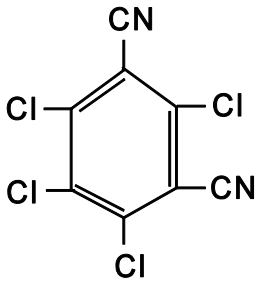
CHLOROTHALONIL

RISK CHARACTERIZATION DOCUMENT

FOR DIETARY EXPOSURE



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I. TECHNICAL SUMMARY

This risk assessment assessed the dietary exposure to chlorothalonil (2,4,5,6-tetrachloro-1,3-benzenedicarbonitrile), SDS-3701, and hexachlorobenzene (HCB) under the mandate of AB 2161 (known as the Food Safety Act) of California.

INTRODUCTION

Chemical Identification- Chlorothalonil is a broad-spectrum fungicide used on fruits, vegetables, ornamentals, turf grass, paints, and wood. The mechanism of action in yeast cells involves the inhibition of glycolytic and respiratory enzymes. The current product registrants are Syngenta Crop Protection, Inc., GB Sciences Inc., and Sipam Agro. The reregistration process at the U.S. Environmental Protection Agency was completed in 2003. In California, chlorothalonil is listed under Proposition 65 as a chemical known to the State of California to cause cancer.

Environmental Fate- Chlorothalonil was hydrolyzed in basic solutions with the formation of metabolites, SDS-19221 and SDS-3701. It was not photodegraded under sunlight, but was biotransformed in both aerobic and anaerobic soil conditions with SDS-3701 as the major metabolite. SDS-3701 was resistant to hydrolysis, photodegradation, and microbial degradation. Chlorothalonil and the metabolites were more mobile in sandy-type than clay-type soils. Foliar application and soil application resulted in chlorothalonil residues on crops. The residues declined with time, washing, and processing. Field trial studies showed metabolites (such as SDS-3701 and HCB) at or near the detection limits.

TOXICOLOGY PROFILE

Pharmacokinetics- In rats, the oral absorption for chlorothalonil was 34% while the dermal absorptions were 1.22%, and 1.34% for chlorothalonil in Bravo^{TM} 720 formulation, latex paint, and alkyd stain, respectively. *In vitro* and *in vivo* studies showed that chlorothalonil was metabolized in the gastrointestinal tract before absorption. Chlorothalonil equivalents were found mostly in the blood, kidneys, and liver. The half-lives of radioactivity in the blood, as well as bile, fecal, and urinary excretions were dose-dependent and increased with the dose. After oral and dermal exposures, the primary route of excretion was in the feces. The excretion of thiol metabolites was influenced by the dosing regimen and involved active secretion in the kidneys. Higher levels of the metabolites were found in the rat compared with those in the dog and monkey. There is no pharmacokinetics study with the inhalation route of exposure.

Acute Toxicity- In general, technical chlorothalonil and formulations are relatively nontoxic by the oral and dermal routes as the LD50s are in the Toxicity Category of III or IV. They are more toxic by the inhalation route with the LC50s generally in Toxicity Category I or II. Chlorothalonil is an eye and skin irritant. Some studies showed chlorothalonil or formulations to be a skin sensitizer. Non-lethal acute effects observed in laboratory animals from oral exposure included clinical signs (soft stools, decreased motor activity, discharges from the eyes, nose, and urogenital area), reduced food consumption and decreased body weights, reduced liver weights, alteration of glutathione levels, and kidney damage (epithelial vacuolation and degeneration)

Subchronic Toxicity- Subchronic exposure of rats and mice to chlorothalonil by the oral route resulted in reduced body weights, discolored urine, and changes in serum chemistry. Lesions were found in the kidney (tubular epithelial hyperplasia, hypertrophy, and vacuolar degeneration), and forestomach (epithelial hyperkeratosis, hyperplasia, thickening of mucosa, erosion, and ulceration). Forestomach lesions were observed after treatment with chlorothalonil, but not with the mono-glutathione conjugate. Increased labeling indices as an indication of cellular proliferation were observed in both the kidney and forestomach tissues. Dermal exposure of rabbits and rats to chlorothalonil resulted in skin lesions and clinical signs (rats only). Reduced plasma alanine transaminase (ALT) levels were observed in rats (dietary), dogs (oral), and rabbits (dermal) after chlorothalonil treatment.

Chronic Toxicity- Rats, mice, and dogs exposed to chlorothalonil showed decreased body weight gain, increased kidney weight, kidney lesions, forestomach lesions, and other effects after chronic oral exposure. Kidney lesions included tubular adenomas and carcinomas, tubular cysts, and tubular epithelial hyperplasia/degeneration. Lesions in the gastrointestinal tract involved the forestomach (hyperkeratosis, erosion, ulcer, papilloma and/or squamous cell carcinoma), glandular stomach (erosion), esophagus (hyperplasia/ hyperkeratosis), and duodenum (hypertrophy). Male rats were more susceptible than female rats, mice, and dogs to chlorothalonil-induced kidney lesions. Chlorothalonil also reduced serum ALT activity in rats and dogs. There are no studies on the effect of chronic inhalation and dermal exposure to chlorothalonil.

Genotoxicity- Chlorothalonil and metabolites (including SDS-3701) were tested negative in bacterial and mammalian cell gene mutation assays and most structural chromosomal assays. At high doses, chlorothalonil was positive in a hamster assay and in an *in vitro* Chinese hamster ovary cell chromosomal aberration assay. DNA studies showed that chlorothalonil and SDDS-3710 did not cause cell transformation in rat cell lines, and chlorothalonil did not bind to rat kidney DNA. However, chlorothalonil caused DNA damage in human peripheral blood lymphocytes.

Reproductive Toxicity- In 2- and 3- generation reproductive toxicity studies, rats showed decreased food consumption, lower body weights, kidney lesions, and forestomach lesions after exposure to chlorothalonil in the diet. The only effect in the pups was a reduction in body weight exposed to chlorothalonil or SDS-3701 *in utero*.

Developmental Toxicity- Chlorothalonil did not cause developmental toxicity in rats or rabbits. However, dams treated with chlorothalonil showed increased mortality, clinical signs (excess lacrimation, vaginal and nose discharges, and anogenital stains), decreased food consumption, and reduced body weight.

Human Exposure- Allergic contact dermatitis and anaphylaxis have been reported in humans exposed to chlorothalonil.

RISK ASSESSMENT

Hazard Identification- The critical acute NOEL for chlorothalonil was 15 mg/kg/day in

pregnant rabbits based on a LOEL of 30 mg/kg/day for reduced food consumption which lead to decreased body weights in the treated rabbits. The critical subchronic NOEL for chlorothalonil was 1.5 mg/kg/day for kidney lesions in rats after 13-weeks of exposure and increased labeling index in rat kidney after 28 days of exposure. The critical chronic NOEL for chlorothalonil was 1.8 mg/kg/day for effects in the kidney observed at 3.8 mg/kg/day in rats. The non-neoplastic kidney lesions included chronic progressive nephropathy, focal epithelial hyperplasia, clear cell hyperplasia, cortical cysts, and pelvic epithelial hyperplasia. The weight of the evidence showed that chlorothalonil was oncogenic in experimental animals studies. Chronic and oncogenicity studies showed that chlorothalonil caused kidney and forestomach tumors in rats (both sexes) and mice (males only) after more than 1 year of exposure in the diet. Kidney tumors were also observed in rats at a higher dosage after shorter-term exposure. The potency factors were $7.5x10^{-3}$ and $1.1\ x10^{-2}$ mg/kg/day^{-1} for q_1 and q_1*, respectively.

For HCB, the chronic NOEL was 0.08 mg/kg/day for liver effects (centrilobular basophilic chromogenesis) in rats. The potency factor for liver tumor was 1.02 mg/kg/day^{-1}.

Exposure Assessment- The dietary exposures were based on monitoring data from USDA Pesticide Data Program and DPR, or tolerances and on the USDA consumption surveys. At the 99th percentile, the acute dietary exposure to chlorothalonil and SDS-3701 ranged from 0.0056 mg/kg/day (females 13-19 not pregnant or nursing, males 20+ years old) to 0.0165 mg/kg/day (nursing infants <1 year old). Exposures at the 95th and 97.5th percentiles were also determined. For chronic dietary exposure to chlorothalonil and SDS-3701, the exposures ranged from 0.00011 mg/kg/day (females 20+ years old, not pregnant or nursing) to 0.00042 mg/kg/day (non-nursing infants). The lifetime exposure was 0.00014 mg/kg/day for the Western region. The chronic dietary exposure to HCB ranged from $4.5x10^{-7}$ mg/kg/day (females 20+ years old, not pregnant or nursing) to $1.92\ x10^{-6}$ mg/kg/day (non-nursing infants). The lifetime exposure to HCB was $7x10^{-7}$ mg/kg/day for the Western region.

RISK CHARACTERIZATION

For acute dietary exposure, the MOEs of all subgroups at 95th to 99th percentiles were greater than 900. For chronic exposure, the MOEs ranged from 4304 (non-nursing infants) to 15732 (females 20+ years old not pregnant or nursing). The oncogenic risks were 1.1×10^{-6} to 1.5×10^{-6} for the population in the Western region with an estimated lifetime exposure of 0.00014 mg/kg/day. The MOEs for chronic exposure to HCB exceeded 40,000 for all population groups. The lifetime risk for HCB exposure was $7\ x10^{-7}$ for the Western region population. Based on a MOE and oncogenic risk benchmarks of 100 and 10^{-6}, respectively, the dietary exposures of chlorothalonil and HCB did not exceed the benchmarks.

RISK APPRISAL

The uncertainties in the hazard identification of chlorothalonil included the selection of 15 mg/kg/day based on reduced food consumption as the acute NOEL, and the assumption of a non-threshold mechanism for oncogenicity. The uncertainties in the dietary exposure assessment included the use of tolerance, 100% crop treatment, and no loss of residues from processing.

The evaluation of the MOEs for potential exposures to chlorothalonil were based on a benchmark of 100, which assumes that the average human is 10 times more sensitive to the effects of a chemical than the most sensitive laboratory animal, and that a sensitive individual is 10 times more susceptible than an average individual. For oncogenic risk, the current DPR default is 10^{-6}, the probability of one in a million.

As for issues related to the Food Quality Protection Act, there was no evidence of chlorothalonil-induced increased pre- or postnatal sensitivity or neurotoxicity. There could be a potential for aggregate exposure to chlorothalonil and this will be addressed in the occupational/residential risk characterization document yet to be prepared. Since the mechanism of chlorothalonil toxicity is unknown, the potential cumulative toxicity between chlorothalonil and other chemicals with a similar mechanism of toxicity could not be evaluated at this time. Chlorothalonil has not been shown to cause endocrine disruption.

TOLERANCE ASSESSMENT

For acute exposure to individual commodities at tolerance levels of chlorothalonil and including background exposure for all commodities, the MOEs were greater than 100 for all population subgroups.

CONCLUSION

The dietary exposure to chlorothalonil residues in food was evaluated in this Risk Characterization Document. The critical toxicity endpoints were derived from experimental animals, and the NOELs were based on reduced food consumption for acute exposure and kidney lesions for chronic and lifetime exposures. The toxicity endpoints for HCB were liver effects in rats after chronic and lifetime exposures. For non-oncogenic effects, the risks of exposure were assessed with a MOE of 100 as the benchmark to determine the scenarios of potential health concern. For oncogenicity, the benchmark was 10^{-6}, the probability of one in a million.

The acute, chronic, and lifetime dietary exposures of chlorothalonil and SDS-3701 were based on monitored residue data and tolerances, when residue data were not available. The analyses at the tier 2 level, with 100% crop treatment assumed, showed relatively low exposure for all population groups. These exposures did not exceed the benchmarks of concern. In the tolerance assessment, the MOEs for acute exposure to chlorothalonil at the tolerance for selected commodities with potential high exposures (cranberry, green bean, pumpkin, broccoli, celery, corn, peach, summer squash, winter squash, and tomato) did not exceed the benchmark of 100. The chronic and lifetime dietary exposures to HCB also did not exceed the benchmarks of concern. While this risk assessment concluded that the dietary exposure to chlorothalonil treated commodities did not pose a health concern, this conclusion should be viewed in the context of the limitations and uncertainties discussed. Furthermore, this assessment did not include considerations of occupational and residential settings. These additional exposures will lead to reductions in the MOEs estimated in this assessment. Dietary exposure may have to be reevaluated using refinements such as percent of crop treated information.

II. INTRODUCTION

A human health risk assessment for dietary exposure to the pesticide, chlorothalonil was conducted under the mandate of California Assembly Bill 2161, known as the Food Safety Act. In experimental animals, adverse effects have been identified in acute toxicity, chronic toxicity, oncogenicity, and chromosomal effects studies with chlorothalonil. A risk characterization document for occupational and residential exposures is pending the completion of the exposure assessment. This assessment also addressed the potential risk associated with dietary exposure to SDS-3701, a metabolite of chlorothalonil; and hexachlorobenzene (HCB), a contaminant in the chlorothalonil formulations.

II.A. CHEMICAL IDENTIFICATION

Chlorothalonil (2,4,5,6-tetrachloro-1,3-benzenedicarbonitrile; tetrachloroisophthalonitrile), is a contact (non-systemic) broad-spectrum fungicide (Ware, 1989). It is fungistatic and is used on fruits, vegetables, ornamentals, turf, paint, stains, and wood. A list of commodities with U.S. Environmental Protection Agency (U.S. EPA) established food use tolerances for chlorothalonil and SDS-3701 is in Appendix A.

Chlorothalonil fungicidal activity involves the inhibition of several enzymes. In yeast, chlorothalonil reacts with glutathione to form substituted glutathione-chlorothalonil derivatives that inhibits specific nicotine-adenosine dinucleotide (NAD) thiol-dependent glycolytic and respiratory enzymes such as glyceraldehyde-3-phosphate dehydrogenase, alcohol dehydrogenase and malate dehydrogenase (Tillman *et al.*, 1973). Chlorothalonil also inhibits yeast *a*-chymotrypsin activity (Long and Seigel, 1975). Chlorothalonil affects the catalytic activity of this enzyme by reacting with the sulfhydryl sites (cysteine-149) of the protein subunits responsible for the binding of glyceraldehyde 3-phosphate.

II.B. REGULATORY HISTORY

II.B.1. Chlorothalonil

Chlorothalonil was first introduced by Diamond Shamrock Corporation in 1965 (Edwards *et al.*, 1991). Current registrants of chlorothalonil-containing products are: Syngenta Crop Protection, Inc. (a merger between Novartis Crop Protection, Inc., and Zeneca Ag Products, Inc.), GB Sciences Inc. (previously ISK Biosciences Corp.), and Sipam Agro USA (formerly Sostram Corporation). Previous registrants included SDS Biotech Corporation, Fermenta Plant Protection, and Fermenta ASC Corporation.

The U.S. EPA issued the first Registration Standard in 1984 and concluded that additional data were necessary for health evaluation. In 1988, U.S. EPA revised the Standard and issued the draft guidance for the reregistration of chlorothalonil (U.S. EPA, 1988). The Reregistration Eligibility Document (RED) was issued in 1999 (U.S. EPA, 1999a) and the reregistration process was completed in 2003 (U.S. EPA, 2003). The RED concluded that HCB, as a contaminant in technical chlorothalonil and manufacturing-use products, needed to be reduced to 40 ppm in order to protect humans from oncogenic concerns. Workers needed additional protective

measures, which included improved packaging (*i.e*. water-soluble bags), additional worker protective clothing (masks, gloves, respirators), and change in work practices (handling of treated sod by mechanical means instead of by hand). To mitigate residential handler exposure, the use of chlorothalonil on home lawns was deleted from labels (U. S. EPA, 1999b). For wildlife, protective measures included reduced seasonal maximum application rates and buffer zones. Additional data were required for studies on the effect of chlorothalonil on marine/estuarine fish, mollusk, and shrimp, fish early life stage, and aquatic plant growth; foliar residue dissipation; post-application dermal and inhalation passive dosimetry exposures; residue study for SDS-3701 on foliage; use patterns on cut flowers; as well as exposure data for handlers, both workers and residents who might be involved in wood pressure treatment or use of treated wood. In 2001, the U.S. EPA approved additional food uses, which included almonds, asparagus, mangoes, non-bell peppers, pistachios, and ginseng (U.S. EPA, 2001a and b). Tolerances were established for the metabolite SDS-3701 for milk and meat commodities (U.S. EPA, 2001a).

The U.S. EPA acute reference dose (RfD) is 0.58 mg/kg/day for increased cell proliferation and lesions in forestomach and kidney tissues with a lowest-observed-effect level (LOEL) of 175 mg/kg/day in a rat subchronic toxicity study (Ford and Killeen, 1987a; U.S. EPA, 1999a). The chronic RfD is 0.02 mg/kg/day based on a no-observed-effect level (NOEL) of 2 mg/kg/day and an uncertainty factor of 100 for forestomach and kidney lesions in a 2-year feeding study in rats (Wilson and Killeen, 1989; Whiting, 1997). U.S. EPA considered chlorothalonil as a compound likely to be a human carcinogen by all routes of exposure. The calculated cancer potency factor (q_1*) is 7.66 x 10^{-3} $(mg/kg/day)^{-1}$ as human equivalents based on renal (adenoma and carcinoma) tumors found in female rats (Wilson *et al.*, 1985c) (Fisher, 1995). More detailed discussion of U.S. EPA reference doses is in **IV. D.** The U.S. EPA longer-term drinking water health advisory level is 0.2 mg/L for a 10-kg child (U.S. EPA, 1994). Since appropriate short-term data were not available, the longer-term level is also used for one-day and ten-day health advisories. This level is based on the finding of kidney lesions in rats. For adults, the longer-term and lifetime health advisory levels are 0.5 mg/L and 0.15 mg/L, respectively, for a cancer risk probability of 1 x 10^{-4}.

In California, chlorothalonil was listed in 1989 under California Proposition 65 as a chemical known to the State to cause cancer. The Office of Environmental Health Hazard Assessment calculated an expedited human cancer potency factor of 0.0031 $(mg/kg/day)^{-1}$ based on rat kidney tumors from a National Cancer Institute (NCI) study (NCI, 1978a) and a No Significant Risk Level for Carcinogens of 200 *u*g/day (Cal/EPA, 1994). An additional No Significant Risk Level of 60 *u*g/day is listed based on the potency factor (q_1*) of 0.011 for kidney tumors in female rats calculated by the U.S. EPA (Engler, 1994). A potency factor (q_1*) of 0.011 $(mg/kg/day)^{-1}$ based on kidney tumors in female rats has been established by the International Agency for Research on Cancer (Engler, 1994). In addition, chlorothalonil has been identified as a potential toxic air contaminant under California Assembly Bills 1807 and 3219 (Kelley and Reed, 1996).

At the international level, the World Health Organization (WHO) calculated an acceptable daily intake (ADI) of 0.03 mg/kg/day based on a 2-year feeding study in dogs (Black, 1993; IPCS, 1994). The no-observed-adverse-effect level (NOAEL) was 120 ppm (3.0

mg/kg/day) and an uncertainty factor of 100 was applied. In evaluating the data, WHO noted quantitative differences in the pharmacokinetics of chlorothalonil in rats, germ-free rats, monkeys, and dogs. Since the mechanism of toxicity was based on thiol levels, WHO concluded that the dog or the monkey would be a more suitable model than the rat for assessment of risk in humans. Health and Welfare Canada reached the same conclusion as the WHO regarding species differences (Health and Welfare Canada, 1994). However, the Canadian ADI (0.015 mg/kg/day) was calculated based on kidney lesions in rats because of concerns regarding limited information on dogs and monkeys.

II.B.2. Impurities and Metabolites

SDS-3701, a major metabolite, is found after the metabolism of chlorothalonil in plant, soil, and cows. Since SDS-3701 was found in milk and meat of cows fed SDS-3701, the U.S. EPA established tolerances for this metabolite in animal tissues and milk (U.S. EPA, 2001a). A review of the limited database showed SDS-3701 was not oncogenic in rats or mice, not teratogenic (> 5mg/kg) in rabbits under experimental conditions, but caused a reduction of weanling body weights in a reproductive toxicity study. The oral LD_{50} was 422 mg/kg for male rats and 242 mg/kg for female rats.

Hexachlorobenzene (HCB) is an impurity from the production of chlorothalonil (U.S. EPA, 1988). The current U.S. EPA approved upper-certified limit is 0.05% for HCB in technical chlorothalonil. ISK Biosciences reported a reduction of HCB to 0.004% (Hawkins, 1996). Hexachlorobenzene is classified by U.S. EPA as a B_2 carcinogen based on an increased incidence of tumors in the liver, thyroid and kidney in hamsters, mice, and rats (U.S. EPA, 1996). The potency factor (q_1*) for carcinogenicity is 1.6 $(mg/kg/day)^{-1}$ based on hepatocellular carcinomas in female rats and hamsters. The chronic reference concentration was 0.0008 mg/kg/day for liver effects (centrilobular basophilic chromogenesis) in rats.

II.C. TECHNICAL AND PRODUCT FORMULATIONS

In 2003, 48 chlorothalonil-containing products were registered for use in California. They are in forms of concentrates, dust/powder, solution, granules/ flakes, and paint coating (DPR, 2003). Chlorothalonil is also mixed with other fungicides (mefenoxam in Flouronil™, propamocarb hydrochloride in Tattoo™, thiophanate methyl in Spectro™, 3-iodo-2-propynyl butyl carbamate in Bioflex™) and a biocide (tributyltin oxide in Cuprinol™). The amount of active ingredients in these products ranged from 0.087% to 98%.

Chlorothalonil is a known eye and skin irritant, as well as a skin sensitizer (Pearson, 1999). The product labels contain warnings concerning eye and skin contacts that may cause injury, allergic reactions, skin sensitization, and bronchial irritation.

II.D. USAGE

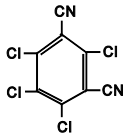
The Department of Pesticide Regulation (DPR) Full-Use Reports showed an average of 749,000 pounds used per year (1,183,053 pounds in 1998 to about 630,000 pounds in 2002) (DPR, 1998-2002). Over these years, the highest was 1.2 million pounds in 1998. In 2002, the

major uses (and percentages of the total amount used) were: tomatoes (fresh and processing, 29%), landscape (11%), potato (9%), celery (8%), onions (8%), and nursery (6%).

II.E. ILLNESS REPORTS

From 1994 through 2001, there were 122 reported cases of illness/injury associated with exposure to chlorothalonil alone (Mehler, 2003). The illness/injury cases were caused primarily by accidental exposure (including drift). Common complaints included: weakness, difficulty in breathing or shortness of breath, lung irritation, eye irritation (sore, burning, itchy, red, conjunctivitis), dizziness, nausea, vomiting, headache, skin irritation (rash, red, itchy, burning, blistery). Additional information from case reports in the published literature is described in section **III.I. HUMAN EXPOSURE.**

II.F. PHYSICAL AND CHEMICAL PROPERTIES [a]

Chemical and a common name:	Chlorothalonil
CAS Registry number:	1897-45-6
Trade names:	Acticide, Add-2, All Pro, Bioflex, Biotrend, Black Leaf, Bonide, Bravo, Bravado, Busan, Clortram, Countdown, Cuprinol, Daconil, Dexol, Echo, Ensign, Fluoronil, Fung-onil, Gardentech, Jomax House, M-1, Manicure, Nexgen, Nuocide, Prescription Treatment, Ridomil, Spectro, Tatto.
Molecular formula:	$C_8Cl_4N_2$
Molecular weight:	265.89 g/mole
Chemical structure:	
Physical appearance:	White crystalline solid, odorless in pure form
Solubility:	Practically insoluble in water (0.6 mg/L at 25°C); soluble in organic solvent at 25°C: xylene 80 g/kg, cyclohexane 30 g/kg, acetone 20 g/kg, kerosene < 10 g/kg.
Boiling point:	350°C at 760mm Hg
Melting point:	250°-251°C
Vapor pressure:	5.72×10^{-7} torr at 25°C
Octanol-water coefficient:	7.62×10^{2}
Henry's Law constant:	1.40×10^{-7} atm. m^3/mole

a/ References: The Merck Index, 1989; Farm Chemicals Handbook, 1997; Edwards *et al.*, 1991; Formanik and Walls, 1987; Formanik and Walls, 1988; Manning, 1980; De Pablo, 1980; Szalkowski *et al.*, 1981; Cryberg, 1983; Cryberg, 1987a; Cryberg, 1986; Cryberg, 1987b, Fermenta Plant Protection, 1988; and Leffingwell, 1989.

II.G. ENVIRONMENTAL FATE

Summary: Chlorothalonil was hydrolyzed in basic solutions with the formation of metabolites, SDS-19221 and SDS-3701. It was not photodegraded under sunlight, but was biotransformed in both aerobic and anaerobic soil conditions with SDS-3701 as the major metabolite. SDS-3701 was resistant to hydrolysis, photodegradation, and microbial degradation. Chlorothalonil and the metabolites were more mobile in sandy-type than clay-type soils. Foliar application and soil application resulted in chlorothalonil residues on crops. The residues declined with time, washing, and processing. Field trial studies showed metabolites (such as SDS-3701 and HCB) at or near the detection limits.

II.G.1. Hydrolysis

In the absence of light, chlorothalonil was degraded in basic buffered (pH 9) solutions via hydrolysis and substitution reactions (Szalkowski, 1976). The degradation followed first order kinetics and the degradation products were 3-cyano-2,4,5,6-tetrachlorobenzamide (SDS-19221, 55%) and 4-hydroxy-2,5,6-trichloro-isophthalonitrile (SDS-3701, 22%). SDS-3701 was not hydrolyzed at any pH levels (pH 5, 7, or 9).

II.G.2. Photolysis or Photodegradation

Chlorothalonil and SDS-3701 were not photodegraded when placed on soil thin films and exposed to the equivalent of 168 days of sunlight (12 hours of sunlight per day) (Szalkowski and Stallard, 1983). Neither compound adsorbed to the treated soils. On the other hand, chlorothalonil in aqueous solution was photolyzed when exposed to artificial sunlight for 118 days (Nelson, 1987). The major metabolite detected was SDS-3701.

II.G.3. Microbial Degradation

Chlorothalonil was degraded in soils under aerobic and anaerobic conditions. The following is a summary of several studies. The half-life for chlorothalonil in the soil was dependent on the soil type, temperature, moisture content, and presence of microbial organisms. In field tests with different types of soil (clay loam, sandy loam, and silt loam), the average half-lives for chlorothalonil in the soil was 1 to 2 months (Stallard, 1971). Degradation was more rapid in soils with lower clay content and higher sand content. Wolfe and Stallard (1968) reported half-lives ranged from 36 days for sandy loam soil to 220 days for clay soil. High soil temperature (100°F *vs*. 76°F) increased the degradation rate (Stallard, 1971). Further investigation by Stallard (1971) showed that chlorothalonil was rapidly degraded in unsterilized soil and moist soil. The half-lives of chlorothalonil ranged from 10 to 36 days in non-sterile soils and were 2-6 fold longer in sterile soils (Szalkowski and Stallard, 1976b; Doran, 1988). The half-lives increased from 6 days to > 70 days for 9% to 0.6% moisture. Under anaerobic conditions, the half-life of chlorothalonil was 6-9 days in sandy loam and silty loam soils (Nelson *et al.*, 1985a). In these degradation studies, the metabolites were SDS-3701 (major) and SDS-19221 (Duane, 1970; Szalkowski and Stallard 1976 a and b; Stallard, 1971; Doran, 1988). SDS-3701 was apparently not further degraded in soil (Szalkowski and Stallard, 1976a).

II.G.4. Mobility (Soil, Air, Water, Plants)

Chlorothalonil was relatively immobile in soils (Szalkowski *et al.*, 1979; Szalkowski and Stallard, 1976a). When the adsorption and desorption of chlorothalonil were examined in different soil types, approximately 90% of the chlorothalonil in solution was adsorbed to the silty and silty clay loam soils (Capps *et al.*, 1982). The sandy loam and sand soils adsorbed 84% and 47% of the chlorothalonil, respectively. The adsorption constants (K) for silt, silty clay loam, sandy loam, and sand soils were 29, 26, 20, and 3, respectively. There was no definite correlation between the adsorption constant and the organic matter content of the soils. Chlorothalonil adsorbed strongly (2 to 5% desorbed) to most of the soil types and was not expected to leach significantly from silt, silty clay loam, and sandy loam soils. It may leach to some extent (10-28% desorbed) in sandy soils.

On the other hand, SDS-3701 had medium mobility potential and was more mobile in soils with high sand and low clay contents (Wolfe and Stallard, 1968; Szalkowski *et al.*, 1979; Szalkowski and Stallard, 1976a and 1983; Nelson *et al.*, 1985b; Doran, 1988). The calculated Freundlich isotherm coefficient based on organic content, K_{oc}, ranged from 251 to 491 for adsorption, and from 276 to 451 for desorption (Archer, 1991).

Two field dissipation studies were conducted in Greenfield, CA and Phelps, NY. Earlier studies (Formanik, 1989; Rose and Ballee, 1988; Ballee *et al.*, 1987) were considered unacceptable due to inadequate sampling depth. In Greenfield, CA, the fields were planted with broccoli and treated with multiple applications of BravoJ 500 (2.25 pints/acre) (King, 1989; Peplowski, 1991). The highest chlorothalonil residue in soil was 2.2 ppm at the depth of 0 to 3 inches after the last application. Chlorothalonil was not detected (minimum detection limit, MDL, =0.01 ppm) below 9-12 inches after 62 or more days. SDS-3701 was the only metabolite detected (highest value of 0.28 ppm) in all samples of 0-6 inches deep. After 18 months, the SDS-3701 level decreased to 0.10 ppm at 0-6 inches. The levels were either at or below the detection limit (0.01 ppm) for deeper soil samples. Other metabolites (SDS-46851, SDS-47525, SDS-47523/24, and SDS-19221), and hexachlorobenzene (HCB) were detected either at low levels or not detected (MDL range 0.01- 0.03 ppm). Pentachlorobenzonitrile (PCBN) was detected up to the depth of 9 inches. The calculated half-lives for chlorothalonil were 40 days by the investigators and 51.0 days by DPR (Leffingwell, 1991).

In the NY trial, fields were planted with potatoes only or with potatoes followed by rotational crops (Kenyon and Ballee, 1991). Chlorothalonil residues were found primarily in the first 6 inches of soil; the highest mean level was 4.71 ppm at 0-3 inch depth and 6 days after the last application. Plowing, planting, and harvesting activities occasionally increased the residue level. SDS-3701 residues were found at depths up to 9 inches for all samples and were generally low (0.01-0.18 ppm). Findings for the other metabolites were similar to those reported for the CA study.

II.G.5. Plant Residues/Metabolism

Early studies showed that chlorothalonil (^{14}C) did not translocate after topical applications on cucumber, bean, or tomato leaf (Kunkel, 1967a). Chlorothalonil residues were

found in food crops grown in chlorothalonil-treated soil (Kunkel, 1967b) and after foliar applications to vegetables, fruits, and other commodities (Dillon *et al.*, 1985; Diamond Shamrock Corporation, 1985; Stallard, 1970; Ballee, 1976; Markle, 1979; Ballee *et al.*, 1980a and b; Diamond Shamrock Corporation, 1979a and b, 1980a and b, 1981; Nelson *et al.*, 1983; Huhtanen, 1993). Numerous field trials have been conducted and summaries of the more recent studies are discussed in the following paragraphs.

Field trials for soybean, coffee bean, cocoa bean, dry bean, and peanut were conducted (Dillon *et al.*, 1985). Samples with zero residues were assigned a value of 0.05 ppm, which was the lowest detected level. There were seven field trials with soybean; the highest residue was 0.08 ppm, and the mean residue level was 0.037 ppm. For coffee bean, the four trials showed the highest residue at 0.11 ppm and an overall mean of 0.063 ppm. Both cocoa bean and dry bean showed residue levels of zero in all four trials. There were also four field trials for peanut; the highest residue level was 0.29 ppm and the overall mean was 0.12 ppm.

Field trials in several states (Maine, Georgia, Mississippi, North Carolina, New Jersey, and Michigan) were conducted with blueberries at various growing stages (bud break to pink berry) and 1 to 5 applications of chlorothalonil (Bravo 720, 3 to 25 pints/acre) with preharvest interval ranged from 42 to 101 days (MacGregor, 1990). There was no obvious correlation between residues and application rates, plant stage, or preharvest intervals. Chlorothalonil residues ranged from <0.010 ppm to 0.595 ppm (4 applications at 3 pints per acre, applied at bud break to petal fall, 75 days PHI). None of the metabolites (SDS-3701, SDS-46851) or manufacturing impurities (HCB or PCBN) residues was detected. The detection limits were 0.01 ppm (SDS-3701), 0.03 ppm (SDS-46851), 0.003 ppm (HCB), and 0.005 (PCBN).

Five field trials were conducted in Florida with several variety of mangos (Tommy Atkins, Keitt, and VanDyke) treated with chlorothalonil (Bravo 500, 1.3 lbs per acre, PHI 0 to 21 days, 7 to 19 applications) (Biehn, 1991). The ranges of chlorothalonil residues (and PHI) in these varieties were: 0.347 ppm to 1.202 ppm (7 days), 0.085 ppm to 0.803 ppm (14 days), and 0.055 ppm to 0.289 ppm (21 days). Residues for the metabolites (SDS-3701, SDS-46851) and manufacturing impurities (HCB or PCBN) were close to or below the detection limit for all samples. The detection limits (range for all trials) were 0.02 ppm-0.05 ppm (SDS-3701), 0.02 ppm-0.05 ppm (SDS-46851), 0.01 ppm (HCB), and 0.01 (PCBN).

Four field trials were conducted in several states (Michigan, Oklahoma, California, and Washington) with chlorothalonil (Bravo 500 at 3 to 6 pints/acre, or Bravo 720 at 1.50 to 4.00 pints/acre, 3-8 applications, PHI 97 to 262 day) on asparagus ferns during the fall (Ruhland, 1991). Chlorothalonil, metabolite (SDS-3701), and impurities (HCB and PCBN) were not detected on the asparagus spears harvested in the following spring. SDS-46851 was detected in treated plots in Michigan and Oklahoma; however, the significance of these levels was unclear since the levels (0.03 ppm to 0.05 ppm) were the same as those in the untreated control.

Four field trials were conducted in California with chlorothalonil (Bravo 500, 6 pints/acre, PHI 148 to 170 days) on almond nutmeats and hulls (King and Prince, 1995). In the nutmeat, chlorothalonil residues were <0.01 ppm to 0.04 ppm while SDS-3701 and HCB residues were at below the detection limits of 0.01 and 0.00025 ppm, respectively. In almond

hulls, chlorothalonil residues were <0.01 ppm to 1.07 ppm. SDS-3701 and HCB were close to or below the detection limits.

Another 3 field trials on almond nutmeats and hulls were conducted in California using chlorothalonil (Echo 720, 3.1 lbs/acre, 6 applications at pink bud to shuck split, PHI 146 to 152 days) (Jones, 2002). For all three locations, nutmeat residues of chlorothalonil, SDS-3701, and HCB were below the detection limits, which were 0.01 ppm, 0.01 ppm, and 0.005 ppm, respectively. In the hulls, the mean resides for the sites ranged from 0.139 ppm to 0.339 ppm for chlorothalonil, and from 0.04 ppm to 0.0631 ppm for SDS-3701. HCB residue in the hulls was at or below the detection limit.

A field trial was conducted in California with chlorothalonil (Echo 720, 2 pints/acre, 10 applications, PHI 0 day) on carrots (Alcaraz, 2002). After the tops were removed, the carrots were found to contain 0.5 ppm chlorothalonil and <0.05 ppm SDS-3701.

The effect of spray-tank adjuvant on the persistence, distribution, and degradation of chlorothalonil (Bravo 720, 6.4 L/ha, 2 applications) on cranberry plants and fruits were studied in a commercial cranberry bog (Putnam *et al*., 2003). Foliage samples of growing cranberry plants were collected at 1 hour; 3, 7, 13, and 28 days after each application. Fruits were collected during late fruit development and until cranberry harvest (76 days after the second application). Soil sample was collected on the last sampling period. On the foliage, the estimated half-life was 12 days and 13 days after the second application in the presence and in the absence of the adjuvant, respectively. On the mature fruits, chlorothalonil levels were 0.076 ppm and 0.049 ppm in the presence and in the absence of the adjuvant, respectively. SDS-3701 (Compound II) was 0.04 ppm, about 60% of the chlorothalonil level. The combined chlorothalonil and SDS-3701 levels were 0.129 ppm and 0.0795 ppm in the presence and in the absence of the adjuvant, respectively. The other metabolites detected were 1,3-dicarbamoyl-2,4,5,6-tetrachlorobenzene (Compound III) and 2,5,6-trichloro-4-methoxyisophthalonitrile (Compound IV) but were at relatively low levels (0.007 ppm and 0.021 ppm, respectively). Compounds V (1-carbamoyl-3-cyano-4-hydroxy-2,5,6-trichlorobenzene), VI (2,4,5-trichloroisophthalonitrile), and VII (2,5,6-trichloro-4-methylisophthalonitrile) were below the detection limits (0.025 to 0.001 ppm). Soil analysis showed chlorothalonil and six metabolites (Compounds II to VIII; Compound VIII is isophthalonitrile). Compounds II and III were the major metabolites with the others at much lower levels. Compounds III, V, VI, and VII had not previously been detected in chlorothalonil treated soils.

Three field trials (two in Pennsylvania and one in California) were conducted with chlorothalonil (Bravo 500, 0.26 lbs and 0.13 lbs active ingredients/1000 square feet of mushroom bed surface, 2 applications) on Agaricus mushrooms (Thompson, 1995). Mushrooms were collected from the first harvest at 5 days and 7 days after the second application, and the second harvest 2 days later. Additional samples were collected to determine the effect of one-time washing and rinsing on the residues. The highest residues were detected on the first break and 7 day PHI samples. The residues were 0.51 ppm for chlorothalonil and 0.174 ppm for SDS-3701; the combined total residue was 0.684 ppm. Much lower levels were found in the second crop; maximal residues were 0.119 ppm and <0.01 ppm for chlorothalonil and SDS-3701, respectively.

No HCB was detected (detection limit of 0.003 ppm) in any samples. Washing of the day 5 samples removed the compost materials on the mushrooms and reduced the residues by more than 75%. Maximum chlorothalonil and SDS-3701 residues in these washed samples were 0.037 ppm and 0.046 ppm, respectively.

Three field trials (one in Arizona and two in California) were conducted with chlorothalonil (Bravo 720, 4.5 lbs active ingredient/acre, 5 applications, PHI 14 days) on pistachio trees (Thompson, 1996). The maximum residues from the three trials were 0.141 ppm (range <0.01 to 0.141 ppm) chlorothalonil, <0.01 ppm SDS-3701, and <0.003 ppm HCB.

II.G.6. Plant Residues - Processing

Washing and processing reduced residue levels on the treated commodities (Marks, 1985; Diamond Shamrock Corporation, 1979c; Szalkowski *et al.*, 1980). Bravo 500J (4.25 pints/acre, the recommended rate, and 8.5 pints/acre) was applied to tomatoes (Szalkowski *et al.*, 1980). After seven applications, the mean chlorothalonil residue levels were 2.5 and 4.7 ppm for the above rates. SDS-3701 levels were at or below the detection limit of 0.01 ppm. Washing reduced the residues by 74%. Chlorothalonil residues were detected in the pomace (2.23 and 3.82 ppm for the two rates), juice (0.02 and 0.78 ppm), condensate (<0.0003 ppm, MDL), and paste (<0.01 and 0.02 ppm). The DPR calculated processing factors were 0.008 (0.02 ppm/2.5 ppm) for juice, and 0.004 (0.01 ppm/2.5 ppm) for paste. SDS-3701 residues in these fractions were below the detection limit, except 0.02-0.04 ppm in the pomace, and 0.01-0.03 ppm in the paste.

Additional processing studies and metabolite analyses have been conducted on carrot (King and Prince, 1990a), potato (King and Prince, 1993), snap bean (Ballee *et al.*, 1980c), cucumber (King and Ballee, 1987), winter squash (King and Prince, 1990b), cherry (Ballee, 1997a), and peach (Ballee, 1997b) using Bravo 500, 702, and 6F. The results of these studies are summarized in Table 1. Chlorothalonil residues were detected in carrot, snap bean, cucumber, winter squash, cherry, and peach. Processing reduced the chlorothalonil and metabolite residues close to or below the detection limit. The reduction factors for washing were 0.01 for cherry, peach, and snap bean; 0.08 for cucumber; and 0.005 for carrot. The reduction factors for cooking were 0.01 for cherry and snap bean; 0.001 for peach, 0.015 for cucumber, 0.003 for winter squash, and 0.005 for carrot.

Table 1. Chlorothalonil and metabolite residues in raw agricultural commodities and processed forms.

Commodity (Formulation)	Rate pt/A	PHI	Form	Mean Residue Levels (as a range for 1x to 2x application rate, ppm)[a]					Ref[b]
				CTL	3701	46851	HCB	PCBN	
Tomato Bravo 500 (40% CTL)	4.25, 8.5	?	RAC Pomace Juice Condensate Paste	2.5-4.7 2.23-3.82 0.02-0.78 <0.0003 <0.01-0.02	ND ND-0.02 ND-0.04 ND 0.01-0.03	NA	NA	NA	1
Carrot Bravo 720 (54% CTL)	2, 20	0	unpeel processed[c]	0.04-2.23 ND	ND-0.06 ND	ND	ND	0.008 0.058-ND	2
Potato Bravo 720 (54% CTL)	1.35 13.5	21	RAC and all forms[d]	ND	ND	ND	ND	NA	3
Snap bean Bravo 6F (40% CTL)	?	88	RAC air cleaned processed[e]	0.84 0.54-ND ND	ND	NA	NA	NA	4
Snap bean Bravo 500F	?	10	RAC processed[f]	0.78 ND-0.09	ND	NA	NA	NA	4
Cucumber Bravo 500 (40% CTL)	4.66	12 hrs	RAC washed processed[g]	1.32 0.71-0.52 ND-0.38	0.01 ND ND	ND	ND	0.011 0.006-ND 0.008-ND	5
Winter Squash Bravo 720 (54% CTL)	3	2.75 hrs	RAC processed[h]	3.23 ND	0.02 ND	0.06 ND-0.04	ND	0.043 ND	6
Cherry Bravo 6F (54% CTL)	3	7	RAC washed-canned	2.74 0.38-0.52 0.03	ND	NA	NA	NA	7
Peach Bravo 6 F (54% CTL)	?	7	RAC washed canned	12.9 0.21-5.86 0.21	ND	NA	NA	NA	8

a/ Detection limits: <0.01 ppm chlorothalonil, <0.01 ppm SDS-3701, <0.03 ppm SDS-46851, <0.03 ppm HCB, and <0.005 ppm PCBN. Abbrevations: PHI=preharvest interval, CTL=chlorothalonil, RAC=raw agricultural commodities, ND=below detection, NA=not analyzed.

b/ References: 1. Szalkowski *et al.*, 1980; 2. King and Prince, 1990a; 3. King and Prince, 1993; 4. Ballee et al., 1980c; 5. King and Ballee, 1987; 6. King and Prince, 1990b; 7. Ballee, 1997a; and 8. Ballee, 1997b.

c/ peeled, pureed, partially cooked, or baby food

d/ washed RAC, french fries, potato chips, potato granules

e/ after washing, blanching, or canning

f/ beans only after second wash, sliced and chopped before blanching, or after steam or water blanching

g/ brined sliced pickle, cold canned pickles, cold canned pickle juice, hot canned pickles, or hot canned pickle juice

h/ peeled squash, milled squash, partially cooked squash, or baby food.

III. TOXICOLOGY PROFILE

Pharmacokinetic and toxicity studies of chlorothalonil are summarized in this section. Acceptability of the studies (except genotoxicity studies) by DPR where noted, was determined by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guidelines. The acceptability of the genotoxicity studies is based on the Toxic Substances Control Act guidelines (Federal Register, 1985 and 1987). The toxicology summary for studies reviewed for The Birth Defect Prevention Act of 1984 (SB 950) is included in Appendix B.

While this document is for the risk characterization of dietary exposure to chlorothalonil, this toxicology profile is a comprehensive review of all studies and will serve as a reference for the risk characterization of inhalation exposure. When the actual dosage (in term of mg chlorothalonil/kg/day) is not given in the study, a default consumption rate is used to convert ppm of chlorothalonil in the diet to the dosage unit (Appendix C). For the inhalation studies, the air concentrations were determined by either gravimetric or analytical methods. The exposure dose was corrected for % of active ingredient and converted to equivalent dosage terms using default respiration rates for experimental animals and amortized for daily exposure (Appendix C). The dosages in the study summaries are not corrected for absorption because the exposure estimates were in terms of residue levels on the commodities, not internal doses. Summary tables for selected toxicity studies considered for NOELs and LOELs for oral exposures are in Tables 4, 8, and 14 for acute, subchronic, and chronic exposures, respectively.

III.A. PHARMACOKINETICS

Summary: In rats, the oral absorption for chlorothalonil was 34% while the dermal absorptions were 1.22%, and 1.34% for chlorothalonil in Bravo™ 720 formulation, latex paint, and alkyd stain, respectively. *In vitro* and *in vivo* studies showed that chlorothalonil was metabolized in the gastrointestinal tract before absorption. Chlorothalonil equivalents were found mostly in the blood, kidneys, and liver. The half-lives of radioactivity in the blood, as well as bile, fecal, and urinary excretions were dose-dependent and increased with the dose. After oral and dermal exposures, the primary route of excretion was in the feces. The excretion of thiol metabolites was influenced by the dosing regimen and involved active secretion in the kidneys. Higher levels of the metabolites were found in the rat compared with those in the dog and monkey. The biotransformation of chlorothalonil in the rat is presented in Figure 1. There is no pharmacokinetics study with the inhalation route of exposure.

III.A.1. Oral - Rat, Dog, and Monkey

III.A.1.a. Absorption

The oral absorption of chlorothalonil was determined in Sprague-Dawley rats (8 males and 4 females) with bile ducts cannulated (Marciniszyn *et al.*, 1985c). In 50% of the animals of each sex, a second cannula was inserted into the bile duct leading into the duodenum for the infusion of sodium taurocholate (50 mg/ml) to study the effect of bile salt on biliary excretion. All animals were then given a single dose of ^{14}C-chlorothalonil (radiochemical 95.5% pure, technical 99.7% pure; 5 mg/kg) by gavage. Bile was collected hourly for 48 hours. Blood and

urine samples were collected 6, 24, and 48 hours after dosing. Fecal samples were collected 24 and 48 hours after dosing. The radioactivity in the blood was maximal (< 0.4% of dose) at the earliest sampling time (6 hours) and decreased with time. The presence of sodium taurocholate did not affect the radioactivity level in the bile or urine. However, more bile (about 2-fold) was excreted in rats treated with sodium taurocholate than those without treatment. The excretion of radioactivity in the bile was rapid with peak concentrations occurring within 2 hours after dosing. At 48 hours after dosing, distribution of the 5 mg/kg dose (as average % of dose for both sexes) was: bile (19%), urine (10%), and carcass (2%). The absorbed dose was 34% (31% corrected for 91% recovery), the sum of the 3 compartments. The non-absorbed dose was about 60% (56% in the feces and 6% in the gastrointestinal tract).

The absorption of chlorothalonil in the dog was less than that for the rat. Male beagle dogs (4) with cannulated bile ducts were given a single oral dose of ^{14}C-chlorothalonil (radiochemical 99.5% pure; 50 mg/kg) by gavage (Savides *et al.*, 1995b). The average percentages of the administered dose in the bile, urine, liver, kidney, and carcass were 5.12%, 1.44%, 0.05%, 0.02%, and 1.13%, respectively. The total absorbed dose was 7.75% with the remainder of the dose in the feces (81%) and in the gastrointestinal tract (0.9%). The use of methylcellulose as the vehicle (Savides *et al.,* 1989b) or regurgitation of the dose (Magee *et al.,* 1992) resulted in lower absorption factors in these studies.

III.A.1.b. Distribution

After oral dosing, most of the radioactivity was found in the gastrointestinal tract. Male Sprague-Dawley rats (5/group) were given a single dose of ^{14}C-chlorothalonil (98% pure; 0, 5, 50, or 200 mg/kg) by gavage (Lee *et al.*, 1982). Seventy-six to 80 percent of the initial radioactivity was in the small intestine (2 hours) while 87-95% was in the large intestine contents after 2 hours (Lee *et al.*, 1982). At this time period, the gastrointestinal tract contents contained chlorothalonil equivalents proportional to the dose intervals. However, for the later time points, more *u*g equivalents were found in the gastrointestinal tract of the 50 and 200 mg/kg animals and were not proportional to the dose interval. The result suggested saturation of tissue clearance of chlorothalonil and its metabolites at higher doses (50 and 200 mg/kg).

Chlorothalonil equivalents in the blood were also dependent on the dose. Sprague-Dawley rats (4/sex/group) were given ^{14}C-chlorothalonil (≥ 95.5% pure; 5, 50, or 200 mg/kg) by gavage and sacrificed 2, 9, 24, 96, and 168 hours later (Marciniszyn *et al.*, 1984a; Marciniszyn *et al.*, 1985a). The only clinical sign noted was loose stools in the 200 mg/kg group. The peak blood radioactivity for all groups was less than 1% of the dose and occurred between 2 (for 5 mg/kg) to 9 hours (for other doses). In males, there was a dose-related difference in the half-lives of radioactivity of chlorothalonil and equivalents in the blood; 7 hours for 5 and 50 mg/kg, and > 10 hours for 200 mg/kg. Radioactivity levels in the blood of males were lower (50%) than those for the females at 5 and 50 mg/kg, but were the same as the females at 200 mg/kg. Dose-related differences in the blood levels have also been reported in other studies (Lee *et al.*, 1982; Pollock *et al.,* 1983*;* Savides *et al.*, 1985b and 1986b*).*

The effect of multiple dosing on the blood levels was studied with Sprague-Dawley rats (4/sex/group for a single dose; 4 male/group for multiple doses) given ^{14}C-chlorothalonil

(radiochemical 95.5-98.6% pure, technical 99.7% pure; 1.5, 5, 50, or 160 mg/kg/day) by gavage for 5 days (Savides *et al.*, 1985b; Savides *et al.*, 1986b). The peak blood level was reached 2 hours after the fifth dose for all dose groups. The urinary excretion of radioactivity decreased with increased dose levels; however, the difference was < 2% between single and multiple dosing.

Kidneys and liver contained the highest levels of radioactivity for chlorothalonil (Marciniszyn *et al.*, 1984a; Marciniszyn *et al.*, 1985a; Lee *et al.*, 1982). In the kidneys, chlorothalonil equivalents were distributed to organelles. Male Sprague-Dawley rats (12/group) were given a single dose of ^{14}C-chlorothalonil (97.1% pure; 50 mg/kg) by gavage and then sacrificed 6 hours later (Kidon *et al.*, 1987). The distribution of radioactivity (as % of the homogenate) was: nuclear pellets (0.2%), cellular debris fraction (6.3%), heavy mitochondrial fraction (7.0%), light mitochondrial-lysosomal fraction (3.2%), microsomal fraction (2.0%), and soluble fraction (81.2%).

There was limited information to compare the distribution of chlorothalonil in rats with other species. In the Rhesus monkey (4 males) treated with a single dose of ^{12}C and ^{14}C-chlorothalonil (radiochemical 96.3% pure, technical 98.9% pure; 50 mg/kg) by gavage, the half-life of chlorothalonil in the blood ranged from 7 to 35 hours (Savides *et al.*, 1990a). In beagle dogs given a single dose of ^{14}C-chlorothalonil (radiochemical 99% pure; 50 mg/kg) by gavage, 70 percent of the dose remained in the gastrointestinal tract at 2-9 hours after dosing (Magee *et al.*, 1992). Peak tissue levels (less than 0.5% of dose) were reached by 2 hours and continued to decline over the 96 hours. The highest tissue level was in the gallbladder.

III.A.1.c. Biotransformation

In vitro studies showed that chlorothalonil was metabolized in the intestinal tract. When ^{14}C-chlorothalonil (97.1% pure; 2.5 mg/incubation) was placed in the lumen of the jejunum from male Sprague-Dawley rats, the distribution of radioactivity was: lumen (mucosal side, 91%), buffer (serosal side, 7%), and intestinal sac (2%) (Mead *et al.*, 1986). Chlorothalonil and metabolites (6% of dose) were found on the mucosal side. It was not clear whether the metabolites found in the serosal side are glutathione conjugates since they were not substrates for gamma-glutamyl transpeptidase. Glucuronide conjugates were not detected.

Intestinal microflora metabolism of chlorothalonil was studied using germ-free Sprague-Dawley rats (9 males) given a single dose of ^{14}C-chlorothalonil (radiochemical 96.3% pure, technical 98.9% pure; 50 mg/kg) by gavage (Magee *et al.*, 1990a; Larsen and Bakke, 1988). After 4 days, the distribution (% dose) of radioactivity was: urine (3%), feces (87%), and tissues (0.47%). The urine of germ-free rats contained thiols (di- and/or tri- thiols) at 1/50 (0.032% of dose versus 1.5% of dose) level of the non-germ-free rats in a previous study (Savides *et al.*, 1986c). It should be noted that the percentage of the dose in the urine of germ-free rats (2-3%) was lower (50%) than that for non-germ-free rats (5-6%) (Savides *et al.*, 1985c). *In vitro* studies with isolated rat (Sprague-Dawley) stomach and intestinal mucosal cells under non-sterile conditions showed that chlorothalonil was metabolized to mono-, di-, tri-, and tetra- (probably) glutathione conjugates (Savides *et al.*, 1986a). In a species comparative study, more chlorothalonil was metabolized when incubated with dog colon contents (70% of chlorothalonil

metabolized) or human feces (77%), than with rat cecum contents (53%) (Hillenweck *et al.*, 1997). Analysis of the metabolites indicated that *B*-lyases were involved.

Other published studies using isolated gastrointestinal sacs of conventional and germ-free Sprague-Dawley rats showed that intestinal mucosa enzymes were also involved in the metabolism of chlorothalonil and the glutathione and cysteine conjugates and converting these to methylthiolated metabolites (Hillenweck *et al.*, 1998).

Glutathione conjugate levels in the urine were affected by the presence of gamma-glutamyl transpeptidase in the blood. Male Sprague-Dawley rats (3/group) were given AT-125 (acivicin, no purity stated; 0, 10 mg/kg), an inhibitor of gamma-glutamyl transpeptidase, by intraperitoneal injection and followed by ^{14}C-chlorothalonil (97.1% pure; 50 mg/kg) one hour later by gavage (Marciniszyn and Killeen, 1987; Savides *et al.*, 1988b). AT-125 did not affect blood levels, liver levels, urinary excretion rate, and total radioactivity in the urine. However, AT-125 caused an increase of radioactivity (0.88% of dose versus 0.33% of dose in non-AT-125 treated controls) in the kidneys. Analysis of non-extractable fractions of the 0-24 hours urine samples from the AT-125 treated rat urine showed di-glutathione and tri-glutathione conjugates, possibly due to the inhibition of gamma-glutamyl transpeptidase activity.

In a published study, male SD rats were given acivicin and had bile ducts cannulated prior to administration of single oral doses of 0.66 or 2.64 mg/kg chlorothalonil (Rosner *et al.*, 1996). The only biliary product reported was a small amount of 4,6-bis (gluthathion-*S*-yl)-2,5-dichloroisophthalonitril (chlorothalonil was not detected). Other male and female SD rats were dosed with chlorothalonil for urinary metabolite evaluation (presumably without acivicin pre-treatment). The only identified product was 4,6-bis (*N*-acetylcystein-*S*-yl)-2,5-dichloroiso-phthalonitril, which was found in only minor amounts, with no gender difference in amount detected. Most of the administered chlorothalonil was excreted unchanged in the feces. The only other metabolite assayed was 4-(*N*-acetylcystein-*S*-yl)-2,5-trichloroisophthalonitril. There was no report of possible mono-, di-, or tri-thiol compounds in the excreta.

The distribution and metabolism of a conjugate were studied in male Sprague-Dawley rats (8/group) given a single dose of mono-glutathione conjugate of ^{14}C-chlorothalonil (SDS-66382, radiochemical 91.27% pure; 60 mg/kg) by either gavage or intraperitoneal injection and sacrificed 6 hours later (Savides *et al.*, 1986e). No toxic effects were observed. Compared with orally-dosed animals, the intraperitoneally-dosed animals had higher levels (about 10-fold) of radioactivity in the urine, kidneys, and blood. Urine from the orally-dosed rats contained tri-thiols (9% of the dose) and di-thiols (5% of the dose). In contrast, no tri-thiol and low level (less than 1% of dose) of di-thiol metabolites were found in the urine of the intraperitoneal group. The difference in thiol levels between the two routes of exposure might be due to SDS-66382 biotransformation to cysteine metabolites and/or other products in the gastrointestinal tract before absorption.

Since gamma-glutamyl transpeptidase is involved in the metabolism of chlorothalonil, the enzyme levels in the blood, liver, and kidneys were determined in the dog (Gelin and Killeen, 1991a). Transpeptidase activity was highest in the kidney (2-fold higher in the cortex than medulla), lower level in the liver, and negligible in the serum.

III.A.1.d. Excretion- Rat

The data on the excretion of chlorothalonil has already been discussed in the previous sections. The major route of chlorothalonil excretion was via the feces in rats (Skinner, 1965; Skinner *et al.*, 1967; Ryer, 1966) and the amount excreted was dose-dependent (Marciniszyn *et al.*, 1984a and 1985a). Eighty-three percent or more of the dose was found in the feces collected 168 hours after dosing. Excretion in the feces in the first 24 hours was faster at the low dose (60% of dose in the feces) than at higher doses (≤ 38% of dose for 50 and 200 mg/kg).

Chlorothalonil equivalents were excreted in the bile. Male Sprague-Dawley rats were given a single dose of ^{14}C-chlorothalonil (98% pure; 5 mg/kg) intraduodenally (Marciniszyn *et al.*, 1983). One to 6% of the administered radioactivity was excreted into the bile within 24 hours. When the bile pooled from the first 6 hours post-dosing was administered intraduodenally to a group of untreated rats, 19 percent of the administered radioactivity was excreted in the bile within 24 hours after dosing. The bile was not analyzed for metabolites. In another report, di- and perhaps tri-glutathione conjugate were detected in the bile (Savides *et al.*, 1985c).

The excretion of chlorothalonil equivalents in the rat bile was dose dependent. At 1.5, 5, or 50 mg/kg of ^{14}C-chlorothalonil (radiochemical 97.7-98.4% pure, technical 99.7% pure), approximately 19% and 8% of the dose (for all dose levels) were excreted in the bile and urine, respectively (Savides *et al.*, 1986d). However, lower levels of radioactivity were found in the bile (7.7% of dose) and urine (4.7%) of the 200 mg/kg group. The excretion of radioactivity in the bile was prolonged at 50 and 200 mg/kg. Radioactivity in the blood of cannulated rats was less than 50% of those in non-cannulated rats.

The urinary excretion of radioactivity occurred primarily in the first 24 hours and was also dose dependent (Marciniszyn *et al.*, 1984a and 1985a). After 168 hours, the percentages of the dose in the urine (male/female) were 6.65%/11.45%, 5.74%/8.78%, and 5.30%/5.43% from the low to the high dose groups. Urinary excretion was higher in females than males (similar to finding in Marciniszyn *et al.*, 1985c bile duct cannulation study).

To identify the urinary metabolites, male Sprague-Dawley rats (4/group) were given a single dose of ^{14}C-chlorothalonil (radiochemical 98.6% pure, technical 99.7% pure; 200 mg/kg) by gavage (Marciniszyn *et al.*, 1985b). Urine samples (0-24 hours) contained 2.3% of the administered dose. Trimethylthio-chloro-isophthalonitrile and dimethylthio-dichloro-isophthalo-nitrile, as free thiols and methylated derivatives (Figure 1), were detected which may be derived from glutathione conjugates of chlorothalonil.

The ratio of metabolites in the urine with multiple dosing was different from single dosing (Savides et *al*., 1986c). The samples from Savides *et al.* (1986b) showed 16% of the metabolites as tri-thiols for all dose levels on the first day. The excretion of di-thiol metabolites increased (5% to 15%) with the dose (5 to 160 mg/kg/day). After 4 days of dosing, there was an apparent change in the metabolic pathway of the high dose group as less di-thiols were found. The sulfur-containing metabolites identified are shown in Figure 1. The 4-hydroxy metabolite (SDS-3701) was not detected.

The excretion of chlorothalonil involved active secretion in the kidney. Male Sprague-Dawley rats were pretreated with probenecid (0, 143 mg/kg), an inhibitor of active secretion, intraperitoneally in corn oil 1 hour before given ^{14}C-chlorothalonil (≥ 99% pure; 50 mg/kg) by gavage (Savides *et al.*, 1985a). Compared with chlorothalonil-only rats (controls), higher plasma levels (146-156% of control) and lower urinary (40-50%) and kidney levels (60-70%) of radio-activity were found in rats pretreated with probenecid. Analysis of the urine showed identical metabolite profiles for both groups; however, the total radioactivity for each component of the profile was lower in the probenecid group than in the control group. The tri-methylthiol (both groups), and di-methylthiol (only in the control) metabolites were identified, with the tri-methylthiol metabolite at 3 times higher in the control than the probenecid group. The 4- and 5-hydroxy (SDS-3701 and SDS-5635), and 4- and 5-dechlorinated (SDS-5473 and SDS-5885) metabolites of chlorothalonil, and the mono-sulfhydryl conjugate (SDS-13353) were not detected.

III.A.1.e. Excretion- Monkey and Dog

In the monkey, chlorothalonil was also excreted primarily in the feces (52-92% of dose) with only 2-4% in the urine (Savides *et al.*, 1990a). In the urine, tri-thiol (0.001% of dose) and di-thiol (0.01% of dose) isophthalonitriles were detected, while mono-methylthio-isophthalonitrile (< 0.001%) was not detected.

In the dog, chlorothalonil was excreted unchanged and primarily in the feces. When mongrel dogs (4/group) were given a single dose (500 mg/kg) in capsules or fed (0.15%, 1.5%, or 3%) in the daily diet for ten months, 87% to 90% of the dose (by capsule) was recovered in the feces sampled between 24 and 72 hours after dosing (Skinner, 1965; Skinner *et al.*, 1967). With dietary administration, chlorothalonil levels in the feces were 12%, 69%, 86% of the total amount consumed for 0.15%, 1.5%, and 3% diet, respectively. Trichlorodicyanoaniline was identified as a metabolite in the feces. At the 1-year and 2-year sacrifices, no chlorothalonil or water-soluble metabolites were identified in the fat. In these studies, chlorothalonil was not detected in any of the urine or blood samples.

In another dog study, 99.6% of the dose was recovered in the feces of dogs given ^{14}C-chlorothalonil (radiochemical 96.3% pure, technical 98.9% pure; 50 mg/kg) in capsules (Savides *et al.*, 1989b). The presence of white material resembling methylcellulose, the vehicle, in the samples suggested that chlorothalonil was not absorbed at all.

The excretion of chlorothalonil given to dogs by gavage was also examined. When male beagle dogs (3/group) were given a single dose of ^{14}C-chlorothalonil (radiochemical 96.3% pure, technical 98.9% pure; 50 mg/kg) by gavage, total excretion (% of dose) was 0.7 to 1.9% in the urine and 83-99% in the feces (Savides *et al.*, 1990b). Mono-, di-, and tri-thiols were not detected in the urine (MDL= 0.0001 to 0.00001% of dose). These results were similar to those reported by Magee *et al.* (1991 and 1992). The di-methylthio and tri-methylthio derivatives, but not the mono-methylthio derivative, were detected in the urine (Magee *et al.*, 1992).

In dogs, the excretion of radioactivity into the bile was highest between 10 and 14 hours after dosing and was essentially complete by 26 hours (Savides *et al.*, 1995b). Glutathione

conjugates were found in the bile. In the urine, there was a broad peak that may be mono-glutathione conjugate, mono-thiols, and mono-thiols with S-methyl substituents. Di-thiol, tri-thiol; or mono-, di-, and tri-S-methyl derivatives were not detected.

III.A.2. Dermal - Rat, Human, and Monkey

The dermal absorption of chlorothalonil in different vehicles was studied on the clipped backs (42 cm^2) of male Sprague-Dawley rats (3/group/time) (Andre *et al.*, 1991b). ^{14}C-chlorothalonil (radiochemical purity 96.3%, chemical purity 99.6%; 0.1, 0.5, or 5.0 mg/kg; 2.2, 11, and 110 *u*g/cm^2) in acetone or BravoJ 720 formulation base were applied to the backs and the rats were sacrificed at 1, 2, 4, 10, 24, 48, 72, 96 or 120 hours. Urine, feces, blood, non-occlusive patch, treated areas of the skin, cage washes, liver, kidneys, and carcass, were analyzed for radioactivity. Chlorothalonil when administered in acetone was excreted primarily in the feces of the low dose groups (0.1 and 0.5 mg/kg) and in the urine of 5.0 mg/kg. However, the primary route of excretion was via the feces for all doses of chlorothalonil in the formulation base. The amount of chlorothalonil absorbed through the skin was dose and vehicle dependent (Table 2). The percentages of absorption (% administered dose in the carcass, urine, feces, cage washes, blood, kidney, liver, and skin bounded residues), and the percentages of absolute absorption (excluding skin residues) showed that the higher absorption occurred at lower doses. The DPR Worker Health and Safety Branch estimated a dermal absorption factor of 5% based on absorption at 10 hours for the 0.5 mg/kg dose in Bravo 720 (Thongsinthusak, 1995). The magnitude of the absorption was similar to that (5.6%) obtained in an earlier study with Sprague-Dawley rats (3/group/time) treated with ^{14}C-chlorothalonil (radiochemical purity 99%, chemical purity 99.7%; 5 mg/kg) in acetone (Marciniszyn *et al.*, 1984b; Fermenta Plant Protection, 1987). However, there was a significant loss of the dose within the first 2 hours of application.

Table 2. The dermal absorption of chlorothalonil in the rat.[a]

Dose	% Absorption[a]	% Absolute absorption[a]	% Absorption[b]
	10 hours	10 hours	10 hours
Chlorothalonil in Acetone			
0.1 mg/kg	42.7	15.1	14.9
0.5 mg/kg	27.4	7.2	8.7
5.0 mg/kg	3.3	1.5	3.0
Bravo™ 720 Formulation			
0.1 mg/kg	20.7	2.2	1.2
0.5 mg/kg	26.3	3.6	**5.4**
5.0 mg/kg	5.7	0.4	5.7

a/ Data from Andre *et al.*, 1991b. Absolute absorption excluded the amount bound in the skin.
b/ Based on log-linear regression of the % absolute absorption (Thongsintusak, 1995).

To determine the excretion of thiol metabolites after dermal exposure, the clipped backs (25 cm^2) of male Sprague-Dawley rats (5/group) were treated with chlorothalonil (5 mg/kg) (Savides *et al.*, 1989a). Urine samples collected at 24 and 48 hours after dosing contained 1.5% and 3.1% of the dose, respectively. A maximum of 0.07% of the dose were thiol metabolites.

The dermal absorption of chlorothalonil from paints was studied by applying ^{14}C-chlorothalonil (radiochemical purity 99.6%, chemical purity 99.6%; 1% w/w)-containing alkyd stain or latex paint on the clipped back (10 cm^2) of male Sprague-Dawley rats (1/control; 6/treated group) for 8 or 24 hours (Savides *et al.*, 1995a). A third group was exposed to the paints for 24 hours and then the skin site was washed for the determination of additional absorption 24 hours later. The paints were washed either with soap and water (latex paint) or with paint thinner followed by soap and water (alkyd stain). After washing, more chlorothalonil (2.99% to 4.49%) was absorbed from the alkyd stain application, but none from the latex paint. The mean percentages of the dose absorbed (in the urine, feces, blood, carcass, and skin) for latex/alkyd paints were 1.22%/1.34% and 2.43%/2.99% after 8 and 24 hours of exposure, respectively. The Worker Health and Safety Branch used the absorption values for 8 hours of exposure to estimate painter exposure: 1.22% for latex paint and 1.34% for alkyd stain.

In human abdominal epidermis obtained *post mortem,* the absorption rates for the neat and acetone applications (0.1 g/cm^2 as neat or 40 *u*g/cm^2 in acetone) were 2.98 and 0.034 *u*g/cm^2-hour, respectively (Ward and Scott, 1989a). When ^{14}C-chlorothalonil (radiochemical 97.5% pure, technical 98.2% pure) was included in the Bravo 720 formulation, the dose-dependent absorption rates were 11.5, 0.256, 0.180, and 0.005 *u*g/cm^2-hour, for 72,000 *u*g; 7,000 *u*g; 530 *u*g; and 53 *u*g chlorothalonil; respectively (Ward and Scott, 1989b).

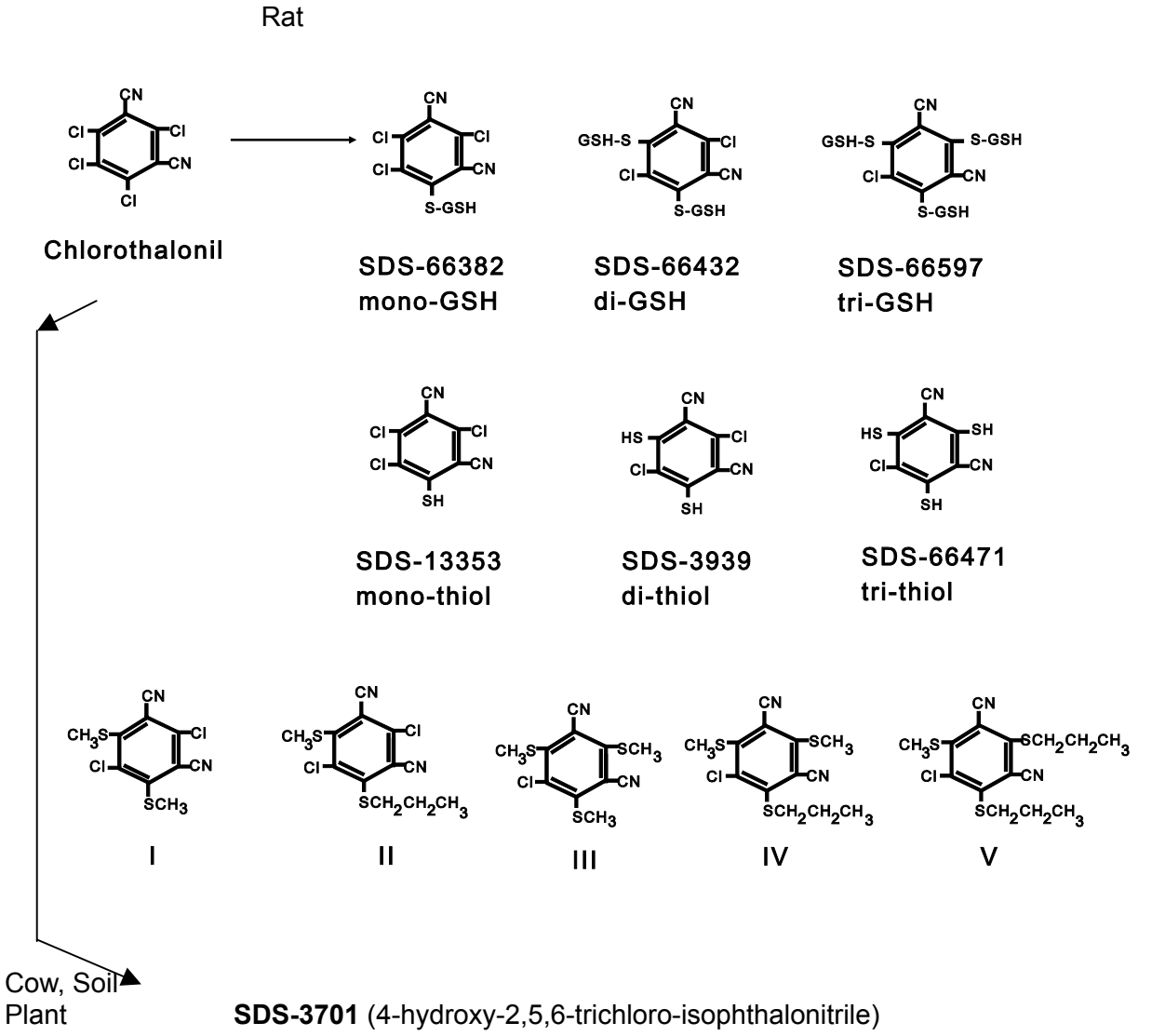
The dermal absorption of chlorothalonil was also studied in monkeys. Male Rhesus monkeys (1 control, 4/treated) were exposed to ^{14}C-chlorothalonil (radiochemical 96.3% pure, technical 98.9% pure; 5 mg/kg) dermally (180 cm^2 area) for 48 hours (Magee *et al.*, 1990b). Two treated monkeys were sacrificed after 48 hours of exposure (48 hour-group), while the remaining two were sacrificed 72 hours later (120 hour-group). Blood, urine, and feces were collected from all monkeys during exposure. Urine and feces were collected for an additional 72 hours from the 120-hour group. Radioactivity was determined in urine, feces, blood, liver, kidney, intestine, non-occlusive patch, skin, and skin washing. The majority (90%) of the radioactivity was in the patch and washing. Low levels of radioactivity were found in the tissues and constituted 0.44% and 0.08% of the dose for 48 hour and 120 hour groups, respectively. After 48 hours of exposure, the highest radioactivity was in the intestine (0.37% of dose), and lesser amounts in the liver (0.06%) and kidneys (0.015%). In the 120-hour group, the amounts of the radioactivity in the tissues were 16-40% of those at 48 hours. The lack of an increase in radioactivity in the tissues and excreta of the 120-hour group suggested no further absorption of radioactivity occurred after the removal of chlorothalonil. For both groups, 2.3% of the dose was absorbed and excreted in the urine (1%) and feces (1%). In the skin, radioactivity levels extractable from the skin and bound to the skin were 0.5% and 2.0% of the dose, respectively. Analysis of the urine did not detect methylated thiol metabolites. The Worker Health and Safety Branch did not use these results to determine dermal absorption because most of the chlorothalonil was found on the nonocculsive patch (Sanborn, 1995).

III.A.3. Diet - Cow

An earlier study showed that neither chlorothalonil residues nor conjugates of acidic or phenolic derivatives were detected in the milk, urine, or feces of cows fed chlorothalonil for 4 days (Gutenmann and Lisk, 1966). Two metabolites were detected, though not identified, in the rumen fluid.

In a longer-term study, dairy cows (4/group) were fed chlorothalonil (purity not stated; 0, 25, 75 or 250 ppm equivalent to 0, 1.1, 3.3, or 11.0 mg/kg/day) in the diet for 30 days (Wolfe and Stallard, 1970a). Milk samples were collected on days 0, 2, 4, 8, 14, 18, 22, 26, and 30 during the study. Low residue levels (<0.02 ppm to 0.04 ppm) were detected in pooled morning and evening milk samples. Two potential metabolites, 2,4,5-trichloro-isophthalonitrile and 4-amino-2,5,6-trichloro-isophthalonitrile, were also not detected. When chlorothalonil (25 ppm to 250 ppm) and SDS-3701 (0.2 to 2.0 ppm) were administered in combination to dairy cows (4/group) for 30 days, no chlorothalonil was detected in the tissues. SDS-3701 was detected in some tissues (kidneys, liver, muscle, and fat) (Wolfe and Stallard, 1970b). However, the SDS-3701 levels declined to undetectable level (detection limit=0.1 ppm) after a 32-day withdrawal period. In the milk, the maximum SDS-3701 levels were reached by day 18 and were 0.14 ppm to 0.71 ppm for the 3 doses (Wolfe and Stallard, 1970c). SDS-3701 was not detectable (MDL= 0.03 ppm) in milk samples after withdrawal.

Figure 1. Biotransformation of chlorothalonil.[a]



a/ Data from Wolfe and Stallard, 1970 a, b, and c; Marciniszyn *et al.*, 1985b and c; and Savides *et al.*, 1986c. The hypothetical pathway in the rat was: chlorothalonil was conjugated with glutathione (GSH) to form GSH-conjugates (SDS-66382, SDS-66432, and SDS-66597). These conjugates were bioactivated and then formed free thiols or methylated thiols (I-V). The free thiols were: SDS-13353 (2,5,6-trichloro-4-thio-isophthalonitrile), SDS-3939 (2,5-dichloro-4,6-bismercapto-isophthalonitrile), SDS-66471 (5-chloro-2,4,6-trismercapto-isophthalonitrile). The extractable methylated thiols in the rat urine were: I. Dimethyl-thio-dichloro-isophthalonitrile, II. Propylthio-methylthio-dichloro-isophthalonitrile, III. Trimethylthio-chloro-isophthalonitrile, IV. Propylthio-dimethylthio-chloro-isophthalonitrile, and V. Dipropylthio-methylthio-chloro-isophthalonitrile. SDS-3701 has only been found in plants and cow tissues.

III.B. ACUTE TOXICITY

Summary: In general, technical chlorothalonil and formulations are relatively nontoxic by the oral and dermal routes as the LD50s are in the Toxicity Category of III or IV. They are more toxic by the inhalation route with the LC50s generally in Toxicity Category I or II. Chlorothalonil is an eye and skin irritant. Some studies showed chlorothalonil or formulations to be a skin sensitizer. Non-lethal acute effects observed in laboratory animals from oral exposure included clinical signs (for example, soft stools, decreased motor activity, discharges from the eyes, nose, and urogenital area), reduced food consumption and decreased body weights, reduced liver weights, alteration of glutathione levels, and kidney damage (epithelial vacuolation and degeneration) (Table 4).

III.B.1. Acute Toxicity Category Studies

The acute Toxicity Category studies used to support current chlorothalonil formulations are summarized in Table 3. Some of these studies as well other acute studies are included in the study summaries for the acute toxicity database for the purpose of identification NOEL and endpoint for hazard identification.

Technical chlorothalonil and formulations are relatively nontoxic by the oral and dermal routes. The oral LD50s are in the 2g/kg to >5 g/kg range with Toxicity Category of III or IV. There was one study where the oral LD50 was >500 and <1500 for males and 353 mg/kg for females resulting a Toxicity Category of II (Kuhn, 1992b). The dermal LD50s are greater than 2 g/kg in all cases and the Toxicity Category was designated as III or IV. The acute inhalation LC50s are in the Toxicity Category I or II for both the technical and formulations. Inhalation exposure to the formulation, however, may be negligible because of chlorothalonil low volatility and unlikelihood for the liquid formulation to generate respirable aerosols under use conditions (Parsons, 1999).

Chlorothalonil and formulations are eye irritants in most cases; they cause various effects such as corneal opacity, iritis, conjunctivitis, and chemosis. Some studies showed chlorothalonil and formulations to be skin irritants and skin sensitzers. There are also case reports for skin sensitization for workers handling chlorothalonil (**III.I. HUMAN EXPOSURE**). Boman (2000) showed that chlorothalonil was a potent contact allergen and can induce skin sensitization by the dermal route. Skin sensitization was demonstrated by a dose-related increased ^{3}H-thymidine uptake using the local lymph node assay (LLNA) in mice. The LLNA has been recognized as a useful test for quantitative estimation of skin-sensitizing potency (Kimber *et al.*, 2001). Boman (2000) also showed that chlorothalonil induction (at 3%) resulted in enhanced skin reactions from subsequent chlorothalonil challenge at much lower doses (0.0003% to 0.03%) in guinea pigs using the cumulative contact enhancement test.

Table 3. The acute toxicity of chlorothalonil.[a]

Study types	Results (Toxicity Category)	Reference
Chlorothalonil technical		
Acute oral LD50	>5050 mg/kg (IV) (M) 680 mg/kg (F) 353 mg/kg (II)	*Kuhn, 1992a, *Moore, 2000 *Kuhn, 1992b
Acute dermal LD50	>2020 mg/kg (III)	*Kuhn, 1992c, Johnson, 2000a (?*), *Kuhn, 1992d
Acute inhalation LC50	(M) 0.032 mg/L (F) 0.013 mg/L (I) (M) 0.094 (F) 0.925 mg/L (II) (M and F) 0.19 mg/L (II)	*Holbert, 1993a *Shults *et al*.,1981 *Holbert, 1992b
Eye irritation	Corneal opacity (I) Conjunctival irritation, chemosis (I)	*Kuhn, 1992e *Kuhn, 1992f
Dermal irritation	None (IV) Edema, erythema (III) Edema, erythema (II)	*Kuhn, 1992g *Johnson, 2000b *Kuhn, 1992h
Dermal sensitization	None Sensitization	Kuhn, 1992i *Kuhn, 1992j
T-127-1 (96%)		
Acute oral LD50 Acute inhalation LC50 Eye irritation Dermal irritation	>16.24 g/kg (IV) (M/F) 0.11 mg/L (II) Corneal opacity, iritis, chemosis (I) Erythema, edema (III)	*Lundberg *et al*., 1980a *Lundberg *et al*., 1980b *Lundberg *et al*., 1980c *Lundberg *et al*., 1980d
ASC-66518-0101-1203 (82.5%)		
Acute oral LD50 Acute dermal LD50 Eye irritation Dermal irritation Dermal sensitization	>5 g/kg (IV) >2 g/kg (III) Corneal opacity, irritation (I) Erythema (III) Positive	*Shults *et al*., 1991a. *Shults *et al*., 1991b *Shults *et al*., 1991c *Shults *et al*., 1991d *Shults *et al*., 1991e
Spectro 90 WDG (72%)		
Acute Oral LD50 Acute Dermal LD50 Acute Inhalation LC50 Eye Irritation Dermal Irritation	<5000 mg/kg > 5 g/kg/ (III) 0.066 mg/L (II) Iritis, conjunctivitis, corneal opacity (I) No effect (IV)	Moore, 1999a *Moore, 1999b *Moore, 1999c *Moore, 1999d *Moore, 1999e
Bravo 720 SC formulation (54.51%), Bravo 6-F (54 or 55.7% ai), Bravo 720 (T-194-1, 55.7%), Bravo 720 SC (WF 2782, 54%), Daconil WeatherStik (53.9%)		
Acute inhalation LC50 Acute dermal LD50 Eye irritation	>0.704 mg/L (III) (M) >1.5 mg/L, (F) 0.86-1.50 m/L (III) >2 g/kg (III) Corneal opacity, iritis, conjunctivae (II) Corneal opacity, iritis, conjunctivae (III)	*Rattray, 2002 *Kilgore, 1999b *Shults *et al*., 1986a *Shults *et al*., 1986b, *Johnson, 2000d *Kuhn, 2003

Table 3. The acute toxicity of chlorothalonil (continued).[a]

Chlorothalonil 720 G/L (52.7%)		
Acute Oral LD50	(M) 3600 (F) 2950 mg/kg (III)	*Kuhn, 1993a
Acute Dermal LD50	>2020 mg/kg (III)	*Kuhn, 1993b
Acute Inhalation LC50	(M) 0.14 (F) 0.10 mg/L (II)	*Hobart, 1993b
Eye Irritation	Corneal opacity, iritis, conjunctivitis (III)	*Kuhn, 1993d
Dermal Irritation	No effect (IV)	*Kuhn, 1993c
Dermal Sensitization	No reaction	*Kuhn, 1993e
Compound SO-1 Chlorothalonil 75 WDG (solid, used as 50% mixture)		
Acute Oral	(M and F) 6.2 g/kg (III)	*Cerven, 1991a
Acute Dermal	>2 g/kg (III)	*Cerven, 1991b
Eye Irritation	Iritis, chemosis (I)	*Cerven, 1991c
Dermal Irritation	No effect (IV)	*Cerven, 1991d
Bravo 500 (40.4%)		
Dermal sensitization	Positive	*Shults *et al*., 1990
SO-2, Chlorothalonil flowable (40.8 %)		
Acute Oral	(M and F) 4.1 g/kg (III)	*Cerven, 1992a
Acute Dermal	>2000 mg/kg (III)	*Cerven, 1992b
Eye Irritation	Conjunctival irritation (III)	*Cerven, 1992c
Dermal Irritation	No effect (IV)	*Cerven, 1992d
Dermal Sensitization	No reaction	*Cerven, 1992e
Chlorothalonil 345 g/l SC (30.4%)		
Eye irritation	Corneal opacity, iritis, conjunctivae, chemosis, discharge (III)	Johnson, 2000c (?*)
Bioflex (0.93% Nuocide, 0.78% Troyzan)		
Acute Oral	> 5 g/kg (IV)	*Merkel, 2001a
Acute Dermal	>5 g/kg (III)	*Merkel, 2001b
Acute Inhalation	> 2.04 mg/L (IV)	*Merkel, 2001c
Eye Irritation	All cleared by 72 hours (IV)	*Merkel, 2001d
Dermal Irritation	No effect (IV)	*Merkel, 2001e
Dermal Sensitization	No reaction	*Merkel, 2001f

a/ The toxicity studies used to support the currently registered products are shown in this Table. Not all submitted studies are included in this Table; representative studies were selected for different levels of chlorothalonil. Studies which have been determined to be acceptable under FIFRA guidelines are noted with asterisks (*). The experimental animal species and genders for each type of studies were: acute oral LD50 (rat, M and F), acute dermal LD50 (rabbit, M and F), acute inhalation LC50 (rat, M and F), eye irritation (rabbit, M and F), dermal irritation (rabbit, M and F), and dermal sensitization (guinea pig, M). M=males, F=females.

III.B.2. Gavage/Intraperitoneal - Rat

Male Fischer 344 rats (6/group) were given chlorothalonil (97.2% pure; 0, 40 80, or 175 mg/kg/day) by gavage twice per day (50% of the dose each time) for 2 days (Gelin and Killeen, 1991b). The purpose of the experiment was to examine the subcellular morphological changes in the kidneys. No clinical signs were observed in the treated groups. The body weight gain was decreased (92% of control) only in the 175 mg/kg/day group. There was a dose-related increase in the incidence and severity of tubular epithelial vacuolation in the proximal convoluted tubules of all treated groups. The severity of the vacuolation and the incidences (number affected/total examined) were: slight/mild (3/6) at 40 mg/kg/day; slight mild (3/6) and moderate (1/6) at 80 mg/kg/day; slight mild (1/6), moderate (2/6), and moderately severe (3/6) at 175 mg/kg/day. Tubular epithelial degeneration was also observed in the 175 mg/kg/day group. The LOEL was 40 mg/kg/day for tubular epithelial vacuolation.

Male Fischer 344 rats (5/group) were given chlorothalonil (97.9% pure; 0 or 175 mg/kg/day) by gavage twice per day (50% of the dose each time, 8 hours apart) for 1 or 2 days (Killeen, 1993). The one-day rats were sacrificed at 16 or 24 hours after the initial dose. The two-day rats were sacrificed 48 hours after the initial dose. Soft stools and dry rales were observed in the treated groups after 1 or 2 days of exposure. In addition, respiratory distress, stain on the chin, and weight loss were noted after 2 days of exposure. At the earliest sacrifice time, there was focal swelling of the epithelium of the proximal tubules. With increased time, the vacuoles were larger and included stippled material. The vacuolar degeneration originated in the cisternae of the rough endoplasmic reticulum of the proximal tubule cells. Electron microscopy showed stippled material of unknown composition in many vacuoles. The LOEL was 175 mg/kg/day for tubular epithelial vacuolation and clinical signs.

Male Sprague-Dawley rats (3-5/group) were given chlorothalonil (97.8% pure) as a single dose by intraperitoneal injection (5 mg/kg) or by gavage (5000 mg/kg) (Sadler *et al.*, 1985a). Assuming absorptions of 34% and 100% for oral and intraperitoneal administrations, the respective absorbed doses were 1700 mg/kg and 5 mg/kg. Animals were sacrificed 2 hours after intraperitoneal treatment or 24 hours after oral treatment. Chlorothalonil, when given by the intraperitoneal route, did not affect the hepatic or renal glutathione levels and no clinical signs were observed. In comparison, treatment by the oral route at higher dosage resulted in a reduction (67 to 88% of control) of the hepatic and an increase (152-178% of control) of the renal glutathione levels. These animals also showed clinical signs that included: soft stool, anogenital staining, decreased motor activity, and hunched posture. The oral NOEL was <5000 mg/kg/day.

In a follow-up study, the time course for the effect of chlorothalonil on body weight, liver and kidney weights, and liver and kidney glutathione level was studied. Male Sprague-Dawley rats (5/group) were given a single dose of chlorothalonil (97.8% pure; 5000 mg/kg) by gavage and sacrificed 1, 3, 9, 18, 24, or 48 hours later (Sadler *et al.*, 1985b). Clinical signs similar to those in the previous study (Sadler *et al.*, 1985a) were observed. Significant ($p < 0.05$) effects included: reduction of body weight (85% of control at 24 and 48 hours after dosing), liver weight (71 to 78% of control at 18 to 48 hours), and hepatic glutathione (60 to 75% of control at 18 to

24 hours), but increase of renal glutathione (121-201% of control from 9 to 48 hours). The LOEL was 5000 mg/kg/day for clinical signs and cited effects.

Sprague-Dawley rats (5/sex/group) were given a single dose of Nopcocide N-96 (96% chlorothalonil; 6.33, 8.01, 10.14, 12.83, or 16.25 g/kg) by gavage (Lundberg *et al.*, 1980a). Clinical signs were observed intermittently and included: lethargy, piloerection, ptosis, chromorhinorrhea and chromodacryorrhea in all groups throughout the 14-day study. Diarrhea was observed in most of the animals in the first 3 days, and sporadically for the rest of the study. The LOEL was 6330 mg/kg for clinical signs.

Sprague-Dawley rats (5/sex/dose) were given a single dose of technical chlorothalonil (100% purity; 0, 250, 500, 1500, or 5050 mg/kg) by gavage (Kuhn, 1992b). The mortality incidences were: 1/5 (M) and 1/5 (F) for 250 mg/kg, 0/5 (M) and 4/5 (F) for 500 mg/kg, and all dead in the 1500 and 5050 mg/kg groups. The LD50 was >500 and <1500 mg/kg (extrapolated at 680 mg/kg) for males, and 353 (247-506) mg/kg for females. Except for the high dose group which died within 0.5 hours, all other treated groups showed piloerection and the 1500 group showed lacrimation, decreased activity, ataxia, and tremors. Necropsy showed signs of salivation, discoloration of contents of the stomach and small intestine and gas distension of stomach. The Toxicity Category was II and the study was considered acceptable. The LOEL was 250 mg/kg for clinical signs.

III.B.3. Inhalation (Whole Body) - Rat

Sprague-Dawley rats (5/sex/group) were exposed to technical chlorothalonil (100% purity; gravimetric concentrations of 0, 0.26, 0.43, and 1.12 mg/L) powder by whole-body inhalation for 1 hour (Shults *et al.*, 1991e). The equivalent dosages were 0, 10.4, 17.2, and 44.8 mg/kg/day. Mortality rates were 0/10 (control) and 1/10, 6/10, and 8/10 for the low to high dose groups. Signs of toxicity were observed in all treated groups and included: partial closing of the eyes, irregular breathing, piloerection, and restless behavior. The lungs were congested and swollen. The LOEL was 0.26 mg/L (10.4 mg/kg/day) based on mortality, clinical signs, and lung pathology.

Sprague-Dawley rats (10/sex/group) were exposed to technical chlorothalonil (97.4% purity; gravimetric concentrations of 0, 0.07, 0.13, 0.28, or 0.41 mg/L) powder by whole-body inhalation for 1 hour (Shults *et al.*, 1984). The equivalent dosages were 0, 2.7, 5.1, 10.9, and 16.0 mg/kg/day. Deaths occurred in all treated groups and were 3/20, 7/20, 18/20, and 16/20 with increasing doses. All treated groups showed gasping, lethargy, and nasal staining. The lungs were swollen, mottled, and patchy. The LOEL was 0.07 mg/L (2.7 mg/kg/day) based on mortality, clinical signs, and lung pathology.

Sprague-Dawley rats (10/sex/group) were exposed to technical chlorothalonil powder (purity not reported; gravimetric concentrations of 0, 167, 223, 332, or 548 *u*g/L) for 1 hour by whole body exposure (Breckenridge *et al.*, 1981). The equivalent dosages were 0, 6.7, 8.9, 13.3, and 21.9 mg/kg/day. The mortality resulted from the exposure was: 2/20 for 167 *u*g/L, 14/20 for 223 *u*g/L, 18/20 for 332 *u*g/L, and 18/20 for 548 *u*g/L. Deaths occurred within 1 to 5 days of exposure. The reported LC50 (95% confidence limit) were 220 (189 to 257) *u*g/L for males and

259 (193 to 347) *u*g/L for females. Clinical signs included severe respiratory rales accompanied by bloody nasal discharge and gasping. Histological evaluation of the tissues revealed pulmonary congestion and /or edema, bronchitis, an increase in alveolar macrophages and hepatic vesiculation. A Toxicity Category was not assigned and the study was considered supplemental because the animals were exposed for one hour rather than the 4 hours recommended in the guidelines. The LOEL was 167 *u*g/L (6.7 mg/kg/day)

Sprague-Dawley rats (5/sex/group) were exposed to an aerosol of Bravo 6F (a 25% or 50% aqueous suspension; average nominal concentrations were 27.8 mg/L and 7.0 mg/L) by whole-body inhalation for 4 hours (Holliday, 1973a). All rats from the 50% group died 2 days after exposure. They showed ptosis, clear nasal discharge, salivation, gasping, and rhinitis. Mild to severe diffuse discoloration in the lungs was observed at necropsy. Only 1 rat died in the 25% group, and the survivors also showed ptosis, clear nasal discharge and rhinitis. There were no lesions found at necropsy. This study was unacceptable to DPR according to FIFRA guidelines and not upgradeable (air concentration of the test article was not determined).

Sprague-Dawley rats (5/sex/group) were exposed to Nopcocide N-96 dust (96% chlorothalonil; gravimetric concentrations of 0, 0.03, 0.04, 0.06, 0.10, 0.25 or 0.39 mg/L) by whole-body inhalation for 4 hours (Lundberg *et al.*, 1980b). The equivalent dosages were 0, 4.6, 6.1, 9.3, 15.4, 38.4, or 59.2 mg/kg/day. There were deaths in 4 groups: 1 of 10 in the 0.04 mg/L, 5 of 10 in the 0.10 mg/L, all of 0.25 mg/L, and 9 of 10 in the 0.39 mg/L groups. The earliest death for each group occurred on the first day after exposure. Clinical signs were observed in all groups during exposure and included: shallow, irregular or rapid breathing, labored breathing or gasping, and excessive ocular, nasal and oral secretions. The highest dose group (0.39 mg/L) was most affected with the earliest signs observed within 30 minutes of exposure. Treatment-related body weight reduction was observed primarily in the 0.25 and 0.39 mg/L groups. On day 7, the body weight of the survivors was 50% of control. All treated groups showed dose-related increases in incidences (4/10, 7/10, 5/10, 10/10, 9/10, and 10/10 from the lowest to the highest dose groups) of mottled lung, discoloration of lung and/or dark red foci on lungs. The LOEL was 0.03 mg/L (4.6 mg/kg/day) based on lung pathology and clinical signs. This study was considered acceptable by DPR according to FIFRA guidelines.

Sprague-Dawley rats (5/sex/group) were exposed to aerosolized chlorothalonil technical powder (98% pure; analytical concentrations: 0.00208, 0.0226, 0.0829, or 0.510 mg/L) by whole-body inhalation for 4 hours (Holbert, 1993a). The equivalent dosages were 0.3, 3.7, 13.3, or 81.6 mg/kg/day. Clinical signs were observed in all groups within 6 hours after exposure and included: decreased activity, piloerection, ptosis, and respiratory gurgle. At the lowest dose, these signs were described as slight or mild, and only respiratory gurgle was observed 1 day after treatment. At higher doses, the observed signs were more severe and included gasping, lacrimation, nasal discharge, polyuria, salivation, staggered gait, and death. Some effects persisted for several days after treatment. There were deaths in 3 groups: 6 of 10 in the 0.0226 mg/L, 9 of 10 in the 0.0829 mg/L, and all animals in the 0.510 mg/L groups. The earliest death in each group was on the first day after exposure. At 0.510 mg/L, all animals were dead by day 2. Necropsy showed discolored gastrointestinal tract, discolored and swollen lungs, and distended stomach. The LC_{50} for the males and females were 0.032 mg/L and 0.013 mg/L, respectively. The acute lowest-observed-adverse-effect level (LOAEL) was 0.00208 mg/L (0.3

mg/kg/day) based on clinical signs. This study was considered acceptable by DPR according to FIFRA guidelines.

Sprague-Dawley rats (5/sex/group) were exposed to aerosolized Hammer-milled chlorothalonil powder (98.2% pure; gravimetric concentrations: 0, 0.08, 0.14, or 0.21 mg/L) by whole-body inhalation for 4 hours (Shults *et al.*, 1993a). The equivalent dosages were 12.6, 22.0, and 33.0 mg/kg/day. The mortality rates were 0/10, 4/10, 6/10, and 9/10 for control to the highest dose group; and the LD_{50} was 0.10 mg/L for both sexes. Clinical signs observed in all treated groups were: gasping, restlessness, exaggerated respiratory movements, brown stain around head and face, noisy respiration, lethargy, swollen abdomen, immobile, and reduced weight gain. Some signs persisted several days after exposure. At necropsy, fluid-filled stomach, swollen and congested lungs and white frothy fluids in the trachea were found. The LOEL was 0.08 mg/L (12.6 mg/kg/day) based on mortality and clinical signs. This study was considered acceptable by DPR according to FIFRA guidelines.

Sprague-Dawley rats (10/sex/group) were exposed to technical chlorothalonil (100% purity; gravimetric concentrations of 0, 0.0648, 0.0925, 0.1008, or 0.2195 mg/L) powder by whole-body inhalation for 4 hours (Shults *et al.*, 1981). The equivalent dosages were 0, 10.4, 14.8, 16.1, and 35.1 mg/kg/day. The mortality rates were 0/20, 1/20, 9/20, 17/20, and 19/20 for control and increasing doses. The LC50 were 94.0 (70.3 to 125.7) *u*g/L for males, and 92.5 (79.4 to 107.8) *u*g/L for females. All treated groups showed clinical signs, which included: respiratory rales, nasal discharge, and gasping. Gross pathology was observed in the 0.0925 mg/L groups and consisted of: diffuse congestion in the lungs; congestion and loss of granular staining and/or vacuolization of hepatocytes; and increased accumulation of eosinophilic amorphic material in the convoluted renal tubules and renal congestion. The LOEL was 0.0648 mg/L (10.4 mg/kg/day) based on mortality, clinical signs, and pathology. This study was considered acceptable.

Sprague-Dawley rats (5/sex/group) were exposed for 4 hours by inhalation to aerosolized chlorothalonil flowable 720 (54.9% pure; analytical concentrations of 0.0916, 0.11, 0.128, 0.190, and 0.249 mg/L) in water at the two lowest doses and undiluted at the higher doses (Holbert, 1993b). The equivalent dosages were 14.7, 17.6, 20.5, 30.4, and 39.8 mg/kg/day. The mortality rates were 4/10, 6/10, 4/10, 8/10, and 7/10 from the lowest dose to the highest dose group; and the LC50 was 0.11 mg/L for both sexes. In addition to mortality, clinical signs were observed in all groups and included: piloerection, decreased activity, ptosis, nasal discharge, lacrimation, gasping, and respiratory chirps or gurgle. Necropsy showed dark red and swollen lungs, distended gastrointestinal tract, and mottled liver. The LOEL was 0.092 mg/L (14.7 mg/kg/day) based on mortality and clinical signs. This study was considered acceptable by DPR according to FIFRA guidelines.

Sprague-Dawley rats (5/sex/group) were exposed to aerosolized chlorothalonil flowable 500G/L liquid (40.8% chlorothalonil; measured concentrations of 0.0109, 0.115, 0.229, 0.418, 0.536, 1.12 and 2.74 mg/L by gravimetric and analytical methods) in filtered air by whole-body inhalation for 4 hours (Holbert, 1992a). The equivalent dosages were 1.7, 1.4, 36.6, 66.9, 85.8, 179.2, and 438.4 mg/kg/day. The mortalities in increasing concentrations were: 0/5, 3/5, 3/5, 2/5, 2/5, 2/5, and 5/5 for males; and 0/5, 4/5, 5/5, 5/5, 3/5, 5/5, and 5/5 for females. The

LC_{50} values were 0.088 mg/L and 0.25 mg/L for females and males, respectively. Three or more rats in each group showed piloerection and decreased activity within 0.5 hours after exposure. At 0.115 mg/L and higher concentrations (both sexes), the incidences and severity of the piloerection and decreased activity were increased. Additional clinical signs included gasping, respiratory chirp, salivation, nasal discharge, and polyuria were observed after exposure on the same day. Some signs persisted for several days after exposure. At necropsy, the liver and lungs were discolored and the gastrointestinal tract was distended with gas. The LOEL was 0.0109 mg/L (1.7 mg/kg/day) based on clinical signs (piloerection and decreased activity) with mortality and respiratory effects at higher doses. This study was considered unacceptable to DPR according to FIFRA guidelines because the dose-response for mortality in females was not adequately determined.

Sprague-Dawley rats (5/sex/group) were exposed to aerosolized Bravo 825 (81.2% chlorothalonil) diluted in water (5.4% chlorothalonil; gravimetric concentration of 0.91 mg/L) by whole-body inhalation for 4 hours (Shults *et al.*, 1993b). The equivalent dosage was 7.9 mg/kg/day. Clinical signs observed were urine stain or colored urine (7/10), swollen eyelids (10/10), dark material around nose and/or mouth (6/10), salivation (6/10), labored and/or congested breathing (3/10), gasping (2/10), decreased activity (2/10), rough coat (2/10), lacrimation (1/10), and rales (1/10). Two female rats died on day 2. At necropsy, the findings were abnormal colored mucoid contents in the small intestine and/or stomach, blackish-purple spleen, and mottled or dark red consolidated lungs. The LOEL was 0.91 mg/L (7.9 mg/kg/day) based on mortality, clinical signs, and pathology.

Sprague-Dawley rats (5/sex/group) were exposed to aerosolized Bravo 500 liquid (40.4% chlorothalonil; gravimetric concentration of 2.4 mg/L) by whole-body inhalation for 4 hours (Shults *et al.*, 1995). The formulation was diluted to 5% with water. The equivalent dosage was 155.1 mg/kg/day. The treated group showed wet fur, partially closed eyes, exaggerated respiration movements, gasping, and wet snout. The lungs were congested. Two of the 10 rats in the treated group died. The LOEL was 2.4 mg/L (155.1 mg/kg/day) for mortality, clinical signs, and lung effects.

Sprague-Dawley rats (5/sex/group) were exposed to aerosolized Bravo 500 liquid (40% chlorothalonil; gravimetric concentration of 1.07 mg/L) by whole-body inhalation for 4 hours (Killeen, 1977). The equivalent dosage was 27.4 mg/kg/day. No mortalities were observed. Dry rales were noted in 2/10 animals during the 4-hour post-exposure period. During the 14-day observation period, dry rales (7/10), excessive salivation (1/10) and nasal discharge (2/10) were noted. Necropsy showed lung discoloration (mottled light and dark red, with or without white spots) in 8 of 10 rats and cecum distension in 2 of 10 rats. This study was considered unacceptable and not upgradeable to DPR because only 1 dose level was used.

Sprague-Dawley rats (5/sex/group) were exposed to chlorothalonil liquid (12.5%; gravimetric concentrations of 0 or 2.71 mg/L) by whole-body inhalation for 4 hours (Robbins, 1991). The equivalent dosage was 6.8 mg/kg/day. No mortality was reported. The only clinical sign was perineal staining (yellow) in 5 of 10 animals after exposure and it was resolved within 5 hours. This study was considered acceptable to DPR.

Sprague-Dawley rats (5/sex/group) were exposed to Spectro™ 90 WDG (72% purity) powder for 4 hours by whole-body exposure (Moore, 1999c). The gravimetric concentrations were 0.025, 0.055, 0.52, and 2.07 mg/L. The equivalent dosages were 2.9, 6.3, 59.9, and 238.5 mg/kg/day. The mortality incidences were: 0/10 for 0.025 mg/L, 4/10 for 0.055 mg/L, 10/10 for 0.52 mg/L, and 10/10 for 2.07 mg/L. The LC50 was 0.066 (0.021-0.159) mg/L. At 0.025 mg/L, clinical signs included ocular and nasal discharge, irregular respiration, dyspnea, hunched posture and hypoactivity. At 0.055 mg/L and 0.52 mg/L, additional signs were observed and they were: dry rales, reduced fecal volume and/or prone posture. Clinical signs were also reported for the 2.07 mg/L group with 5/10 of the animals dying during exposure and the remaining 5 animals described to have developed a prone posture prior to death. The LOEL was 0.025 mg/L (2.9 mg/kg/day). The Toxicity Category was II and the study was considered acceptable to DPR.

HSD:(SD) rats were exposed chlorothalonil (purity not reported; 0, 0.186, 0.194, 0.205 and 0.242 mg/L) as an aerosol (undiluted liquid mixed with air) for 4-hour whole body exposure (Holbert, 1992b). Assuming 100% purity, the equivalent dosages were 29.8, 31.0, 32.8, and 38.7 mg/kg/day. The mortality incidences were: 1/10 for 0.186 mg/L and 8/10 for 0.205 mg/L groups; and all died in 0.194 and 0.242 mg/L groups. The LC50 was 0.1878 (0.1851-0.1906) mg/L for males, and 0.1938 (0.1621-0.2318) mg/L for females. Clinical signs were observed in treated groups and include one or more of the following: convulsions, decreased activity, body tremors, emaciation, gasping, lacrimation, nasal discharge, piloerection, polyuria, ptosis, respiratory gurgle, salivation and staggered gait. Necropsy showed signs of nasal discharge, polyuria and salivation, discoloration of contents of gastrointestinal tract, gas distention of stomach, discoloration of liver and lungs and swollen lungs. The LOEL was <0.186 mg/L (<29.8 mg/kg/day). The Toxicity Category was II, and the study was considered acceptable.

III.B.4. Inhalation (Nose only) - Rat

Sprague-Dawley rats (6/sex/group) were exposed to HGB 2205 668 F (40% chlorothalonil, 10% tebuconazole) as a liquid aerosol for 4 hours by nose-only exposure (Warren and Halliburton, 1996). The analytical concentrations for chlorothalonil were 0, 3.26, 13.92, and 26.40 mg/m^3. Mortalities in males (0/6, 0/6, 4/6, and 5/6, respectively) and females (0/6, 0/6, 1/6, and 3/6, respectively) were observed between days 0 to 2. Clinical signs were observed in ≥13.92 mg/m^3 groups and included dyspnea, hypoactivity, oral staining, perianal staining, and rales. The observations were generally first noted on day 0-1. Necropsy findings revealed lacrimation, nasal stain, reddened turbinates, reddened lungs, salivation, and ventral staining in decedents. The reported LC_{50} levels for male and female were 0.0308 mg/L and 0.067 mg/L, respectively. This study was unacceptable to DPR but possibly upgradeable with submission of data, standard curve and calculations used to determine the analytical concentration of the test article. The toxicity observed in this study was likely due to chlorothalonil and not tebuconazole since a study with technical tebuconazole showed no mortality or clinical signs up to 0.818 mg/L, the highest dose tested (Heiman, 1983).

Alpk:AP$_f$SD (Wistar-derived) rats (5/sex/group) were exposed to chlorothalonil 500 G/L SC (41.2% purity; 75% dilution with water) for 4 hours by nose-only exposure (Kilgour, 1999a).

The analytical concentration was 1.96 mg/L and the equivalent dosage was 313.6 mg/kg/day. One female was euthanized *in extremis* on day 2. Clinical signs for this animal included difficulty in breathing, decreased activity, reduced reflexes, and being cold to the touch. Other animals also displayed signs of abnormal respiratory noise, decreased activity, ocular irritation and salivation. Signs persisted in some animals to the end of the observation period. No treatment-related lesions were noted in the necropsy examination. The Toxicity Category was III and the study was considered acceptable.

Alpk:AP$_f$SD (Wistar-derived) rats (5/sex/group) were exposed to chlorothalonil 720 G/L SC (52.7% purity; 50% dilution with water) for 4 hours by nose-only exposure (Kilgour, 1999b). The analytical concentration was 1.50 mg/L. An additional group of 5 females were exposed to 0.86 mg/L (analytical concentration). The equivalent dosages for these two groups were 137.6 and 240 mg/kg/day. Two and four females were euthanized *in extremis* on days 2 and 3 at the lower and higher exposure concentrations, respectively, due to breathing difficulties (0.86 mg/L) or severe ocular effects (1.50 mg/L). Clinical signs included hunched posture, abnormal respiration, piloerection, salivation, stains around nose, chromodacryorrhea, discharge from eyes and stained eye lids. Gross necropsy examination of the animals revealed gas distension in the gastrointestinal tract and reddened eyelids among the females which were euthanized. The LC50s were > 1.50 mg/L for males, and between 0.86 mg/L and 1.50 mg/L for females. The Toxicity Category was III and the study was considered acceptable.

Alpk:AP$_f$SD Wistar-derived rats (5/sex/group) were exposed nose-only to a spray strength dilution of chlorothalonil Bravo 720 SC formulation (0.7 mg/L; chlorothalonil concentration 7 *u*g/L or equivalent dosage of 1.1 mg/kg/day) for 4 hours (Rattray, 2002). There were no effects on survival, body weights, or organs examined. Only minor respiratory irritation (4/5 males, 2/5 females) was noted on the day of exposure. This sign was also observed up to day 3 post exposure with complete recovery in all animals by day 4. The Toxicity Category was III, and the study was considered acceptable.

III.B.5. Dermal - Rabbit

New Zealand white rabbits (5/sex/group) were exposed to chlorothalonil (purity not stated; 2.020 g/kg, 60 mg/cm^2) dermally for 24 hours (Kuhn, 1992c). There was no mortality. Clinical signs were limited to decreased defecation with no treatment-related lesions. There was no report of skin effects. The acute dermal NOAEL was 2.02 g/kg. This study was acceptable to DPR according to FIFRA guidelines.

Rabbits (breed not specified, 3/sex/group) were exposed to Nopcocide N-96 (95% chlorothalonil; 6.76, 8.13, 9.77, 11.75, and 14.13 g/kg; 77.7 to 162 mg/cm^2) applied to the clipped back for 14 hours (Lundberg *et al.*, 1980c). Three animals died, one each on day 3 (14.13 g/kg), day 7 (9.77 g/kg), and day 14 (6.76 g/kg). Edema, erythema, and skin flaking were observed in all doses. Body weight gain was reduced in a dose-related manner. Diarrhea, ataxia, lethargy, tachypnea, and ptosis were observed in all groups within hours of exposure. The acute dermal NOAEL was <6.76 g/kg. This study was unacceptable to DPR according to FIFRA guidelines because an inadequate number of animals was tested.

New Zealand white rabbits (5/sex/group) were exposed to chlorothalonil (100% purity; 2020 mg/kg) for 24 hours with occlusive wrap (Kuhn,1992g). There was no mortality. Clinical observations included decreased defecation in one male on days 6 and 7 post exposure. The skin at the application site was reported to appear normal. The LD50 for both males and females were > 2020 mg/kg. The Toxicity Category was III, and the study was considered acceptable.

In a subchronic toxicity study, New Zealand white rabbits (6/sex/group) were exposed to chlorothalonil (98.4% pure in methylcellulose; 0. 0.1, 2.5, or 50.0 mg/kg/day) dermally on the back (10% of body surface area) for 6 hours/day for 21 days (Shults *et al.*, 1986d). Dermal irritation was noted on day 3 in the 2.5 and 50.0 mg/kg/day groups and was accompanied by minimal to slight histopathologic changes (acanthosis and hyperkeratosis). The skin effect progressed from slight erythema/ edema to moderate erythema/edema with desquamation with repeated exposure. The acute dermal NOEL was 0.1 mg/kg/day based on dermal irritation.

III.B.6. Special Studies

Several studies were conducted with isolated mitochondria to establish the role of thiol metabolites in the proposed mechanism of chlorothalonil-induced kidney tumors. Liver and kidney mitochondria were isolated from male Sprague-Dawley rats (Savides *et al.*, 1988a; Andre *et al.*, 1991a). For assays with succinate as the substrate, the metabolite concentrations were 340 to 382 nmoles/mg mitochondrial protein. For assays with glutamate as the substrate, the metabolite concentrations were from 320 to 382 nmoles/mg mitochondrial protein. Only the respiration at site II (succinate as the substrate), not site I (glutamate) was inhibited by the metabolites. Specifically, the mono-thiol (SDS-13353) and di-thiol (SDS-3939) inhibited both liver and kidney mitochondrial state 3 respiration (ADP phosphorylation to form ATP). The tri-thiol (SDS-66471), and the mono-glutathione conjugate (SDS-66382) inhibited only the kidney mitochondria. No effects were observed with the di-glutathione (SDS-66432) and tri-glutathione (SDS-66597) conjugates.

Isolated rat renal proximal tubular cell mitochondria were incubated with mono- or di-glutathione conjugates (0, 0.5, 1.0, or 5.0 mM) of chlorothalonil in the presence or absence of aminooxyacetic acid, a *B*-lyase inhibitor; and diphenyl-p-phenylenediamine, an inhibitor of lipid peroxidation (van de Water *et al.*, 1994). The mono-glutathione conjugate (5 mM) reduced both cell viability and mitochondrial membrane potential by 50% (estimated from graphed data). These effects were prevented by diphenyl-p-phenylenediamine, but not aminooxyacetic acid, suggesting that the mono-glutathione conjugate lipid peroxidation compound. The di-glutathione conjugate did not have any effects on the cells.

Additional studies for the consideration of acute toxicity are described in the **III.C. SUBCHRONIC TOXICITY**, and **III.G. DEVELOPMENTAL TOXICITY** sections and are included in Table 4.

Table 4. Selected no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) of chlorothalonil for acute effects after oral exposure.[a]

Species/ Route	Exposure Duration	NOEL/ LOEL (mg/kg/day)	Effects	Ref[b]
Oral				
Rat	2 days	<40/40	Kidney-tubular epithelial vacuolation with degeneration at 175 mg/kg/day	1
Rat	1-2 dose	<175/175	Kidney-tubular epithelial vacuolation, clinical signs (soft stools, dry rales, respiratory distress, stain on chin), and body weight loss	2
Rat	1 dose	<5000/5000	• body weight, • liver weight, • hepatic GSH, • renal GSH, and clinical signs (soft stools, anogenital staining, • motor activity, hunched posture)	3
Rat	1 dose	<6330/ 6330	Lethargy, piloerection, ptosis, chromorhinorrhea, chromodacryorrhea, and diarrhea	4
Rat	1 dose	<250/250	Piloerection	5
Rat[c] (diet)	4 days	<175/175	Kidney lesion (vacuolar degeneration) by day 4	6
Rat[d]	gd 6-15	100/400	Death (6 doses), diarrhea, alopecia, • food consumption (day 6 to 15) and body weight (day 9 to 12)	7*
Dog[c]	5 days	500/750	Mortality (day 3), vomiting and anorexia on day 5	8, 9
Dog[c]	1 week	<50/50	• body weight gain (females) by week 1	10
Rabbit[d]	**gd7-19**	**15/30**	**• body weight & food consumption**	**11**
Rabbit[d]	gd7-19	10/20	Marginal decrease (93% control) in fetal mean body weight	12

a/ Studies in bold are used to determine the critical NOELs in Hazard Identification (**IV.A.**). Abbreviation: hrs=hours, gd=gestation day, GSH=glutathione. Unless specified, oral administration was via gavage.

b/ * after the reference number indicates the study was acceptable to DPR according to FIFRA guidelines. References: 1. Gelin and Killeen, 1991b; 2. Killeen, 1993; 3. Sadler *et al.*, 1985a and b; 4. Lundberg et al., 1980a; 5. Kuhn, 1992b; 6. Ford and Killeen, 1987a; 7. Mizens *et al.*, 1983a; 8. Fillmore, 1992a and b; 9. Fillmore and Laveglia, 1993; 10. Fillmore and Laveglia, 1992; 11. Mizens12. Wilson and Killeen, 1988a; 13. Wilson and Killeen, 1988b.

c/ The study is described in **III.C. SUBCHRONIC TOXICITY**.

d/ The study is described in **III.G. DEVELOPMENTAL TOXICITY**.

III.C. SUBCHRONIC TOXICITY

Summary: Subchronic exposure of rats and mice to chlorothalonil by the oral route resulted in reduced body weights, discolored urine, and changes in serum chemistry. Lesions were found in the kidney (tubular epithelial hyperplasia, hypertrophy, and vacuolar degeneration), and forestomach (epithelial hyperkeratosis, hyperplasia, thickening of mucosa, erosion, and ulceration. Forestomach lesions were observed after treatment with chlorothalonil, but not with the mono-glutathione conjugate. Increased labeling indices as indication of cellular proliferation were observed in both the kidney and forestomach tissues. Dermal exposure of rabbits and rats to chlorothalonil resulted in skin lesions and clinical signs (rats only). Reduced plasma alanine transaminase levels was observed in rats (dietary), dogs (oral), and rabbits (dermal) after chlorothalonil treatment. A summary of the studies is in Table 8.

III.C.1. Gavage - Rat

Male Fischer 344 rats (15/group) were given chlorothalonil (97.9% pure; 75 mg/kg/day), the mono-glutathione conjugate of chlorothalonil (92.5% pure; 150 mg/kg/day), or the vehicle (0.5% methylcellulose) by gavage for 90 days (Ford and Killeen, 1987b; Wilson *et al.*, 1990). Results showed that kidney toxicity was similar for both compounds, although the effects occurred in higher incidences with chlorothalonil than the conjugate. Histopathological examination showed tubular epithelial hyperplasia and hypertrophy in most rats of both treated groups, with karyomegaly in some chlorothalonil-treated rats. Additional staining of the tissue slices showed vacuolar degeneration, tubular ectasis, tubular casts, interstitial fibrosis, and foci of basophilic tubules in both treatment groups, with the chlorothalonil group generally more affected. There were quantitative and qualitative differences in the urinary thiol metabolites between the two treated groups. The urine of the chlorothalonil group consistently contained a higher (3-5 fold) tri-thiol level than did the urine of the conjugate group (e.g., a mean of 101.8 *u*g/rat versus 22.3 *u*g/rat on day 1). The difference persisted to week 4. By week 8, the tri-thiol metabolite was not detected in either group. Furthermore, the di-thiol metabolite was found in the chlorothalonil urine samples for day 1, but was not found in the conjugate group urine samples. Dark-yellow urine, reduced body weights, and reduced food consumption were reported in the chlorothalonil group but not in the other groups. Only chlorothalonil induced changes in the forestomach (thickening and occasional ulcerations of the mucosa and hyperplasia, hyperkeratosis, erosion, and ulceration of the epithelium). This study was considered by DPR to be an acceptable ancillary study. The LOEL was 75 mg/kg/day for chlorothalonil induced kidney and stomach lesions.

Male Fischer 344 rats were given either vehicle (0.5% methylcellulose), chlorothalonil (SDS-2787, 97.9% pure; 150 mg/kg/day), or mono-glutathione conjugate (SDS-66382, 92.5% pure; 75 mg/kg/day) by gavage for 90 days (Ford *et al.*, 1987). Both chlorothalonil and the mono-glutathione conjugate, at equimolar doses, caused increased (113-114% of control) kidney weights, and histopathological lesions in the kidneys (proximal tubular epithelial hyperplasia, tubular dilation, vacuolar degeneration, and interstitial fibrosis). While the tri-thiol was found in the urine of both groups, the di-thiol was observed only in the 1 hour sample of the chlorothalonil group. Thickening of the mucosa of the non-glandular stomach was seen only

with chlorothalonil treatment. The LOEL was 150 mg/kg/day for chlorothalonil increased kidney weight, and kidney and stomach lesions.

III.C.2. Dietary - Rat

Male Fischer 344 rats (90/group) were fed diets containing chlorothalonil (97.9% pure; 0, 175 mg/kg/day) (Ford and Killeen, 1987a). Groups of 10 rats were sacrificed on days 4 and 7 and at the end of weeks 2, 4, 6, 8, 10, 12, and 13 of treatment. There was no mortality or clinical signs of toxicity. The mean body weights of the treated groups were lower than the control during the experiment. Lesions were found primarily in the forestomach and kidneys. As early as day 4 to week 8, chlorothalonil caused ulceration, erosion, gastritis, and squamous hyperplasia and hyperkeratosis of the stomach mucosa. During the latter part of the study, there was thickening of the mucosa from squamous epithelial hyperplasia and hyperkeratosis. The range (for measurements during the study) of absolute kidney weight, mean weight relative to body weight, and mean weight relative to brain weight were increased significantly ($p < 0.05$) by 5-24%, 9-33%, and 6-28%, respectively, when compared to the controls. While there were no gross pathological lesions, the kidneys showed proximal tubular vacuolar degeneration by day 4. Regeneration of the epithelium was noted as early as week 7. However, there were increased incidences and severity of kidney lesions with repeated dosing. Urine analysis showed only the tri-thiol, but not the di-thiol conjugate, in all samples (except those collected on day 7 and week 6). The acute LOEL was 175 mg/kg/day for kidney and stomach lesions starting from day 4.

Charles River rats (20/sex/group) were fed diets containing chlorothalonil (98% pure; 0, 1.5, 3.0, 10.0, and 40.0 mg/kg/day) for 13 weeks when 50% of the rats were necropsied and the rest continued on an untreated diet for 13 weeks (recovery period) (Wilson *et al.*, 1983a; Wilson *et al.*, 1985a; Wilson *et al.*, 1984). Satellite groups (5/sex/group) were necropsied at 6 weeks. No clinical signs were observed in the treated groups. At the 13-week sacrifice, there was a statistically significant ($p < 0.05$) decrease in the serum alanine transaminase (ALT; also known as serum glutamic pyruvic transaminase, SGPT) levels in the ≥ 3.0 mg/kg/day male (87% of control) and 40.0 mg/kg/day female (67% of control) groups (Table 5). During recovery, serum ALT activities were higher (males) or at the same level (females) as the control.

Absolute kidney weights at 6 weeks were significantly ($p < 0.05$) higher in the treated groups (≥ 10 mg/kg/day males only) than those for the controls. At 13 weeks, the absolute kidney weights were increased in the treated groups (≥ 3.0 mg/kg/day) of both sexes (Table 5). However, there were no treatment-related differences in the kidney weights between treated and control animals after the recovery period. Incidences of dilated medullary tubules were elevated in all treated groups (25 to 40% compared with 5% for controls) at 13 weeks. In the reevaluation of the renal tissue for evidence of hyperplasia, hyperplasia was noted primarily in the 10.0 and 40.0 mg/kg/day males after 6 and 13 weeks (Table 5). An increase in tubular size (dilation) was observed in only one male in each of the 10 mg/kg/day group at 6 weeks, and 40 mg/kg/day group at 6, 13, and 24 weeks. The increased incidences of hyperplasia and dilation were also observed after 13 weeks of recovery. Increased incidences of irregular, intracytoplasmic inclusion bodies were detected in the proximal tubular cells from treated animals (Table 5). Neutral red analysis (selective stain for inclusion bodies) showed an elevated incidence and/or degree of inclusions at all dose levels tested by week 13 (end of dosing phase). After recovery

period, residual changes were evident at ≥ 3 mg/kg/day. The investigators concluded that these bodies were not related to identifiable toxicological lesions in the kidneys, including chronic progressive nephropathy.

An increase (20%) in liver absolute weight was observed only for the 40 mg/kg/day males at 13 weeks, but not after the recovery period. Microscopic examination of the non-glandular stomach of the treated groups at 6 and 13 weeks showed a dose-related increase in the incidence (10-100%) of hyperplasia and hyperkeratosis of the squamous epithelium in the ≥3.0 mg/kg/day groups of both sexes. At the end of the recovery phase, low incidences (0 to 30%) of hyperplasia and hyperkeratosis were reported for stomachs from both control and treated groups. The NOEL was 1.5 mg/kg/day based on decreased serum ALT, increased kidney weights, and increased incidences of cytoplasmic inclusion bodies in the renal tubules at 3.0 mg/kg/day.

Table 5. Effects of chlorothalonil in rats after 13-week dietary exposure.[a]

Effects	**Dosage (mg/kg/day)**				
	0	**1.5**	**3.0**	**10**	**40**
ALT[b] (% C)					
Male	100	90	87*	67**	67**
Female	100	76	59	87	67*
Kidney weight[b] (% C)					
Male	100	98	113*	112*	113*
Female	100	109	119*	120*	114*
Stomach (incidences)					
Lesions	1/20 (5%)++	0/20	2/20 (10%)	15/20 (75%)**	20/20 (100%)**
Kidney (incidences, males only)					
Hyperplasia 6 weeks	0/5 ++	1/5	0/5	2/5 (40%)	4/5 (80%) *
13 weeks	0/12 +	0/10	0/10	0/10	10/10 (100%)**
Dilation 6 weeks	0/5	0/5	0/5	1/5 (20%)	1/5 (20%)
13 weeks	0/12	0/10	0/10	0/10	1/10 (10%)
Inclusion bodies 13 weeks					
Slight	4/10	0	4/10	1/10	0
Minimal	1/10	6/10	2/10	2/10	3/10
Moderate	0	2/10	2/10	7/10	7/10
Inclusion bodies (recovery)[c]					
Slight	1/7	2/10	5/10	5/10	2/10
Minimal	0	1/10	4/10	3/10	3/10
Moderate	0	0	1/10	1/10	4/10

a/ Data from Wilson *et al.*, 1983a and Wilson *et al.*, 1985a. Statistical significance * at $p \leq 0.05$ or ** at $p \leq 0.01$. The stomach lesions were hyperplasia and hyperkeratosis of the non-glandular stomach. Level of statistical significance, $p \leq 0.05$ (* or +) or $p \leq 0.01$ (** or ++), is indicated after each incidence. Significance at the control value was based on a dose-weighted chi-square trend test, and the pair-wise significance at the dosed groups was based on the Fisher's Exact Test.

b/ ALT= serum alanine transaminase. Average enzyme level or average absolute organ weight.

c/ Recovery period- 13 weeks in control diet after 13 weeks on chlorothalonil-containing diet.

Charles River rats (20/sex/group) were fed diets containing chlorothalonil (98% pure; 0, 40, 80, 175, 375, 750, or 1500 mg/kg/day) for 90 days (Wilson *et al.*, 1981a; Wilson *et al.*, 1985b; Diamond Shamrock Corporation, 1983a). Clinical signs were observed primarily in the 750 and 1500 mg/kg/day groups and were: soft stool, mucus in the stool, red nasal discharge or dark crusty material around the nose, decreased fecal output, swelling and/or irritation of the anal area, and generally poor physical condition. Mean body weights and/or food consumption were significantly ($p < 0.01$) reduced at doses > 175 mg/kg/day. Mean organ weights were decreased for the brain (males at ≥ 375 mg/kg/day, $p <0.01$), heart (both sexes at ≥ 375 mg/kg/day, $p<0.05$), liver (males at 750 mg/kg/day, $p<0.05$), testes (≥ 750 mg/kg/day, $p<0.01$). However, the mean kidney weights were increased ($p<0.05$) for males at ≥ 40 mg/kg/day and females at ≥ 80 and mg/kg/day. Kidney weights were 118% and 110% of control values for the 40 mg/kg/day males and 80 mg/kg/day females, respectively. The increase in kidney weights was not statistically significant for some high dose groups (375 mg/kg/day females, 750 mg/kg/day males, and 1500 mg/kg/day both sexes). The urinalysis at 30 and 90 days showed significantly ($p < 0.01$) increased specific gravity (101-103% of control) at ≥ 375 mg/kg/day, and decreased urine volume (21-58% of control, depending on dose group) in the males. Histopathological examination showed lesions in the stomach (focal acute gastritis) and kidneys (tubular hyperplasia and enlarged proximal tubules). The incidences for renal tubular hyperplasia in the control and the 6 dose levels (40 to 1500 mg/kg/day) of both sexes were 0/40, 17/40, 16/40, 30/40, 22/40, 34/40, and 37/40. Similar dose-related trends were observed for incidences of increased tubule size. In addition to hyperplasia, an elevated incidence of neutral red positive material was found in the kidneys of all treated groups. The NOEL was < 40 mg/kg/day based on increased kidney weights, and stomach and kidney lesions.

In a cell proliferation study, male F-344 rats (7-14/group) were fed chlorothalonil (0 or 175 mg/kg/day) mixed in the diet (Mizens, 1996a). Fourteen animals per group were sacrificed on day 7, and 7 per group each on days 28 and 91. Bromodeoxyurdine was administered by osmotic pump for 3.5 days (also 6.5 days for the day 7 group) before the respective day of sacrifice. The renal proximal convoluted tubular epithelium of treated rats showed degeneration, hyperplasia, and hypertrophy. These changes were evident in the presence of immuno-histochemical staining which suggested cell proliferation occurred in association with the histopathology lesions. The mean labeling indices in the treated kidneys were significantly increased ($p< 0.01$) when compared to control (range 1.24 to 2.67). The highest mean labeling index was 28.84 on day 7 (3.5-day pump) (Figure 2a). However, the indices decreased with increased duration of exposure. There was also a significant increase ($p<0.01$) in the absolute kidney weight with increased exposure duration. Forestomach lesions consisted of hyperkeratosis and hyperplasia of the squamous epithelium, often with submucosal edema, erosions, and ulcerations. Histopathology in both organs persisted from day 7 to the end of the study on day 91. This study was considered by DPR to be an acceptable ancillary study with minor deficiencies.

F344 male rats (6/group) were fed chlorothalonil (0, 1.5, 15, or 175 mg/kg/day) in the diet for 7, 14, 21, or 28 days (Hironaka, 1996). Kidney sections were stained with PC10, which contained an antibody to the proliferation cell nuclear antigen (PCNA). Forestomach tissues were evaluated by bromodeoxyuridine (BrdU) immunostaining. Rats were administered 0.1 g/kg BrdU 1 hour before autopsy. Increased labeling indices were observed to some extent at 15

mg/kg/day and substantially at 175 mg/kg/day in the kidney (Table 6 and Figure 2b). Responses generally decreased over time in kidney proximal tubular epithelial cells at both of these dose levels. Vacuolar changes were detected in the kidneys primarily at the high dose of 175 mg/kg and the incidences also decreased with time (Table 6). On the other hand, the labeling indices in the forestomach remained elevated for the entire duration (Table 6, Figure 2c). Histopathological examination of the forestomach showed extensive damage which included edema, hemorrhage, erosion, infiltration, hyperkeratosis, and hyperplasia. The incidences for these lesions increased with repeated exposures. Neither histopathology nor evidence of cellular proliferation was seen at 1.5 mg/kg/day in either tissue. The NOEL was 1.5 mg/kg/day for increased labeling indices in the kidney and forestomach tissues.

Wistar rats (30/sex/control group, 15/sex/treated groups) were fed diets containing chlorothalonil (97.8% pure; 0, 1, 2, 4, 15, 30, 60, or 120 ppm) for 4 months (Bio/Tox Research Laboratories, Inc., 1975). The dosages were estimated to be 0.05 to 6 mg/kg/day based on a default value of 5% body weight as the daily food consumption rate. Dose analysis was not reported. No effects were observed in body weight, food consumption, survival, and kidney histopathology. The apparent NOEL was >120 ppm. This was a supplemental study to evaluate kidney histopathology.

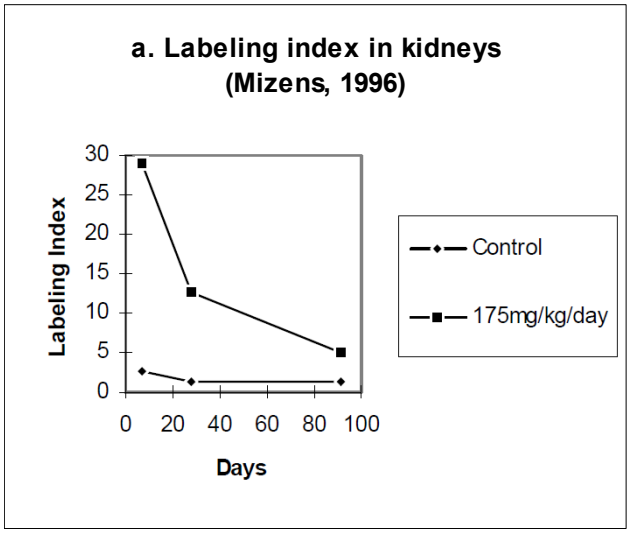
Table 6. Effects of chlorothalonil in rats in a 28-day dietary exposure study.[a]

Effect/ Days of treatment		Dosage (mg/kg/day) 0	1.5	15	175
Labeling index-Kidney					
7		0.58	0.50	1.21**	6.86***
14		0.72	0.84	1.98**	4.31***
21		0.90	1.17	1.35**	3.10***
28		0.94	0.87	1.10	2.78***
Labeling index-Stomach					
7		4	5	7	267***
14		7	5*	6*	319***
21		5	4	20	305***
28		5	9	20*	250***
Histopathology- Kidney[b]					
7		0/6	0/6	0/6	6/6**
14		0/6	0/6	0/6	6/6**
21		0/6	0/6	0/6	5/6**
28		0/6	0/6	1/6	3/6
Histopathology- Forestomach[c]					
7-	Edema	0/6	0/6	0/6	2/6**
	Hemorrhage	0/6	0/6	0/6	2/6
	Erosion	0/6	0/6	0/6	5/6**
	Infiltration	0/6	0/6	0/6	6/6**
	Hyperkeratosis	0/6	0/6	0/6	6/6**
	Hyperplasia	0/6	0/6	0/6	6/6**
14-	Edema	0/6	0/6	0/6	6/6**
	Hemorrhage	0/6	0/6	0/6	3/6
	Erosion	0/6	0/6	0/6	4/6*
	Infiltration	1/6	0/6	0/6	6/6**
	Hyperkeratosis	0/6	0/6	0/6	6/6**
	Hyperplasia	0/6	0/6	0/6	6/6**
21-	Edema	0/6	0/6	4/6*	6/6**
	Hemorrhage	0/6	0/6	1/6	2/6
	Erosion	0/6	0/6	2/6	3/6
	Infiltration	0/6	0/6	4/6	6/6**
	Hyperkeratosis	0/6	0/6	1/6	6/6**
	Hyperplasia	0/6	0/6	3/6	6/6**
28-	Edema	0/6	0/6	5/6**	6/6**
	Hemorrhage	0/6	0/6	1/6	2/6
	Erosion	0/6	0/6	2/6	4/6*
	Infiltration	0/6	0/6	6/6**	6/6**
	Hyperkeratosis	0/6	0/6	3/6	6/6**
	Hyperplasia	0/6	0/6	2/6	6/6**

a/ Data from Hironka, 1996. *,**, *** Statistically significant at $p<0.5$, $p<0.01$, and $p<0.001$, respectively.
b/ Incidence (number affected/total examined) of kidney effect (vacuolar change).
c/ Incidence (number affected/total examined) of forestomach effects included: edema, hemorrhage, erosion, inflammatory infiltration, hyperkeratosis, and squamous cell hyperplasia.

Figure 2. Labeling indices in rats treated with chlorothalonil in the diet.

Labeling indices were measured in rats toward the end or at the end of the exposure period (Mizens, 1996; Hironaka, 1996). They were detected by bromodeoxyuridine immunostaining.



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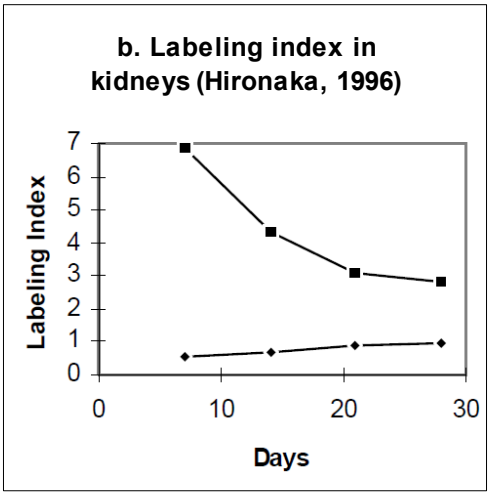

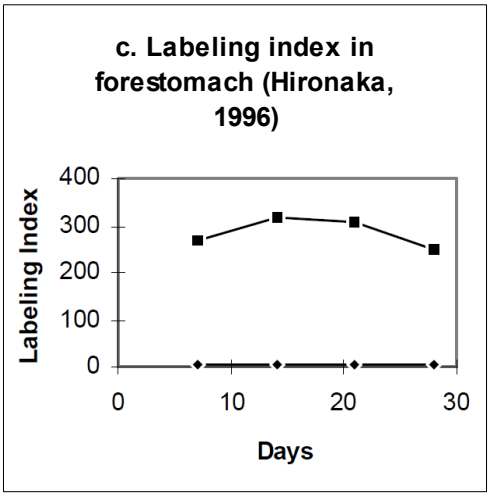

III.C.3. Dermal - Rat

The shaved backs of male Fischer 344 rats (10/group) were exposed to chlorothalonil (98.9%; 0, 60, 100, 250, or 600 mg/kg/day) in aqueous methylcellulose for 6 hours per day, 5 days per week for a 21-day period (Mizens, 1996b). Treated skin at all dose levels showed erythema, yellow discoloration and desquamation at necropsy, as well as hyperkeratosis, and squamous epithelial hyperplasia and vacuolation in histological sections. The dermal NOEL was <60 mg/kg/day. Body weight and food consumption were 83-88% of control on the first week ($p<0.01$) and serum ALT was 67-79% of control ($p<0.01$;Table 7). At ≥ 250 mg/kg/day, kidney weights (relative to brain weight) were increased. Daily clinical observations showed dose- and time- related increased incidences (Table 7). Anogenital stains and material around the nose were observed at 600 mg/kg/day on days 1-5 and could be the used as the basis for an acute NOEL at 250 mg/kg/day. The subchronic NOEL (exclusive of application site) was 60 mg/kg/day based on increased incidences of rough coat at 100 mg/kg/day, and of colored materials around the eyes/nose and anogenital staining at higher doses during the 21-day study. There were no histopathological changes in the kidneys. This study was considered by DPR to be an acceptable ancillary study.

Table 7. Effects of chlorothalonil in rats after 21-day dermal exposure.[a]

	Dose (mg/kg/day)				
Effects	**0**	**60**	**100**	**250**	**600**
Observations					
Colored material/nose and eyes					
Days 1-5	1 (1/10)	0	1 (1/10)	1 (1/10)	4 (3/10)
6-10	0	1 (1/10)	0	0	0
11-15	0	0	0	1 (1/10)	2 (2/10)
16-21	0	0	0	5 (2/10)	18 (3/10)
Rough coat					
Days 1-5	0	0	0	0	0
6-10	0	0	1 (1/10)	4 (4/10)	8 (8/10)
11-15	0	0	5 (1/10)	18 (8/10)	28 (10/10)
16-21	0	0	3 (1/10)	22 (6/10)	37 (8/10)
Anogenital staining					
Days 1-5	0	0	1 (1/10)	1 (1/10)	8 (3/10)
6-10	0	0	0	0	3 (1/10)
11-15	0	0	0	2 (1/10)	2 (2/10)
16-21	0	0	0	1 (1/10)	0
Alanine Transaminase[b]	100	93	86	79**	67**

a/ Data from Mizens, 1996b. Observation data were total number of incidences (number of animals affected/total numbers) per 5 day period (1 week), except for the last week (days 16-23).

b/ Percent of control and sampled at 21-day at necropsy. ** Statistically significant at $p< 0.01$.

III.C.4. Inhalation - Rat

Sprague-Dawley rats (15/sex/group) were exposed to aerosolized water or Bravo 6F (purity not stated; average nominal concentration was 12.2 mg/L) for 6 hours per day, 5 days per week, for 3 weeks (Holliday, 1973b). No effects on body weight, survival, or tissues as determined by gross pathology were reported. This study was considered inadequate to evaluate by DPR because of deficiencies (achieved concentration and size of particles not adequately tested, and control and treated animals had chronic murine pneumonia).

III.C.5. Dietary - Mouse

CD-1 mice (10/sex/group) were fed chlorothalonil (98.4% pure; 0, 7.5, 15, 50, 275, or 750 ppm) in the diet for 90 days (Shults *et al.*, 1983; Shults *et al.*, 1985). The calculated mean doses for both sexes of the 5 treatment groups were 0, 1.3, 2.8, 9.2, 50.0, 132.4 mg/kg/day. Five additional mice were treated with chlorothalonil for an interim sacrifice on week 6. The only significant clinical chemistry finding was an increase (145% of control, $p < 0.01$) in alkaline phosphatase for the 750 ppm females at the terminal necropsy. Serum ALT was not affected; however, the standard deviation of the control value was large (more than 50% of the mean). Statistically significant changes in the kidney weights were only observed in the males at 6 weeks, and the females at 13 weeks. The absolute kidney weights were increased in the 750 ppm males (125% of control, $p \leq 0.05$), as well as 275 and 750 ppm females (113% of control, $p \leq 0.01$). The forestomach showed hyperplasia and hyperkeratosis of the squamous epithelial cells. These changes were observed in both sexes of the 275 and 750 ppm groups at the interim sacrifice and ≥ 50 ppm groups at the terminal sacrifice. In the kidney, generalized vacuolation of the cortical tubular epithelial cells or hyperplasia of the epithelial cells of the proximal convoluted tubules was observed at ≥ 275 ppm at 6 weeks and later. The NOEL was 15 ppm (2.8 mg/kg/day) based on forestomach at ≥ 50 ppm (9.2 mg/kg/day) and kidney lesions at ≥ 275 ppm.

III.C.6. Dietary - Dog

Beagle dogs (4/sex/group) were fed chlorothalonil (99.18% pure; 0, 160, 1600, or 16000 ppm) for 13 weeks (Spencer-Briggs *et al.*, 1994). ALT levels were reduced at all dose levels, and no NOEL was established for this endpoint. There was treatment-related hypertrophy of the zona fasciculata of the adrenals in males at 1600 ppm (seen in both sexes at 16000 ppm). There was an apparent reduction in the non-protein thiols in the urine of both sexes at 1600 and 16000 ppm; however, the data were considered equivocal. Additional findings at 16000 ppm included modest body weight and food consumption decrements, an apparent increase in non-protein thiol concentration in liver and kidney tissues, decreased serum albumin, increased serum cholesterol, an equivocal increase in urinary protein in females, increased adrenal weight in males, and an increased width of the zona glomerulosa in females. The NOEL was 160 ppm (5.6 mg/kg/day) for effects observed (adrenal hypertrophy, decreased urinary non-protein thiols) at 1600 ppm. The study was considered acceptable by DPR.

Beagle dogs (4/sex/group) were fed chlorothalonil (purity not stated; 0, 250, 500, or

750 ppm) in the diet for 16 weeks (Hazleton Laboratories, Inc., 1967a). The only finding was an elevation (about 2- to 3-fold) of protein-bound iodine levels in all treated groups; the toxicological significance of this finding was considered minimal. The NOEL was >750 ppm. This study was considered incomplete because of deficiencies: no NOEL established, lack of information on test material, test animals, and randomization; no feed analysis; insufficient serum chemistry, ophthalmology, and histopathology; and lack of data analysis.

III.C.7. Oral - Dog

Beagle dogs (4/sex/group) were dosed with chlorothalonil (purity not stated; 0, 15, 150, or 750/500 mg/kg/day) in gelatin capsules once daily for 90 days (Fillmore and Laveglia, 1993; Fillmore, 1992a and 1992b). The 750 mg/kg/day dose was reduced to 500 mg/kg/day on day 5 because of one death on day 3. All dogs in the high dose group showed excessive vomiting/anorexia and the one death was attributable to bronchitis and pneumonia subsequent to the aspiration of vomitus. For the remainder of the study, there were no differences in the physical observations, food consumption, and hematology between control and treated groups. The incidence of emesis was slightly elevated in the 500 mg/kg/day group. In the 150 and 500 mg/kg/day groups (males), there was a reduction in mean body weight (0-44%, 14-40% of control, respectively), which was statistically significant ($p \leq 0.05$) on weeks 1, 5, 10, and 13. Treatment-related clinical chemistry results included: decreased (0-5% of control value) serum ALT levels in all treated groups, increased serum cholesterol (138 to 168% of control) in 150 (females) and 500 mg/kg/day (both sexes) groups, and decreased (88-94% of control) serum albumin levels in 150 (males) and 500 mg/kg/day (both sexes) groups. Relative liver weights were elevated (120-131% of control) in both sexes of the 500 mg/kg/day group. No NOEL was established for the decrease in serum ALT since all dose groups were affected. For other effects, the NOEL was 15 mg/kg/day, based on decreased body weight gain (males), decreased albumin levels (males), and increased cholesterol levels (females). An acute NOEL of 500 mg/kg/day could be established based on mortality on day 3 and clinical signs (vomiting and anorexia) at 750 mg/kg/day.

Beagle dogs (2/sex/group) were dosed with chlorothalonil (97.9% pure; 0, 50, 150, or 500 mg/kg/day) in gelatin capsules once daily for 30 days (Fillmore and Laveglia, 1992). There was no effect on survival. At 500 mg/kg/day, there were increased incidences of emesis. Lower weight gain (and weight loss in some cases) was observed in all female groups and 500 mg/kg/day males; the effect was evident by week 1. Food consumption was lowered (qualitatively evaluated as portions consumed) only in the 500 mg/kg/day males. At the end of the study, clinical chemistry showed lowered serum ALT in all treatment groups (average of 20%, 18%, and 13% of controls for 50, 150, and 500 mg/kg/day, respectively). Only the liver weights of the 500 mg/kg/day females were increased (112% of control) compared with controls. No lesions were observed by microscopic examination of the tissues. The NOEL was < 50 mg/kg/day based on decreased serum ALT. For other effects, the NOEL was <50 mg/kg/day for decreased body weight gain of all female groups.

III.C.8. Dermal- Rabbit

Chlorothalonil (purity not stated; 0.001%, 0.01%, and 0.1%) in acetone was applied successively to shaved areas of six New Zealand rabbits for an open and semi-occlusive (sites were covered with gauze) cumulative irritation (abraded and unabraded) assays for 3 weeks (Flannigan *et al.*, 1986). Control sites on the same animal were treated with acetone only. Effects on the skin were evaluated by gross (erythema and edema) observations every 24 hours and histopathological (acanthosis, hyperkeratosis, isolated cell damage, and spongiosis) examinations. In both assays, no effects were observed at the 0.001% level. Mild irritation was evident at 0.01%. Moderate irritation with histological findings (not specified) was found at 0.1%. There was no difference in the extent of irritation between abraded versus unabraded, and open versus occluded treatments.

In three range-finding studies, New Zealand white rabbits (2/sex/group) were exposed to chlorothalonil (98.4% pure) dermally on the back (5-10% of body surface area) (Shults *et al.*, 1986c). The doses and duration of exposure were 100, 500, or 1000 mg/kg/day for 7 days in the first study; 1.0, 10.0, or 100 mg/kg/day for 14 days in the second study; and 0.1, 1.0, and 10.0 mg/kg/day for 14 days in the third study. There were no effects on survival, body weight, and general physical condition. Mild dermal irritation (erythema) was observed at 1.0 mg/kg/day while more severe irritation (erythema, edema, subcutaneous hemorrhage, and desquamation) was noted at higher doses. The NOEL was 0.1 mg/kg/day based on dermal irritation.

In the definitive study, New Zealand white rabbits (6/sex/group) were exposed to chlorothalonil (98.4% pure in methylcellulose; 0. 0.1, 2.5, or 50.0 mg/kg/day) dermally on the back (10% of body surface area) for 6 hours/day for 21 days (Shults *et al.*, 1986d). Chlorothalonil did not affect survival, general physical condition, skin condition, body weight, food consumption, hematology, clinical chemistry and urinalysis parameters, and organ weights. No treatment-related effects were observed under gross and microscopic examinations of the organs (including kidneys). Dermal irritation was noted on day 3 in the 2.5 and 50.0 mg/kg/day groups and was accompanied by minimal to slight histopathologic changes (acanthosis and hyperkeratosis). The slight erythema/ edema progressed to moderate erythema/edema with desquamation with repeated exposures. There was also a statistically significant ($p \leq 0.05$) decrease in the mean serum ALT levels in these groups. The serum ALT levels (M/F) were 20/30% and 11/11% of controls for the 2.5 and 50.0 mg/kg/day groups, respectively, at the end of the study. Sulfur-containing metabolites, such as thiols, glutathione conjugates and other biotransformation products were not detected in the urine of the 2.5 and 50.0 mg/kg/day groups. The NOEL was 0.1 mg/kg/day based on skin irritation, skin histopathological changes (acanthosis and hyperkeratosis) and decreased serum ALT.

Table 8. Selected no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) of chlorothalonil from oral subchronic toxicity studies[a].

Species	Route/ Duration	NOEL/LOEL (mg/kg/day)	Effects	Ref.[c]
Chlorothalonil				
Rat	gavage, 13 w	<75/ 75	Kidney and forestomach lesions	1
Rat	gavage, 13 w	<150/ 150	Kidney weights, kidney and forestomach lesions	2
Rat	diet, 4d-13w	<175/175	Kidney and forestomach lesions	3
Rat	**diet, 13 w**	**1.5/ 3.0**	**ALT (87% of C), kidney weights, inclusion bodies in kidneys**	**4**
Rat	diet, 13 w	< 40/ 40	Kidney weights, kidney and forestomach lesions	5
Rat	diet, 7-91 d	<175/ 175	Labeling indices in kidney, forestomach and kidney lesions	6
Rat	**diet, 28 d**	**1.5/ 15**	**Labeling indices in kidney and stomach, forestomach and kidney lesions**	**7**
Mouse	diet, 13 w	2.8/ 9.2	Forestomach lesions, kidney lesions at higher doses	8
Dog	diet, 13 w	5.6/ 56	Hypertrophy of the adrenals, urine non-protein thiols	9
Dog	cap, 13 w	15 / 150	Body weight gain, serum chemistry changes	10
Dog	cap, 30 d	< 50 / 50	ALT (20% of control), body weight gain	11

a/ Studies in bold are used to determine the critical NOELs in Hazard Identification (**IV.A.**). Common kidney lesions included tubular epithelial hyperplasia, hypertrophy, or/and vacuolation. Common stomach lesions included epithelial hyperkeratosis, hyperplasia, or/and thickening of mucosa. Effects specific to the study and additional effects and are provided in the study summaries.

b/ Abbreviations: w=weeks, d=days, ALT =serum alanine transaminase, C=control, cap=capsules.

c/ References: 1. Ford and Killeen, 1987b; 2. Ford *et al.*, 1987; 3. Ford and Killeen, 1987a; 4. Wilson *et al.*, 1983a; Wilson *et al*., 1985a; Wilson *et al*., 1984; 5. Wilson *et al.*, 1981a; 6. Mizens, 1996a; 7. Hironaka, 1996; 8. Shults *et al.*, 1983; Shults *et al*., 1985; 9. Spencer-Briggs *et al.*, 1994; 10. Fillmore and Laveglia, 1993; 11. Fillmore and Laveglia, 1992.

III.D. CHRONIC TOXICITY AND ONCOGENICITY

Summary: Rats, mice, and dogs exposed to chlorothalonil showed decreased body weight gain, increased kidney weight, kidney lesions, forestomach lesions, and other effects after chronic oral exposure. Kidney lesions included tubular adenomas and carcinomas, tubular cysts, and tubular epithelial hyperplasia/degeneration. Lesions in the gastrointestinal tract involved the forestomach (hyperkeratosis, erosion, ulcer, papilloma and/or squamous cell carcinoma), glandular stomach (erosion), esophagus (hyperplasia/ hyperkeratosis), and duodenum (hypertrophy). Male rats were more susceptible than female rats, mice, and dogs to chlorothalonil-induced kidney lesions. Chlorothalonil also reduced serum ALT activity in rats and dogs. There are no studies on the effect of chronic inhalation and dermal exposure to chlorothalonil. A summary of selected studies is in Table 14.

III.D.1. Dietary - Rat

Crl:CD (SD) BR rats (50/sex/group) were given chlorothalonil (99.28% pure; 0, 15, 60, 240, or 1200 ppm) in the diet for 2 years (Spencer-Briggs, 1995a). Additional groups (20/sex/group) were dosed for the 1 year interim sacrifice. The estimated mean chlorothalonil intakes for both sexes were: 0, 0.8, 3.0, 12.3, and 62 mg/kg/day. The serum ALT was reduced when measured after 13, 26, 52, 54, 78, and 104 weeks of treatment. The reduction was statistically significant primarily at 240 ppm and 1200 ppm. On week 104, the ALT activities (male/female) were 38%/54% ($p < 0.01$) of control levels. When the ALT activity was assayed in the presence of pyridoxal-5'-phosphate, the ALT activity was restored to 60%/90% of control. The investigators concluded that the decrease in ALT activity was due to the depletion of pyridoxal-5'-phosphate, a cofactor, by *B*-lyase in the metabolism of chlorothalonil.

As with short-term studies, the forestomach and kidneys were the target tissues after chronic exposure. Epithelial hyperplasia and hyperkeratosis of the non-glandular forestomach were dose-related in both sexes and all dose levels. Additional common findings in the forestomach at 60 ppm and above included ulceration and submucosal fibrosis and inflammatory cell infiltration. Squamous cell tumors were reported in two 240 ppm females (one papilloma and one carcinoma), one 1200 ppm female (papilloma), and three 1200 ppm males (one papilloma and two carcinoma). For the kidneys, the weights were elevated (117% of control, $p < 0.01$) in 240 ppm males at interim sacrifice and in high dose males (121% of control, $p < 0.01$) and females (107% of control) at terminal sacrifice. The only microscopic lesion was chronic progressive glomerulonephrosis at elevated incidence or degree in high dose rats. Kidney adenomas were found in one 15 ppm male, one 1200 ppm male, and one 1200 ppm female while carcinomas were found in one 60 ppm female. Other effects included increased urinary protein (250% of control, $p < 0.01$) and centrilobular hepatocyte hypertrophy, which were also observed in high dose rats. The NOAEL was 60 ppm (3.0 mg/kg/day) based on forestomach squamous cell tumors at ≥ 240 ppm[1]. A NOEL of 60 ppm could also be established for non-tumor effects of increased kidney weights, ALT, and urinary proteins. This study was considered acceptable by DPR according to FIFRA guidelines.

[1] The assignment of a NOAEL for the tumor effect was part of data review process; it does not imply that it was formed by a threshold mechanism.

Fischer 344 rats (60/sex/group) were given chlorothalonil (98.1% pure; 0, 40, 80 or 175 mg/kg/day) in the diet for 27 months (males) or 30 months (females) (Wilson *et al.*, 1985c; Wilson *et al.*, 1986a). The 175 mg/kg/day dosage may have exceeded the maximum tolerated dose because the weight decrement was greater than 10%. At 12, 24, and 27 months of exposure, the body weights (male/female) of this group were: 88%/90%, 80%/85%, 71%/75% of control, respectively. The body weight decreases for each week were statistically significant ($p \leq 0.05$). At 80 mg/kg/day, body weights (male/female) were 90/88% of control at 27 months. The serum ALT levels (M/F) at 115 weeks were significantly decreased ($p \leq 0.05$), and were 23/58%, 23/73%, and 21/55% of control at 40, 80, and 175 mg/kg/day, respectively. Other effects included: enlarged parathyroids, decreased alkaline phosphatase, increased blood urea nitrogen (BUN), increased creatinine, and decreased serum albumin.

At all doses, there were significant treatment-related lesions in the kidneys (Tables 9 and 10). The lesions included: glomerulonephritis, tubular cysts, cortical and medullary hyperplasia, tubular adenomas and carcinomas. Adenoma and carcinoma were found in both genders with significant increased combined incidences in the 40 mg/kg/day males (Table 10). In the forestomach, incidences of papilloma and carcinoma were 0/60, 1/60, 1/60, and 3/60 for males; and 0/60, 1/60, 2/60, and 7/60 for females. Additional lesions in the gastrointestinal tract of all treated groups included: hyperplasia/hyperkeratosis and submucosal inflammation of the stomach; mucosal hypertrophy of the duodenum, and hyperplasia/ hyperkeratosis of the esophagus. No NOEL was established in this study, and the LOEL was 40 mg/kg/day based on decreased serum ALT, and kidney and stomach lesions. This study was considered acceptable by DPR according to FIFRA guidelines.

Table 9. Non-oncogenic kidney lesions in rats after chronic exposure to chlorothalonil in the diet.[a]

Effects	**Dosage (mg/kg/day)**			
	0	**40**	**80**	**175**
Number examined[a]	120	120	117	120
Glomerulonephritis very slight/slight moderate/marked	 72 23++	 55 54**	 30 79**	 10 106**
Tubular cysts	6 ++	29 **	45 **	71 **
Cortical hyperplasia	0 ++	15 **	29 **	39 **
Medullary hyperplasia	1 ++	7 *	13 **	12 **

a/ Data from Wilson *et al.*, 1985c. Data for both sexes were combined since there was no sex difference in the incidences. Level of statistical significance, $p \leq 0.05$ (* or +) or $p \leq 0.01$ (** or ++), is indicated after each incidence. Significance at the control value was based on a dose-weighted chi-square trend test, and the pair-wise significance at the dosed groups was based on the Fisher's Exact Test.

Table 10. Neoplastic kidney lesions in rats after chronic exposure to chlorothalonil.[a]

Effect	Dosage (mg/kg/day)			
	0	**40**	**80**	**175**
MALES				
Number at risk[b]	60	60	58	60
Adenoma	0++	3 (5%)	5 (9%) *	7 (12%) **
Carcinoma[c]	0+	4 (7%)	2 (3%)	13 (22%) **
Combined[d]	0++	7 (12%) **	7 (12%) **	18 (30%) **
FEMALES				
Number at risk[b]	60	60	59	60
Adenoma	0++	3 (5%)	10 (17%) **	15 (25%) **
Carcinoma[c]	0++	1 (2%)	0 (0%)	11 (18%) **
Combined[d]	0++	4 (7%)	10 (17%) **	23 (38%) **

a/ Data from Wilson *et al.*, 1985c.

b/ Incidences were expressed as the number of animals bearing tumors. All animals examined were considered at risk, except for those which died before day 365 of the study. The first tumor was diagnosed on day 417. Level of statistical significance, $p \leq 0.05$ (* or +) or $p \leq 0.01$ (** or ++), is indicated after each incidence. Significance at the control value was based on a dose-weighted chi-square trend test, and the pair-wise significance at the dosed groups was based on the Fisher's Exact Test.

c/ Tubular carcinomas in all groups and anaplastic renal carcinomas in one male (80 mg/kg/day) and 3 females (175 mg/kg/day).

d/ Rats with either adenoma or carcinoma only, or both.

Fischer 344 rats (65/sex/group) were fed chlorothalonil (98.3% pure; 0, 1.8, 3.8, 15.2, or 183 mg/kg/day) in the diet (Wilson and Killeen, 1989 and 1987a). Satellite groups (10/sex/group) were sacrificed on week 56. The high dose satellite group showed reduced (88-93% of control) mean body weights and increased incidences of dark urine. The decrease in body weights was significant after 1 week of exposure to the end of the study. Macroscopic examinations of the satellite groups showed a granular appearance of the kidney (183 mg/kg/day males), and a thickening of the forestomach (15.2 and 183 mg/kg/day groups).

In the main group, the exposure duration was 99 weeks for the 183 mg/kg/day males, 111 weeks for all other males, and 125 weeks for all females. Survival was affected by chlorothalonil treatment and was 80% by the end of 99 weeks and 125 weeks for the high dose males and females, respectively. There was a significant ($p \leq 0.05$) decrease in the mean body weight of 10% or more compared with the control values. The overall average body weights for the males/females were 365 gm/227 gm, 358 gm/230 gm, 357 gm/230 gm, 346 gm/229 gm, and 310 gm/204 gm for the 0, 1.8, 3.8, 15.2, and 183 mg/kg/day groups, respectively. There were no effects on food consumption and hematology. The significant clinical chemistry findings were: decreased (1.027 versus 1.038 in controls at 23 months, $p \leq 0.05$) urine specific gravity in 183 mg/kg/day group after 18 and 23 months; and decreased serum ALT in 15.2 mg/kg/day females (54% of control, $p \leq 0.05$) and higher doses of both sexes (32-50% of control) after 23-24 months of exposure. The absolute kidney weight, relative kidney to body weight, and relative kidney to brain weight were increased in a dose-related manner. At 183 mg/kg/day, all three measurements were statistically significant ($p \leq 0.05$) and ranged from 120 to 146% of control for both sexes. At 3.8 and 15.2 mg/kg/day, a statistically significant ($p \leq 0.05$) increase

was noted for at least one of these ratios. High dose males and females had increased clear fluid in thoracic cavities, and enlarged parathyroids at terminal sacrifice.

Histological examinations showed dose-related increases in the incidence of lesions in the kidneys, forestomach, and glandular stomach (Tables 11 and 12). The examination of the kidney slides was conducted "blinded" as to treatment. Lesions found were: chronic progressive nephropathy, focal epithelial hyperplasia, clear cell[2] hyperplasia, cortical cysts, pelvic epithelia hyperplasia, tubular adenoma, and carcinoma. Tubular epithelial hyperplasia was elevated in both incidence and degree at 3.8 mg/kg/day and above. This hyperplasia was confirmed in every animal bearing tubular cell tumors, except 4 cases in which autolysis and/or chronic nephropathy prevented a definitive diagnosis. The association was considered strong evidence that the hyperplasia was a preneoplastic lesion. In the stomach, several lesions were found: papilloma and/or squamous cell carcinoma, epithelial hyperplasia, hyperkeratosis, erosion, and ulcer in the forestomach; and mucosal erosion in the glandular stomach. The incidence of non-oncogenic lesions was increased at 3.8 mg/kg/day and progressed with increasing frequency and severity at the higher doses. The NOEL for non-oncogenic effects was 1.8 mg/kg/day based on kidney and stomach lesions at 3.8 mg/kg/day and other effects at higher doses. This study was considered an acceptable supplementary study since the data requirement was already filled by the study from Wilson *et al.* (1985c).

[2] Clear cells have dense nuclei wih small, condensed chromatin. They may be filled with glycogen or lipid. H&E stained paraffin sections show cytoplasm as transparent and without structure.

Table 11. Non-oncogenic kidney and stomach lesions in rats after chronic exposure to chlorothalonil in the diet.[a]

Effects	Dosage (mg/kg/day)				
	0	**1.8**	**3.8**	**15.2**	**183**
Number examined	110	108	109	107	110
Kidney					
Chronic progressive nephropathy					
moderate/severe	45++	53	63**	66**	103**
all levels	80++	85	87**	86	106**
Epithelial hyperplasia, focal					
moderate/severe	18++	21	29*	38**	94**
all levels	33++	40	48*	58**	99**
Epithelial hyperplasia, diffuse	12	10	12	15	9
Clear cell hyperplasia					
moderate/severe	0++	1	1	6*	33**
all levels	1++	3	2	9**	39**
Cortical cysts	21++	11	20	28	80**
Pelvic epithelia hyperplasia	3++	4	3	11*	18**
Stomach					
Mucosal erosion, glandular					
moderate/severe	9	4	6	15	13
all levels	21 ++	14	14	29	62 **
Epithelial hyperplasia, non-glandular					
moderate/severe	10++	10	33**	37**	69**
total	15++	14	47**	91**	102**
Hyperkeratosis, non-glandular					
moderate/severe	8++	10	25**	35**	65**
total	13++	12	38**	87**	102**
Erosion, non-glandular	1	0	6	9**	6
Ulcer, non-glandular	14++	13	32**	37**	35**

a/ Data for both sexes were combined (Wilson and Killeen, 1989). Incidences indicated were those for moderate to severe (if data show different levels of severity) and total incidences. Data for other levels of severity are available in the study report. Level of statistical significance, $p \leq 0.05$ (* or +) or $p \leq 0.01$ (** or ++), is indicated after each incidence. Significance at the control value was based on a dose-weighted chi-square trend test, and the pair-wise significance at the dosed groups was based on the Fisher's Exact Test.

Table 12. Neoplastic and pre-neoplastic lesions of the kidney and stomach in rats after chronic exposure to chlorothalonil.[a]

Effect	Dosage (mg/kg/day)				
	0	**1.8**	**3.8**	**15.2**	**183**
MALES					
Number at risk	55	54	54	54	55
Kidney					
Tubular adenoma	1 (2%) ++	1 (2%)	1 (2%)	3 (6%)	17 (31%) **
Tubular carcinoma	0 (0%) ++	0 (0%)	0 (0%)	1 (2%)	7 (13%) **
Combined[c]	1 (2%) ++	1 (2%)	1 (2%)	4 (7%)	23 (42%) **
Stomach					
Papilloma	0 (0%) ++	0 (0%)	3 (6%)	2 (4%)	5 (9%) *
FEMALES					
Number at risk	55	54	55	53	55
Kidney					
Tubular adenoma	0 (0%) ++	0 (0%)	0 (0%)	0 (0%)	24 (44%) **
Tubular carcinoma	0 (0%) ++	0 (0%)	0 (0%)	0 (0%)	11 (20%) **
Combined[c]	0 (0%) ++	0 (0%)	0 (0%)	0 (0%)	32 (58%) **
Stomach					
Papilloma	1 (2%) ++	1 (2%)	2 (4%)	4 (8%)	7 (13%) *
Squamous cell carcinoma	1 (2%) +	0 (0%)	0 (0%)	1 (1%)	3 (5%)

a/ Data from Wilson and Killeen (1989).

b/ Incidences were expressed as the number of animals bearing tumors (with % incidence in parenthesis). All animals examined were considered at risk, except for those which died before day 365 of the study. The first tumor was diagnosed on days 497 and 525 for the kidney and stomach, respectively. Level of statistical significance, $p \leq 0.05$ (* or +) or $p \leq 0.01$ (** or ++), is indicated after each incidence. Significance at the control value was based on a dose-weighted chi-square trend test, and the pair-wise significance at the dosed groups was based on the Fisher's Exact Test.

c/ Rats with either adenoma or carcinoma only, or both.

Osborne Mendel rats (10/sex/control groups; 50/sex/treated groups) were fed chlorothalonil (98.5% and 98% pure; two samples used) in the diet for 80 weeks and observed for 110 weeks (NCI, 1978a; Wilson and Heilman, 1980; Wilson *et al.*, 1981b; Ketron, Inc., 1982). Doses were initially at 20,000 and 10,000 ppm for the first week of dosing; then they were lowered to 10,000 and 5,000 ppm, respectively, for the remaining 79 weeks. The time-weighted average doses were 5,063 and 10,126 ppm. Significant findings in both groups were: weight loss, rough and discolored hair coats, bright-yellow urine, pale mucous membranes, ataxia, tachypnea, epistaxis, dermatitis, hematuria, hyperactivity, and vaginal bleeding. The incidences of tumors (adenomas and carcinomas) in the kidney tubular epithelium were 0/10, 2/46, and 1/49 for the males and 0/10, 0/48, and 3/50 for the females for the control, low, and high dose groups, respectively. This study was considered unacceptable by DPR according to FIFRA guidelines because of the following deficiencies: only two doses, doses lowered during the study, test material changed during dosing, dosing only for 80 weeks, missing individual data, and too few control animals.

Charles River C-D rats (50/sex/group) were fed chlorothalonil (purity not stated; 0, 4, 10, 20, 30, 40, or 60 ppm) in the diet for 2 years (Hazleton Laboratories, Inc., 1970a). Based on the default consumption rate of 5% body weight, the estimated dosages were: 0, 0.2, 0.5, 1.0, 1.5, 2.0, or 3.0 mg/kg/day. There were interim sacrifices at week 13 and 1 year. No treatment-related effects were observed in growth, food consumption, survival, clinical laboratory tests, organ weights, and gross pathology. The major finding was renal tubular vacuolization and hypertrophy in the 40 and 60 ppm groups at the 1-year interim sacrifice. The renal findings were not substantiated at terminal sacrifice. This study was considered unacceptable by DPR according to FIFRA guidelines because of the following deficiencies: incomplete histopathology in some animals, early deaths, test article and treated feed not characterized, and no diet analysis.

Charles River C-D rats (70/sex/group for control; 35/sex/group for treated) were fed chlorothalonil (93.6% pure; 0, 0.15, 1.5, or 3.0% by weight) in the diet for up to 2 years (Hazleton Laboratories, Inc., 1967b). Based on the default consumption rate of 5% body weight, the estimated dosages were: 0, 75, 750, or 1500 mg/kg/day. Degradative products in the chlorothalonil preparation included: 3.0% tetrachloro-terephthalonitrile, tetrachloro-phthalonitrile 1.1%, and pentachloro-benzonitrile 2.3%. There were two interim sacrifices at 13 and 16 weeks for the high dose group, and at 13 and 52 weeks for the other groups. Dietary levels of chlorothalonil for the 1.5 and 3.0% groups were decreased during part of the study because of food refusal and poor weight gain. The survival rates were poor and were 39%, 20%, and 20% for the control, 0.15, and 1.5% groups, respectively. There was a decrease in body weight gain and an increase in kidney weights (102-126% of control) and organ/body weight ratios (127-146% of control, statistically significant but p value not specified) in all treated groups. Histopathological alterations were found in the thyroid, stomach, kidney, and liver. Kidney changes (tubular hyperplasia and hypertrophy) were found in all treated groups. The NOEL was < 0.15% (< 75 mg/kg/day) based on treatment-related toxicity in all treatment groups. This study was considered unacceptable by DPR according to FIFRA guidelines because of the following deficiencies: doses were too high; changes in doses during the experiment; lack of information on test material; no feed analysis; excessive mortality; insufficient observations, serum chemistry, necropsies, ophthalmology, and histopathology; and missing data.

To follow-up on the previous study (Hazleton Laboratories, Inc., 1967b), two supplemental studies were conducted with lower doses from the same mixture (Hazleton Laboratories, Inc., 1967c and 1967d). In the first supplemental study, Charles River C-D rats (35/sex/group) were fed chlorothalonil (93.6% pure; 0, 0.5% by weight) in the diet for up to 2 years (Hazleton Laboratories, Inc., 1967c). There were interim sacrifices at 13 and 52 weeks. Based on the default consumption rate of 5% body weight, the estimated dosage for chlorothalonil was 250 mg/kg/day. The treated group showed reduced weight gain as the terminal mean body weight was 85-91% of the control group. Food consumption was significantly higher in males during weeks 26-52. Survival was only 12% in treated males by the end of the study, compared with 27% in the control group, but it was higher in treated females (60%) than in control females (40%). Both kidney/body weight ratios and liver/body weight ratios of treated rats were significantly (p value not specified) elevated (108-115% of control value for liver; 131-140% of control value for kidneys). Kidneys of treated rats were enlarged, abnormal in color, and showed some cyst-like foci or large cysts. Histopathological examination of the kidneys showed tubular hypertrophy of the renal cortex, and degeneration of the proximal

tubule epithelium. The NOEL was < 0.5% (< 250 mg/kg/day) based on treatment-related findings. This study was considered a supplementary study by DPR. There were major deficiencies in this study: only a single dose level; lack of information on test material; no feed analysis; excessive mortality; insufficient observations, serum chemistry, necropsies, ophthalmology, and histopathology; and missing data.

In the second supplemental study, Charles River C-D rats (15/sex/group) were fed chlorothalonil (93.6% pure; 0, 0.05, 0.1% by weight) in the diet for 76 weeks, at 0.5% for 23 weeks (interrupted for 13 days) (Hazleton Laboratories Inc., 1967d). Based on the default consumption rate of 5% body weight, the estimated dosages were: 0, 25, 50, 250 mg/kg/day. The diet contained the same mixture as described previously (Hazleton Laboratories, Inc., 1967b). There were interim sacrifices (5/sex/group) on week 20 for the 0.05 and 0.1% groups; and on week 23 for the 0.5% group. Survival of the 0.1% group males (30%) was lower than that of the control group (60%). No clinical signs were observed, except for food refusal by the 0.5% group in the first two weeks. Food consumption and body weights were decreased in the high dose group during the first week of dosing and the first week of reinstated dosing (week 5) (data not supplied). Kidneys of the 0.1% males were enlarged and showed a rough or pitted surface. Discolored kidneys were observed in most of males and several females in the 0.5% group. Histopathological examinations of the kidneys showed degenerative changes in the 0.1% and 0.5% groups. The changes were more severe in males than females and were characterized by tubular hypertrophy, epithelial irregularity and vacuolization, and cyst formation. The NOEL was 0.05% (25 mg/kg/day) based on the treatment related findings. This study was considered a supplementary study by DPR and had the following deficiencies: lack of information on test material; no feed analysis; too few animals; test period too short; insufficient observations, hematology, serum chemistry, urinalysis, necropsies, ophthalmology, and histopathology; and no data tables.

In a chronic study, rats (strain and group size not specified) were fed SDS-3701 (purity not specified; 0.5, 3.0, 15, or 30 mg/kg/day) in the diet for 2 years (Diamond Shamrock Corporation, 1983b). The two highest dose levels were reduced or ended during the study because of increased mortality and anemia. No oncogenicity was reported. The NOEL was 3.0 mg/kg/day based on mortality and anemia. This report was a summary and was considered a supplementary study by DPR.

III.D.2. Dietary - Mouse

Crl:CD-1 (ICR) BR mice (50/sex/group) were given chlorothalonil (99.28% pure; 0, 15, 60, 240,or 960 ppm) in the diet for 80 weeks (Spencer-Briggs, 1995b). The mean dosages for both sexes were 0, 2.2, 8.9, 35.5, and 143.5 mg/kg/day. Epithelial hyperplasia, both in the forestomach and at the limiting ridge, was dose-related in incidence and degree at all dose levels in males. Squamous cell papillomas were found in the non-glandular stomach. Effects on the kidneys were observed only in the males. Kidney weights were elevated in the 960 ppm group. There was a dose-related increase in the incidence of cystic atrophic glomerulus with hypertrophic parietal epithelium with the NOAEL at 15 ppm (2.2 mg/kg/day). This study was considered acceptable by DPR according to FIFRA guidelines.

Charles River CD-1 mice (60/sex/group) were fed chlorothalonil (97.7% pure; 0, 750, 1500, or 3000 ppm) in the diet for 24 months (Wilson *et al.*, 1983b; Wilson *et al.*, 1986b; Wilson and Killeen, 1986). The calculated average dosages for both sexes were: 0, 127, 265, 551 mg/kg/day. There were no treatment-related effects on body weight, food consumption, physical condition, and hematological parameters. Serum chemistry analysis was not conducted. Survival of all groups including controls was greater than 50% at 18 months, but less than 50% at 24 months. Of the organs weighed, only the absolute kidney weights were significantly ($p \leq 0.01$) increased in a dose-related manner. The mean absolute kidney weights (male/female) were: 120%/124%, 117%/125%, 127%/137% of control values for 750, 1500, and 3000 ppm, respectively. The kidney to body weight and kidney to brain weight ratios were also increased to a similar extent. Histopathological examinations showed lesions in the esophagus (hyperplasia and hyperkeratosis), stomach (hyperplasia and hyperkeratosis of gastric squamous mucosa, squamous epithelial carcinoma), and kidneys (glomerulonephritis, cortical cysts and tubular degenerations, tubular adenomas and adenocarcinomas in males only) for all treated groups. The incidences of the neoplastic findings for the kidney and stomach are presented in Table 13. The incidences for forestomach hyperplasia and hyperkeratosis were 83% at 750 ppm, 87% at 1500 ppm, and 94% at 3000 ppm. The NOEL was < 750 ppm (<127 mg/kg/day) for kidney and stomach lesions. This study was considered acceptable by DPR according to FIFRA guidelines.

Table 13. Kidney and stomach lesions in mice after chronic exposure to chlorothalonil in the diet.[a]

Effects	Dosage (ppm)			
	0	**750**	**1500**	**3000**
MALES Number at risk[b]	57	60	53	50
Kidney				
Tubular adenoma	0 (0%)	2 (3%)	3 (6%)	3 (6%)
Tubular carcinoma	0 (0%)	4 (7%)	1 (2%)	1 (2%)
Adenoma and/or carcinoma[c]	0 (0%)	6 (10%) *	4 (8%) *	4 (8%) *
Stomach				
Forestomach, squamous epithelium				
carcinoma	0 (0%)	2 (3%)	5 (9%) *	2 (4%)
papilloma	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fundic stomach, glandular epithelium				
carcinoma, glandular	0 (0%)	1 (2%)	2 (4%)	0 (0%)
adenomatous diverticulum or polyp	1 (2%)	1 (2%)	0 (0%)	2 (4%)
FEMALES Number at risk[b]	52	57	54	51
Stomach				
Forestomach, squamous epithelium				
carcinoma	0 (0%)	0 (0%)	5 (10%) *	3 (6%)
papilloma	0 (0%)	2 (4%)	1 (2%)	2 (4%)
Fundic stomach, glandular epithelium				
carcinoma, glandular	0 (0%)	1 (2%)	1 (2%)	2 (4%)
adenomatous diverticulum or polyp	0 (0%)	0 (0%)	2 (4%)	1 (2%)

a/ Data from Wilson *et al.*, 1983b.

b/ Incidences were expressed as the number of animals bearing tumors (% incidence in parenthesis). All animals examined were considered at risk, except those which died before day 365 of the study. The first tumor was diagnosed on day 640 for kidney, and day 524 for stomach. Level of statistical significance, $p \leq 0.05$ (* or +) or $p \leq 0.01$ (** or ++), is indicated after each incidence. Significance at the control value was based on a dose-weighted chi-square trend test, and the pair-wise significance at the dosed groups was based on the Fisher's Exact Test.

c/ Rats with either adenoma or carcinoma only, or both.

In a follow-up study, the doses were lowered to determine a NOEL for kidney lesions in the male mice observed in the previous study. Charles River CD-1 male mice (60/group) were fed chlorothalonil (98% pure; 0, 10/15, 40, 175, or 750 ppm) in the diet for 1 year (Wilson and Killeen, 1987b; Wilson and Killeen, 1987c). The low dose was increased from 10 ppm to 15 ppm at week 18 to ensure a dosage of at least 1.5 mg/kg/day. Nominal dosages were 0, 1.86, 5.35, 23.2, or 99.7 mg/kg/day. Serum chemistry analysis was not conducted. Significant effects were found in the kidneys (organ weights at 750 ppm; and hyperplasia at 175 and 750 ppm) and forestomach (hyperplasia and hyperkeratosis of the squamous mucosa at ≥ 40 ppm, glandular hyperplasia, and possible squamous papillomas). The increased absolute kidney weight of the treated groups was not statistically significant when compared with the control. However, the increase (116% of control) of kidney weight relative to body weight in the 750 ppm group was statistically significant ($p \leq 0.05$). The incidences of kidney tubular hyperplasia (regardless of severity) were 9/13, 9/17, 8/12, 10/14, and 14/16 for the groups, 0, 10/15, 40, and 175 ppm, respectively. The incidences for lesions in the stomach were 0, 2/17, 3/12, 3/14, and 12/16 for 0, 10/15, 40, 175, and 750 ppm, respectively. The NOELs were 15 ppm (1.86 mg/kg/day) based on stomach lesions, and 40 ppm (5.35 mg/kg/day) based on kidney lesions. This was considered a supplementary study by DPR.

B6C3F1 mice (10/sex/control groups; 50/sex/treated groups) were fed chlorothalonil (98% pure) in the diet for 80 weeks (NCI, 1978b). The intended doses of 10,000 and 20,000 ppm were reduced to 2,500 and 5,000 ppm after 2 and 10 weeks of exposure, respectively, because of mortality, changes in body weight and the general condition (not specified in the report) of the animals. No oncogenicity or treatment-related effect was observed. This study was considered unacceptable by DPR according to FIFRA guidelines because of the following deficiencies: only two doses, doses lowered during the study, missing individual data, too few control animals, and higher frequencies of spontaneous tumors.

Mice (strain not specified) were fed SDS-3701 (purity not stated; 375, 750, or 1500 ppm) in the diet for 2 years (Diamond Shamrock Corporation, 1983c). There was increased liver-to body weight ratio for all dose groups. No oncogenicity was reported. This study was considered unacceptable by DPR because only a summary report was submitted.

III.D.3. Oral - Dog

Beagle dogs (5/sex/group) were given chlorothalonil (98.3% pure; 0, 15, 150, or 500 mg/kg/day) once daily in gelatin capsules for 12 months (Mizens and Laveglia, 1994). There were no treatment-related effects on survival, physical condition, ocular changes, food consumption, hematology, urinalysis parameters, and gross pathology. Emesis was noted more frequently in the high dose group; however, it occurred only occasionally throughout the study. At 500 mg/kg/day, body weights were slightly suppressed ($p \leq 0.05$, 93% and 85% of controls only in males for weeks 10 and 40, respectively) and plasma cholesterol was elevated ($p \leq 0.01$, 171% of control for females on week 27). The reduced circulating serum albumin ($p \leq 0.01$, 84-87% of control for weeks 27 and 52 for both sexes) suggested a minor functional change in the liver. At 150 and 500 mg/kg/day, relative liver weights were elevated and pigmentation of kidney tubular epithelial cells were enhanced. The severity of pigmentation increased from minimal in control and low dose groups, mild in the mid-dose, to moderate in the high dose

involving all animals. Serum ALT levels were decreased in all treatment groups as early as the first week (94-78% of control) and further decreased to 0-2 IU/L for weeks 27 and 52, compared with 20-26 IU/L for controls. The effect on ALT was not associated with any liver lesion. The NOEL was 15 mg/kg/day for increased liver weights and pigmentation of the kidney tubular epithelial cells. The study was considered acceptable by DPR according to FIFRA guidelines.

III.D.4. Dietary - Dog

Beagle dogs (4/sex/group) were fed chlorothalonil (99.28% pure; 0, 160, 1280, or 10240 ppm) in the diet for 1 year (Spencer-Briggs, 1995c; Spencer-Briggs *et al.*, 1994). The mean dosages for both sexes were: 0, 5.5, 44.3, and 364 mg/kg/day. In the stomach, the following were observed: prominent apoptotic bodies in the antrum, erosion of luminal surface epithelium, cellular hypertrophy with increased mucosal thickness, congestion of submucosal vessels, inflammatory cell infiltration in gastric mucosa, mucus and cell debris adherent to the luminal surface, and foci of mucosal mineralization. One high dose female was sacrificed moribund after displaying marked and sustained signs of anemia, reduced food consumption, and serious cardiac pathology (myocardial degeneration, intramyofibrillar hemorrhage and edema, and hemorrhage into the endocardium). There was a sharp drop in ALT (less than 20% for the 160 ppm group and <5% for the other dose groups of the pretreatment levels) in all treated groups for all measured time periods (weeks 13, 26, 39, 52). When the ALT assay was performed with pyridoxal-5'-phosphate, no treatment differences in ALT levels were evident. Other effects included: elevated non-protein thiol concentration in kidneys (10240 ppm of males, all doses for females), body weight decrements (1280 ppm and 10240 ppm males), liver weight increases (1280 and 10240 ppm for both sexes), pigmentation of kidney cortical tubule epithelium (1280 and 10204 ppm for both sexes), adrenal cortical hypertrophy in high dose males only, and vasodilation evident in gums and/or ears in high dose dogs (from week 2 to 24, only one dog after week 28). The NOAEL was 160 ppm (5.5 mg/kg/day) based on the above stomach pathology. Additional effects with this NOEL were decreased body weight, increased liver weight, and pigmentation of the kidney cortical tubule epithelium. The NOEL was <160 ppm (<5.5 mg/kg/day) for reduced ALT in all treated groups. The study was considered acceptable to DPR according to FIFRA guidelines.

Beagle dogs (3/sex/group) were fed chlorothalonil (93.6% pure; 0, 0.15, 1.5, or 3.0% by weight) in the diet for 104 weeks (Hazleton Laboratories, Inc., 1966a; Wilson, 1966). Additional groups (1/sex/group) were sacrificed after 1 year of exposure and no gross findings were observed at necropsy. The average dosages for the 3 treatment groups after 104 weeks were: 45, 440, and 831 mg/kg/day. During the study, all dogs appeared normal, except two dogs (one in each of 1.5% and 3.0%) were anorexic. All treated groups showed reduced weight gain, which was 44%, 18%, and 5% of control level for the 0.15, 1.5, and 3.0% groups, respectively. Absolute liver weights and liver/body weight ratios were slightly increased in the 1.5 and 3.0% groups. Increased absolute kidney and thyroid weights, and relative organ weight ratios were found in some animals of all treated groups. Significant histopathologic findings found in the 1.5% and 3.0% levels included the kidneys (tubular hypertrophy and dilatation; epithelial vacuolation, and pigmentation), liver (pigmentation of hepatocytes and macrophages, and other irregularities), thyroid (pigmentation), and stomach (gastritis). The kidneys lesions were dose-related in severity and frequency. The renal lesions in the 3.0% group were considered moderate

to severe and were found in almost all dogs in this group. Regenerative growth was observed in the kidneys of 2 dogs of the 3.0% group. The LOEL was 0.15% (45 mg/kg/day) based on reduced body weight gain and other findings at higher doses. This study was considered unacceptable by DPR according to FIFRA guidelines because of the following deficiencies: inadequate information on the test material, test animals, and randomization procedure; no feed analysis; insufficient serum chemistry; lack of ophthalmology data; inadequate tissue examination protocol for histopathology; missing data; and the lack of data analysis.

Dogs (8/sex/group) were given chlorothalonil (purity not specified; 0, 60, or 120 ppm) in the diet for 2 years (Hazleton Laboratories, Inc., 1970b; Stemmer, 1970). The dosages were 1.5 and 3 mg/kg/day assuming a consumption rate of 2.5% body weight. Fifty percent of each group was sacrificed after 1 year. No adverse effects were reported. This study was considered unacceptable by DPR according to FIFRA guidelines because of inadequate dosing levels; limited histopathology; test material and treated feed not characterized; and limited data analysis.

Table 14. Selected no-observed-effect levels (NOELs) and lowest-observed-effect levels (LOELs) of chlorothalonil from chronic toxicity studies[a].

Species	Route/ Duration	NOEL/LOEL (mg/kg/day)	Effects	Ref.[b]
Rat	diet, 2 y	3.0 / 12.3	Stomach and kidney tumors, ↓ALT, ↑ Kidney weights and urinary protein	1*
Rat	diet, 27-30 m	< 40/ 40	Kidney and forestomach lesions, ↓ALT	2*
Rat	**diet, 111w**	**1.8 / 3.8**	**Kidney & forestomach lesions, ↓ ALT (female at 15.2 mg/kg/day)**	**3***
Rat	diet, 2 generation	<21.7/ 21.7	Kidney and stomach lesions	4*
Mouse	diet, 2 y	2.2 / 8.9	Glomerular atrophy	5*
Mouse	diet, 2 y	< 127 / 127	↑ Kidney weights, kidney and forestomach lesions	6*
Mouse	diet, 2 y	1.86 / 5.35	Stomach lesions, kidney lesions at $23.2 mg/kg/day	7
Dog	cap, 1 y	15 / 150 < 15 / 15	↑Liver weights, ↑ kidney cell pigmentation ↓ ALT	8*
Dog	diet, 1 y	5.5 / 44.3 <5.5 / 5.5	Stomach lesions, ↓body weight, ↑liver weight, ↑kidney cell pigmentation ↓ ALT	9*
Dog	diet, 2 y	< 45 / 45	↓ Body weight gain; clinical signs; kidney, thyroid, liver, and stomach lesions at ≥ 436 mg/kg/day	10

a/ Studies in bold are used to determine the critical NOELs in Hazard Identification (**IV.A.**). Common kidney lesions included glomerulonephritis, epithelial hyperplasia, hypertrophy, or/and vacuolation. Common stomach lesions included epithelial hyperkeratosis, hyperplasia, or/and thickening of mucosa. Effects specific to the study and additional effects and are provided in the study summary.

b/ Abbreviations: y=years, m=months, w=weeks, cap=capsules

c/ * after the reference number indicates the study was acceptable to DPR according to FIFRA guidelines. References: 1. Spencer-Briggs, 1995a; 2. Wilson *et al.*, 1985c; 3. Wilson and Killeen, 1989; 4. Lucas and Benz, 1990; 5. Spencer-Briggs, 1995b; 6. Wilson *et al.*, 1983b; 7. Wilson and Killeen, 1987b; 8. Mizens and Laveglia, 1994; 9. Spencer-Briggs, 1995c; 10. Hazleton Laboratories, Inc., 1966a.

III.E. GENOTOXICITY

Summary: Chlorothalonil and metabolites (including SDS-3701) were tested negative in bacterial and mammalian cell gene mutation assays and most structural chromosomal assays. At high doses, chlorothalonil was positive in a hamster assay and in an *in vitro* Chinese hamster ovary cell chromosomal aberration assays. DNA studies showed that chlorothalonil and SDDS-3710 did not cause cell transformation in rat cell lines and chlorothalonil did not bind to rat kidney DNA. However, chlorothalonil caused DNA damage in human peripheral blood lymphocytes. A summary of selected studies is in Table 15.

III.E.1. Gene Mutation

III.E.1.a. Chlorothalonil

Chlorothalonil (>97% pure; up to 10 *u*g/plate) was not mutagenic in Ames assays with strains TA98, TA100, TA1537, or TA1538 with and without rat liver S-9 homogenate pretreated with Aroclor 1254 (Microbiological Associates, 1977a; Shirasu *et al.*, 1977a). Chlorothalonil (no purity stated; up to 50 *u*g/plate) was also not mutagenic in the above strains with and without rat kidney S-9 homogenate (Jones *et al.*, 1984). Only the report by Microbiological Associates (1977a) was considered acceptable by DPR.

In a host-mediated Ames assay, male mice (10/group) were given chlorothalonil (>99% pure; 6.5 mg/kg/day) by gavage for 5 days (Legator, 1974a). *Salmonella typhimurium* strains were then injected into the peritoneal cavity and recovered 3 days later. The results were reported as negative; however, no data were provided. This study was considered unacceptable by DPR because of insufficient information to assess mutagenicity.

Chlorothalonil (97.3% pure) was not mutagenic when tested at 0.3 *u*g/ml in Chinese hamster lung fibroblasts (V79) cells, at 0.3 *ug*/ml with activation (rat liver S-9 homogenate pretreated with Aroclor 1254) in mouse BALB/3T3 fibroblasts, and at 0.03 *u*g/ml without activation in BALB/3T3 cells (Microbiological Associates, 1977b). This study was considered unacceptable by DPR because of insufficient information and other deficiencies.

III.E.1.b. Metabolites

Potential metabolites and impurities of chlorothalonil were negative in Ames assays with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 with and without liver or kidney S-9 homogenate (Microbiological Associates, 1977c; Jones *et al.*, 1985a to l; Mizens *et al.*, 1985a and b; Mizens *et al.*, 1986a and b; Mizens *et al.*, 1987). These studies are summarized in Table 15. All studies were considered supplemental data by DPR.

4-Hydroxy-2,5,6-trichloro-isophthalonitrile (SDS-3701, 99% pure; 3 *u*g/ml) was not mutagenic in Chinese hamster lung fibroblasts (V79) cells and mouse BALB/3T3 fibroblasts with and without activation (rat liver S-9 homogenate pretreated with Aroclor 1254) (Microbiological Associates, 1977d). This study was considered supplemental data by DPR.

III.E.2. Structural Chromosomal Aberrations

Male Chinese hamsters (10/group) were given chlorothalonil (98.3% pure; 0, 187.5, 375, or 750 mg/kg/day) by gavage for 5 days (Mizens and Laveglia, 1995). Bone marrow samples were examined at 6 and 24 hours after the last dose. There were 4 deaths at the high dose and the cause of death was not identified. Mean body weights of the 375 and 750 mg/kg/day groups were 91.9 and 87.6% of original body weights, respectively. Clinical signs (piloerection, hunched position, difficulty in breathing) were also observed in these 2 groups and were more severe in the 750 mg/kg/day group. Chlorothalonil did not induce chromosomal aberrations in bone marrow cells. This study was considered acceptable by DPR.

Male SD rats (5/group) were given chlorothalonil (98.85% pure; 0, 500, 1000, or 2000 mg/kg/day) by gavage for 5 days (Kajiwara and Furusho, 1994). Chlorothalonil did not induce chromosomal aberrations in the bone marrow cells. This study was considered acceptable by DPR.

Chlorothalonil (98.2% pure) was given within 24-hours by gavage to Wistar rats (10 males/group; 0, 8, 40, 200, 1000 or 5000 mg/kg/day; Mizens *et al.*, 1983b), Swiss CFLP mice (10 to 13 males/group; 0, 4, 20, 100, 500, or 2500 mg/kg/day; Mizens *et al.*, 1983c), and Chinese hamsters (10 males/group; 0, 4, 20, 100, 500, or 2500 mg/kg/day; Mizens *et al.*, 1983d). Chlorothalonil did not induce bone marrow erythrocyte micronuclei; however, none of the reports contained sufficient information to assess adverse effects. Two hamsters died (one in the 100 mg/kg/day and one in the 500 mg/kg/day groups) following dosing (Mizens *et al.*, 1983d). These studies were considered unacceptable by DPR.

Other investigators also showed that chlorothalonil did not induce micronuclei formation in mice gavaged with chlorothalonil (>99% pure; 6.5 mg/kg/day) for 5 days (Legator, 1974b). This study was considered unacceptable by DPR because there was insufficient information to assess adverse effects.

In a dominant lethal assay, chlorothalonil (>99% pure; about 6.5 mg/kg/day) was given to male mice (strain not specified) by gavage (Legator, 1974c). Treated males were mated to two females each week for 8 weeks. No effects on fertility, implantation, or early death were reported. This study was considered unacceptable by DPR because of the contradictory dose information, too few pregnant females, and no individual data.

Using the same protocol as the micronuclei assay (Mizens *et al.*, 1983b-d), chlorothalonil did not induce chromosomal aberrations in the bone marrow of rats (Mizens *et al.*, 1983e), mice (Mizens *et al.*, 1983f), or hamsters (Mizens *et al.*, 1983g). The bone marrow was sampled 6 hours after the second dose. These studies were considered unacceptable by DPR because there was insufficient information to assess adverse effects and sample times were too short.

Further studies by the same investigators extended the time for bone marrow examination from 6 to 24 and 48 hours after a single treatment. Chlorothalonil (98.2% pure) remained negative for the induction of chromosomal aberration in mice (250 to 2500 mg/kg; Mizens *et al.*, 1985c) and rats (500 to 5000 mg/kg; Mizens *et al.*, 1985d). In hamsters, there was a dose-related

decrease in the mitotic index and a marginally increased aberration frequency for the 48 hours samples for the 2500 and 5000 mg/kg groups (Mizens *et al.*, 1985e). The increases were 4/1000 and 3/700 cells at 2500 and 5000 mg/kg, respectively, for chromosomal breaks, compared with 1/1000 cells for the control. These studies were considered acceptable by DPR.

Chinese hamsters (10-11 males/group) were given chlorothalonil (98.2% pure; 0, 50, 125, or 250 mg/kg/day) by gavage for 5 days (Mizens *et al.*, 1985f). Chromosomal breaks in bone marrow cells were elevated in all treated groups (statistically significant at 50 and 250 mg/kg/day). The incidences were: 3/900 (50 mg/kg/day), 4/900 (250 mg/kg/day), and 1/1000 (control). This study was considered acceptable by DPR.

In an *in vitro* study, chlorothalonil (98.8% pure; 0, 0.6, 1.5, 3.0, and 6.0 *u*g/ml) was tested in Chinese hamster ovary cells with rat liver S-9 homogenate induced with Aroclor 1254 and at 0, 0.03, 0.08, 0.15, and 0.30 *u*g/ml without S-9 homogenate (Mizens *et al.*, 1986c). There were increased (0.63 compared with 0 for control, statistically significant at $p \leq 0.05$) numbers of structural aberrations in cells treated at 0.30 *u*g/ml without the addition of the S-9 homogenate. No increase in aberrations was observed in experiments which included the S-9 homogenate. This study was considered acceptable by DPR.

III.E.3. Other Genotoxic Effects

III.E.3.a. Chlorothalonil

Chlorothalonil (97.8% pure; 0, 2, 10, or 20 *u*g/plate) was added to *Salmonella typhimurium* strains TA1978 (repair competent) and TA1538 (repair deficient) in disc diffusion assays (Microbiological Associates, 1977e). Chlorothalonil caused growth inhibition with both strains with and without rat liver S-9 homogenate; however, there was significantly more growth inhibition of strain TA1538 than of TA1978. This study was considered acceptable by DPR.

Chlorothalonil (99.3% pure; 0, 2, 5, 10, 20, 100 or 200 *u*g/plate) was added to *Bacillus subtilis* strains H17 (repair competent) and M45 (repair deficient) in disc diffusion streak assays (Shirasu *et al.*, 1977c). Chlorothalonil caused more inhibition in M45 than H17 cells. This study was considered unacceptable to DPR because no activation was used, only one plate per dose level was used, and data analysis was not provided.

Chlorothalonil (96% pure; 0.001, 0.0001, or 0.00001 *u*g/ml) was incubated for 7 days with rat cell lines, F1706 P95 and H4536 P+2 infected with RLV, for cell transformation assays (Killeen and Heilman, 1980). Each culture was subcultured 12 times and assayed for foci after two weeks. Subcultures were tested for the formation of macroscopic colonies in semisolid agar and high dose subcultures were tested for the formation of tumors in newborn Fischer rats. No adverse effects were reported. This study was considered acceptable by DPR.

Male Sprague-Dawley rats (4/group) were exposed to a single dose of ^{14}C-chlorothalonil (99% pure; 50 mg/kg) by gavage and sacrificed 6 hours later (Savides *et al.*, 1987). Radioactivity was covalently bound to protein but not to DNA of kidneys from chlorothalonil-treated rats. This study was considered acceptable by DPR.

III.E.3.b. Metabolites

4-Hydroxy-2,5,6-trichloro-isophthalonitrile (SDS-3701) did not cause cell transformation in F1705 or H4536 cells *in vitro* (Diamond Shamrock Corporation, 1983d). When SDS-3701-treated H4536 cells were injected into newborn Fischer rats, no tumors were observed. Late tumors were observed in rats treated with SDS-3701 pretreated F1705 cells; however, they were considered spontaneous transformations. This report was a brief summary and was considered a supplemental study by DPR.

SDS-3701 (99% pure; 0, 2, 10, or 20 *u*g/plate) was negative in disc diffusion DNA damage assays with *Salmonella typhimurium* strains TA1978 (repair competent) and TA1538 (repair deficient) (Microbiological Associates, 1977f). This report was a brief summary and was considered a supplement study by DPR.

III.E.4. Published Studies (these studies are not included in Table 15)

Chlorothalonil induced sister chromatid exchanges in Chinese hamster ovary cells in the presence of S-9 mix from rat liver induced with Aroclor 1254, whereas aberrations were found both with and without the S-9 mix (Galloway *et al.*, 1987).

Chlorothalonil (up to 33 *u*g/plate) was not mutagenic in *Salmonella* strains TA100, TA1535, TA1537, or TA98 (Mortelmans *et al.*, 1986; Wei, 1982). Chlorothalonil (0.1 ml/plate) was not mutagenic in TA1535, TA100, TA1538, and TA98 with or without rat liver S-9 homogenate, and TA102 without S-9 fraction. However, it was mutagenic in TA102 with S-9 fraction (Choi *et al.*, 1985). Chlorothalonil was also not mutagenic in TA98, TA100, TA1538, TA1535, or TA1537 in the presence of Aroclor 1254-induced rat kidney S-9 fraction (Wei, 1982).

Chlorothalonil (0.24 *u*g/ml) was lethal to L5178Y tk+/tk- mouse lymphoma cells (McGregor *et al.*, 1988). At 0.12 *u*g/ml, it induced a significant increase in forward mutations at the thymidine kinase locus in the lymphoma cells.

The interaction of chlorothalonil with the cellular macromolecules apparently depended on the study design. In an *in vitro* study, ^{14}C-chlorothalonil (radiochemical purity 96%) was incubated with mammalian DNA, histones, or isolated rat liver nuclei (Rosanoff and Siegel, 1981). Chlorothalonil was bound to histones (> 50% of radioactivity), nuclei (45%), and DNA (1-3%). In the nuclei, radioactivity (expressed as % recovered) was distributed in the nuclear sap protein (18%), ribonucleoprotein (29%), and deoxyribonucleoprotein (11%). In another study, the liver DNA of rats given chlorothalonil (0.13 mg/kg/day for 10 days) showed a dose-dependent increase in 8-OH-2-deoxyguanosine levels (Lodovici *et al.*, 1997). However, there was no increased adduct formation when chlorothalonil was reacted with calf thymus DNA *in vitro* and analyzed by ^{32}P-postlabeling (Shah *et al.*, 1997).

Chlorothalonil (97% pure; 0.2 to 0.6 *u*g/ml) promoted the morphological transformation (criss-crossing and piling up of cells) in primary Syrian hamster embryo (SHE) cells pre-exposed to benzo(a)pyrene *in vitro* (Bessi *et al.*, 1994). Chlorothalonil alone did not cause the transformation of SHE cells or interfere with junctional intercellular communication (measured

by the transfer of fluorescent lucifer yellow from microinjected cells to other cells) in SHE cells or V79 cells.

Chlorothalonil induced DNA damage in human (male) peripheral blood lymphocytes as detected by single cell gel electrophoresis assay (SCGE assay or comet assay) (Lebailly *et al*., 1997). The cells were incubated with chlorothalonil (0, 10, 50, 100, 250, or 500 *u*M) for 1 hour. While these concentrations were not cytotoxic, there was a dose-related increase in the numbers of cells with damaged DNA, measured as tail moment[3] and image length at chlorothalonil concentration at 50 *u*M and higher concentrations. For cells with a 24-hour post-treatment incubation, there was increased cytotoxicity with 25% to 50% loss of viability for 10 to 500 *u*M. The authors hypothesized that DNA damage was a step toward cell death. The mechanism was possibly through its complexation with compounds such as glutathione via an epigenetic, and not a genotoxic mechanism.

[3] tail moment- the product of the distance between the two barycenters of the head and the tail by the proportion of DNA in the tail.

Table 15. Submitted genotoxicity studies with chlorothalonil or its metabolites.

Test types[a]	Regimen	Effects[b]	Ref.[c]
I. Gene Mutation			
Ames Assays with TA98, TA100, TA1535, TA1537, or TA1538			
Chlorothalonil	0.333 to 6.6 *u*g/plate, " rat liver S-9 1 to 10 *u*g/plate, " rat liver S-9 0.5 to 50 *u*g/plate, "rat kidney S-9 6.4 mg/kg/day, male mice	- - - -	1* 2 3 4
SDS-3701	1 to 100 *u*g/plate, liver enzymes (unspecified)	-	5
SDS-19221	10 to 1000 *u*g/plate, + rat kidney S-9 6.0 to 600 *u*g/plate, - rat kidney S-9	-	6
SDS-47524	20 to 2000 *u*g/plate, "rat kidney S-9	-	7
SDS-47525	40 to 6000 *u*g/plate, + rat kidney S-9 20 to 2000 *u*g/plate, - rat kidney S-9	-	8
SDS-3032	20 to 2000 *u*g/plate, "rat kidney S-9	-	9
SDS-3133	20 to 1000 *u*g/plate, "rat kidney S-9	-	10
SDS-47523	20 to 2000 *u*g/plate, "rat kidney S-9	-	11
SDS-13353	400 to 5000 *u*g/plate, + rat kidney S-9 250 to 2500 *u*g/plate, - rat kidney S-9	-	12
SDS-46851	100 to 10000 *u*g/plate, "rat kidney S-9	-	13
SDS-5473	0.5 to 70 *u*g/plate, "rat kidney S-9	-	14
SDS-2020	4 to 400 *u*g/plate, "rat kidney S-9	-	15
SDS-3176	40 to 4000 *u*g/plate, "rat kidney S-9	-	16
SDS-3297	10 to 1000 *u*g/plate, "rat kidney S-9	-	17
SDS-3939	50 to 10000 *u*g/plate, + rat kidney S-9	-	18
	50 to 4000 *u*g/plate, - rat kidney S-9		
SDS-66382	100 to 10000 *u*g/plate, " rat kidney S-9	-	19
SDS-66471	100 to 10000 *u*g/plate, " rat kidney S-9	-	20
SDS-66474	100 to 10000 *u*g/plate, " rat kidney S-9	-	21
SDS-66473	100 to 10000 *u*g/plate, " rat kidney S-9	-	22
***E. coli* strains WP2 hcr+ and WP2 hcr-**			
Chlorothalonil	10 to 500 *u*g/plate, " rat liver S-9	-	23
Chinese hamster lung fibroblasts (V79) cells and mouse BALB/3T3 fibroblasts			
Chlorothalonil	0.03 to 0.3 *u*g/ml, " rat liver S-9	-	24
SDS-3701	30 *u*g/ml, "rat liver S-9	-	25
II. Structural Chromosomal Aberrations			
Micronucleus Test			
Chlorothalonil	Rat, gavage, 8 to 5000 mg/kg/day (2 doses) Mouse, gavage, 4 to 2500 mg/kg/day (2 doses) Hamster, gavage, 4 to 2500 mg/kg/day (2 doses) Mouse, gavage, 6.5 mg/kg/day (5 doses)	- - - -	26 27 28 29

Table 15. Genotoxicity studies with chlorothalonil or its metabolites (continued).

Test types[a]	Regimen	Effects[b]	Ref.[c]
II. Structural Chromosomal Aberrations (continued)			
Dominant Lethal Test			
Chlorothalonil	Mouse, gavage, 6.5 mg/kg/day	-	30
Chromosomal Aberrations			
Chlorothalonil	Rat, gavage, 8 to 5000 mg/kg/day (2 doses)	-	31
	Mouse, gavage, 4 to 2500 mg/kg/day (2 doses)	-	32
	Hamster, gavage, 4 to 5000 mg/kg/day (2 doses)	-	33
	Mouse, gavage, 250 to 2500 mg/kg/day (1 dose)	-	34*
	Rat, gavage, 500 to 5000 mg/kg/day (1 dose)	-	35*
	Hamster, gavage, 2500 to 5000 mg/kg/day (1 dose)	+	36*
	Hamster, gavage, 50 to 250 mg/kg/day (5 days)	+	37*
	Hamster, gavage, 187.5 to 750 mg/kg/day (5 days)	-	38*
	Rat, gavage, 500 to 2000 mg/kg/day (5 days)	-	39*
	CHO cells, 0.6 to 6 *u*g/ml, + rat liver S-9	-	40*
	CHO cells, 0.03 to 0.3 *u*g/ml, - rat liver S-9	+	40*
III. Other Genotoxic Effects			
Disc Diffusion (Growth Inhibition) Assays			
Chlorothalonil	*S. typhimurium*, 2-20 *u*g/plate	+	41*
	B. subtilis, 2-200 *u*g/plate	+	42
SDS-3701	*S. typhimurium*, 20 *u*g/plate	-	43
Cell Transformation			
Chlorothalonil	Rat cell lines, 0.01-1 ng/ml	-	44*
SDS-3701	Rat cell lines	-	45
DNA Binding/Damage			
Chlorothalonil	Rat, gavage, 50 mg/kg (1 dose)	-	46
Chlorothalonil	Human peripheral blood lymphocytes 10-500*u*M	+	47

a/ Abbreviations are: SDS-3701= 4-hydroxy-2,5,6-trichloroisophthalonitrile, SDS-19221= 2,4,5,6-tetrachloro-3-cyanobenzamide; SDS-47524= 2,5,6-trichloro-3-cyanobenzamide, SDS-47525= 2,5,6-trichloro-4-hydroxy-3-cyanobenzamide, SDS-3032= 2,3,5,6-tetrachloro-benzonitrile, SDS-3133= 2,4,5,6-tetrachloro-dibenzamide, SDS-47523= 2,4,5-trichloro-3-cyano-benzamide, SDS-13353= mono-thiol, SDS-46851= 2,5,6-trichloro-3-carboxy-benzamide, SDS-5473= 2,4,5-trichloro-isophthalonitrile, SDS-2020= 2,3,5,6-tetrachloro-terphthalonitrile, SDS-3176= isophthalonitrile, SDS-3297= pentachlorobenzonitrile, SDS-3939= di-thiol, SDS-66382= mono-glutathione conjugate, SDS-66471= tri-thiol, SDS-66474= S,S'-(2,4-dicyano-3,6-dichlorophenyl)-dicysteine, and SDS-66473= S,S',S"-(2,4-dicyano-6-chlorophenyl)-tricysteine.

b/ - = study result was negative, += study result was positive.

c/ * after the reference number indicates the study was acceptable to DPR. References: 1. Microbiological Associates, 1977a; 2. Shirasu *et al.*, 1977a; 3. Jones *et al.*, 1984; 4. Legator, 1974a; 5. Microbiological Associates, 1977c; 6. Jones, *et al.*, 1985a; 7. Jones *et al.*, 1985b; 8. Jones *et al.*, 1985c; 9. Jones *et al.*, 1985d; 10. Jones *et al.*, 1985e; 11. Jones *et al.*, 1985f; 12. Jones *et al.*, 1985g; 13. Jones *et al.*, 1985h; 14. Jones *et al.*, 1985i; 15. Jones *et al.*, 1985j; 16. Jones *et al.*, 1985k; 17. Jones *et al.*, 1985l; 18. Mizens *et al.*, 1985a; 19. Mizens *et al.*, 1985b; 20. Mizens *et al.*, 1986a; 21. Mizens *et al.*, 1987; 22. Mizens *et al.*, 1986b; 23. Shirasu *et al.*, 1977b; 24. Microbiological Associates, 1977b; 25. Microbiological Associates, 1977d; 26. Mizens *et al.*, 1983b; 27. Mizens *et al.*, 1983c; 28. Mizens *et al.*, 1983d; 29. Legator, 1974b; 30. Legator, 1974c; 31. Mizens *et al.*, 1983e; 32. Mizens *et al.*, 1983f; 33. Mizens *et al.*, 1983g; 34. Mizens *et al.*, 1985c; 35. Mizens *et al.*, 1985d; 36. Mizens *et al.*, 1985e; 37. Mizens *et al.*, 1985f; 38. Mizens and Laveglia, 1995; 39. Kajiwara and Furusho, 1994; 40. Mizens *et al.*, 1986c; 41. Microbiological Associates, 1977e; 42. Shirasu *et al.*, 1977a; 43. Microbiological Associates, 1977f; 44. Killeen and Heilman, 1980; 45. Diamond Shamrock Corporation, 1983d; and 46. Savides *et al.*, 1987.

III.F. REPRODUCTIVE TOXICITY

Summary: In 2- and 3- generation reproductive toxicity studies, rats showed decreased food consumption, lower body weights, kidney lesions, and forestomach lesions after exposure to chlorothalonil in the diet. The only effect in the pups was a reduction in body weight exposed to chlorothalonil or SDS-3701 *in utero*.

III.F.1. Dietary - Rat

III.F.1.a. Chlorothalonil

In a range finding study, CD rats (15/sex/group) were fed chlorothalonil (98.1% pure; 0, 200, 375, 750, 1500, or 3000 ppm) in the diet for 10 weeks before mating, and continuously through the mating, gestation, and lactation periods (Wilson *et al.*, 1989). A reduction in body weight gain was measured only for males with a NOEL of 750 ppm. Enlarged kidneys were noted only in the 3000 ppm F_0 adults (in 5/15 males and 1/15 females). Tissues were not examined microscopically. There was a reduction of pup body weights which was statistically significant ($p \leq 0.05$) at day 21. The developmental NOEL was 1500 ppm based on reduced pup weight.

In the definitive study, Sprague-Dawley rats (35/sex/group) were fed chlorothalonil (98.1% pure; 0, 500, 1500, or 3000 ppm) in the diet for 2 generations (Lucas and Benz, 1990). Treatment was continuous for both successive generations, beginning 10 and 14 weeks before mating for the F_0 and F_1 generation rats, respectively. Because of decreasing food consumption throughout the study, the dosages declined with time. For F_0, the ranges of the dosages from week 1-21 were: 52.8-22.6, 156.9-68.2, and 292.2-154.1 mg/kg/day for males, and 49.8-30.9, 154.0-93.9, and 278.3-200.8 mg/kg/day for females. For F_1, the dosages from week 1-25 were: 56.7-21.7, 178.3-67.5, and 370.3-137.8 mg/kg/day for males; and 60.2-32.8, 181.1-94.6, and 381.7-195.6 mg/kg/day for females.

Dose-related effects were found in all treated groups, and included: tubular epithelial hyperplasia and hypertrophy (both sexes), clear cell hyperplasia, and karyomegaly (males) in the kidneys, as well as hyperkeratosis and squamous epithelial hyperplasia (both sexes) in the forestomach (Table 16). Kidney lesions in males were more severe than in females. Two males in the F_0 3000 ppm group were found to have either an adenoma or an adenocarcinoma at terminal sacrifice (16 weeks of exposure; average dosage for the duration was 200 mg/kg/day). Statistically significant decrements in body weight gain were seen throughout the study in F_0 and F_1 parents (Table 16). The reduction was significant by the first week in some groups. The systemic NOEL was < 500 ppm (<21.7 mg/kg/day, the lowest dosage) based on kidney and forestomach lesions. There was also a significant ($p \leq 0.05$) reduction (9 to 14%) in the 21-day pup weights for all litters at 3000 ppm. No other reproductive effects were observed. The developmental NOEL was 1500 ppm (67.5-178.3 mg/kg/day) based on the reduction of pup weights. This study was considered acceptable by DPR according to FIFRA guidelines.

Table 16. The effects of chlorothalonil in rats in a 2-generation reproductive toxicity study.[a]

Effects	Dosage (ppm)			
	Control	**500**	**1500**	**3000**
MALES				
Body weight gain (percent of control[b])				
F_0 (week 0-1)	100	96	90 **	68 **
F_0 (week 0->21)	100	94	92 *	85 **
F_1 (week 0-1)	100	86 *	97	89 **
F_1 (week 0->25)	100	94	94	89 **
Kidney epithelial hyperplasia (total incidences, 35 animals examined)				
F_O minimal/slight/mild	6	16	23	6
moderate/severe	0	1	12	29
F_1 minimal/slight/mild	1	21	21	11
moderate/severe	0	1	13	24
Kidney tubular hypertrophy (total incidences, 35 animals examined)				
F_O minimal/slight/mild	0	9	19	8
moderate/severe	0	0	5	25
F_1 minimal/slight/mild	0	8	22	12
moderate/severe	0	0	2	19
Forestomach hyperkeratosis (total incidences, 35 animals examined)				
F_O minimal/slight/mild	0	2	35	25
moderate/severe	1	1	0	10
F_1 minimal/slight/mild	0	11	34	27
moderate/severe	0	0	0	8
Forestomach squamous epithelial hyperplasia (total incidences, 35 animals examined)				
F_O minimal/slight/mild	1	9	32	0
moderate/severe	1	0	3	35
F_1 minimal/slight/mild	0	20	32	18
moderate/severe	0	2	2	17

Table 16. The effects of chlorothalonil in rats in a 2-generation reproductive toxicity study (continued).[a]

Effects	Dosage (ppm)			
	Control	500	1500	3000
FEMALES				
Body weight gain (percent of control[b])				
F_O (week 0-1)	100	93	94	70 **
F_O (week 0->21)	100	98	95	87 **
F_1 (week 0-1)	100	95	97	100
F_1 (week 0->25)	100	92	92*	87 **
Kidney epithelial hyperplasia (total incidences, 35 animals examined)				
F_O minimal/slight/mild	0	4	19	32
moderate/severe	0	0	0	0
F_1 minimal/slight/mild	0	1	10	21
moderate/severe	0	0	5	7
Kidney tubular hypertrophy (total incidences, 35 animals examined)				
F_O minimal/slight/mild	0	2	14	26
moderate/severe	0	0	0	0
F_1 minimal/slight/mild	0	0	11	23
moderate/severe	0	0	2	8
Forestomach hyperkeratosis (total incidences, 35 animals examined)				
F_O minimal/slight/mild	0	13	35	35
moderate/severe	0	0	0	0
F_1 minimal/slight/mild	0	25	25	33
moderate/severe	0	0	0	2
Forestomach squamous epithelial hyperplasia (total incidences, 35 animals examined)				
F_O minimal/slight/mild	1	35	35	31
moderate/severe	0	0	0	4
F_1 minimal/slight/mild	0	28	30	29
moderate/severe	0	1	3	6
PUPS				
Body weight (day 21) (percent of control, both sexes)				
F_{1a}/F_{1b}	100/100	99/97	97/92**	93*/86**
F_{2a}/F_{2b}	100/100	94/92*	98/95	91**/88**

a/ Data from Lucas and Benz, 1990.

b/ Statistically significant differences from control group at the 0.05 (*) and 0.01 (*,*) levels were based on Bonferroni t-test in the report.

In a 3-generation reproductive toxicity study, Charles River rats (10 males and 20 females/ group) were given chlorothalonil (purity not stated) in the diet for the first 7 weeks, and then a mixture of chlorothalonil (93.6% pure) plus metabolites for the remainder of the study (Hazleton Laboratories, Inc., 1967e). The intended doses were 0, 1500, 15000, or 30000 ppm of chlorothalonil. The actual dose for the high dose group was 20000 ppm. Both the 15000 and 20000 ppm doses were achieved gradually from 5000 ppm. The observed effects were decreased parental weight gain in all 3 generations, histological changes in the kidney, esophagus, and stomach, and retarded growth of pups with the NOEL at <1500 ppm. This study was considered unacceptable by DPR according to FIFRA guidelines because of multiple changes in the doses, dose levels too high, inadequate characterization of the tested material, insufficient number of doses after the P_1 generation, too few animals, males rotated weekly among females of the same group for mating, and limited histopathology.

In a supplemental study to the previous study 3-generation study (Hazleton Laboratories, Inc., 1967e), chlorothalonil (93.6% pure; 0 or 5000 ppm) plus metabolites were given to Charles River rats (10 males and 20 females/group) in the diet (Hazleton Laboratories, Inc., 1967f). Similar results as in the previous study were observed with a NOEL of < 5000 ppm. This study was considered unacceptable by DPR according to FIFRA guidelines because of the same reasons (except dose changes) as stated in the previous study.

III.F.1.b. Metabolites

Rats (strain and number not specified) were fed SDS-3701 (purity not specified; 0, 10, 20, 30, 60, or 120 ppm) in a one-generation study (Diamond Shamrock Corporation, 1983e). Mean pup weights during lactation were reportedly lower than the controls in the 60 and 120 ppm groups for both litters. This report was a brief summary and was considered a supplemental study by DPR.

Rats (strain and number not specified) were fed SDS-3701 (purity not specified; 0, 10, 60, or 125 ppm) in the diet for three generations (Diamond Shamrock Corporation, 1983f). Mean pup weights during lactation were reduced in the 60 and 125 ppm groups for both litters of all generations. This report was a brief summary and was considered a supplemental study by DPR.

III.G. DEVELOPMENTAL TOXICITY

Summary: Chlorothalonil did not cause developmental toxicity in rats or rabbits. However, dams treated with chlorothalonil showed increased mortality, clinical signs (excess lacrimation, vaginal and nose discharges, and anogenital stains), decreased food consumption, and reduced body weight.

III.G.1. Gavage - Rat

Pregnant Sprague-Dawley rats (25/group) were given chlorothalonil (98% pure; 0, 25, 100, or 400 mg/kg/day) by gavage on gestation days 6 to 15 (Mizens *et al.*, 1983a). At 400 mg/kg/day, maternal toxicity included deaths, diarrhea, alopecia, decreased body weight gain, and decreased food consumption. Three of the 400 mg/kg/day group died (one on each gestation day 12, 15, and 18) and the deaths were considered treatment-related. Food consumption was decreased on days 6 to 15 (64-81% of control) and was accompanied by decreased mean body weight gain (13% of control from day 9 to 12) during treatment but not after gestation day 15. There was also post-implantation loss, not statistically significant when compared with the control, due to early embryonic deaths and/or maternal toxicity. The maternal NOEL was 100 mg/kg/day for mortality and reduced food consumption at 400 mg/kg/day. No developmental effects were observed, and the NOEL was > 400 mg/kg/day. This study was considered acceptable by DPR according to FIFRA guidelines.

III.G.2. Gavage - Rabbit

In a pilot study, pregnant New Zealand white rabbits (7/group) were given chlorothalonil (98.2% pure; 5, 15, 30, or 75 mg/kg/day) by gavage on gestation days 7 to 19 (Wilson and Killeen, 1988a). At 75 mg/kg/day, there were 3 deaths (one each on gestation days 8, 14, or 15) and 3 abortions (gestation days 22 or 23) (Table 17). The food consumption was significantly reduced throughout the study with significant reduction observed after the first few days of dosing: gestation day 7 to 8 for 75 mg/kg/day and gestation days 9 to11 for 30 mg/kg/day. Statistically significant decreased body weight was reported for gestation day 19 and 24 (Table 17). There were increased incidences (and number of dosing days for the first incident) of excess lacrimation (7^{th} day), vaginal discharge (4^{th} day), anogenital stains (4^{th} day), and red nose discharge (4^{th} day) in this group (Table 17). Clinical signs were observed primarily on gestation days 10 and 13. At 30 mg/kg/day, there were premature deliveries (2/7 females), and decreases in food consumption associated with body weight reduction of >10% of control. An acute NOEL of 15 mg/kg/day could be established for decreased food consumption at 30 mg/kg/day, which resulted in significantly reduced body weight. This study supported the selection of 20 mg/kg/day as the highest dose in the definitive study.

In the definitive study, pregnant New Zealand white rabbits (20/group) were given chlorothalonil (98.1% pure; 0, 5, 10, or 20 mg/kg/day) by gavage on gestation days 7 to 19 (Wilson and Killeen, 1988b). The mean food consumption of the 20 mg/kg/day was reduced throughout the study (day 10-11:91% of control, day 13-14:63% of control, day 16-17:65% of control, day 19-20: 70% of control) with statistical significance noted only for day 7 ($p<0.01$; 85% of control). There was no significant difference in the mean maternal body weight between

the control and the treated groups for each weighing period (day 0, 3, 7, 10, 13, 16, and 19). However, the maternal body weights for the 20 mg/kg/day were lower than those for the control for gestation days 16 and 19. On day 19, the mean body weights (group) were 4068 g (control), 4055 g (5 mg/kg/day), 4088 (10 mg/kg/day), and 3978 g (20 mg/kg/day; 98% of control). The mean fetal body weight of viable fetuses in the 20 mg/kg/day group was 93% of the control but was not statistically significant. The report noted that the mean fetal weight for this study was within the range of recent historical control for the laboratory. No other maternal or developmental effects were observed. The NOEL for both maternal and developmental effects was 10 mg/kg/day based on marginal effects on body weights. This study was considered acceptable by DPR according to FIFRA guidelines.

Table 17. Maternal toxicity of chlorothalonil in pregnant rabbits.[a]

Effects	Dosage (mg/kg/day)				
	0	**5**	**15**	**30**	**75**
Mortality	0	0	0	0	3[b]
Food Consumption (% of control[c])					
Gestation day 7-8	100	96	87	62	10**
Gestation day 9-11	100	88	95	55*	2**
Gestation day 16-17	100	89	68	35*	4**
Post treatment day 1-2	100	111	102	53	0**
Mean body weight (% of control[c])					
Gestation day 19	100	98	95	88*	83*
Gestation day 24	100	98	98	88*	(no survivors)
Clinical Signs (number of animals)					
Soft stools	0	1[d]	0	0	0
Anogenital stains	0	0	2[e]	0	5[f]
Excess lacrimation	0	0	0	0	2[g]
Red vaginal discharge	0	0	0	0	2[f]
Red nose discharge	0	0	0	0	1[f]

a/ Data from Wilson and Killeen, 1988a. Treatment started on gestation day 7.
b/ One each on gestation days 8, 14, and 15; 2nd, 8th, and 9th day of dosing.
c/ Statistically significant difference from control group at the 0.05 (*) and 0.01 (**) levels based on Dunnett's test.
d/ First observed on gestation day 16, 10th day of dosing.
e/ First observed on gestation day 0, before dosing.
f/ First observed on gestation day 10, 4th day of dosing.
g/ First observed on gestation day 13, 7th day of dosing.

Pregnant Japanese white rabbits (8/control, 9/treated groups) were given chlorothalonil (99.3% pure; 0, 5, or 50 mg/kg/day) by gavage on gestation days 6 to 18 (Shirasu and Teramoto, 1975; Shirasu and Teramoto, 1984). Maternal toxicity (decreased food consumption and body weights, and increased abortions) was observed at 50 mg/kg/day. No developmental effects were observed. The NOEL for maternal toxicity was 5 mg/kg/day. This study was considered unacceptable by DPR according to FIFRA guidelines because too few doses and animals were used, no description of abortuses was reported, and corpora lutea were not counted.

III.G.3. Capsule - Rabbit

Pregnant New Zealand white rabbits (8/group) were given chlorothalonil (no purity stated) orally in gelatin capsules (Hazleton Laboratories, Inc., 1966b). The dosages were 0, 180, or 375 mg/kg/day for gestation days 8-9, and were changed to 0, 62.5, or 31.25 mg/kg/day, respectively, for days 10-16. Animals were sacrificed on days 22-23 because of maternal toxicity (food consumption reduction, body weight reduction, diarrhea or soft feces, depression, and weakness). Deaths occurred on days 12, 16, and 17 in the high dose group. This study was considered unacceptable by DPR according to FIFRA guidelines because too few animals were used, dosing period was shortened, dosages were reduced, and high and low groups were reversed, and only 2 dose levels were studied.

III.H. NEUROTOXICITY

According to current FIFRA guidelines, a delayed neurotoxicity study is not required for chlorothalonil.

III.I. HUMAN EXPOSURE

Data from a health surveillance program were examined to determine whether there were any chronic effects in employees at the Greens Bayou Plant which produced chlorothalonil (Chelsky, 1990a and b; Noble, 1990). Eyes were examined and tested for visual acuity, phoria, color perception, depth perception, and tonometry. Respiratory system was evaluated by spirometry and chest x-ray. There were no treatment-related chronic effects on eyes or respiratory system with inhalation exposure to chlorothalonil dust at levels up to 932 $u g/m^3$. However, none of the reports were considered by DPR to be an adequate assessment of worker exposure.

Allergic contact dermatitis has been reported in humans exposed to chlorothalonil-containing products (Edwards *et al.*, 1991). A cabin maker developed dermatitis after working 9 months with chlorothalonil containing wood-preservatives (Bach and Pedersen, 1980). The dermatitis disappeared after 3 weeks of sick leave, but reappeared when he returned to work. Similar case histories have been reported for other wood workers (Johnsson *et al.*, 1983), carnation workers (Bruynzeel and Ketel, 1986), and painters (Meding, 1986).

A 49-year-old woman experienced contact urticaria and anaphylaxis after exposure to pesticides used in a redwood plant nursery (Dannaker, *et al.*, 1993). Pruritic eruption, erythema, and edema in the face occurred within 15 to 30 minutes of exposure. She also experienced nasal congestion and tight chest, and was wheezing when examined. Her symptoms were caused by chlorothalonil exposure which were confirmed when Daconil 2787 (75% chlorothalonil) in a 0.01% aqueous solution caused a large wheal and flare reaction. Within 10 minutes of exposure, she experienced facial flushing, eyelid edema, and difficulty in swallowing and breathing.

In a review of industrial-related injury records for a bulk-packaging plant, workers exposed to chlorothalonil dust reported skin rashes, conjunctivitis, as well as pain, burning, and soreness to the nose and pharynx (McAmis *et al.*, 1994). Examination of the nose and pharynx showed mild to moderate diffuse redness of mucous membrane. Palpation and auscultation, and x-ray of the chest were negative.

III.J. TOXICITY OF SDS-3701

The toxicity studies for SDS-3701, based on submitted studies to DPR, was included in the specific test type in the previous sections. Most of the studies were summary reports. These studies and additional studies in the U.S. EPA RED are summarized in the Table 18.

Table 18. The toxicity of SDS-3701.[a]

Studies	**DPR NOEL and endpoints**	**U.S. EPA NOEL and endpoints**
Acute toxicity in rats	NA	Oral LD50 Male- 422 mg/kg, Female-242 mg/kg
Subchronic toxicity-4 month diet	NA	NOEL=5 mg/kg/day Depressed body weight and increased liver weight in male rats
Subchronic toxicity-61-69 days diet	NA	NOEL=20 mg/kg/day Decreased body weight, anemia, renal cortical atrophy in rats
Subchronic toxicity-3 month diet	NA	NOEL=2.5 mg/kg/day Renal tubular degeneration and vacuolation in male dogs
Chronic toxicity in rats	NOEL=3 mg/kg/day Mortality and anemia. No oncogenicity (Diamond Shamrock Corporation, 1983b)	NOEL=3 mg/kg/day Reduced body weight, anemia, hemosiderin and decreased serum potassium. No oncogenicity
Chronic toxicity in mice	NOEL not established. No oncogenicity (Diamond Shamrock Corporation, 1983c)	NOEL not established. No oncogenicity
Developmental toxicity in rabbits	NA	Maternal NOEL=1 mg/kg/day Increase in maternal death and abortion Developmental NOEL=5 mg/kg/day (highest dose tested)
Reproductive toxicity – 1 generation in rats	NOEL not established (Diamond Shamrock Corporation, 1983e)	Parental NOEL=1.5 mg/kg/day Effect not indicated in the RED Off spring NOEL=6.0 mg/kg/day Reduced weanling body weights
Reproductive toxicity – 3 generation in rats	NOEL not established (Diamond Shamrock Corporation, 1983f)	Parental NOEL=0.5 mg/kg/day Reduced pup body weight Reproductive toxicity NOEL=6.25 mg/kg/day (highest dose tested)
Genotoxicity studies	Mostly negative but few positive studies	Mostly negative but few positive studies

NA= study not described in this document. NOELs were not established by DPR when the study reports did not provide sufficient data. U.S. EPA determined NOELs were from U.S. EPA, 1999a.

IV. RISK ASSESSMENT

IV.A. HAZARD IDENTIFICATION

For the hazard identification of chlorothalonil, data from experimental animals were used to assess the risks under acute, subchronic, chronic, and lifetime exposure scenarios. Information from human studies was inadequate to determine the dose-response relationship. The rationale for the selection of toxicity endpoints and critical NOELs are discussed in this section. Only those endpoints considered of toxicological significance, regardless of whether they were designated as adverse in the toxicology summaries, were used for risk characterization. Since this document addressed only dietary exposure, only NOELs and endpoints from oral toxicity studies were considered.

The critical NOELs selected for chlorothalonil would also be applied to SDS-3701 since the database for this metabolite was limited (Table 18). Also, the dietary exposure to SDS-3701 would be expected to be relatively low, compared to chlorothalonil, since it has only been found in meat products and milk. This approach was used by the U.S. EPA in the dietary assessment for SDS-3701 (U.S. EPA, 1999a). In this document, the toxicity database for HCB was not reviewed since the focus was on chlorothalonil and reference dose and potency factors were available from the U.S. EPA. For chronic exposure, the reference dose for HCB was 0.0008 mg/kg/day based on a NOEL of 0.08 mg/kg/day for liver effects (centrilobular basophilic chromogenesis in rats and uncertainty factor of 100 (intraspecies and interspecies extrapolations) (U.S. EPA, 1999a). The potency factor (q_1*) was 1.02 mg/kg/day^{-1} for liver tumors in rats.

IV.A.1. Selection of Toxicity Endpoints

The primary target organ for chlorothalonil toxicity was the kidney. Effects in this organ were found in multiple species and for various durations of exposure. While kidney lesions and tumors were clearly toxicity endpoints of concern, the toxicological significance of other effects was uncertain.

One endpoint that fitted the latter category was the effect of chlorothalonil on serum ALT (or SGPT) activity. ALT and its cofactor, pyridoxal 5'-phosphate (active form of vitamin B6), catalyze the conversion of alanine to pyruvate, which is involved in the metabolism of lipids, proteins, and carbohydrates. ALT activity is highest in the liver and an elevated activity in the serum is generally associated with frank liver toxicity (Plaa and Hewitt, 1989). On the other hand, metabolic changes and chemicals can reduce ALT activity (Waner and Nyska, 1991). Both zinc and vitamin B6 deficiencies have been shown to decrease ALT activity. Vitamin B6 deficiency may be a result of hemodialysis (Ono *et al.*, 1995). ALT activity is reduced after treatment with isoniazid, phenothiazine, delapril hydrochloride, penicillamine, cefazolin, l-canavanine, oxodipine, and vigabatrin (Waner and Nyska, 1991; Evans and Whitehorn, 1995). While the mechanism of the reduction is largely unknown, there is evidence that some chemicals act on ALT (vigabatrin; Foletti *et al.*, 1995) while others have effects on pyridoxal 5'-phosphate (hydrazines, isoniazid, and cefazolin; Waner and Nyska, 1991; Dhami *et al.*, 1979). Studies with oxodipine in rats showed that the reduction in ALT activity was only partially reversible after the

cessation of treatment (Waner *et al.*, 1990). These published studies showed that ALT activity is susceptible to a variety of structurally-unrelated chemicals.

Chlorothalonil reduced serum ALT activity in a dose-related manner in several species (rats, dogs, and rabbits) after repeated oral or dermal exposures (Tables 8 and 14). The reduction of ALT for most studies was not the most sensitive endpoint. The dog was apparently more sensitive than the rat for this effect. The serum ALT activity was reduced to very low levels at ≥160 ppm (≥ 5.5 mg/kg/day) as early as 13 weeks (Spencer-Briggs, 1995c) and to zero in dogs treated with 150 mg/kg/day in capsules for 27 weeks (Fillmore and Laveglia, 1993). Yet, no specific physiological changes were associated with these reductions. The lowest reduction in rats was 79% for males treated with 175 mg/kg/day for 115 weeks (Wilson *et al.*, 1985c). The effect of chlorothalonil on serum ALT in mice is unclear. ALT activity was measured only in one subchronic mouse study (Shults *et al.*, 1983) and any potential effect might be obscured by the large variation in the control values. The reduction of this enzyme in rats after 13 weeks of exposure was apparently reversible as the activity was at or higher than the control activity when rats were no longer treated with chlorothalonil (Wilson *et al.*, 1983a). Also, no treatment-related differences in ALT levels were evident when the ALT activity assay was performed in the presence of added pyridoxal-5'-phosphate (Spencer-Briggs, 1995a and 1995c). One hypothesis was that the decreased ALT activity was due to the depletion of pyridoxal-5'-phosphate from the metabolism of chlorothalonil by *B*-lyase (Spencer-Briggs, 1995a). In humans, pyridoxine deficiency affects the skin (seborrhea-like lesions), nervous system (peripheral neuritis, decreased neurotransmitter levels, and convulsive seizures), and erythropoiesis (anemia) (Marcus and Coulston, 1990). While sustained anemia and ALT depletion were noted in a recent chronic dog study (Spencer-Briggs, 1995c), anemia was not observed in another dog study (Mizens and Laveglia, 1994). Due to the uncertainty of the toxicological significance of ALT reduction, this endpoint was not selected as the basis for the critical NOELs.

Another controversial toxicity endpoint was the forestomach lesion found in rats. The relevancy of this endpoint for human risk assessment has been a subject of debate since humans do not have a forestomach. On the other hand, it is also recognized that the human esophagus tissue is similar to that in the forestomach. Since the lowest NOELs for forestomach lesions are the same or higher than those for kidney lesions (Tables 8 and 14), the critical NOELs based on kidney effects (to be discussed) protected against this endpoint.

IV.A.2. Selection of Critical No-Observed-Effect Level

When a critical NOEL is derived from an experimental animal study, its use for risk characterization assumes that the absorption is the same for animals and humans.

IV.A.2.a. Acute Toxicity

Acute and developmental toxicity studies were evaluated for acute toxicity (Table 8). The critical NOEL was 15 mg/kg/day in pregnant rabbits based on reduced food consumption which led to decreased body weights (Table 17) (Wilson and Killeen, 1988a). The LOEL was 30 mg/kg/day. The reduction in food consumption was interpreted as an early indication of stress in the animals. Since the route of administration was via gavage, palatability should not be a factor

for this endpoint. At 2.5-fold higher dosage, 75 mg/kg/day, clinical signs (anogenital stains, excess lacrimation, nasal and vaginal discharges) and mortality were observed from the 2nd day of dosing. This NOEL and effects were seen in both the range finding and definitive studies. In the definitive study, pregnant rabbits showed a marginal decrease in body weights in maternal (98% of control) and fetal (93% of control) rabbits at 20 mg/kg/day after more than 9 days of treatment (Wilson and Killeen, 1988b). The food consumption was reduced in the 20 mg/kg/day group. The NOEL was 10 mg/kg/day and was lower than the range-finding study. However, it could not be selected as the critical acute NOEL since the reductions were observed only after repeated exposures.

In comparison, the NOEL was <40 mg/kg/day for mild renal tubular vacuolation at 40 mg/kg/day and more severe vacuolation at 80 and 175 mg/kg/day in rats (Gelin and Killeen, 1991b). This study was not used to derive the critical NOEL because it was designed only to examine the changes at the electron microscopy level, and was not a toxicity study[4]. The biological importance of the changes seen with the electron microscope was unknown since no other effects were reported. The results, however, were useful to compare with those from other studies to determine the appropriate critical NOEL to assess acute toxicity. Since the effect at 40 mg/kg/day was graded as slight/mild vacuolation in this study, an uncertainty factor of 3 could be used to estimate a NOEL of 13 mg/kg/day. This is comparable to the critical NOEL of 15 mg/kg/day established in the developmental toxicity study rabbits (Wilson and Killeen, 1988a).

Mortality after acute exposure was also observed at higher doses in pregnant rabbits (75 mg/kg/day), pregnant rats (400 mg/kg/day), dogs (750 mg/kg/day), and rabbits (≤ 6759 mg/kg/day) (Wilson and Killeen, 1988a; Mizens *et al.*, 1983a; Fillmore, 1992a and b; Lundberg *et al.*, 1980a).

IV.A.2.b. Subchronic Toxicity

For subchronic oral exposure, the critical NOEL was determined from subchronic and reproductive toxicity studies. In the reproductive toxicity study, kidney and forestomach lesions were observed in rats at the lowest dose of 500 ppm (21.7-56.7 mg/kg/day) (Table 16) (Lucas and Benz, 1990). Two F_0 males of the 3000 ppm group each developed kidney adenomas or adenocarcinomas. The NOEL for the reduction of pup weight was 1500 ppm (67.5-178.3 mg/kg/day). In dogs, chlorothalonil caused a decrease in body weight gain and serum chemistry changes at 150 and 500 mg/kg/day during the 90-day treatment (Fillmore and Laveglia, 1993). The lowest NOEL and the critical NOEL was 1.5 mg/kg/day (adjusted dose of 0.51 mg/kg/day) for kidney lesions in rats after 13-weeks of exposure (Wilson *et al.*, 1983a) and increased labeling index in rat kidney after 28 days of exposure (Hironaka, 1996).

IV.A.2.c. Chronic Toxicity

After chronic oral exposure of rats, mice, and dogs to chlorothalonil, the primary findings in these animals were decreased body weight gain, increased kidney weight, kidney lesions, and forestomach lesions (Table 14). The critical NOEL was 1.8 mg/kg/day for effects in the kidney

[4] FIFRA guidelines only required light microscopic examination of tissues and organs. The electron microscope is 10 to 1,000 times more able to detect changes in the appearance of the tissues.

observed at 3.8 mg/kg/day in rats (Wilson and Killeen, 1989). The non-neoplastic kidney lesions included chronic progressive nephropathy, focal epithelial hyperplasia, clear cell hyperplasia, cortical cysts, and pelvic epithelial hyperplasia. This NOEL was similar in magnitude to other NOELs for kidney effects observed in the rat (3.0 mg/kg/day; Spencer-Briggs, 1995a), mouse (2.2 mg/kg/day; Spencer-Briggs, 1995b), and dog (5.5 mg/kg/day; Spencer-Briggs, 1995c).

IV.A.3. Oncogenicity

The weight of the evidence showed that chlorothalonil was oncogenic in experimental animals studies. Chronic and oncogenicity studies showed that chlorothalonil (15.2 to 183 mg/kg/day) caused kidney and forestomach tumors in rats (both sexes) and mice (males only) after more than 1 year of exposure in the diet (Wilson *et al.*, 1985c; Wilson and Killeen, 1989; Wilson *et al.*, 1983b). Kidney tumors were also observed in rats at a higher dosage after shorter-term exposure. In the reproductive toxicity study, tumors were found in F_0 male rats (2/35 rats) exposed to an average dosage of 200 mg/kg/day for 16 weeks in the diet (Lucas and Benz, 1990). Because of uncertainties associated with the use of forestomach tumors as endpoint for human risk assessment (**IV.A.1. Selection of Toxicity Endpoint**), only kidney tumors were considered for oncogenicity in this document. While there was sufficient evidence to determine the oncogenicity potential of chlorothalonil, genotoxicity study results were mostly negative (Table 15). Few studies showed positive results, which included chromosomal aberration in hamster and CHO cells, growth inhibition in bacteria, and DNA damage in human lymphocytes. The significance of these results on chromosomal aberration and growth inhibition was unclear since there were studies with negative findings for the same endpoints. Lebailly *et al* (1997) suggested an epigenetic mechanism for chlorothalonil-induced DNA damage in isolated human lymphocytes.

IV.A.3.a. Mechanism for Oncogenicity – DPR

The mechanism for chlorothalonil-induced kidney tumors has not been elucidated. The previous registrants for chlorothalonil had proposed a mechanism involving the activation of chlorothalonil glutathione conjugates to reactive thiols by kidney *B*-lyase (Wilkinson, 1995; Killeen, 1995; Wilkinson and Killeen, 1996). These thiols, through a series of molecular and cellular events in the mitochondria supposedly caused the formation of kidney-specific tumors. However, this proposed mechanism was withdrawn by the current registrant of chlorothalonil after their evaluation of the data (Wickramaratne, 1998). DPR also concluded that the database did not support the role of mitochondria or *B*-lyase in tumor formation. On the contrary, the presence of aminooxyacetic acid, an inhibitor of *B*-lyase, did not affect the mono-glutathione conjugate-induced toxicity in renal proximal tubular cells *in vitro* (van de Water *et al.,* 1994). With halogenated alkene and alkanes, the addition of *B*-lyase inhibitors resulted in reduced kidney toxicity *in vivo* (Monks and Lau, 1987; Monks *et al.*, 1990; Koob and Dekant, 1991; Anders *et al.*, 1992; Lash, 1994). Furthermore, the effects of chlorothalonil and metabolites on mitochondria have only been shown *in vitro*. These experiments showed that the mono- and di-thiols inhibited the liver and kidney mitochondria while the tri-thiol and mono-glutathione conjugate inhibited only kidney mitochondria (Savides *et al.,* 1988a; Andre *et al.*, 1991a). The proposed specificity of thiol toxicity to kidney mitochondria, versus liver mitochondria, needed to be supported. Liver tumors have not been observed even though some thiols inhibited liver

mitochondria (Mizens and Laveglia, 1994). Also, the potential effect of chlorothalonil on other mitochondrial functions (such as effects on ATPase activity, uncoupled respiration, transport protein functions) had not been investigated. A review of nephrotoxic compounds showed that multiple mechanisms generally exist, and that mitochondrial dysfunction may be a consequence of other interactions or toxicity (Schnellmann and Griner, 1994). Cephalosporins were selective inhibitors of site II respiration due to the greater binding to succinate transport protein compared with the multiple transport mechanisms in site I. More importantly for the oncogenicity of chlorothalonil, a temporal relationship had not been established between mitochondrial respiration inhibition and kidney tumors in low-dose, long-term studies.

While experimental data showed chlorothalonil-induced hyperplasia and neoplasia, only associative evidence has been provided to link these responses to cell proliferation (Mizens, 1997). Short-term (28 and 90 days) cell proliferation studies in male rats (Hironaka, 1996; Mizens, 1996a) showed, at 175 mg/kg/day, there were both increased labeling indices and lesions in the kidney and the forestomach. Closer examination of the chlorothalonil toxicology database showed a lack of cause and effect relationship between cell proliferation and oncogenicity. First of all, the relationship between cell proliferation and cellular damage was unknown. In the cell proliferation study, there was extensive damage to the forestomach in form of edema, hemorrhage, erosion, and inflammatory infiltration (Table 6). The labeling indices increased at least 40-fold from the control. However, at the same or similar dose after long-term exposure, no forestomach tumors were observed in rats treated at 175 mg/kg/day for two years (Wilson et *al.*, 1985c) and papillomas were detected at low (9%) incidence in rats treated at 183 mg/kg/day for two years (Wilson and Killeen, 1989, Table 12).

Second, the induced proliferation in the kidneys may be short-term and may not be associated with the tumor formation after long-term exposure (Goldsworthy *et al*., 1993). With chlorothalonil, both cell proliferation studies were conducted for short-term exposure. Sustained cell proliferation was observed only in the forestomach (Figure 2). As discussed previously, the incidence of tumors in the forestomach was relatively low (9%). The first forestomach tumor was diagnosed on day 525 (Wilson and Killeen, 1989). However, in both experiments on the kidneys, the labeling indices were highest on the first measured time point (day 7) and decreased with increased exposure duration (to 28 or 91 days) (Figure 2). Proliferation data were not available beyond 91 days. In the chronic toxicity studies, the first kidney tumor was observed on day 417 (Wilson et al., 1985c) and 497 (Wilson and Killeen, 1989). The incidences of kidney tumors in the male rats were 30% for 175 mg/kg/day (Table 10) and 42% for 193 mg/kg/day compared to 0-2% in the controls (Table 12).

Furthermore, enhanced cell proliferation may or may not have any influence on the carcinogenesis process (Melnick *et al.*, 1993; Huff, 1993; Huff, 1995). For example, 1,4-dichlorobenzene caused increased labeling indices in both treated mice and female rats while tumors were only found in mice (Eldridge *et al.*, 1992). For chlorothalonil, cell proliferation studies have only been conducted in male rats. A more convincing case for the proposed mechanism would entail a long-term study in rats with limited or absent capacity to produce di- and trithiols. Such capacity limitations may be achieved by sustained use of inhibitors of gamma-glutamyltranspeptidase or of *B*-lyase or alternatively by using rats genetically deficient in one of these enzymes. The linkage of cell proliferation and oncogenicity requires additional

studies, which examine the duration and nature of the proliferative response (Goldsworthy *et al.*, 1993). These studies would include cell proliferation evaluations after prolonged exposure and conducted in species which have not been shown to have tumors after chlorothalonil treatment.

DPR acknowledged that chlorothalonil has been shown to be non-genotoxic in all short-term bacterial and most of the mammalian genotoxicity studies (**III.E. GENOTOXICITY**). Some metabolites were non-genotoxic by the Ames' assay using *Salmonella* strains. However, chlorothalonil was positive in some chromosomal aberration assays and a DNA damage study. Lebailly *et al* (1997) suggested an epigenetic mechanism for chlorothalonil-induced DNA damage in isolated human lymphocytes. For chloroalkenes, which were biotransformed to reactive thiols before forming DNA adducts, Monks *et al.* (1990) suggested that the nephrocarcinogenicity of this class of compounds be considered intermediate between genotoxic carcinogens and those active via epigenetic or non-genotoxic pathways.

IV.A.3.b. Mechanism for Oncogenicity – U.S. EPA

In July 1998, the U.S. EPA FIFRA Scientific Advisory Panel (SAP) was asked to address several issues relating to the oncogenicity of chlorothalonil (Lewis, 1998). A majority of the SAP concluded that the cytotoxicity and cell proliferation mechanism was plausible and likely to be valid for kidney tumors. However, the SAP indicated that additional information was needed to support the mechanism. The SAP considered a margin of exposure approach appropriate for oncogenicity only if the mode of action was due to sustained cytotoxicity and regenerative cell proliferation. However, the linearity of the dose-response relationship should be considered in determining the appropriate methods for low-dose extrapolation. The SAP acknowledged that there were quantitative differences in gamma-glutamlyl-transpeptidase (GGT) and *B*-lyase levels between rats and humans. However, the relationship between these enzyme levels and oncogenicity was not established. Mice, which have less GGT than rats and only 2-fold higher than that in humans, developed kidney tumors after chronic exposure to chlorothalonil. The database was inadequate to conclude that infants and children are not potentially more sensitive to the nephrotoxicity of chlorothalonil.

IV.A.3.c. Evaluation of Oncogenic Risk

After consideration of the registrant revised proposed mechanism of action and the SAP conclusions, DPR determined that available data were insufficient to support a threshold mechanism for the oncogenicity of chlorothalonil. Therefore, the risk characterization of chlorothalonil-induced kidney tumors utilized a linear dose-response extrapolation method assuming a non-threshold mechanism. The incidences of renal tumors in male rats from two studies (Wilson *et al.*, 1985c; Wilson and Killeen, 1989) were selected to assess the oncogenicity of chlorothalonil (Table 19). The 1989 study had lower doses (1.8 to 15.2 mg/kg/day) than the 1985 study and provided a better estimate of potency at lower levels of exposure. The 1989 study also had a high dose (183 mg/kg/day), which bracketed the doses used in the 1985 study. Additional factors for considering these studies together were: (1) they were performed by the same investigators using the same strain of rats, (2) the dosages and incidences showed a positive dose-response relationship (Table 19), (3) the body weights of the rats were similar, (4) similar oncogenic and non-oncogenic findings were reported, and (5) both were acceptable studies

conducted according to FIFRA guidelines. These considerations are consistent with those discussed by Vater *et al.* (1993) when combining carcinogenicity data for quantitative risk assessment.

Table 19. The incidences of kidney tumors in rats treated with chlorothalonil.[a]

Gender	Dosage (mg/kg/day)							
	0	**1.8**	**3.8**	**15.2**	**40**	**80**	**175**	**183**
Males	1/155++ (1%)	1/54 (2%)	1/54 (2%)	4/54 (7%)	7/60* (12%)	7/58* (12%)	18/60** (30%)	23/55** (42%)
Females	0/115++	0/54	0/55	0/53	4/60 (7%)	10/59** (17%)	23/60** (38%)	32/55** (58%)

a/ Data from Tables 10 and 12 (Wilson *et al.*, 1985c; Wilson and Killeen, 1989). Incidences were expressed as the number of animals bearing tumors per animals at risk. All animals examined were considered at risk, except for those which died before day 365 of the study. Level of statistical significance, $p \leq 0.05$ (* or +) or $p \leq 0.01$, (** or ++) is indicated after each incidence. Significance at the control value is based on a dose-weighted chi-square trend test, and pair-wise significance at the dosed groups is for the Fisher's Exact Test.

The linearized multistage model, Global 86 (Howe *et al.*, 1986), was used to extrapolate the dose-response relationship obtained from experimental animal data at higher dose levels to the lower dose range that is generally more typical of human exposures. Both potency factors, the maximum likelihood estimate (MLE, q_1) and the 95% upper confidence limit (q_1*) of the linear term of the multistage model, are presented as estimates of the oncogenic potency. The potency factors were 2.0×10^{-3} and 2.9×10^{-3} $(mg/kg/day)^{-1}$ for q_1 and q_1*, respectively, based on administered doses (Table 20). They were similar to the potency factors calculated for the individual studies which were: 2.1×10^{-3} and 2.7×10^{-3} for the 1985 study and 2.9×10^{-3} and 4.1×10^{-3} for the 1989 study. Since the pharmacokinetics of chlorothalonil at the high dose (200 mg/kg) was different than that for lower doses (5 and 50 mg/kg), the potency factors based on all doses (1.8 mg/kg/day to 183 mg/kg/day) and lower doses (1.8 to 80 mg/kg/day) were compared. The comparison showed no significant difference in the potency factors with or without the high doses because of the linear relationship between dose and tumor incidences. The potency factors in terms of absorbed doses were also calculated and will be used in combined exposure scenarios (occupational and dietary exposures).

The potency factors calculated from the rat data were extrapolated to humans, assuming an interspecies dose equivalence factor based on the body weight to the 3/4 power (see Equation 4 in Appendix C). Using this assumption, a factor of 1/4 power of the human-to-animal body weight ratio was applied. A body weight of 350 grams for rats was used to represent the mean body weight of all groups during the experiments. Since the potency factors for the male rats were higher than those for the female rats, they were used to quantify the risk for potential human exposure (Table 20).

IV.A.4. Critical NOELs and Endpoints

A summary of the critical NOELs and endpoints for risk characterization is presented in Table 21. The reference concentrations were based on a margin of exposure of 100, 10-fold each for intraspecies and interspecies extrapolation. For risk characterization, both the NOEL and the dietary exposure would be expressed as dose and were not adjusted for absorption.

Table 20. The potency factors for kidney tumors in rats treated with chlorothalonil.[a]

Gender	Potency Factor mg/kg/day^{-1}			
	Rat		Human equivalents[b]	
	q1	q1*	q1	q1*
Males				
Administered dose	2.0×10^{-3}	2.9×10^{-3}	7.5×10^{-3}	1.1×10^{-2}
Absorbed dose[c]	5.8×10^{-3}	8.4×10^{-3}	2.2×10^{-2}	3.1×10^{-2}
Females				
Administered dose	5.1×10^{-4}	1.8×10^{-3}	not determined[d]	
Absorbed dose[c]	1.5×10^{-3}	5.4×10^{-3}		

a/ Potency factors were determined for two oncogenicity studies (Table 19; Wilson *et al.*, 1985c; Wilson and Killeen, 1989). The q_1 and q_1* based on the administered doses for the individual studies were: 2.1×10^{-3} and 2.7×10^{-3} for the 1985 study and 2.9×10^{-3} and 4.1×10^{-3} for the 1989 study.

b/ The human equivalent q_1 and q_1* were calculated by (Appendix C Equation 4 for derivation):
q_1 human = q_1 animal x (human body weight/animal body weight)$^{1/4}$
where the human body weight = 70 kg, male rat body weight = 0.35 kg.
For example: male rat to human extrapolation: q_1 human = 0.002 x $(70/0.35)^{1/4}$ = 0.0075 (mg/kg/day)$^{-1}$

c/ Absorbed dose was calculated by administered dose multiplied by 0.34 (oral absorption factor).

d/ Not determined because potency factors will not be used.

Table 21. The critical no-observed-effect levels (NOELs) and potency factors for risk characterization[a]

Exposure Scenario	NOEL (mg/kg/day)	Endpoints	Reference Concentration (mg/kg/day)	Ref.
Chlorothalonil (and SDS-3701)				
Acute	15	Reduced food consumption in pregnant rabbits	0.15	1
Chronic	1.8	Kidney lesions (nephropathy, hyperplasia) in rats	0.018	2*
Lifetime	Potency factor[b] q_1=7.5×10^{-3} q_1*=1.1×10^{-2}	Kidney tumors in rats	NA	2*,3*
Hexachlorobenzene				
Chronic	0.08	Liver effects (centrilobular basophilic chromogenesis) in rats	0.0008	4
Lifetime	q1*=1.02	Liver tumors in rats	NA	4

a/ * study was considered acceptable by DPR according to FIFRA guidelines. References: 1. Wilson and Killeen, 1988a; 2. Wilson *et al.*, 1985c; 3. Wilson and Killeen, 1989; 4. U.S.EPA, 1999a. Reference concentration was based on an uncertainty factor of 100, 10 each for inter- and intra-species extrapolation.

b/ Human equivalent potency factor for administered dose (mg/kg/day^{-1}) from Table 20.

IV.B. DIETARY EXPOSURE ASSESSMENT

IV.B.1. Introduction

DPR evaluates the risk of dietary exposure to the pesticide residues using two processes: (1) total dietary exposure to all commodities potentially treated with chlorothalonil, and (2) dietary exposure to an individual commodity at the tolerance level. The latter process is described in **VI. TOLERANCE ASSESSMENT**. For both processes, the exposures are estimated based on input of residue values and consumption data using a software program.

The total dietary exposure involves a tiered approach to determine the residue value for each commodity (DPR MT-3, 2004). Tier 1 is a point estimate analysis with the assumption that all foods consumed in a given day contained residues at the tolerance levels. If the estimated exposures from this analysis result in any population subgroup with a margin of exposure lower than the criterion of 500[5], a tier 2 analysis is conducted. Tier 2 analysis represents the first level of refinement on the residue values by using measured residues rather than the tolerances. Both tiers 1 and 2 analyses assume 100% crop treatment. In tier 2, the preference for the residue is the use of data from the USDA Pesticide Data Program (PDP; USDA 1998-2002) since the sampling and analysis were specifically designed for the data to be used in risk assessment. In this tier, the highest detected value for each commodity is used for acute dietary exposure and the mean of all detected values is used for chronic dietary exposure. For samples with residues below the detection limit, the limit of detection and ½ of the LOD are used as the residue levels for acute and chronic dietary exposures, respectively. For commodities with no residue data, the tolerances are used as the highest possible residue value. Further refinement of the residues is included in tiers 3 and 4, which take into consideration residue loss due to processing, % of crop treatment, and probability distribution of residue levels for each commodity. In tier 3 acute and chronic dietary exposures, the mean residue value is used for the blended foods if the residue was derived from the raw agricultural commodity. The assumption is that the blended foods contain a mixture of residue levels. The residue value for the raw agricultural commodity can be reduced if there are processing data, which show loss of residues, for example from washing and peeling of the fruit skin. Tier 4 uses Monte Carlo analysis to select the residue value based on the probabilistic considerations of the database.

For consumption data, DPR has selected the most recent consumption survey by the USDA. The Continuing Survey of Food Intakes by Individuals (CSFII; USDA, 1994-1998) is a representative consumption database, which provides information on a 2-day food intake by 20,607 individuals of all ages from 62 geographical areas. The database consists of the 1994-1996 food consumption survey, along with the 1998 Supplemental Children's Survey, which includes additional 5,559 children from birth to 9 years old.

[5] The criterion is set at 500 when the NOEL was derived from experimental animal study; it is a guide to determine if further refinement is needed. It is higher than the conventional benchmark of 100 for health concern because there may be additional considerations in the risk characterization and risk appraisal that warrant a higher MOE as the benchmark.

The acute and chronic dietary exposures are calculated using the Dietary Exposure Evaluation Model (DEEM)™ software program (Exponent[6], Inc., version 7.81). The acute dietary exposure is based on per user-day (a day of consuming at least one commodity included in the analysis) basis. The chronic dietary exposure is calculated using per-capita mean consumption (the entire population subgroup regardless whether the analyzed foods were consumed).

IV.B.2. Chlorothalonil Dietary Exposure

For chlorothalonil, the dietary exposure assessment was conducted for acute, chronic, and lifetime exposures to raw agricultural and processed commodities allowed on the labels. Seasonal exposure was not estimated since almost all commodities could be consumed through out the year. The exposure would likely be close to that estimated for chronic exposure (see **V.D. Risk Characterization**). A list of the commodities with tolerances for chlorothalonil is in Appendix A. The potential exposure from chlorothalonil in drinking water was not included in this assessment because exposure by this route was considered negligible. Between 1986-1992 in California, chlorothalonil was detected in only one of 1036 wells sampled (DPR, 1992). The level was 0.8 to 0.11 ppb in an unsealed well. These levels are well below the U.S. EPA drinking water health advisories, which are 200 ppb for one-day and longer-term exposure for children and 500 ppb for longer-term exposure for adults (U.S. EPA, 1994). In the RED, the U.S. EPA showed that exposure to chlorothalonil and metabolites in the drinking water was relatively low with margins of exposure greater than 100,000 (U.S.. EPA, 1999a; 2001a and b).

The dietary exposure to SDS-3710 was also addressed since this metabolite might be present in the meat and milk. In addition, hexachlorobenzene was included since it is a known contaminant in chlorothalonil formulations, and it is an oncogen.

IV.B.2.a. Tier 1 Analysis

In Tier 1 analysis, the tolerance and ½ tolerance for chlorothalonil and SDS-3701 were used as the residue value to determine the acute and chronic exposures, respectively, to all commodities potentially treated with chlorothalonil products. The adjustment factor for dehydration and processing was set to 1 since residues for all food forms cannot exceed the tolerance. This analysis showed high exposures with margins of exposures of less than 500 for many population subgroups (data not shown).

IV.B.2.b. Tier 2 Analysis

Since the margins of exposure from tier 1 analysis was less than 500 for some population groups after acute or chronic exposures, tier 2 analysis was performed with measured residue levels for commodities with adequate monitoring data (Table 22) and 100% crop treatment.

[6] The program was formerly developed by Novigen Sciences, Inc.

Table 22. Residue values for chlorothalonil dietary exposure assessment.[a]

Commodities	Acute residue	Chronic residue	Adj. Factor	Data Source
Almonds	0.05	0.025	1	Tolerance
Apricots and juice*	0.01	0.005	1	DPR 2002, n=79
Apricots-dried*	0.01	0.005	6	
Asparagus*	0.02	0.005	1	DPR 2002, n=34
Bananas	0.022	0.003	1	PDP 2001, n=189
Bananas-dried	0.022	0.003	3.9	
Bananas-juice	0.022	0.003	1	
Beans-dry-all types	0.1	0.05	1	Tolerance
Beans-succulent-green	1.2	0.012	1	DPR 99-00, n=246
Beans-succulent-all others	0.15	0.008	1	DPR 99-02, n=60
Blueberries	0.41	0.039	1	DPR 01-02, n=29
Broccoli	0.008	0.0025	1	PDP 2001, n=208
Brussels sprouts*	0.01	0.005	1	DPR 2002, n=30
Cabbage-green and red*	0.01	0.005	1	DPR 2002, n=96
Carrots	0.008	0.0025	1	PDP 2001, n=215
Casabas	5	2.5	1	Tolerance
Cauliflower*	0.01	0.005	1	DPR 2002, n=36
Celery, juice, seed	1.3	0.008	1	PDP 2001, n=213
Cherries*	0.005	0.0025	1	PDP 2001, n=57
Chocolate-cocoa butter	0.05	0.025	1	Tolerance
Coffee	0.2	0.1	1	Tolerance
Corn grain/sugar/hfcs*	0.01	0.005	1.5	DPR 2002, n=51
Corn grain/sugar-molasses*	0.01	0.005	1	
Corn grain-others*	0.01	0.005	1	
Corn/sweet*	0.01	0.005	1	
Cranberries, juice	5	0.06	1	Tolerance, DPR 98-01, n=17
Crenshaws	0.01	0.005	1	Honeydew surrogate
Cucumbers	0.017	0.003	1	PDP 2000, n=211
Filberts (hazelnuts)	0.1	0.05	1	Tolerance
Garlic*	0.01	0.05	1	Dried onion surrogate
Ginseng	0.1	0.05	1	Tolerance
Mangoes*	0.01	0.005	1	DPR 2002, n=44
Meat[b]-fat w/o bones	0.1	0.05	1	Tolerances for SDS-3701
Meat-kidney	0.5	0.25	1	
Meat-lean (fat/free) w/o bones	0.03	0.015	1	
Meat-meat byproducts	0.05	0.025	1	
Melons-cantaloupes-juice, pulp	0.008	0.0025	1	PDP 1999, n=237
Melons-honeydew*	0.01	0.005	1	DPR 01-02, n=66
Melons-persian*	0.01	0.005	1	Honeydew surrogate

Table 22. Residue values for chlorothalonil dietary exposure assessment (continued).[a]

Commodities	Acute residue	Chronic residue	Adj. Factor	Data Source
Milk- all forms*	0.003	0.0015	1	PDP 1998, n=139
Mushrooms	0.008	0.003	1	PDP 2001, n=53
Nectarines*	0.005	0.0025	1	PDP 2001, n=80
Onions-dehydrated or dried*	0.01	0.005	1	DPR 2002, n=68
Onions-green	0.34	0.022	1	DPR 2002, n=77
Papayas-dried	0.05	0.005	1.8	DPR 2002, n=32
Papayas-juice	0.05	0.005	1.5	
Papayas-pulp	0.05	0.005	1	
Parsnips	1	0.5	1	Tolerance
Passion fruit, juice	3	1.5	1	Tolerance
Peaches, juice*	0.01	0.005	1	DPR 00-02, n=99
Peaches-dried*	0.01	0.005	7	
Peanuts-butter, hulled, oil	0.3	0.15	1	Tolerance
Peppers-other	0.32	0.008	1	DPR 2002, n=254
Pistachio nuts	0.2	0.1	1	Tolerance
Plums (damsons)*	0.01	0.005	1	DPR 2002, n=100
Plums/prune-juice*	0.01	0.005	1.4	DPR 2002, n=100
Plums-prunes (dried)*	0.01	0.005	5	
Potatoes/white-dry*	0.005	0.0025	6.5	PDP 2001, n=162
Potatoes/white-peel only*	0.005	0.0025	1	
Potatoes/white-peeled*	0.005	0.0025	1	
Potatoes/white-unspecified*	0.005	0.0025	1	
Potatoes/white-whole*	0.005	0.0025	1	
Pumpkin	5	2.5	1	Tolerance
Shallots*	0.01	0.005	1	Dry onion surrogate
Soybean-all forms	0.2	0.1	1	Tolerance
Squash-summer	0.21	0.009	1	DPR 00-02, n=102
Squash-winter	0.42	0.019	1	DPR 99-02, n=42
Tomatoes-catsup	0.08	0.005	2.5	PDP 1999, n=104 for tomato
Tomatoes-dried	0.08	0.005	14.3	PDP 1999, n=104 for tomato
Tomatoes-juice	0.08	0.005	1.5	PDP 1999, n=104 for tomato
Tomatoes-paste*	0.005	0.0025	1	PDP 2002, n=83 for paste
Tomatoes-puree	0.08	0.005	3.3	PDP 1999, n=104 for tomato
Tomatoes-whole	0.08	0.005	1	PDP 1999, n=104 for tomato
Watermelon	0.04	0.006	1	DPR 01-02, n=46

a/ The data sources were USDA Pesticide Data Program (1998-2002), DPR monitoring program (1999-2002), or the tolerance. Adjustment factors were defaults from the DEEM program. High residue values (the highest detected value, limit of detection, or tolerance) are used for acute dietary exposure and the mean of all residue values (detected value, ½ limit of detection or tolerance) are used for chronic and lifetime dietary exposure analyses. PDP limit of detections: 0.005 ppm for almost all commodities and 0.003 ppm for milk. DPR limit of detection was 0.01 ppm for all commodities. All meats from cow (including calf), pig, goat, horse, and sheep. *=residues were at the detection limit. Adj.=adjustment factor for increase in residue due to concentration or dehydration.

The residue data sources were the USDA Pesticide Data Program (PDP; USDA, 1998-2002) and DPR marketplace monitoring program (DPR, 1999-2002). The PDP limits of detection were 0.005 ppm for most commodities and 0.003 ppm for milk. The DPR LOD was 0.01 or 0.02 ppm for all commodities. For some commodities, data from several years were combined to increase the number of samples, when the residue levels were similar for those years. Tolerances were used when there were no recent residue monitoring data or suitable surrogates. Table 22 also included the default adjustment factor for processed food forms to account for potential increase in residues due to processing such as drying and concentration. The factor was one for the raw agricultural commodity and when the tolerance was used as the residue.

Both the PDP database for California samples and DPR databases showed chlorothalonil residue levels remained relatively low and constant in the 5 years examined. These levels were generally lower than those obtained from field trials (see **II.G.5. Plant Residues/Metabolism**). This low residue level was expected since chlorothalonil is a contact fungicide with residues primarily on the outerleaves and the residues can be removed with washing before the produce reaches the marketplaces. Several commodities did not contain any residues (at below the detection limit); these included apricot, asparagus, Brussels sprouts, cabbage, cherry, corn, honeydew, mango, milk, nectarine, onion (dried), peach, plum, potato, and tomato paste. Most of the commodities with positive samples were limited to a few samples collected (less than 10% of samples collected). Celery (50% of samples) and cranberry (59% of samples) showed high percentages of samples with positive residues. Yet, the average for all the samples was relatively low. For example, the highest residue detected was 1.3 ppm in a sample of celery; yet, the mean of all samples was 0.008 ppm.

With cranberry, there were few samples in the database. DPR residue database showed that 17 samples were collected from 1998 to 2001. The levels were less than 0.1 ppm except for two samples (0.39 ppm and 0.23 ppm); the mean residue was 0.06 ppm. Considering the high residue levels in those samples, the tolerance (5 ppm) was selected for acute exposure. On the other hand, the average value, rather than ½ of the tolerance, seemed more reasonable for chronic and lifetime exposures. While the database had few samples, the average residue values were consistent with the data from a recent field trial study which showed that chlorothalonil residues were 0.049 ppm and 0.076 ppm, without and with spray adjuvant, on fruits 76 days after the last application (Putnam et al., 2003) (see **II.G.5. Plant Residues/ Metabolism**). In addition, the primary consumed food form is cranberry juice, which is a mixture of samples from various sources and would be unlikely to contain residues at ½ of tolerance.

Tolerances for meat, meat byproducts, and milk for SDS-3701 were used in the dietary exposure analyses due to lack of monitoring data. For lifetime exposure using the potency factors for chlorothalonil, these commodities were excluded because SDS-3701 has not been found to be oncogenic. They were also excluded from the chronic and lifetime dietary analyses for HCB since SDS-3701 is not a metabolite of HCB.

The acute and chronic dietary exposures to chlorothalonil, SDS-3701, and HCB are shown in Table 23. For acute exposure to chlorothalonil and SDS-3701, three percentiles (95^{th}, 97.5^{th}, and 99^{th}) of exposure are presented to account for all potentially exposed individuals. At

the 99th percentile, the acute dietary exposure ranged from 0.0056 mg/kg/day (females 13-19 not pregnant or nursing, males 20+ years old) to 0.0165 mg/kg/day (nursing infants <1 year old). As a group, the infants (all, non-nursing, or nursing) have the highest exposures. Commodity contribution analysis showed that the major contributor to the exposure of infants was green beans accounting for 73-75% of the total exposure.

For chronic dietary exposure to chlorothalonil and SDS-3701, the exposures ranged from 0.00011 mg/kg/day (females 20+ years old not pregnant or nursing) to 0.00042 mg/kg/day (non-nursing infants) (Table 23). The lifetime exposure was represented by the Western region since this group consisted of mostly Californians across the ages and was 0.00014 mg/kg/day (Table 23).

IV.B.3. Hexachlorobenzene Dietary Exposure

The acute dietary exposure HCB was not estimated since the U.S.EPA did not establish an acute reference concentration. The chronic dietary exposure to HCB was calculated as 0.05% of chlorothalonil chronic exposures; this factor was equivalent to the maximum HCB level allowed in the chlorothalonil formulations (U.S. EPA, 1999a). The exposures to HCB ranged from 4.5×10^{-7} mg/kg/day (females 20+ years old not pregnant or nursing) to 1.92×10^{-6} mg/kg/day (non-nursing infants) (Table 23). The lifetime exposure was 7×10^{-7} mg/kg/day for the Western region.

Table 23. Estimated dietary exposures to chlorothalonil and hexachlorobenzene (HCB).[a]

Population groups	Chlorothalonil (mg/kg/day)					HCB (mg/kg/day)	
	Acute Exposure			Chronic Exposure	Lifetime Exposure[b]	Chronic Exposure	Lifetime Exposure
	95%	97.5%	99%				
U.S. population	0.0029	0.0044	0.0072	0.00016	0.00012	6.2 x10-7	NA
Western region	0.0027	0.0044	0.0070	0.00018	0.00014	7.0 x10-7	$7x10^{-7}$
Hispanics	0.0027	0.0040	0.0067	0.00020	0.00015	7.4 x10-7	NA
Non-hispanic whites	0.0029	0.0044	0.0073	0.00016	0.00012	6.1 x10-7	
Non-hispanic blacks	0.0029	0.0045	0.0070	0.00016	0.00012	5.9 x10-7	
Non-hisp/non-white/ non-black	0.0029	0.0047	0.0069	0.00016	0.00012	5.9 x10-7	
All infants	0.0071	0.0108	0.0147	0.00034	0.00031	15.5 x10-7	
Nursing infants	0.0075	0.0124	0.0165	0.00012	0.00011	5.7 x10-7	
Non-nursing infants	0.0071	0.0103	0.0142	0.00042	0.00038	19.2 x10-7	
Children 1-6 yrs	0.0060	0.0091	0.0147	0.00036	0.00026	12.8 x10-7	
Children 7-12 yrs	0.0033	0.0047	0.0076	0.00025	0.00019	9.3 x10-7	
Females 13+ (P/NN)	0.0020	0.0030	0.0059	0.00012	0.00009	4.4 x10-7	
Females 13+ (N)	0.0029	0.0034	0.0119	0.00024	0.00021	10.5 x10-7	
Females 13-19 (NP or NN)	0.0019	0.0029	0.0056	0.00014	0.00010	5.2 x10-7	
Females 20+ (NP or NN)	0.0026	0.0037	0.0059	0.00011	0.00009	4.5 x10-7	
Females 13-50 yrs	0.0023	0.0034	0.0059	0.00012	0.00009	4.7 x10-7	
Males 13-19 yrs	0.0020	0.0029	0.0060	0.00020	0.00015	7.6 x10-7	
Males 20+ yrs	0.0023	0.0034	0.0056	0.00013	0.00010	4.9 x10-7	
Seniors 55+	0.0027	0.0039	0.0063	0.00012	0.00009	4.7 x10-7	

a/ Exposures were estimated from 1994-1998 food consumption surveys, anticipated residues or tolerances, and the DEEM™ software. For chlorothalonil, acute and chronic exposures were based on all commodities while lifetime exposure did not include meat and milk. HCB chronic and lifetime exposures were 0.05% of chlorothalonil lifetime exposures. Abbreviations: P=pregnant, NP=not pregnant, NN=not nursing, N=nursing.

b/ Only the lifetime exposure for the Western region represented the lifetime exposure of individuals across the ages. The lifetime exposures of other groups were presented in this Table to provide the numerical basis for the calculation of the HCB chronic exposures.

IV.C. RISK CHARACTERIZATION

The potential health risk associated with the dietary exposure to chlorothalonil was evaluated using the critical NOELs and endpoints selected in the Hazard Identification section (**IV.A.2.**), and the dietary exposures estimated (**IV.B.2**). For potential non-oncogenic effects, the risks were characterized in terms of margins of exposure (MOE), defined as the ratio of the critical NOEL (Table 21) to the exposure level. For oncogenic effects, the risk was characterized as the theoretical probability of excess cancer risk in a lifetime and was the product of potency (Table 20) and the lifetime exposure based on chronic exposure of the Western region (Table 23).

The MOEs for tier 2 acute and chronic dietary exposures for chlorothalonil are presented in Table 24. For acute dietary exposure, the MOEs of all subgroups at 95th to 99th percentiles were greater than 900. The MOEs ranged from 907 (99th percentile exposure for nursing infants) to 7794 (95th percentile for females 13-19 years old, not pregnant or nursing). For chronic exposure, the MOEs ranged from 4304 (non-nursing infants) to 15732 (females 20+ years old not pregnant or nursing). The oncogenic risks were 1.1×10^{-6} and 1.5×10^{-6} for q_1 [0.0075 (mg/kg/day^{-1})] and q_1* [0.011 (mg/kg/day^{-1})], respectively, for the population in the Western region with an estimated lifetime exposure of 0.00014 mg/kg/day.

The potential health risk for exposure to HCB as a contaminant of chlorothalonil was assessed using critical NOEL and potency factor derived by the U.S. EPA (U.S. EPA, 1999a). The MOEs for chronic exposure exceeded 40,000 for all population groups. The lifetime risk for the Western region population was 7×10^{-7} based on the q1* .

Table 24. Margins of exposure and oncogenic risks for dietary exposures to chlorothalonil and hexachlorobenzene (HCB).[a]

Population groups	Chlorothalonil					HCB	
	Acute Exposure MOE			Chronic Exposure MOE	Lifetime Exposure risk	Chronic Exposure MOE	Lifetime Exposure risk
	95%	97.5%	99%				
U.S. population	5210	3412	2093	10950	NA	>50000	NA
Western region	5497	3428	2155	9978	$1.1x10^{-6}$ to $1.5x10^{-6}$	>50000	$7x10^{-7}$
Hispanics	5641	3725	2249	9252	NA	>50000	NA
Non-hispanic whites	5169	3400	2051	11229		>50000	
Non-hispanic blacks	5165	3337	2129	11036		>50000	
Non-hisp/non-white/non-black	5112	3194	2162	11070		>50000 >50000	
All infants	2100	1395	1019	5344		>50000	
Nursing infants	1996	1211	907	14711		>50000	
Non-nursing infants	2107	1452	1057	4304		41775	
Children 1-6 yrs	2508	1654	1019	5069		>50000	
Children 7-12 yrs	4602	3205	1974	7236		>50000	
Females 13+ (P/NN)	7407	5077	2536	14574		>50000 >50000	
Females 13+ (N)	5096	4476	1260	7430		>50000	
Females 13-19 (NP, NN)	7794	5218	2697	13160		>50000	
Females 20+ (NP, NN)	5740	4029	2529	15732		>50000	
Females 13-50 yrs	6469	4399	2563	14916		>50000	
Males 13-19 yrs	7450	5186	2511	9000		>50000	
Males 20+ yrs	6447	4439	2677	13549		>50000	
Seniors 55+	5481	3870	2388	15183		>50000	

a/ Exposure levels were the 95th, 97.5th, and 99th percentile for acute and mean annual level for chronic exposures and are based on the USDA Continuing Survey of Food Intakes of Individuals (1994-1998) (Table 23). For chlorothalonil, acute margins of exposure were based on a NOEL of 15 mg/kg/day for reduced food consumption in pregnant rabbits (Wilson and Killeen *et al.*, 1988a; Wilson and Killeen, 1988b). Chronic margins of exposure were based on a NOEL of 1.8 mg/kg/day for kidney lesions in rats (Wilson and Killeen, 1989). The probability for oncogenic risk was based on the potency factors of 0.0075 $mg/kg/day^{-1}$ and 0.011 $mg/kg/day^{-1}$ for kidney tumors in rats (Wilson *et al*., 1985c). For HCB, chronic margins of exposure was based on a NOEL of 0.08 mg/kg/day for liver effects in rats, and lifetime risk was based on a potency factor of 1.02 $mg/kg/day^{-1}$ for liver tumors in rats (U.S. EPA, 1999a). Abbreviations: P=pregnant, NP=not pregnant, NN=not nursing, N=nursing, NA=not applicable.

IV. D. COMPARISON OF RISK ASSESSMENT WITH THE U.S. ENVIRONMENTAL PROTECTION AGENCY

The risk characterization for dietary exposure conducted in this document was compared with those performed by the U.S. EPA in the Reregistration Eligibility Document (U.S. EPA, 1999a), and tolerance assessments (U.S. EPA 2001 a and b). The U.S. EPA assessments were comprehensive and included worker and residential exposures, as well as aggregate exposures (dietary, water, and residential exposures). For this document, comparisons were made only for dietary exposures.

IV.D.1. Hazard Identification and Reference Concentrations

There were several differences in the NOELs/endpoints between DPR and the U.S.EPA. They are presented in Table 25 and summarized below:

1. DPR determined an acute NOEL (15 mg/kg/day) from a developmental toxicity study, which showed acute effects (reduced food consumption) in pregnant rabbits (Wilson and Killeen et al., 1988a). This NOEL was lower than the U.S. EPA extrapolated acute NOEL of 60 mg/kg/day from a single dose (175 mg/kg/day) short-term study with effects observed after 4 days of exposure. These effects were increased cell proliferation and kidney lesions which were observed in many studies.

2. DPR and U.S. EPA both selected the same study to address chronic exposure. There were slight differences in the magnitude of the NOEL due to differences on how the ppm in the diet was converted to dosage (mg/kg/day).

3. For oncogenicity, both DPR and U.S. EPA based the potency factor on kidney tumors in rats. DPR calculated the potency factors by combining the incidences of renal tumors in male rats from two studies (Wilson *et al.*, 1985c; Wilson and Killeen, 1989 (discussed under **IV.A.3. Oncogenicity**). U.S. EPA used data only from Wilson *et a*l. (1985c).

4. For the evaluation of lifetime exposures, DPR considered only the non-threshold approach as a default since the data did not provide sufficient evidence for a threshold mechanism of oncogenicity. On the other hand, the U.S. EPA calculated the risks assuming both threshold and non-threshold mechanism for oncogenic risks (U.S. EPA, 1999a). Since the U.S. EPA had not resolved the issues regarding the mechanism of action or the appropriate MOE at which to regulate cancer risk based on the threshold method, regulatory decisions were based on risk from the non-threshold method.

5. Both DPR and U.S. EPA used a 100-fold uncertainty factor to determine the reference concentrations from the NOEL or estimated NOEL.

Table 25. Comparison of critical no-observed-effect levels (NOELs) and endpoints for risk characterization.[a]

Exposure Scenario	DPR NOEL and endpoint	USEPA NOEL and endpoint
Chlorothalonil		
Acute	Reduced food consumption in pregnant rabbits NOEL=15 mg/kg/day RfD=0.15 mg/kg/day (Wilson and Killeen *et al.*, 1988a)	Cell proliferation, renal and gastric lesions in rats LOEL= 175 mg/kg/day Estimated NOEL=58 mg/kg/day (UF=3) RfD=0.58 mg/kg/day (Ford and Killeen, 1987a)
Chronic	Kidney lesions in rats NOEL=1.8 mg/kg/day RfD=0.018 mg/kg/day (Wilson and Killeen, 1989)	Kidney effects in rats NOEL=2 mg/kg/day RfD=0.02 mg/kg/day (Wilson and Killeen, 1989)
Lifetime	Nonthreshold Kidney tumors in rats Potency factors[b] q_1=7.5x10^{-3} mg/kg/day^{-1} q_1*=1.1x10^{-2} mg/kg/day^{-1} (Wilson *et al.*, 1985c; Wilson and Killeen, 1989)	Nonthreshold Kidney tumors in rats q_1*=7.66 x10^{-3} mg/kg/day^{-1} (Wilson *et al.*, 1985c)
Hexachlorobenzene		
Acute	Adopt U.S. EPA values (U.S. EPA, 1999a)	No acute endpoint available
Chronic		Liver effect (centrilobular basophilic chromogenesis) in rats NOEL=0.08 mg/kg/day RfD=0.0008 mg/kg/day (U.S. EPA, 1999a)
Lifetime		liver tumors in hamsters and rats q_1*=1.02 mg/kg/day^{-1} (U.S. EPA, 1999a)

a/ Both DPR and U.S. EPA used a factor of 100 for interspecies and intraspecies extrapolation to derive the reference concentrations from the NOEL or estimated NOEL.

b/ Human equivalent potency factor for administered dose (mg/kg/day^{-1}) from Table 20.

IV.D.2. Exposure Assessment

U.S. EPA and DPR used different residue and consumption databases and software to estimate the exposures primarily due to data availability when the analyses were done. DPR was able to use more current data compared to those used by U.S. EPA in 1999. Also, DPR relied on residue data only for samples collected in California to better estimate exposure in this State, rather than at the national level. The factors which contribute to differences in the exposure levels were the use of percentage of crop treatment (PCT) and the tolerances. DPR did not adjust the detected residues with this PCT factor since tier 2 dietary analyses showed MOEs greater than the benchmark of concern, and no further refinements were needed (see **IV.B.2.b.**). Tolerances were used only when there were no residue data. The U.S. EPA, on the other hand, used Theoretical Maximum Residue Contribution (TMRC) based on the tolerance or anticipated residues for acute exposure, TMRC with percentage of crop treatment adjustment for chronic exposures, and anticipated residues (excluding meat, milk, poultry, and eggs) for lifetime exposures (U.S. EPA, 1999a). For HCB, DPR and U.S. EPA used the same conversion factor (0.05% of chlorothalonil).

For drinking water, DPR considered the exposure via this route to be negligible (**IV.B.2.**). The U.S. EPA included this route in the RED because relatively high residue levels were found in groundwater samples from New York due to the use of chlorothalonil for potatoes, and in surface water samples from Florida (U.S. EPA, 1999a).

IV.D.3 Risk Characterization

A comparison of margins of exposures showed a difference in magnitude of the margins of exposure and oncogenic risks between DPR and the U.S. EPA (Table 26). These differences were a result of aforementioned differences in hazard identification and exposure assessment. However, both DPR and U.S. EPA concluded that dietary exposure to chlorothalonil was below levels (MOE of 100 or >100% of RfD, and oncogenic risk of $>10^{-6}$) of health concern.

Table 26. Comparison of risk characterization.[a]

	DPR	U.S. EPA
Chlorothalonil		
Acute Exposure	MOE ≥ 900	Food MOE ≥ 875 Water MOE ≥ 110,000
Chronic Exposure	MOE ≥ 4304 (≤ 23% RfD)	Food ≤ 60% of RfD Water ≤ 1% RfD
Lifetime Exposure	risk =1.1x 10^{-6} (q_1) to 1.5 x 10^{-6} (q_1*)	Food risk=1.2 x 10^{-6} (q_1*) Water risk=8 x10^{-9} (q_1*)
HCB		
Chronic Exposure	≥ 41775, ≤ 1% RfD	Food ≤ 1% RfD
Lifetime Exposure	7 x 10^{-7}	Food risk= 2.4 x 10^{-7}

a/ Based on U.S. EPA (1999a). Abbreviations: CSFII= Continuing Survey of Food Intake by Individuals, DEEM=Dietary Exposure Evaluation Model, DRES=Dietary Risk Evaluation System, HCB=hexachlorobenzene, PCT=percent of crop treatment, TMRC=theoretical maximum residue contribution.

V. RISK APPRAISAL

V.A. INTRODUCTION

The human health risk assessment of chlorothalonil was conducted for dietary exposure. Risk assessment is the process used to evaluate the potential for human exposure and the likelihood that adverse effects of a substance will occur under specific exposure conditions. Every risk assessment has inherent limitations on the application of existing data to estimate the potential risk to human health. Therefore, certain assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. This, in turn, results in uncertainty in the risk characterization, which integrates all the information from the previous three processes. Qualitatively, risk assessments for all chemicals have similar uncertainties. However, the degree or magnitude of the uncertainty can vary depending on the availability and quality of the data, and the types of exposure scenarios being assessed. Specific areas of uncertainty associated with this risk assessment of chlorothalonil are delineated in the following discussion.

V.B. HAZARD IDENTIFICATION

The uncertainties associated with the selection of the endpoints and the NOELs have already been discussed under **IV.A. HAZARD IDENTIFICATION**. The acute endpoint and NOEL was 15 mg/kg/day based on reduced food consumption (Table 17; Wilson and Killeen, 1988a). This endpoint and NOEL appeared to be conservative since body weight reduction was not observed until gestation day 19 (after 12 exposures). However, given the severity of the toxicity (mortality and clinical signs) observed at 75 mg/kg/day, it was considered appropriate for use to address acute exposure. Since the kidney is a known target organ, this NOEL was comparable to an estimated NOEL of 13 mg/kg/day for kidney histological changes (mild vacuolation) (Gelin and Killeen, 1991b). As discussed under **IV.D**., the U.S. EPA had selected effects in rat kidneys as the critical endpoint, but from another acute toxicity study (Killeen, 1993) with an estimated NOEL of 58 mg/kg/day (based on a LOEL of 175 mg/kg/day and an uncertainty factor of 3).

There was less uncertainty in the endpoints for chronic and lifetime exposures since they were based on effects on the kidneys, and the NOELs were supported by other studies. The weight of the evidence for chlorothalonil oncogenicity was discussed in **IV.A.2.d.Oncogenicity.** In the absence of data, the induction of kidney tumors was assumed to be due to a non-threshold mechanism. This default approach might have overestimated or underestimated the oncogenic risks.

V.C. DIETARY EXPOSURE ASSESSMENT

The uncertainties in the dietary exposure assessment concerned the consumption database and the residue values to calculate exposure levels. For consumption rates, the analyses used the most recent consumption database for this type of analysis even though the survey was conducted between years 1994-1998. The current consumption pattern was assumed to be the same as in this database. The residues were primarily from the most recent monitoring data for chlorothalonil. However, the residue values were likely overestimates due to the assumption of

100% crop treatment for all commodities. Residue values for processed forms were also overestimated when the residues were based on the raw agricultural commodities and no adjustment for potential loss in residues from processing. The exposures would be lower if these assumptions were adjusted with such data through tier 3 analysis, which was deemed unnecessary in this document due to the large margins of exposures.

For some commodities, the tolerances were used and would overestimate the risk especially with the assumption of 100% crop treatment. This was the case for cranberry where the tolerance (5 ppm) was used as the residue value. Both DPR monitoring data and the cited field study showed residues at much lower levels. However, additional monitoring with more samples per monitored sites were needed. For commodities with residue at the detection limit, the use of the detection limit (100% for acute exposure and 50% for chronic exposure) as the residue levels could overestimate or underestimate the potential exposure. In terms of exposures, the acute exposures were represented by 3 percentiles (95^{th}, 97.5^{th}, and 99^{th}) to ensure that they account for all potentially exposed individuals.

V.D. RISK CHARACTERIZATION

The MOEs for potential exposures to chlorothalonil were based on NOELs for toxicity observed in laboratory animals. When the NOEL for non-oncogenic effects is based on animal data, a MOE of at least 100 is generally considered the benchmark to determine the acceptability of the exposure. This benchmark of 100 includes an uncertainty factor of 10 for interspecies extrapolation and a factor of 10 for intraspecies variability. These uncertainty factors assume that the average human is 10 times more sensitive to the effects of a chemical than the most sensitive laboratory animal, and that a sensitive individual is 10 times more susceptible than an average individual (Davidson *et al.*, 1986; Dourson and Stara, 1983).

For chlorothalonil, previous registrants had proposed that data from dogs, not rats, should be used to assess human exposure. Their rationales were based on three reasons. First, dogs and humans are phylogenetically related (Killeen, 1995). Second, chlorothalonil was unlikely to be toxic in humans because of a 10-fold lower *B*-lyase activity in humans compared with the rat. Third, chlorothalonil toxicity was dependent on the metabolism of chlorothalonil in the gastrointestinal tract. The gastrointestinal microbial flora of rats is different from that in humans. DPR disagreed with this proposal and considered the rat as the most sensitive species for risk characterization. Kidney tumors were identified in rats (both sexes) and mice (males) (**III.D. CHRONIC TOXICITY AND ONCOGENICITY**) with the male rat as the most sensitive laboratory animal. DPR acknowledges that there are species-specific effects such as $alpha_{2u}$-globulin accumulation in male rats, which are not appropriate for human risk assessment. However, available data have not met the U.S. EPA criteria for the involvement of $alpha_{2u}$-globulin in chlorothalonil toxicity (Baetcke *et al.,* 1991). Furthermore, the data did not support the sole role of *B*-lyase for the mechanism of toxicity. There was no evidence for specific bacterial species found only in rats for the biotransformation of chlorothalonil to the active metabolite. Differences in gut flora level within and between species exist due to factors such as diet, pH, oxygen tension, gender, age, stress, xenobiotics, drugs, and disease (Rowland, 1988; Drasar, 1989; Chadwick *et al.*, 1992; Roland *et al.*, 1993). More than 400 species of bacteria have been identified in the gastrointestinal tract (Rowland, 1988). Both human and rat feces

contained species from the major genera (Chadwick *et al.*, 1992). In addition, the conjugation of chlorothalonil with glutathione can also occur in other tissues such as the rat liver cytosol (Rosner *et al.,* 1996). Therefore, DPR considered a benchmark of 100 with 10-fold factor each for intraspecies and interspecies extrapolation appropriate for chlorothalonil. Using this benchmark, the MOEs were greater than 100 for acute and chronic dietary exposures to chlorothalonil and HCB.

For oncogenic risk, the current DPR default is 10^{-6}, the probability of one in a million. Using this benchmark, the lifetime dietary exposures to chlorothalonil and HCB did not exceed this risk.

In this document, the subchronic/seasonal exposure was not evaluated. In a subchronic exposure scenario, individuals in a population subgroup could potentially have higher than chronic (average) exposure depending on the consumption pattern and residues on the seasonal commodities. The overall exposure for the group is, however, expected to be closer to the chronic than acute exposure because it is highly unlikely that individuals would consume commodities containing residue levels at the highest detected residues (under the acute exposure scenario) for the entire season. Using the chronic exposure estimates in the RCD (Table 23) and the critical subchronic NOEL of 1.5 mg/kg/day based on kidney effects in the rats (**IV.A.2.b.**), the margins of exposure ranged from 3571 (nonnursing infants) to 16667 (seniors, 55+ years old). Even if assuming seasonal exposure at the unlikely acute exposure level at the 95th percentile, the margins of exposure would be above the benchmark of 100 for health concern, ranging from 200 (nursing infants) to 789 (females 13 to 19 years old). Therefore, there is no additional concern with subchronic/seasonal exposure.

V.E. ISSUES RELATED TO THE FOOD QUALITY PROTECTION ACT

V.E.1. Pre- and Post-natal Sensitivity

There was no evidence of increased pre- or postnatal sensitivity to chlorothalonil. In the rat developmental toxicity study, the developmental NOEL (>400 mg/kg/day for no effects observed) was greater than the maternal NOEL (100 mg/kg/day) (Mizens *et al.*, 1983a). In the rabbit developmental toxicity, both the developmental and maternal NOELs were 10 mg/kg/day for marginal effects on the body weights (Wilson and Killeen, 1988b). In the rat reproductive toxicity study, the developmental NOEL (1500 ppm for decreased pup weight) was much higher than that (<500 ppm for decreased body weight gain) for the maternal NOEL (Lucas and Benz, 1990). There was no evidence of chlorothalonil-induced neurotoxicity in the database. The U.S. EPA had concluded that the additional uncertainty factor to address potential increased sensitivity of infants and children was not needed (U.S. EPA, 1999a).

V.E.2. Aggregate Exposure

There could be a potential for aggregate exposure to chlorothalonil and this will be addressed in the occupational/residential risk characterization document to be prepared. With HCB, there could be additional dietary exposures since it is also a contaminant in other pesticides (dacthal, picloram, pentachloronitrobenzene, endosulfan, chlorpyrifos-methyl,

atrazine, simazine, and clopyrilid) with food uses. The U.S. EPA calculated a lifetime dietary risk of 1.3×10^{-6} for HCB from all known pesticides sources (U.S. EPA, 1999a). This risk level was considered an overestimation since the HCB levels were assumed to be at the same ratio to the active ingredient as was present in the applied formulations. The actual risk might be lower due to environmental dissipation and lower HCB levels in the current formulations.

V.E.3. Cumulative Toxicity

Since the mechanism of chlorothalonil toxicity is unknown, the potential cumulative toxicity between chlorothalonil and other chemicals with a similar mechanism of toxicity could not be evaluated at this time.

V.E.4. Endocrine Effects

Chlorothalonil has not been shown to cause endocrine disruption.

VI. TOLERANCE ASSESSMENT

VI.A. INTRODUCTION

VI.A.1. U.S. EPA

A tolerance is the legal maximum residue concentration of a pesticide that is allowed on a raw agricultural commodity or processed food. The tolerances are established at levels necessary for the maximum application rate and frequency, and not expected to produce deleterious health effects in humans from chronic dietary exposure (U.S. EPA, 1991). The U.S. EPA is responsible for setting tolerances for pesticide residues in raw agricultural commodities (Section 408 of FFDCA) and processed commodities (Section 409 of FFDCA) under the Federal Food, Drug, and Cosmetic Act (FFDCA). The data requirements for tolerances include: (1) residue chemistry, (2) environmental fate, (3) toxicology, (4) product performance such as efficacy, and (5) product chemistry (Code of Federal Regulations, 1996). The field studies must reflect the proposed use with respect to the rate and mode of application, number and timing of applications and formulations proposed (U.S. EPA, 1982).

In 1996, the Food Quality Protection Act (FQPA) amended the overall regulation of pesticide residues under FIFRA and FFDCA (U.S. EPA, 1997). One major change was the removal of the Delaney Clause that prohibited residues of cancer-causing pesticides in processed foods. The tolerances must be health-based and the same standards are used to establish tolerances for both the raw agricultural commodities and their processed forms. FQPA required an explicit finding that tolerances are safe for children. U.S. EPA was required to use an extra 10-fold safety factor to take into account potential pre- and post-natal developmental toxicity and the completeness of the data unless U.S.EPA determined, based on reliable data, that a different margin would be safe. In addition, the evaluations of the tolerance must take into account: (1) aggregate exposure from all non-occupational sources, (2) effects from cumulative exposure to the pesticide and other substances with common mechanisms of toxicity, (3) effects of *in utero* exposure; and (4) potential for endocrine disrupting effects. (Discussion of these issues specific to chlorothalonil is in **V.E. ISSUES RELATED TO THE FOOD QUALITY PROTECTION ACT**).

Under FQPA, U.S. EPA is also required to reassess all existing tolerances and exemptions from tolerances for both active and inert ingredients by 2006 (U.S. EPA, 1997). Previously, U.S. EPA reassessed tolerances as part of its reregistration and Special Review processes. In the evaluation of tolerances, the U.S. EPA uses a tiered approach and the assessment includes all label-use commodities. In 2003, U.S. EPA announced the closure of chlorothalonil reregistration eligibility decision (RED) and tolerance reassessment decision (TRED) (U.S. EPA, 2003).

VI.A.2. California

In California, U.S. EPA established tolerances are evaluated under the mandate of Assembly Bill 2161, generally referred to as the Food Safety Act (Bronzan and Jones, 1989). The Act requires DPR to conduct an assessment of dietary risks associated with the consumption

of produce and processed food treated with pesticides. When the risk is considered deleterious to human health, DPR can promulgate regulations to mitigate the exposure.

VI.B. ACUTE DIETARY EXPOSURE

At DPR, the tolerance assessment is conducted for a single individual label-approved commodity (DPR MT-3, 2004). The commodities are selected with potential for high exposures based on commodity contribution analyses. The exposure is the sum of the 97.5th percentile exposure to the individual commodity with the residue level set at the tolerance and a background exposure. For each analysis, the background exposure is the chronic dietary exposure for all commodities. While this approach results in double counting of the commodity of interest, it conserves time and resources since chronic exposure analysis would have been conducted. If the MOEs for the sum of the exposures indicate potential health concern, then the total exposure is refined with the commodity of interest eliminated from the background exposure.

For chlorothalonil, the tolerances for the following commodities were evaluated: cranberry, green bean, pumpkin, broccoli, celery, corn, peach, summer squash, winter squash, and tomato. These commodities were selected because of high consumption rates and consumption frequency (e.g., green bean, broccoli, corn, and peach) as well as high tolerance levels (e.g. cranberry, celery, pumpkin, squashes, and tomato). With the total acute exposure as the sum of acute exposure for the commodity and the chronic exposure values from Table 23 for all commodities, the total acute exposure ranged from 1.69 *u*g/kg/day (peach, females 20+ years old) to 112.51 *u*g/kg/day (cranberry, Hispanics) (Table 27). The MOEs for all commodities and all population groups were greater than 100, ranging from 267 to 17783. Since the MOEs are greater than the benchmark of 100, no further analysis to refine the background exposure was conducted.

VI.C. CHRONIC DIETARY EXPOSURE

A chronic exposure assessment using residues equal to the established tolerances for individual or combinations of commodities was not conducted because it is highly improbable, that an individual would habitually consume single or multiple commodities with pesticide residues at the tolerance levels. Support for this conclusion comes from FDA and DPR pesticide monitoring programs which indicate that less than 1 percent of all sampled commodities have residue levels at or above the established tolerance.

Table 27. Acute total exposure and margins of exposure for individual commodities at the tolerance levels[a].

Commodities (Tolerance)	Range of Acute Total Exposure (*u*g/kg/day, 97.5th percentile)	Range of Margins of Exposures
Cranberry (5 ppm)	112.51-8.75	133-1720
Bean, green (5 ppm)	73.93-13.92	203-1080
Broccoli (5 ppm)	85.84-18.00	175-837
Celery (15 ppm)	34.62-12.43	435-1213
Corn (1 ppm)	14.89-2.76	1010-5601
Peach (0.5 ppm)	9.34-1.69	1609-9276
Pumpkin (5 ppm)	51.18-7.49	294-2028
Squash, summer (5 ppm)	104.3-20.09	144-747
Squash, winter (5 ppm)	80.59-34.1	186-441
Tomato (5 ppm)	57.10-19.86	263-758

a/ Total exposure was the sum of acute exposure at the 97th percentile based on the tolerance for each commodity and the chronic exposure for all commodities (Table 23) for each population subgroup. The NOEL was 15 mg/kg/day for reduced food consumption in pregnant rabbits (Wilson and Killeen *et al.*, 1988a; Wilson and Killeen, 1988b). A total of 19 population groups were considered (see Table 23) for complete list. The MOEs for the following population subgroups were not presented because there were less than 25 user-days in the group: Hispanic (winter squash), non-Hispanic blacks (pumpkin, winter squash), non-Hispanic others (pumpkin, winter squash), all infants (pumpkin), nursing infants (cranberry, broccoli, pumpkin, summer squash), nonnursing infants (pumpkin), children 7-12 years (winter squash), females 13+ years pregnant/nonnursing (cranberry, green beans, broccoli, peach, pumpkin, summer squash, winter squash), females 13+ years nursing (cranberry, green beans, broccoli, celery, peach, pumpkin, summer squash, winter squash), females 13-19 years not pregnant or nursing (pumpkin, summer squash, winter squash), females 13-50 years (winter squash), males 13-19 (pumpkin, summer squash, winter squash)

VII. CONCLUSION

The dietary exposure to chlorothalonil residues in food was evaluated in this Risk Characterization Document. The critical toxicity endpoints were derived from experimental animals, and the NOELs were based on reduced food consumption for acute exposure and kidney lesions for chronic and lifetime exposures. The toxicity endpoints for HCB were liver effects in rats after chronic and lifetime exposures. For non-oncogenic effects, the risks of exposure were assessed with a MOE of 100 as the benchmark to determine the scenarios of potential health concern. For oncogenicity, the benchmark was 10^{-6}, the probability of one in a million.

The acute, chronic, and lifetime dietary exposures of chlorothalonil and SDS-3701 were based on monitored residue data and tolerances, when residue data were not available. The analyses at the tier 2 level, with 100% crop treatment assumed, showed relatively low exposure for all population groups. These exposures did not exceed the benchmarks of concern. In the tolerance assessment, the MOEs for acute exposure to chlorothalonil at the tolerance for selected commodities with potential high exposures (cranberry, green bean, pumpkin, broccoli, celery, corn, peach, summer squash, winter squash, and tomato) did not exceed the benchmark of 100. The chronic and lifetime dietary exposures to HCB also did not exceed the benchmarks of concern. While this risk assessment concluded that the dietary exposure to chlorothalonil treated commodities did not pose a health concern, this conclusion should be viewed in the context of the limitations and uncertainties discussed. Furthermore, this assessment did not include considerations of occupational and residential settings. These additional exposures will lead to reductions in the MOEs estimated in this assessment. Dietary exposure may have to be reevaluated using refinements such as percent of crop treated information.

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IX. APPENDICES

APPENDIX A

U.S. ENVIRONMENTAL PROTECTION AGENCY TOLERANCES FOR CHLOROTHALONIL

Tolerances for combined residues of chlorothalonil and its metabolite 4-hydroxy-2,5,6-trichloroisophthalonitrile in or on the following raw agricultural commodities:
(Code of Federal Regulations Part 40: 180.275)

Commodities	Tolerances	Commodities	Tolerances
Raw Agricultural Commodities – Tolerances for chlorothalonil			
Almond Almond, hull	0.05 1.0	Ginseng, roots	0.1
Apricot	0.5	Mango	1.0
Asparagus	0.1	Melon	5.0
Banana Banana pulp	0.5 0.05	Mint, hay	2.0
Bean, dry Bean, snap Bean, succulent, green	0.1 5.0 5.0	Mushroom	1.0
Blueberry	1.0	Nectarine	0.5
Broccoli	5.0	Onion, dry bulb Onion, green	0.5 5.0
Brussel sprouts	5.0	Papaya	15.0
Cabbage	5.0	Parsnip, roots	1.0
Carrot	1.0	Peach	0.5
Cauliflower	5.0	Peanut	0.3
Celery	15.0	Pepper, non-bell	5.0
Cherry (sweet and tart)	0.5	Pistachio	0.2
Cocoa bean	0.05	Plum, prune	0.2
Coffee bean	0.2	Potato	0.1
Corn	1.0	Pumpkin	5.0
Cranberry	5.0	Soybean	0.2
Cucumber	5.0	Squash, summer	5.0
Filbert	0.1	Squash, winter	5.0
Fruit, passion	3.0	Tomato	5.0
Secondary residues – Tolerance for SDS-3701			
Cattle, Goat, Hog, Horse, or Sheep Fat Kidney Meat Meat byproducts	 0.1 0.5 0.03 0.05		
Milk	0.1		

APPENDIX B

TOXICOLOGY SUMMARIES

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
CHLOROTHALONIL

Chemical Code # 677, Tolerance # 275, SB 950 # 033

Original Date: June 23, 1987

Revised 1/7/88, 1/30/89, 5/9/89, 10/05/89, 6/6/90, 10/11/91, 10/6/94, 5/17/95, 6/21/95, 7/26/95, 10/20/95, 1/11/96, 4/21/97, 8/21/97, and 2/17/98

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All relevant record numbers through 159189 (Document No. 275-317), and all relevant 900000-series studies have been examined. This includes all records on file at DPR as of 2/5/98. Aldous, 2/5/98.

In the 1-liners below:
** indicates an acceptable study.
Bold face indicates a possible adverse effect.

File name: T980217
Revised by Aldous, 2/17/98

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may identify additional effects.

COMBINED, RAT

Both chronic and oncogenicity study data gaps are filled. There are several studies listed under both headings.

CHRONIC TOXICITY, RAT

Four chronic rat studies were reported during the period 1967 to 1970. In addition, a 1978 Gulf South Research Institute oncogenicity study was submitted, and two rat oncogenicity studies compatible with current oncogenicity study guidelines were subsequently completed. Of the latter two studies, the 1985 IRDC study (Volumes 100-104) was accepted to fill the oncogenicity study data requirement, and the subsequent study in Vol. 164 provided limited ophthalmology and a NOEL for the most sensitive treatment effects. Additional shorter term studies have been submitted, which have some relevance in understanding possible chronic effects. Collectively, the array of rat chronic, oncogenicity, and subchronic studies adequately address the rat chronic and oncogenicity requirements of DPR (i.e. data gaps are filled). No essential new information is likely to be gained by initiating further rodent chronic studies, with the possible exception of oncogenicity mechanistic studies, if desired (see "ONCOGENICITY, RAT" section below). C. Aldous, 10/4/89, 7/21/97.

040 941874 "Two-Year Dietary Administration - Rats. Daconil-2787 (Technical) Final Report." (Hazleton Labs., 6/26/70) Chlorothalonil (purity not given) at 0, 4, 10, 20, 30, 40 or 60 ppm in the diet to 50 rats/sex/group. Possible adverse effect: renal tubular vacuolization and hypertrophy. Systemic NOEL = 30 ppm. Incomplete. Unacceptable: histopathology incomplete in number of animals, deaths during the study, and reports; test article and treated feed not characterized; too few animals continued to 2 years; missing diet analysis. Christopher 3/15/85, Davis 12/2/86.

115 035818 (K. L. Stemmer, University of Cincinnati, 6/19/70) Letter and report evaluating chronic rat study (040 941874). Dr. Stemmer contests the nephrotoxicity reported in the study and concludes that there is no toxicity. CDFA reviewer did not change the possible adverse effect conclusion. Apostolou 12/6/85, Davis 12/2/86.

275-263 143376 Duplicate copy of 040:941874, preceded by Dr. Stemmer's letter of 6/19/70 (see 115:035818, above).

039 941898 "Statement and Evaluation of Kidney Histopathology of Daconil 2787 in Rats and Dogs" by Dr. Klaus Stemmer, University of Cincinnati. (6/19/70) Stemmer concludes there is no nephrotoxicity in either study; presents experimental evidence for artifactual basis of anomalies in the rat study. Analysis of other rat studies shows histological kidney alterations at higher doses. NOEL < 500 ppm. In summary, it is not nephrotoxicity in rats at issue, but rather the dose level. CDFA agreed that there is no nephrotoxicity in the dog study, but found positive evidence in the rat study. Davis 12/2/86. EPA ONE-LINER (040 941874): Systemic NOEL = 60 ppm (HDT). Oncogenic NOEL > 60 ppm. Levels tested = 0, 4, 10, 20, 30, 40 and 60 ppm. CORE GRADE = Not stated
129 050480 "Two-Year Dietary Feeding - Rats. Final Report." (Hazleton Laboratories, Inc., Project No. 200-148, 1/20/67). Chlorothalonil (93.6% purity) plus a mixture of three related compounds, fed to 35 rats/sex/group at 0, 0.15, 1.5, or 3.0 % by weight for up to 104 weeks. One interim kill for three groups, with two interim kills and termination at 47 weeks for the high dose group. Possible adverse effect: dose-related reductions in body weight gain and food efficiency; elevated kidney weights; liver weight changes; histopathological changes in the thyroid,

stomach, kidney and liver. NOEL < 0.15%. Incomplete. unacceptable: dose levels too high; changes in dose level during the experiment; lack of information on test material; no feed analysis; excessive mortality; insufficient observations, serum chemistry, necropsies, ophthalmology, and histopathology; and missing data. Davis, 5/8/87. EPA ONE-LINER: Systemic NOEL = 0.15% (LDT). Systemic LEL = 1.5%. Depression of growth, kidney nephritis. CORE GRADE = Not stated

N.B. The following two chronic feeding studies (Records 050891 and 050892) are supplementary to the previous study (Record 050480) and therefore not guideline studies.

129 050891 "Two-Year Dietary Feeding: Rats. Final Report." (Hazleton Laboratories, Inc., Project No. 200-154, 4/12/67). Chlorothalonil (93.6% purity) plus a mixture of three related compounds, fed to 35 rats/sex/group at 0 or 0.5 % by weight for 104 weeks. Interim kills of 5/sex/group at weeks 13 and 52. Possible adverse effect: Reductions in body weight gain and food efficiency in both sexes; some reduced coagulation times in females; elevated kidney/body weights and liver/body weights; kidneys enlarged, abnormal in color, and showing some cyst-like foci or large cysts; dilatation of the cecum; histopathological degeneration in kidneys. NOEL < 0.5%. Supplementary study: single dose level; lack of information on test material; no feed analysis; excessive mortality; insufficient observations, serum chemistry, necropsies, ophthalmology, and histopathology; and missing data. Davis, 5/11/87. EPA ONE-LINER: Systemic NOEL less than 0.5% (single dose tested). Kidney hypertrophy. CORE GRADE = Not stated

129 050892 "Long Term (76 Weeks) Feeding Study: Rats. Final Report." (Hazleton Laboratories, Inc., Project No. 200-175, 8/16/67). Chlorothalonil (93.6% purity) plus a mixture of three related compounds, fed to 15 rats/sex/group at 0, 0.05, or 0.1 % by weight for 76 weeks, or 0.5 % by weight for 23 weeks (interrupted for 13 days). Interim kills of 5/sex/group at week 20. Possible adverse effect: Reductions in body weight gain and food consumption; decreased survival; elevated kidney weights and ratios and cecum weights; kidneys enlarged, abnormal in color, and showing a rough or pitted surface; histopathological degeneration in kidneys. NOEL = 0.05% for 76 weeks. Supplementary study: lack of information on test material; no feed analysis; too few animals; test period too short; insufficient observations, hematology, serum chemistry, urinalysis, necropsies, ophthalmology, and histopathology; and no data tables. Davis, 5/12/87. EPA ONE-LINER: Systemic NOEL < 0.05% (LDT). Growth depression, tubular hypertrophy. CORE GRADE = Not stated

COMBINED, RAT (SUPPLEMENTARY DATA, NOT USING CHLOROTHALONIL)

070 025237 "Summary of DS-3701 Toxicology Studies: Chronic Toxicity and Tumorigenicity/ DS-3701 Rat Study" Document No. 100-5TX-80-0016-007; Lab and report date not stated; 18-month interim report of 24-month feeding study with 4-hydroxy-2,5,6-trichloroisophthalonitrile (DS-3701, a chlorothalonil metabolite); dose levels of 0.5, 3.0, 15, or 30 mg/kg/day with the two highest levels reduced or dropped during the study. Reversible toxicological effects (unspecified). No tumorigenicity. Systemic NOEL = 3.0 mg/kg/day. Supplementary study: one paragraph summary of study with a related compound. Davis 12/3/86.

SUBCHRONIC: RAT (SUPPLEMENTAL)

275-316 159184 Mizens, M., "A 90-day pilot study for the evaluation of cell proliferation in the kidneys of male rats following the oral administration of technical chlorothalonil", Ricerca, Inc., 9/26/96, Document No. 6704-96-0010-TX-003. Male F-344 rats were dosed continuously in diet with 0 or 175 mg/kg/day chlorothalonil. Fourteen/group were sacrificed at day 7, and 7/group were sacrificed on days 28 and 91, respectively. Primary objectives were to examine

kidney proximal tubular epithelial cell proliferation as evidenced by uptake of BrdU, which was administered by osmotic pump for 3.5 days before respective day of sacrifice. Kidney tissues were examined by H & E staining and by immunohistochemical staining (toward BrdU). The proximal convoluted tubular epithelium underwent degeneration and hyperplasia in treated rats, and tubules were commonly hypertrophied. These changes were evident in the presence of heavy immunohistochemical staining, suggesting that considerable cell proliferation occurred in association with the histopathology lesions. The strong association between proliferation and histopathology is consistent with, but does not prove that a threshold phenomenon was in force. Forestomach lesions consisted of hyperkeratosis and hyperplasia of the squamous epithelium, often with submucosal edema, erosions, and ulcerations. Histopathology in both organs persisted from day 7 to the end of the study on day 91. This is an acceptable ancillary study, with minor deficiencies, as noted in the review. Aldous, 1/29/98.

275-317 159189 Hironaka, M., "Analysis of hyperplastic changes in the stomach and kidney of male rats after 28-day induction by chlorothalonil technical", Center for Safety Assessment of Food, Agricultural Chemicals and Medicinal Drugs (Japan), 9/25/96, Test # 2913 (063-002), Report No. 3561. F-344 male rats were dosed with 0, 1.5, 15, or 175 mg/kg/day chlorothalonil in diet for 7, 14, 21, or 28 days (6 rats per dose/time combination). Primary objectives were to evaluate forestomach and kidney histopathology and cellular proliferation. Kidney sections were stained with PC10, which contained an antibody to proliferating cell nuclear antigen (PCNA). Forestomachs were evaluated by BrdU immunostaining. Rats were administered 0.1 g/kg BrdU 1 hr before autopsy. A stain attached to BrdU monoclonal antibody was used to visualize tissue uptake of BrdU. Additional sections of both tissues were stained with H&E. Increased labeling indices were observed to some extent at 15 and substantially at 175 mg/kg/day in kidney and forestomach. Responses generally decreased over time in kidney proximal tubular epithelial cells at both of these dose levels, and increased over time for forestomach in the 15 mg/kg/day group. Neither histopathology nor evidence of cellular proliferation was seen at 1.5 mg/kg/day in either tissue. This study shows that dose levels previously shown to elicit tumors in these tissues also increased cellular proliferation. No such proliferation was seen at 1.5 mg/kg/day, which was below the level which produced tumors in these tissues. Aldous, 2/17/98.

275-316 159181 An interpretive summary of records 159184 and 159189, above. No worksheet.

129 050893 "4-Month Dietary Toxicity Study: Rats. Chlorothalonil. Final Report". (Bio/Toxicology Research Laboratories, Inc., Project No. 24-201, 9/4/75). Chlorothalonil (purity unknown) fed to 15 rats/sex/group at 1, 2, 4, 15, 30, 60, and 120 ppm for 17 weeks. No effects on the parameters examined (growth, food consumption, survival, kidney histopathology). NOEL > 120 ppm for 17 weeks. Supplementary study: The objective of this study was to examine kidney histopathology. Davis, 5/13/87. EPA ONE-LINER: Systemic NOEL = 120 ppm (HDT). CORE GRADE = Not stated

144 059033 "A 90-Day Feeding Study in Rats with Chlorothalonil" (In-Life Phase: IRDC; Histopathology: Experimental Pathology Labs and C.E.R.T.I., France; Supervision: Ricerca, Inc., Sponsor no. 85-0079, 6/8/87) Technical chlorothalonil (97.9%) fed to 90 male rats each at 0 and 175 mg/kg/day with sacrifices of 10 each on days 4 and 7 and at the end of weeks 2, 4, 6, 8, 10, 12, and 13 of treatment. Possible adverse effect: Kidney: vacuolar degeneration in the proximal convoluted tubules epithelium, proximal tubular epithelial hyperplasia, and tubular hypertrophy; Forestomach: gastritis, multifocal ulceration and erosion of the mucosa followed by gross thickening, epithelial hyperplasia and hyperkeratosis. Supplementary study. Davis 10/6/87.

105-8 034368-034371, 034374, 034376, 034377 Wilson, N.H., J. Laveglia, J. C. Killeen, and J. A. Ignatoski, "A Subchronic Toxicity Study of Technical Chlorothalonil in Rats". Primary contract laboratory: Huntingdon Research Centre, England (6/24/83). Document No. 562-5TX-81-0213-004. Technical Chlorothalonil (98% purity) fed at 0, 1.5,

3.0, 10.0 and 40.0 mg/kg/day to 20 rats/sex/group for 13 weeks, at which time half were necropsied and half were continued on an untreated diet for 13 weeks. Satellite groups of 5 rats/sex/dose were necropsied at 6 weeks. Possible adverse effects include increased kidney and liver weights, decreased circulating liver enzymes, tubular hypertrophy and hyperplasia of the epithelial cells of the proximal convoluted tubules, and hyperplasia and hyperkeratosis in the stomach epithelium. There is no NOEL in this dosage range: inclusion bodies were found in tubules of male renal cortex at all dose levels (Record No. 034377). This effect was evidently not associated with toxicologically important changes, hence the NOAEL = 1.5 mg/kg/day for 13 weeks [based on elevated kidney weights, and decreased alanine aminotransferase activity (of questionable toxicological significance)]. Hyperplasia and hyperkeratosis of non-glandular stomach epithelium was elevated at 10 and 40 mg/kg/day. Supplementary study: 034377 is an EM and light microscopic evaluation of kidney tissue. 034374 is a histopathology re-evaluation specifically to evaluate renal tubular hyperplasia. NOTE: Record Nos. 034374 and 034377 were re-examined by C. Aldous in Oct., 1995, and brief additional worksheets were made, indicating conclusions below. Davis, 5/19/87, and Aldous, 10/20/95.

275-108 034374, Wilson, N.H., J.C. Killeen, and J.A. Ignatoski, "Histopathologic re-evaluation of renal tissue from a subchronic toxicity study of technical chlorothalonil in rats (5TX-81-0213)". The report was produced by SDS Biotech Corp., based on evaluations by Dr. W.M. Busey of EPL. Re-evaluation report was dated July 9, 1985. CD rats received 0, 1.5, 3, 10, or 40 mg/kg/day chlorothalonil for 6 wk (5/sex/group), 13 wk (10/sex/group), or for 13 wk with a 13 wk recovery period (10/sex/group). THIS PARTICULAR RE- EVALUATION WAS FOCUSED ON DETERMINING WHETHER A TREATMENT EFFECT WAS PRESENT FOR A CHARACTERISTIC RENAL TUBULAR HYPERPLASIA, WHICH HAD PREVIOUSLY BEEN SHOWN TO CORRELATE WITH RENAL TUMORS. Only males indicated renal tubular hyperplasia in this study. The NOEL for this characteristic renal hyperplasia appears to be 3 mg/kg/day, based on tubular hyperplasia incidences of 0, 1, 0, 2, and 4 in controls through high dose groups, respectively, at the 6-wk sacrifice. (Investigators considered the NOEL to be 10 mg/kg/day, due to the low incidence of hyperplasia at this and lower dose levels). Aldous, 10/12/95

275-107 034377 Wilson, N.H., J.C. Killeen, B.L. Haley, and J.A. Ignatoski, "A Subchronic Toxicity Study of Technical Chlorothalonil in Rats" [Amendment No. 1]. Supplementary report by Huntingdon Research Centre: supplementary study directed by John Colley. ["Amendment 1" date: 11/14/83]. This report includes EM and light microscopy re-evaluations of rat kidney sections, from tissues used in SDS Biotech Corp. Document No. 562-5TX-81-0213-004 (DPR Document Nos. 275-105 to -107). An initial survey of sections by EM revealed elevated incidence and degree of "irregular intracytoplasmic inclusion bodies" in proximal tubule epithelial cells. These bodies were either electron dense (usually amorphous, sometimes needle-shaped) or heterogeneous under EM. These structures, considered to be lysosomal, are common in male rats, but not found in female rats nor in mice. After establishing the treatment effect and characterizing the structures by EM, investigators evaluated sections from all males on study by light microscopy following treatment by Neutral Red, which had been shown to selectively stain the inclusion bodies. Neutral Red analyses found elevated incidence and/or degree of inclusions at all dose levels tested by week 13 (end of dosing phase), with residual changes evident at 3 mg/kg/day and above after a 13-week recovery period. Thus there is no NOEL for these inclusion bodies over this dose range, however the "NOEL" for inclusion bodies remaining after the recovery phase was 1.5 mg/kg/day. Investigators concluded that these bodies were not related to identifiable toxicological lesions in kidneys, including chronic progressive nephropathy. Presence of these inclusion bodies had not been considered previously by CDFA or DPR in setting the overall NOEL for this subchronic study. The NOAEL is 1.5 mg/kg/day, since slightly higher dose levels were associated with "possible adverse effects" (see Record No. 074770). Aldous, 10/16/95.

130, 131, 108 050894-6, 034373 "A 90-Day Toxicity Study of Technical Chlorothalonil in Rats". (Concord Woods Animal Facility, Diamond Shamrock Corporation, 10/19/81). Technical chlorothalonil (98% purity) was fed to 20

rats/sex/group at 0, 40, 80, 175, 375, 750, and 1500 mg/kg/day for 13 weeks. Possible adverse effects include hyperplasia and other morphologic changes of the kidney tubules; altered stools and generally poor physical condition; depressed mean body weights and food consumption; decreased brain, heart, liver, gonad, and kidney weights; altered blood and urine parameters; and focal acute gastritis. NOEL < 40 mg/kg/day for 13 weeks. Toxic effects were found at all dose levels. Supplementary study. 034373 is supplementary histopathology report. Davis, 5/15/87. EPA ONE-LINER: NOEL < 40 mg/kg/day (relative kidney weights increased at all test levels; urinary vol. and Specific Gravity affected at all test levels). Levels tested-0, 40, 80, 175, 375, 750 and 1500 mg/kg/day in Charles River CD strain. CORE GRADE Minimum

275-297 150595 Mizens, M., "A 21-day repeated dose dermal toxicity study in rats with Technical Chlorothalonil", Ricerca, Inc., Sept. 5, 1996. Document No. 6859-96-0113-TX-002. Ten F-344 male rats/group were dosed dermally in 0.2% aqueous methylcellulose for five days/wk, 6 hr/day, for a 21-day period (i.e. 15 treatment applications). Daily doses were 0, 60, 100, 250, or 600 mg/kg/day of technical chlorothalonil, 98.1% purity, covered by a porous gauze patch. Assessed in-life parameters included body weight and food consumption effects, and clinical observations. At termination, clinical chemistry parameters were assayed, followed by histopathology on kidney, forestomach, and skin lesions. "Application site NOEL" < 60 mg/kg/day: all dose levels showed erythema of treated skin, confirmed by yellow discoloration and desquamation at necropsy, and histological findings of hyperkeratosis, and squamous epithelial hyperplasia and vacuolation. NOEL (exclusive of application site) = 60 mg/kg/day (clinical observations of "rough coat"). Other noted findings were transient body weight and food consumption decrements, small decreases in ALT, and increased kidney weights at 250 mg/kg/day and above (relative to brain weight). There was no associated kidney histopathology. This is an acceptable ancillary study with no adverse effects indicated. Aldous, 11/6/96 (re-evaluated by Aldous on 2/3/98 in consideration of rebuttal comments in Record No. 157407).
275-287 148283 Protocol for Record No. 150595, above, plus U.S. EPA comments on protocol. No DPR worksheet.

275-256 143356 "Histopathologic Evaluation of Kidneys in Male Fischer 344 Rats Following the Oral Administration of Technical Chlorothalonil", (Authors: Gelin, Mark D., and James C. Killeen, Jr.; Ricerca, Inc., Painesville, OH; Lab Report No. 3618-91-0153-TX-002; 12/5/91); Chlorothalonil Technical (Lot No. SDS-2787-0901; purity = 97.2%), dosed as suspensions in 0.5% aqueous methyl cellulose; 0 (vehicle), 40, 80, 175 mg/kg/day for two days; 6 males/group; terminated 16 h after the last dose; Histopathology (kidneys) - epithelial vacuolation (minimal to moderately severe), incidence and severity were dose-related in all treatment groups; epithelial degeneration in proximal convoluted tubules (minimal to moderate) in high-dose group only; Supplemental. (Duncan, 1/29/96)

275-194 133338 Ford, W. H. and Killeen, J.C. Jr., "A 90-day study in rats with the monoglutathione conjugate of chlorothalonil", IRDC (in-life phase), 3/3/87. IRDC Project ID# 293-143. Approximately equimolar amounts of technical chlorothalonil (75 mg/kg/day, purity 97.9), or the monoglutathione conjugate [S-(2,4-dicyano-3,5,6-trichlorophenyl)-glutathione] (150 mg/kg/day, 92.5% purity), or control vehicle (0.5% methylcellulose) were administered by gavage daily for 90 days to 15 male F-344 rats/group. The primary purpose was to investigate whether kidney toxicity was associated with the monoglutathione conjugate. Systematic histopathology evaluations were limited to kidney and stomach, known target organs for chlorothalonil. Both test articles caused substantial kidney lesions. Standard H&E staining revealed epithelial hyperplasia and tubular hypertrophy in the majority of rats in both treated groups, with karyomegaly in some chlorothalonil rats. Specialized staining was performed on additional kidney tissue samples by C.E.R.T.I. Laboratoire d'histopathologie, Versailles, France. C.E.R.T.I. evaluation showed vacuolar degeneration, tubular ectasis, tubular casts, interstitial fibrosis, and foci of basophilic tubules in both treatment groups, with the chlorothalonil group generally more affected. Only chlorothalonil caused lesions of the epithelium of the nonglandular stomach: hyperplasia, hyperkeratosis, erosions, and ulcers. Both test articles underwent further metabolism. A common trithiol metabolite was 3 to 5-fold more

abundant in urine of the chlorothalonil group, suggesting that the monoglutathione conjugate was less available than chlorothalonil for further metabolism. Results indicated that glutathione conjugation was involved in kidney toxicity associated with chlorothalonil. "Acceptable ancillary study". No "adverse effects" indicated, except to characterize previously recognized effects. Aldous, 6/20/95.

275-138 054950 The same report as Record No. 133338, above. It had been submitted by 1987 and had received a brief review by B. Davis on 12/11/87.

SUBCHRONIC: MOUSE (SUPPLEMENTAL)

132, 108 050898-9, 034375 "A 90-Day Feeding Study in Mice with Technical Chlorothalonil" (Concord Woods Animal Facility, SDS Biotech Corporation, 9/2/83, Study No. 5TX-83-007). Technical Chlorothalonil (98.4% purity) fed to 15 mice/sex/group at 0, 7.5, 15, 50, 275, and 750 ppm for 13 weeks with an interim sacrifice of 5 mice/sex/group at 6 weeks. Possible adverse effects: increased alkaline phosphatase levels, elevated kidney weights, slight hyperplasia of renal epithelium, hyperplasia and hyperkeratosis of the gastric epithelium. NOEL = 15 ppm (2.5-3.0 mg/kg/day) for 13 weeks. Supplementary study. 050899 and 034375 are supplementary histopathology evaluations. Davis, 5/26/87. EPA ONE-LINER: NOEL = 15 ppm. LEL = 50 ppm - hyperplasia and hyperkeratosis of gastric mucosa. CORE GRADE Minimum

SUBCHRONIC: RABBIT (SUPPLEMENTAL)

138, 139 054951, 054952 "21-Day Repeated Dose Dermal Toxicity Study in Albino Rabbits With Technical Chlorothalonil", Sponsor Reference No. 5TX-85- 0023. (SDS Biotech Corporation, WIL Research Laboratories, Inc., Experimental Pathology Labs 4/11/86) Dermal application of chlorothalonil to 6 New Zealand White rabbits/sex/group at 0, 0.1, 2.5, or 50.0 mg/kg/day (dose volume of 1.0 ml/kg) for 21 days. No toxicity except dermal irritation accompanied by minimal to slight histopathologic changes. Urinalysis of 2 high dose animals showed no sulfur-containing metabolites. NOEL = 0.1 mg/kg/day. No adverse effect; Supplementary study. Davis 12/15/87.

CHRONIC TOXICITY, DOG

OVERALL “ADVERSE EFFECTS” EVALUATION: There are several dog studies ranging from 3 months to two years in duration. The 1995 Huntingdon Life Sciences study (Record # 153914) was the only study considered to have elicited a “possible adverse effect”. This was based on an atypical response in one high dose female (mean dose for this group was about 354 mg/kg/day) and on stomach pathology at that dose level. The latter study involved dietary administration. An acceptable chronic study, completed in 1994 by Pharmaco LSR, used gelatin capsule administration of test article shortly after feeding half of the daily ration. The balance of the daily ration was presented about 30 minutes after dosing. Although the high dose level in the latter study was 500 mg/kg/day, there was no remarkable stomach pathology, nor were there treatment-related deaths nor serious pathology. There were no adverse effects noted in the acceptable 90-day subchronic study (also capsule administration) which preceded the LSR chronic study. None of the other dog studies on file indicated adverse effects. Evidently the split-feeding capsule dosing methodology reduced the extent of stomach irritation to an insignificant extent. It is noteworthy that both the 1994 Pharmaco LSR study and the 1966 Hazleton 2-year dietary study involved higher dosage ranges than the 1995 Huntingdon study. Collectively, the data do not indicate chronic adverse effects in dogs. Aldous, 4/21/97.

**275-215 134264 Mizens, M. and Laveglia, J., "A chronic (12-month) oral toxicity study in dogs with technical chlorothalonil", Pharmaco LSR Inc., 12/19/94. Pharmaco LSR Study No. 92-3125. Chlorothalonil, purity 98.3%, was

administered in gelatin capsules to 5 beagles/sex/group at 0, 15, 150 or 500 mg/kg/day for 12 months. No NOEL was found: plasma ALT levels were markedly reduced at all dose levels tested. There were no evident functional deficits nor liver microscopic lesions accompanying this change. The NOEL for other findings is 15 mg/kg/day, based on elevated relative liver weights and an enhancement over the normal extent of pigmentation of kidney tubular epithelial cells. At 500 mg/kg/day, body weights were slightly suppressed, and slightly elevated plasma cholesterol and slightly reduced circulating albumin suggested minor functional change in liver. Ophthalmology was negative. Study is acceptable, with no adverse effects. (Kishiyama and Aldous, 5/17/95).

**275-227 138982 Fillmore, G. E. and Laveglia, J., "A 90-day oral dosing study in dogs with chlorothalonil". Bio/dynamics (Study No. 92-3820), April 6, 1993. Four beagles/sex/group were dosed with 0, 15, 150, or 500 mg/kg/day chlorothalonil by gelatin capsule for 3 months. [The high dose was initiated at 750 mg/kg/day, but dose was reduced to 500 mg/kg/day on day 5 due to a death of a 750 mg/kg/day male on day 3. The death was attributed to test article, since there was associated emesis in all 750 mg/kg/day dogs, and no apparent food consumption in this particular dog on day 2. Necropsy of this dog was consistent with death due to aspiration of vomitus, which led to severe pulmonary edema, hemorrhage, necrotizing bronchitis, and diffuse pneumonia.] The adjusted (500 mg/kg/day) high dose was much better tolerated. Emesis was slightly elevated at that dose. This valid study does not indicate a "possible adverse effect". There is no absolute NOEL for this study, due to marked reductions of SGPT activity at all dose levels. Excluding this finding, the NOEL is 15 mg/kg/day, based on decreased body weight gain (males) and serum chemistry changes of decreased albumin levels (males), and increased cholesterol levels (females). These serum chemistry changes were observed in both sexes at 500 mg/kg/day, consistent with modest increases in relative liver weights. There were no direct treatment-related histopathological responses. Data support dose levels chosen for the chronic study of 0, 15, 150, and 500 mg/kg/day (see Record No. 134264). Aldous, 7/26/95.

275-177 118621 Interim report reviewed by Aldous, 9/19/94. Subsequently superseded by Record No. 138982, above).

275-177 118620 Commentary by G. Fillmore on 177:118621, above (no unique data, no DPR worksheet). Aldous, 9/19/94.

275-177 118622 "A 30-day oral toxicity study in dogs with T-117-12" (Final Report). Fillmore, G. E. and Laveglia, J., Bio/dynamics Study No. 91-3762. This study employed dose levels of 0, 50, 150, or 500 to 2/beagles/sex for 30 days. Findings were comparable to study 177:118621. In addition, histopathology was completed in this study, and was negative. No adverse effects indicated. No DPR worksheet. Aldous, 9/19/94.

****275-306 153914** Spencer-Briggs, D. J., "Chlorothalonil: Toxicity to dogs by repeated dietary administration for 52 weeks", Huntingdon Life Sciences, Ltd., HRC Project No. VCM/14, 12/21/95. Four beagles/sex/group were dosed in diet with 0, 160, 1280, or 10240 ppm chlorothalonil (99.28% purity) for 1 year. NOAEL = 160 ppm (stomach pathology; including prominent apoptotic bodies in the antrum, erosion of luminal surface epithelium, cellular hypertrophy with increased mucosal thickness, congestion of submucosal vessels, inflammatory cell infiltration in gastric mucosa, mucus and cell debris adherent to the luminal surface, and foci of mucosal mineralization). One high dose female was sacrificed moribund after displaying marked and sustained signs of anemia, reduced food consumption, and serious cardiac pathology. None of these signs were characteristic responses of other dogs at any dose level in the study. The above stomach pathology, and the anemia and heart pathology characterizing the atypical response of one dog, constitute a **"possible adverse effect"**. No NOEL was demonstrated for the adaptive response of elevated non-protein thiol concentration in kidneys of females. Findings of limited toxicological importance and/or apparent adaptive responses included body weight decrements, clinical chemistry changes, liver

weight increases, pigmentation of kidney cortical tubule epithelium, adrenal cortical hypertrophy in high dose males only, and vasodilation evident in gums and/or ears in high dose dogs (judged to be a local irritant response). Study was classified as unacceptable in the 1997, requesting stability data on treated diet. Data were provided in Record No. 157567, below. This chronic study is re-classified as acceptable. Aldous, 4/18/97 (upgraded 2/5/98).

**275-315 157567 Spencer-Briggs, D. J., K. W. Ashman, D. P. Buist, D. Crook, A. Anderson, I. S. Dawe, R. M. Read, C. Gopinath, L. F. Chasseaud, and M. Hall, [Study submitted to upgrade chronic dog study (DPR Record No. 153914)]. "Chlorothalonil toxicity to dogs by dietary administration for 13 weeks", Huntingdon Research Centre, 11/4/94, Laboratory Study # VCM 12/920413. Chlorothalonil (99.18%) was administered in diet to 4 beagles/sex/group at 0, 160, 1600, or 16000 ppm for 13 weeks. In addition to usual subchronic study measurements, this study measured urinary non-protein thiol and thioether concentrations, and non-protein thiol concentrations in liver and kidneys. There is no NOEL for reduced ALT levels. This finding has been reported in several other studies, and does not correspond to liver histopathology, even at the highest dose level. NOEL (other than for ALT) = 160 ppm (5.6 mg/kg/day). The most definitive treatment response at 1600 ppm is hypertrophy of the zona fasciculata of the adrenals in males (seen in both sexes at 16000 ppm). There was an apparent reduction in concentration of non-protein thiols in urine of males and females at 1600 to 16000 ppm, however data are equivocal. Additional findings at 16000 ppm included modest body weight and food consumption decrements, an apparent increase in non-protein thiol concentration in liver and kidney tissue, decreased serum albumin, increased serum cholesterol, an equivocal increase in urinary protein in females, increased adrenal weight in males, and an increased width of the zona glomerulosa in females. Study is acceptable, with no adverse effects. The data on formulated diet stability suffice to upgrade the chronic dog study performed at the same laboratory (Record No. 153914). Aldous, 2/5/98.

132 050901 "Two-Year Dietary Administration - Dogs. Final Report." (Hazleton Laboratories, Inc., Project No. 200-149, 11/7/66). Chlorothalonil (93.6% purity) plus a mixture of three related compounds, fed to 4 dogs/sex/group at 0, 0.15, 1.5, or 3.0 % by weight in the diet for 104 weeks. An interim kill of one dog/sex/group at one year with the remainder sacrificed to terminate the study at two years. Original CDFA review (6/2/87) considered this study to represent a "possible adverse effect", apparently based on reductions in body weight gain and upon elevated kidney and thyroid weights at all dosages. The study was re-examined on 10/4/89, and CDFA determined that (1) the data do not indicate a "possible adverse effect", (2) a provisional NOEL could be established by considering the major chronic dog studies together, and (3) a major non-reconcilable deficiency (considering the overall chronic study data base) was lack of acceptable ophthalmology. Organs which appeared to indicate treatment effects at 1.5% to 3% level in this study were kidney (primarily tubular degeneration observed: hypertrophy, dilatation; also epithelial vacuolation, pigmentation, and regenerative growth), liver (pigmentation of hepatocytes and macrophages, and an increase over the normal range of hepatocellular irregularities), thyroid (pigmentation), and stomach (gastritis). Re-examination of the data available on 10/11/91 (below) suggests that an upgrade is not possible. Incomplete. Unacceptable. A replacement dog study is required. Deficiencies originally noted by B. Davis included: no NOEL established; inadequate information on test material, test animals, and randomization; no feed analysis; insufficient serum chemistry; complete lack of ophthalmology or of microscopic examinations of eyes; inadequate tissue examination protocol for histopathology; missing data; and lack of data analysis. Davis, 6/2/87, Aldous, 10/4/89 and 10/11/91. EPA ONE-LINER: Systemic NOEL < 0.15% (LDT). Kidney and liver pigmentation. CORE GRADE = Not stated

275-172 096393, 096394, and 096395 Three records of human medical surveillance data and limited chlorothalonil exposure data, detailed separately, below. Data relate to the non-rodent chronic study data gap requirement. The most rigorous of existing animal chronic studies is the dog study, 275-132:050901. New data are sponsored by ISK Biotech Corp. (formerly Fermenta ASC Corporation). The major data for possible persistent effects on workers' eyes

are in Record 096393. These data indicate that there were no treatment-related chronic effects on eyes of workers at a major chlorothalonil production facility (Greens Bayou Plant in Texas). None of the records provides adequate assessment of worker exposure to facilitate risk assessment. Data are not acceptable: not upgradeable. A repeat dog study will therefore be needed. A memorandum from M. O'Malley (Worker Health and Safety Branch of this Department) is appended to this review. Aldous, 10/11/91.

155 066795 Letter from N. H. Wilson to Fermenta Plant Protection Company addressing the issue of lack of ophthalmology in the 1966 dog study. Supplement to 050901. Gee, 1/24/89. (Discussed by CDFA in 1/30/89 rebuttal response).

039 941872 "104-Week Dietary Administration-Dogs. Daconil 2787 (Technical). Final Report." (Hazleton Laboratories, Inc., Project No. 200-206, 5/6/70) (831) Chlorothalonil (purity not stated) at 0, 60 or 120 ppm in the diet for 2 years to 8 dogs/group/sex with a 1 year interim sacrifice of half of the dogs. No adverse effects reported. Incomplete. Unacceptable: cannot be upgraded. Dose levels too few and too low; histopathology limited (only 3 organs examined); test material and treated feed not characterized; limited data analysis. Christopher 3/14/85, Davis 6/15/87. (This study was considered in Aldous review of 10/4/89).

115 035817 (K. L. Stemmer, University of Cincinnati, 6/19/70) Letter and report evaluating chronic dog study (039:941872). Dr. Stemmer disagrees with the report conclusion that there were kidney tissue anomalies in high dose males. The CDFA reviewer did not analyze this submission since the study in question is unacceptable and cannot be upgraded. Apostolou, 12/6/85.

039 941898 "Statement and Evaluation of Kidney Histopathology of Daconil 2787 in Rats and Dogs by Dr. Klaus Stemmer, University of Cincinnati" (6/19/70). Reference to chronic dog study (039:941872). Stemmer concludes there is no nephrotoxicity in either study; presents experimental evidence for artifactual basis of anomalies in the rat study. Analysis of other rat studies shows histological kidney alterations at higher doses. NOEL < 500 ppm. In summary, it is not nephrotoxicity in rats at issue, but rather the dose level. CDFA agreed that there is no nephrotoxicity in the referenced dog study, but concluded positive evidence in the rat study. Davis 12/2/86. EPA ONE-LINER: Systemic NOEL = 60 ppm. Systemic LEL = 120 ppm (histopathological changes in kidneys). Levels tested = 0, 60 or 120 ppm. CORE GRADE = Not stated.

133 050902 "16-Week Dietary Feeding - Dogs. Final Report." (Hazleton Laboratories, Inc., Project No. 200-200, 12/4/67). Chlorothalonil (purity unknown) fed to 4 dogs/sex/group at 0, 250, 500, or 750 ppm for 16 weeks. No adverse effect reported; NOEL > 750 ppm. Incomplete, unacceptable: Not an SB-950 study; Additional deficiencies include failure to establish a NOEL; lack of information on test material, test animals, and randomization; no feed analysis; insufficient serum chemistry, ophthalmology, and histopathology; and lack of data analysis. Davis, 6/3/87. EPA ONE-LINER: Systemic NOEL < 250 ppm (LDT). Increased PBI. CORE GRADE = Not stated

ONCOGENICITY, RAT

The data gap is filled by the IRDC study (volumes 100-104, record numbers 34366, 34367, 34348-34352, 34372). The finding of renal tubular adenomas and carcinomas in this study was confirmed by an unacceptable oncogenicity study done by Gulf South Research Institute. In addition, an ancillary study (Vol. 164) involving Fischer 344 rats confirmed the presence of kidney and forestomach tumors in males and females, and determined NOEL's for lesions in both organs. Kidney lesions in rats, including renal tubular tumors, are consistent with the results of mouse studies (see ONCOGENICITY: MOUSE below), although oncogenicity in mice was restricted to males and did not appear to be dose related. See also the documentation for the 8/27/87 meeting with Fermenta Plant Protection Company (summary dated 9/9/87 and CDFA comments dated 1/11/88). Davis, 1/88, amended by Aldous, 10/4/89.

See also comment under heading “CHRONIC, RAT” on page 2, and a section below entitled “ONCOGENICITY, RAT, INTERPRETIVE INFORMATION” (Aldous, 8/21/97).

****100-104, 131 034366, 034367, 034348-034352, 034372, 050897** Wilson, N.H., J.C. Killeen, and J. A. Ignatoski, "A Tumorigenicity Study of Technical Chlorothalonil in Rats" (SDS Biotech Document No. 099-5TX-80-0234-008; (IRDC, 5/28/85). Chlorothalonil (purity 98.1%) given in the diet to achieve 0, 40, 80 or 175 mg/kg/day to 60 F-344 rats/group/sex for 27 months (males) or 30 months (females). Possible adverse effect indicated based principally on renal tubular adenomas and carcinomas, forestomach papillomas and squamous carcinomas, and a dose-related exacerbation of chronic progressive nephropathy. Complete; acceptable. 050897 is a histopathologic reevaluation. Apostolou 9/20/85; Davis 5/27/87. The data were re-examined by Aldous on 9/28/94 (see next paragraph).

275-100 to -104 034366 to 034367, 034348 to 034352, and 034372 and supplementary information in 275-131 050897. Primary report (beginning with Record No. 034366) was Wilson, N.H. et al., "A tumorigenicity study of technical chlorothalonil in rats", SDS Biotech Corp., Painesville, OH, 5/28/85. Report as previously amended was already accepted. The original CDFA review, performed in 1985, was designed as a data survey rather than as a detailed analysis. This study is a pivotal one because it identifies tumor responses in the kidney and non-glandular stomach, so that an analysis of the principal oncogenic and other chronic findings is needed to support risk assessment. This review presents the primary findings of the 1985 study, then evaluates the data along with that of the subsequent study in a lower dose range (the 1989 Ricerca study; Record No. 074770). The combined data indicate "possible adverse effect", based on tumors of renal tubular epithelium and of the non-glandular stomach mucosa, as well on the relatively low NOEL for chronic progressive nephropathy (based on Record No. 074770), which is 4 mg/kg/day in males and 2 mg/kg/day in females. The highest dose level used in each of the two studies (about 175 mg/kg/day) exceeded body weight and survival criteria for the MTD, however the major findings extended to lower dose levels. Aldous, 9/28/94.

164 074770 Wilson, N.H., and J.C. Killeen, "A tumorigenicity study of technical chlorothalonil in rats". Ricerca, Inc. (study was subcontracted to other facilities), June 7, 1989. Dietary admixture of 0, 1.8, 3.8, 15.2, or 183 mg/kg/day chlorothalonil (mean values based on extractability of technical. from assayed diet) to Fischer 344 rats, 65 sex/group (of which 10/sex/group were designated for 1-yr interim sacrifice). Duration of principal phase was 99 wk (183 mg/kg/day males), 111 (all other males), or 125 (all females): termination times based on survival. The pathologist examining kidney slides was "blinded" as to treatment (p. 18). The expected "possible adverse effects" were observed (with 53 to 55/sex/group "at risk" in all cases): incidence of renal tubular adenomas/carcinomas for controls through increasing dosages in M = 1, 1, 1, 4, 23; in F = 0, 0, 0, 0, and 32. Tubular-epithelial hyperplasia in kidneys was elevated in incidence and degree at 3.8 mg/kg/day and above. This hyperplasia was confirmed present in every animal bearing tubular cell tumors, except for 4 cases in which autolysis and/or chronic nephropathy prevented a definitive diagnosis. The association was considered to be strong evidence that the hyperplasia is a preneoplastic lesion. Incidence of forestomach papillomas/carcinomas for controls through increasing dosages was 0, 0, 3, 2, 5 for males and 1, 1, 2, 5, and 9 for females. These tumors were associated with hyperplasia, hyperkeratosis, or erosions or ulcers in the forestomach. NOEL = 2 mg/kg/day in both sexes, based on hyperplasia and hyperkeratosis of non-glandular stomach, and on modest increases in kidney tubular-epithelial hyperplasia (the latter most evident at 1-yr interim sacrifice). Ophthalmology examinations were performed late in the study, and were negative. These observations contribute significantly to the chronic rodent study data requirements. The co-existence of non-neoplastic lesions with tumors in respective tissues is consistent with the possibility that non- neoplastic lesions were part of a progression toward tumors: however the possibility of independent mechanisms cannot be excluded. C. Aldous, 10/4/89; minor editing changes without new worksheet by Aldous on 9/18/95.

275-264 143378 (exact duplicate of 275-164:074770, except that this copy lacks original prints of micrographs).

****275-307 153915** Spencer-Briggs, D. J., "Chlorothalonil: Potential tumorigenic effects in prolonged dietary administration to rats", Huntingdon Life Sciences, Ltd., 1/17/96, Laboratory Study # VCM 15. Fifty Crl:CD®(SD)BR rats/group were dosed with 0, 15, 60, 240, or 1200 ppm chlorothalonil in diet for 2 yr in the oncogenicity study. An additional 20/sex/group were dosed for 1 yr before interim kill. No NOEL was identified in this study. Epithelial hyperplasia and hyperkeratosis of the non-glandular forestomach were dose-related in both sexes over all dose levels. NOAEL = 60 ppm ["**possible adverse effect**" = squamous cell tumors (papilloma or carcinoma) in two 240 ppm females, one 1200 ppm female, and three 1200 ppm males]. Additional common findings in forestomach at 60 ppm and above included ulceration and submucosal fibrosis and inflammatory cell infiltration. Forestomach surface was often grossly "thickened", "roughened", and/or "white". The above tumors were likely to have resulted from chronic irritation of the non-glandular surface of the forestomach. Kidney weights were elevated in 240 ppm males and in high dose males and females. The only characteristic kidney microscopic lesion was chronic progressive glomeruloneprosis at elevated incidence or degree in high dose rats. Urinary protein was commonly elevated in high dose rats, possibly reflecting kidney disfunction. Centrilobular hepatocyte hypertrophy was elevated in high dose rats. This is an **acceptable** oncogenicity study. Aldous, 4/18/97.

087 941883 "Bioassay of Chlorothalonil For Possible Carcinogenicity" (Gulf South Research Institute for the National Cancer Institute Carcinogenesis Testing Program, 1978) Chlorothalonil (98.50% and 98% purity for the two samples used) at 5,063 or 10,126 ppm in the diet (time-weighted averages) to 50 Osborne-Mendel rats/sex/group; 10 matched negative control rats/sex; Doses initially 20,000 & 10,000 first week of dosing, then lowered to 10,000 & 5,000 for remaining 79 weeks; Dosed for 80 weeks, observed for 110 weeks; Possible adverse effect; Oncogenicity NOEL < 5063 ppm (Neoplasms of renal tubular epithelium). Chronic toxicity NOEL < 5063 ppm (Weight loss, rough and discolored hair coats, bright-yellow urine, pale mucous membranes, ataxia, tachypnea, epistaxis, dermatitis, hematuria, hyperactivity, and vaginal bleeding). Incomplete. Unacceptable. Only two doses, doses lowered during the study, test material changed during dosing, dosing only 80 weeks, missing individual data, too few control animals. See also the important criticisms raised in 069 031892. Christopher, 3/14/85 and Davis, 12/4/86.

069 031892 Diamond Shamrock 2/14/80 "A Position Statement: The Carcinogenicity Assessment of Chlorothalonil (Daconil)" Doc. No. 280-5TX-79- 0133-001; Supplemental information to 087 941883; Critical review of rat oncogenicity study points out deficiencies in dose selection, reporting, analysis, and conclusion. Does not change CDFA conclusion of a possible adverse effect (renal oncogenicity) or the view that the study is unacceptable. Davis, 12/5/86.

069 031893 Diamond Shamrock 5/4/81 "Concerns About The Reporting of Data From The 'Bioassay of Chlorothalonil For Possible Carcinogenicity' In Rats"; Document No. 280-5TX-81-0123-001; Supplemental information to 087 941883; Critical review of rat oncogenicity study points out problems with grouping renal neoplasms, with spontaneous neoplasm frequencies, and with the study pathologists' views. Does not change CDFA conclusion of a possible adverse effect (renal oncogenicity) or the view that the study is unacceptable. Davis, 12/5/86.

069 028412 Kentron, Inc., Arlington, VA 5/12/82; "Environmental risk assessment of the use of chlorothalonil. Phase II: Hazard analysis." KTR 221-81. Supplemental information to 087 941883; Review of rat oncogenicity study criticizes negative controls, spontaneous frequency of renal neoplasms in this rat strain, unreported high frequency of nephritis, and choice of doses. Does not change CDFA conclusion of a possible adverse effect (renal oncogenicity) or the view that the study is unacceptable. Davis, 12/8/86. EPA ONE-LINER: Neoplasms of the renal tubular epithelium in both males and females. CORE GRADE = Not stated

137 054947 "Report of the Status of A Tumorigenicity Study of Technical Chlorothalonil in Rats" (In-Life Phase: IRDC; Histopathology: Experimental Pathology Labs; Supervision: Ricerca, Inc., Sponsor no. 84-0103, 2/12/87) 56 week report for a supplementary study; no significant effects. Davis 12/9/87.

069 28409, 28410 "Summary of Data Report and Evaluation, Section 4" (IARC Expert Committee 7/21/82) Possible adverse effect-Third draft of IARC report states that chlorothalonil produced adenomas and adenocarcinomas in rat kidneys but no oncogenicity in mice. (No worksheet done. Davis 1/7/88)

ONCOGENICITY, RAT, INTERPRETIVE INFORMATION

275-311 154982 Wilkinson, C. F., and J. C. Killeen, "A mechanistic interpretation of the oncogenicity of chlorothalonil in rodents and an assessment of human relevance", *Regul. Pharmacol. Toxicol.* **24**, 69-84 (1996). The article addresses relevance to humans of forestomach and renal tumors seen in chlorothalonil-treated rodents. It is primarily a review of studies performed by the registrants, many of which are reported in Document Nos. 275-165 and 275-191 to -197. Rodent forestomach tumors were considered of limited relevance because humans lack forestomachs, and the squamous epithelium of the esophagus in humans is not exposed to dietary toxins for extended periods as is the rodent forestomach. Authors gave several reasons why rodent renal tumors are of limited relevance. Some haloalkenes had previously been shown to be metabolized by GSH conjugation, followed by a series of hydrolytic cleavages of the GSH moieties, eventually producing toxic thiols through the action of β-lyase. Chlorothalonil also produces GSH addition and cleavage products, which can undergo β-lyase activation to toxic thiols. Studies have shown that di- and tri-thiols of chlorothalonil interfere with electron transfer from succinate to coenzyme Q in rat kidney cortical mitochondrial preparations. There was no such interference with mono- and di-GSH analogs of chlorothalonil. This disturbance in energy metabolism would be expected to lead to intracellular ion transport failure, decline in ATP levels, and altered cellular membrane permeability. Ultimately, tubular epithelial cells die, followed by compensatory proliferation, hyperplasia, and neoplasia. Rats have much higher renal activities of γ-GT and of β-lyase than do humans. Also, rats excrete much higher levels of chlorothalonil-derived thiols in urine than do other species such as dogs or monkeys. Thus it appears that humans are far less susceptible than rats to renal toxicity which is predisposing to tumor development. Other studies show that chlorothalonil residues bind primarily to proteins, but not DNA. This, coupled with the negative mutagenicity studies, suggests that chlorothalonil oncogenicity is a threshold effect. Thus data support the mediation of thiol formation in renal tumor development, but do not prove this association, because it is not proven that the renal tumors result directly and exclusively from action of di- and trithiol metabolites. A more convincing case for the "toxic thiol" hypothesis would entail a long-term study in rats with limited or absent capacity to produce di- and tri-thiols. As indicated in this article, such capacity limitations could be achieved by sustained use of inhibitors of γ-GT or of β-lyase, or alternatively by using rats genetically deficient in one of these enzymes. Aldous, 8/21/97.

275-251 143345 Wilkinson, C. F, "A mechanistic interpretation of the induction of rodent forestomach and renal tumors by chlorothalonil" (April, 1995). Rats and mice have demonstrated forestomach tumors, as well as renal proximal tubular tumors, in response to chlorothalonil. Chlorothalonil and its major metabolites are considered non-genotoxic, suggesting that the above tumors should have thresholds. Both forestomach and renal tumors are preceded by cytotoxicity and compensatory cell proliferation and hyperplasia, suggesting that tumors may arise from "fixation" of spontaneous mutagenic events, which would not otherwise become manifest. The two tumor types in rodents do not apply to humans because (1) humans lack a forestomach, and (2) the metabolic events leading to rodent renal tumors occur only at very low levels in humans. Thus, it is proposed that chlorothalonil be assigned "carcinogenicity" classification of "Group D" or, at worst, "Group C". Various international expert committees have

reviewed chlorothalonil oncogenicity data, and have concluded that it is not genotoxic, and should be regulated on a NOEL - Safety Factor approach. (No SB-950 review is relevant, since this is not a "study". Aldous, 1/11/96).

ONCOGENICITY, MOUSE

The data gap is filled by the Bio/dynamics Inc. study (volumes 077-082, record numbers 941877-941882). The findings of renal tubular adenomas and carcinomas and forestomach neoplasms in this study are consistent with the findings of rat studies (see ONCOGENICITY: RAT above). See also the documentation for the 8/27/87 meeting with Fermenta Plant Protection Company (summary dated 9/9/87 and CDFA comments dated 1/11/88). Davis, 1/88.

**275-077 to -082 941877-941882 Wilson, N.H., J.C. Killeen, and J.A. Ignatoski, "A Chronic Dietary Study in Mice with Technical Chlorothalonil", Bio/dynamics Inc. Study No. 5TX-79-0102, 2/24/83. Chlorothalonil (purity at least 97.7%) was administered at 0, 750, 1500 or 3000 ppm in diet to 60 Charles River CD-1 mice/sex/group for 24 months. Two tumor types were associated with treatment: kidney tubular adenomas and/or carcinomas in males only (incidence of 0, 6, 4, and 4 in controls through increasing dosage groups), and squamous cell papillomas and/or carcinomas in forestomachs of males and females (incidence of 0, 2, 5, and 2 in males, and 0, 2, 6, and 5 in females for respective controls through increasing dosage groups). These are "possible adverse effects". Both tumor types had associated lesions which may have been preneoplastic. All treated groups had a characteristic renal tubular hyperplasia, which was much more common and of higher severity in males, and which was absent in controls of either sex (see Record No. 050900). The majority of treated mice of either sex had hyperkeratosis and/or hyperplasia of the forestomach squamous mucosa, and the squamous cell tumors often arose from within these lesions. Dose-related incidences of esophageal hyperkeratosis were seen in both sexes at all dose levels. There were other treatment-related lesions of lesser importance in kidneys or nonglandular stomach, mainly at higher dose levels. Acceptable. Other relevant records are 050900 (kidney tissue reevaluation), 054948 (stomach tissue reevaluation), and 059034 and 058175 (ancillary low dose range study in males to establish NOEL's). Christopher, 3/15/85; Davis, 12/10/87; and Aldous, 9/27/95. EPA ONE-LINER: Oncogenic NOEL < 750 ppm (LDT) (renal neoplasms in males and evidence of hyperplasia and/or tumorigenesis in the squamous cell and epithelial layer of the esophagus and stomach in both sexes). Systemic NOEL < 750 ppm (LDT) (decreased ovary weight, hyperplastic bone marrow, hyperplasia of splenic red pulp in males, increased kidney weight with surface irregularities, pelvic dilation, cysts, nodules, masses, tubular degeneration). Levels tested by diet in CD-1 strain 0, 750, 1500, and 3000 ppm. CORE GRADE = Supplementary for chronic effects; no NOEL demonstrated. Guideline for oncogenic effects.

275-132 050900 Wilson, N.H., J.C. Killeen, and J.A. Ignatoski, "Histopathologic reevaluation of renal tissue from a mouse tumorigenicity study with chlorothalonil (5TX-79-0102)", March 7, 1986. Kidney slides from the 2/24/83 Bio/dynamics study (Record Nos. 941877-941822) were examined by a recognized specialist in renal pathology, William M. Busey. This report was examined by B. K. Davis in 1987, and was also incorporated into the 1995 review of the primary study (see above).

275-137 054948 Wilson, N.H. and J.C. Killeen, "Histopathologic reevaluation of stomach tissue from a mouse tumorigenicity study with technical chlorothalonil (5TX-79-0102)", 10/20/86. Stomach slides from the 2/24/83 Bio/dynamics study (Record Nos. 941877-941822) were re-examined by the primary study pathologist, W. Ray Brown. This report was examined by B.K. Davis in 1987, and was also incorporated into the 1995 review of the primary study (see above).

070 941871 Brief (6-page) version of Record No. 941877, above.

275-145 and -146 059034 and 058175 Wilson, N.H. and J.C. Killeen, "A Chronic Dietary Study in Mice with Technical Chlorothalonil". (In-Life Phase: IRDC. Histopathology: Experimental Pathology Labs. Supervision: Ricerca, Inc., Sponsor no. 84-0077, 6/12/87). Study was performed to establish NOEL's for Record No. 941877. Only males were used, since they were the more sensitive sex for kidney lesions, and as sensitive as females for forestomach effects. Chlorothalonil (98%) was fed to 60 CD-1 males/group at 0, 10/15, 40, 175, and 750 ppm (equivalent to 0, 1.57, 4.50, 21.3, and 97.8 mg/kg/day after correction for extractability from diet). Ten per group were sacrificed at the end of the first year, the rest maintained for 2 yr. The low dose was increased from 10 ppm to 15 ppm at week 18 to ensure mean exposure of at least 1.5 mg/kg/day. Possible adverse effect: very low NOEL for hyperplasia and hyperkeratosis of the squamous mucosa of the forestomach (15 ppm), and possibly treatment-related squamous cell tumors of the forestomach (2, 0, 0, 1, and 4 affected in controls through increasing dosage groups, respectively). A conservative NOEL for renal tubular changes was 40 ppm, based on slight increase in tubular hyperplasia and karyomegaly at 175 ppm. Acceptable supplementary study. Davis 10/6/87, 12/9/87: Aldous, 9/27/95.

275-137 054946 Interim report for Record No. 059034, above.

****275-308 153916** Spencer-Briggs, D. J., "Chlorothalonil: Potential tumorigenic effects in prolonged dietary administration to mice", Huntingdon Life Sciences, Ltd., 12/20/95, Laboratory Study # VCM 16. Fifty Crl:CD-1® (ICR) BR mice/sex/group were dosed in diet with 0, 15, 60, 240, or 960 ppm chlorothalonil (99.28% purity) for 80 weeks. Report is **acceptable**. There is no NOEL for this study (epithelial hyperplasias, both in the forestomach and at the limiting ridge, were dose-related in incidence and degree at all dose levels in males). Findings noted at 15 ppm appear to be reversible, so that 15 ppm can be considered as a chronic NOAEL, based largely upon cystic glomerular atrophy in kidneys of males. Appearance of squamous cell papillomas in the non-glandular stomach is a "**possible adverse effect**". These benign tumors appear to result from chronic insult to the surface of the forestomach, causing non-neoplastic forestomach lesions at dose levels much lower than those eliciting tumors. Aldous, 4/18/97.

087 038930 "Bioassay of Chlorothalonil For Possible Carcinogenicity" Gulf South Research Institute (for the National Cancer Institute Carcinogenesis Testing Programs, 1978). Chlorothalonil (98% purity) at 2688 or 5375 ppm (time-weighted average dose) to male B6C3F1 hybrid mice (50 group); and at 3000 or 6000 ppm (time-weighted average dose) to female B6C3F1 hybrid mice (50/group); dosed 80 weeks, then observed for 11-12 weeks; no adverse effects indicated. Incomplete. Unacceptable; Only two doses, doses lowered during the study, missing individual data, too few control animals, high frequencies of spontaneous tumors. Christopher, 3/14/85 and Davis, 12/4/86. EPA ONE-LINER: Oncogenic potential negative. CORE GRADE = Not stated

070 025236 "Summary of DS-3701 Toxicology Studies: Mouse Study"; Document No. 098-5TX-78-0024-0010; Lab & Report Date not stated; 4-Hydroxy-2,5,6- trichloroisophthalonitrile (DS-3700, possible chlorothalonil metabolite) fed for two years at 375, 750, or 1500 ppm. No tumorigenicity. Two sentence summary. Incomplete. Unacceptable. Davis, 12/3/86.

REPRODUCTION, RAT

** 275-169 095496 "A Two Generation Reproduction Study in Rats with Technical Chlorothalonil", (F. Lucas and G. Benz, Dept. of Toxicology and Animal Metabolism, Ricerca, Inc., Document # 1722-87-0121-TX-003, 11/9/90). Chlorothalonil, Lot # D-5840923, 98.1% purity, fed in the diet for 2 generations with 2 litters per generation at 0 (control), 500, 1500, and 3000 ppm with 35 Sprague-Dawley (CD-VAF) rats/sex/group. Treatment occurred

continuously through both successive generations, beginning 10 and 14 weeks prior to mating for the F0 and F1 generation rats, respectively. Parental NOEL was not established; the following findings were dose-related down to 500 ppm: Kidney tubular epithelial hyperplasia and hypertrophy (both sexes); kidney clear cell hyperplasia and karyomegaly (no NOEL in males); forestomach hyperkeratosis and squamous epithelial hyperplasia (both sexes). Kidney lesions were typically much more severe in males. Modest, but statistically significant decrements in body weight gain were seen throughout the study in F0 and F1 parents. Reduced 21-day pup weights were indicated for the F1a, F1b, F2a, and F2b litters at 3000 ppm. Developmental NOEL (reduction of litter weight) = 1500 ppm. No adverse effects. Acceptable. (H. Green, T. Kellner and C. Aldous, 9/27/91).

275-166 086558 Wilson, N. H., et al., "Reproduction dose-rangefinding study in rats with technical Chlorothalonil". Ricerca, Inc., 5/18/89. Chlorothalonil, 98.1% purity, was administered in diets of CD rats, 15/sex/group, at dose levels of 0, 200, 375, 750, 1500, or 3000 ppm, for 10 weeks prior to mating, and continuously through mating, gestation, and lactation periods. This rangefinding study did not find adverse effects. Parental NOEL = 750 ppm, based on weight gain decrements in males only (not dose related). Enlarged kidneys were noted in 3000 ppm F0 adults only (in 5/15 males and in 1/15 females). Tissues were not examined microscopically, however kidney lesions have previously been observed in several chronic and subchronic rat studies, and thus kidney findings are presumed to be treatment effects. Reproductive NOEL = 1500 ppm (reduced body weights of pups after day 14 (statistically significant at day 21). Based on this study, the doses to be used in the subsequent 2-generation study will be 500, 1500, and 3000 ppm in diet. Acceptability status is not applicable, since this is a rangefinding study; however this study was performed consistent with guidelines. Doses selected for the definitive study are justifiable, considering this study and previous studies together. Aldous, 5/29/90.

075, 037 941886, 038929, 038844 "Three-Generation Reproduction-Rats. DAC- 2787. Final Report" Doc. No. 1000-5TX-67-0005-001; (Hazleton Labs., 2/2/67) Chlorothalonil (purity not given) dosed first 7 weeks, then a blend of chlorothalonil (93.6%) plus metabolites dosed for remainder of study; 0, 1500, 15000 or 30000 ppm to 10 males and 20 females/group; top 2 dose groups switched to 0 level dosing during days 3-14; both groups then switched to 5000 ppm, with dosing increased in steps to 20000 ppm for the high dose group until the P1 generation was terminated at week 20, and dosing increased in steps to 15000 ppm for the mid-dose group until the P1 generation was terminated in the 30th week; the 0, 1500, and 15000 ppm groups were continued through three generations. Chronic Toxicity: Decreased parental weight gain in all three generations; histological changes in kidney, esophagus, and stomach (histopathology data for this study found in Record # 38929); growth suppression of pups from birth to weaning shown to be a post-natal effect by cross nursing of control and test litters; Chronic toxicity NOEL < 1500 ppm; Incomplete. unacceptable-multiple dose level changes, dose levels too high, test material changed, test materials insufficiently characterized, only two dose levels after the P1 generation, too few animals, males rotated among females, limited histopathology. Christopher 3/15/85, Davis 6/19/87. EPA ONE-LINER: Reproductive LEL < 0.15% (LDT). Depressed pup weights, gastric and esophageal acanthosis in offspring. Maternal NOEL < 0.15%. Depressed body weight. CORE GRADE = Not stated

075, 037 038929, 038844, 038845 "Three-Generation Reproduction-Rats. DAC- 2787" (834); (Hazleton Labs., 4/5/67) Chlorothalonil (93.6%) plus metabolites at 0 or 5000 ppm in the diet to 10 males and 20 females per group; three generation study; Chronic Toxicity-decreased parental weight gain in all generations; kidney anomalies in P3 males; growth suppression of pups from birth to weaning shown to be a post-natal effect; NOEL < 5000 ppm; Incomplete, unacceptable-supplemental study with one dose level; deficiencies are too few body weights, no feed analysis, males rotated among females, incomplete pathology, too few animals; no histopathology data (the data in the appendix are for 075 941886). Christopher 3/15/85, Davis 6/19/87. EPA ONE-LINER: Reproductive NOEL < 0.5% (single dose tested). Decreased fetal weight. Maternal NOEL < 0.5%; body weight depression. CORE GRADE = Not stated

070 025240 "Summary of DS-3701 Toxicology Studies: Three-Generation Rat Reproduction Study" (Doc. No. 107-5TX-78-0023-002); Lab & report date not stated; 4-Hydroxy-2,5,6-trichloroisophthalonitrile, DS-3701 (chlorothalonil metabolite) at 0, 10, 60 and 125 ppm; Mean pup weights during lactation reduced in the 60 and 125 ppm groups for both litters of all generations; NOEL = 10 ppm. Supplemental study-brief summary of study with related compound. Davis 12/3/86.

070 025239 "Summary of DS-3701 Toxicology Studies: One-Generation Rat Reproduction Study". Doc. No. 529-5TX-81-0193-002; Lab & report date not stated; 4-Hydroxy-2,5,6-trichloroisophthalonitrile, DS-3701 (chlorothalonil metabolite); 0, 10, 20, 30, 60 & 120 ppm; mean pup weights lower during lactation in the 60 & 120 ppm groups for both litterings; Very brief summary. NOEL = 30 ppm. Supplemental study-brief summary of study with related compound. Davis 12/3/86.

TERATOGENICITY, RAT

**075 029668 "A Teratology Study In Rats With Technical Chlorothalonil" (Doc. No. 517-5TX-82-0011-003); Diamond Shamrock Corp. Life Science Toxicology and WIL Research Labs., Inc. 5/13/83; Chlorothalonil (98% purity) at 0, 25, 100 or 400 mg/kg/day to 25 pregnant females/group on days 6-15 of gestation; maternal toxicity (deaths, diarrhea, alopecia, decreased weight gain, and food consumption) at 400 mg/kg/day; Post-implantation loss due to early embryonic deaths ascribed to maternal toxicity; Maternal toxicity NOEL = 100 mg/kg/day; developmental NOEL > 400 mg/kg/day. Complete. Acceptable. Christopher, 3/25/85. EPA ONE-LINER: Teratogenic NOEL > 400 mg/kg/day (HDT), Fetotoxic NOEL > 400 mg/kg/day, Maternal NOEL = 100 mg/kg/day, Maternal LEL = 400 mg/kg/day (mortality, reduced body weight, increased resorptions and post implantation bases (sic). Levels tested by gavage in Sprague-Dawley strain-0, 25, 100 and 400 mg/kg/day; CORE GRADE = Guideline

TERATOGENICITY, RABBIT

** 157 072174 "A Teratology Study in Rabbits with Technical Chlorothalonil." (Bio/dynamics Inc., NJ, 10/4/88, 1544-87-0060-TX-002). Chlorothalonil, technical, 98.1%, Lot D-5840923; given by oral gavage in 0.5% methyl aqueous cellulose at 0 (vehicle), 5, 10 or 20 mg/kg/day, days 7 through 19 of gestation, 20 does/group. Maternal NOEL = 10 mg/kg/day (marginal effect on body weight). Developmental effects NOEL = 10 mg/kg/day (marginal reduction in fetal weights at 20 mg/kg/day). Originally classified "unacceptable" because the data of the primary study alone did not clearly demonstrate that the dose of 20 mg/kg/day was an adequate high dose. Upgraded to acceptable on receipt of the pilot study (see below), which demonstrated that dosages substantially higher than 20 mg/kg/day could not have been tolerated. J. Gee, 1/13/89, C. Aldous, 5/9/89.

158 073489 (pilot study to 157:072174) "A teratology dose range-finding study in rabbits with technical Chlorothalonil". Bio/dynamics, Inc., 9/27/88. Seven NZW rabbits/group dosed with 5, 15, 30, or 75 mg/kg/day chlorothalonil (purity 98.2%). Treatment days 7-19 of gestation. Vehicle = 0.5% methyl cellulose, aqueous suspension. Findings at 75 mg/kg/day: 3 deaths and 3 abortions, markedly decreased body weight and food consumption, reduced feces and/or soft stool in all 7 females. Findings at 30 mg/kg/day: 2/7 premature deliveries (possibly treatment-related, considering abortions at top dose and the low historical control incidence of premature deliveries), decreases in food consumption associated with modest decreases in dam body weights, and increased incidence of reduced feces and/or soft stool (5/7 females). This study supports selection of 20 mg/kg/day for the primary teratology study. C. Aldous, 5/9/89.

075 941887 "Reproduction Rabbits, DAC-2787, Final Report" (833) (Doc. No. 1000-5TX-66-0003-001 (Hazleton Lab., Falls Church, VA 9/30/66) Chlorothalonil (no purity stated) administered orally in gelatin capsules at 0, 180, or 375 mg/kg/day for days 8-9, changed to 0, 62.5, or 31.25 mg/kg/day respectively for days 10-16 ; 8 does/group; Animals sacrificed days 22-23 because of maternal toxicity; Insufficient information to assess adverse effects; Incomplete. Unacceptable; Too few animals, dosing started day 8 instead of 6, animals sacrificed day 22-23 instead of day 28, dosages drastically reduced because of maternal toxicity and high and low groups reversed, only two dose levels. J. Christopher, 3/25/85.

275-262 143369 Exact duplicate of 275-075:941887, above.

275-037 (No record #) 9/30/66 Cover sheet and page 5 of 075 941887.
075, 070, 133 941884, 038851, 050903 "Teratogenicity Study of Daconil in Rabbits" (Doc. No. 000-5TX-75-2077-001, Institute of Environmental Toxicology, 5/30/75). Chlorothalonil (99.3%) by gavage at 5 or 50 mg/kg/day for days 6-18 of gestation to 9 pregnant dams/group plus 8 negative control dams; Maternal toxicity (decreased food consumption and body weights, and increased abortions at 50 mg/kg) NOEL = 5 mg/kg/day; Developmental toxicity NOEL > 50 mg/kg/day. Incomplete. unacceptable; Can't be upgraded-only two dose levels, too few animals per group, no description of abortuses, corpora lutea not counted. 38851 is a one paragraph summary; 50903 presents individual data. Christopher 3/25/85; Davis 6/3/87. EPA ONE-LINER: Teratogenic NOEL > 50 mg/kg (HDT). Maternal NOEL = 5 mg/kg. Maternal LEL = 50 mg/kg (four spontaneous abortions). Fetotoxic NOEL = not established, additional information needed. Levels tested by gavage in Japanese White (Funabashi) strain-0, 5.0 and 50 mg/kg. CORE GRADE = Supplementary. Supply individual pup data; examination details of aborted embryos in the 50 mg/kg test group.

GENE MUTATION

Bacterial and somatic cell gene mutation assays on chlorothalonil and Ames assays on a number of metabolites and impurities of chlorothalonil are consistently negative. The data gap is filled and there is no adverse effect. B. Davis, 1/88.

** 073 941889 "Activity of DTX-77-0035 in the Salmonella/Microsomal Assay for Bacterial Mutagenicity" Document No. 000-5TX-77-0035-001. (Microbiological Associates, 6/29/77) Ames assay with strains TA98, TA100, TA1535, TA1537 & TA1538; Chlorothalonil (97.8%) at 0.33, 0.66, 1.0, 3.3 or 6.6 ug/plate with and without activation; No mutagenicity; Complete. Acceptable. Christopher 3/26/85.

037 941889 Contains several pages from 073 941889.

100 034458 No date; Summary of 073 941889.

EPA ONE-LINER: Negative for TA-1535; TA-100; TA-1537 and TA-1538 (his) status (sic) of ST DAC-2787 plated at 0.33, 0.66, 1, 3.3, 6.6 ug/plate. CORE GRADE = Not stated

073 038922 (formerly 941893-1) "Report on Mutagenic Testing With DAC 2787" Document No. 000-5TX-74-0013-001. (Brown Univ., 1/2/74) Host-mediated Ames assay with 8 strains (not guideline strains) of Salmonella typhimurium; Chlorothalonil (99+% purity) at 6.5 mg/kg/day by mouth to 10 male mice for 5 days; Bacteria injected into the peritoneal cavity and recovered 3 hours later; Summary with no data; Insufficient information to assess mutagenicity; Incomplete. unacceptable. Christopher 3/26/85.

100 034356 No date; Summary of 073 038922.

073 038924 (formerly 941888-2) "Mutagenicity Testing on Daconil in Microbial Systems" Document No. 000-5TX-61-0002-001. (Institute of Environmental Toxicology, Japan, No study date) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1538; Chlorothalonil (99.3% purity) at 0, 1, 2, 5, or 10 ug/plate without activation and 0, 2, or 10 ug/plate with activation; 2 plates/group; Insufficient information to assess mutagenicity; Incomplete. Unacceptable; no cytotoxicity observed with activation and hence no evidence that top dose was high enough, too few doses, too few replicates. Christopher 3/26/85.
073 038923 (formerly 942888-3) "Mutagenicity Testing on Daconil in Microbial Systems" Document No. 000-5TX-61-0002-001. (Institute of Environmental Toxicology, Japan, No study date) E. coli strains WP2 hcr+ and WP2 hcr-; Chlorothalonil (99.3% purity) at 0, 10, or 100 ug/plate (4 replicate plates/level) with activation and 0, 10, or 100 or 500 ug/plate (2 replicate plates/level) without activation; Insufficient information to assess mutagenicity; Incomplete. Unacceptable; no evidence of cytotoxicity at highest doses. Christopher 3/26/85.

037 038846 No date; 3 pages taken from 073 038924 & 073 038923.

110 034413 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With Technical Chlorothalonil (SDS- 2787)" Document No. 694-5TX-84-0064-002. (Microbiological Associates, 12/25/84) Ames assay with Salmonella typhimurium strains, TA98, TA100, TA1535, TA1537, TA1538; Chlorothalonil (no purity stated) at 0.5 to 50 ug/plate (5 concentrations) with activation or at 0.16 to 16 ug/plate (5 concentrations); renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Incomplete. unacceptable; The only deficiencies are the lack of test material purity information and the lack of a repeat confirming experiment. Christopher 9/23/85.

110 034415 8/31/84 Appendix B: Contract Laboratory Report for 110:034413.

073 941890 "Activity of Chlorothalonil in an In Vitro Mammalian Cell Point Mutation Assay" Document No. 000-5TX-77-0034-001. (Microbiological Associates, 6/29/77) Somatic fibroblasts (Chinese hamster V79 and Mouse BALB/3T3) Chlorothalonil (97.3% purity) in two hour exposures at 0.3 ug/ml tested only without activation for V79 cells, at 0.3 ug/ml with activation for BALB/3T3 cells, and at 0.03 ug/ml without activation for BALB/3T3 cells; Insufficient information for mutagenicity assessment; Incomplete. unacceptable; too little information on methods of calculations, number of plates and cells; negative control frequencies too high for V79 cells; too few 3T3 cells to establish spontaneous mutation frequencies; too few dose levels; no confirmatory assay. Christopher 3/26/85.

100 034354, 034355 No date; One paragraph summary of 073 941890.

EPA ONE-LINER: Negative for Chinese hamster cells V-79 and BALB/3T3 mouse fibroblasts. Dose = 0.3 ug/ml for 2 hours. CORE GRADE = Not stated

037 027705 (formerly 941810) (Microbiological Associates, 6/29/77) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 & TA1538; 4-Hydroxy-2,5,6-trichloroisophthalonitrile (DS-3701), a metabolite of chlorothalonil, (99% pure) at 1, 3.3, 10, 33.3 or 100 ug/plate both with and without activation; Insufficient information to assess mutagenicity; Supplementary study. Christopher 3/15/85.

110 034414 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,4,5,6-Tetrachloro-3-cyano- benzamide (SDS-19221)" Document No. 694-5TX-84-0087-002.

(Microbiological Associates, 1/18/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,4,5,6-tetrachloro-3-cyano-benzamide, a potential metabolite of chlorothalonil, (purity not stated) at 10 to 1000 ug/plate (5 concentrations) with activation of 6.0 to 600 ug/plate (5 concentrations) without activation; renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

110 034416 10/19/84 Appendix B: Contract Laboratory Report for 110:034414

110 034417 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,5,6-Trichloro-3-cyano-benzamide (47524)" Document No. 694-5TX-84-0088-002. (Microbiological Associates, 1/18/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,5,6-trichloro-3-cyano-benzamide, a potential metabolite of chlorothalonil, (purity not stated) at 0, 20, 100, 500, 1000 or 2000 ug/plate with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

110 034418 11/15/84 Appendix B: Contract Laboratory Report for 110:034417.

110 034419 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,5,6-Trichloro-4-hydroxy-3- cyano-benzamide (SDS-47525)" Document No. 694-5TX-84-0089-002. (Microbiological Associates, 1/18/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,5,6-Trichloro-4-hydroxy-3- cyano-benzamide, a potential metabolite of chlorothalonil, (purity not stated) at 40 to 6000 ug/plate (5 concentrations) with activation and 20 to 2000 ug/plate (5 concentrations) without activation; renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

110 034420 10/19/84 Appendix B: Contract Laboratory Report for 110:034419.

110 034421 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,3,5,6-Tetrachlorobenzonitrile (SDS-3032)" Document No. 694-5TX-84-0091-002. (Microbiological Associates, 2/7/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,3,5,6-Tetrachlorobenzonitrile, a potential metabolite of chlorothalonil, (purity not stated) at 0, 20, 100, 500, 1000 or 2000 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

110 034422 12/28/84 Appendix B: Contract Laboratory Report for 110:034421.

110 034423 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,4,5,6-Tetrachlorodibenzamide (SDS-3133)" Document No. 694-5TX-84-0092-002. (Microbiological Associates, 2/7/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,4,5,6-Tetrachlorodibenzamide, a potential metabolite of chlorothalonil, (purity not stated) at 0, 20, 100, 500, 2500, 5000 or 10000 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

110 034424 12/28/84 Appendix B: Contract Laboratory Report for 110:034423.

111 034425 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,4,5-Trichloro-3-cyano-benzamide (SDS-47523)" Document No. 694-5TX-84-0093-002.

(Microbiological Associates, 2/8/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,4,5-Trichloro-3-cyano-benzamide, a potential metabolite of chlorothalonil, (purity not stated) at 0, 20, 100, 500, 1000, or 2000 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

111 034426 12/28/84 Appendix B: Contract Laboratory Report for 111:034425.

111 034427 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,5,6-Trichloro-4-thio- isophthalonitrile (SDS-13353)" Document No. 694-5TX-84-0124-002. (Microbiological Associates, 5/22/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,5,6-Trichloro-4-thio- isophthalonitrile, a potential metabolite of chlorothalonil, (purity > 90%) at 400, 630, 1000, 1600, 2500, 4000, or 5000 ug/plate with activation (plus additional levels of 2000 & 3000 ug/plate with TA100) and 250, 400, 630, 1000, 1600, or 2500 ug/plate without activation; renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

111 034428 3/29/85 Appendix B: Contract Laboratory Report for 111:034427.

111 034429 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,5,6-Trichloro-3-carboxy- benzamide (SDS-46851)" Document No. 694-5TX-84-0139-002. (Microbiological Associates, 6/24/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,5,6-Trichloro-3-carboxy-benzamide, a potential metabolite of chlorothalonil, (99.4% purity) at 0, 100, 500, 2500, 5000, 10000 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

111 034430 3/28/85 Appendix B: Contract Laboratory Report for 111:034429.

111 034431 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,4,5-Trichloroisophthalonitrile (SDS-5473)" Document No. 694-5TX-84-0086-002. (Microbiological Associates, 1/29/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,4,5-Trichloroisophthalonitrile, an impurity and potential metabolite of chlorothalonil, (purity not stated) at 0, 0.5, 2.5, 10.0, 35.0, or 70.0 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

111 034432 10/19/84 Appendix B: Contact Laboratory Report for 111:034431.

111 034433 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,3,5,6- Tetrachloroterephthalonitrile (SDS-2020)" Document No. 694-5TX-84-0090-002. (Microbiological Associates, 1/15/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; 2,3,5,6- Tetrachloroterephthalonitrile, an impurity and potential metabolite of chlorothalonil, (purity not stated) at 0, 4, 20, 100, 200 or 400 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

111 034434 11/15/84 Appendix B: Contract Laboratory Report for 111:034433.

111 034435 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With Isophthalonitrile (IPN) (SDS- 3176)" Document No. 694-5TX-84-0094-002. (Microbiological Associates, 2/19/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538;

Isophthalonitrile, an impurity of technical chlorothalonil, (purity not stated) at 0, 40, 200, 1000, 2000 or 4000 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

111 034436 12/28/84 Appendix B: Contract Laboratory Report for 111:034435.

111 034437 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With Pentachlorobenzonitrile (SDS- 3297)" Document No. 694-5TX-84-0095-002. (Microbiological Associates, 2/14/85) Ames assay with Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; Pentachlorobenzonitrile, an impurity of technical chlorothalonil, (purity not stated) at 0, 10, 50, 250, 500 or 1000 ug/plate tested with and without renal activation system; triplicate plates; acetone vehicle controls; No adverse effect indicated; Supplementary study. J. Remsen (Gee) 9/23/85.

111 034438 12/28/84 Appendix B: Contract Laboratory Report for 111:034437.

133 050908 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 2,5,-Dichloro-4,6- bismercaptoisophthalonitrile (SDS-3939)" Study Number 5TX-85-0042. (Microbiological Associates, 10/22/85) This potential metabolite (90.5 + 2% purity) of chlorothalonil was tested at 50 to 4000 ug/plate (5 concentrations) without activation and 50 to 10,000 ug/plate (5 concentrations) with activation; Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; renal activation system; triplicate plates; partial repeat assays; No adverse effect indicated; Supplementary study. Davis 6/8/87.

133 050909 "Salmonella/Mammalian-Microsome Plate Incorporation Assay (Ames Test) With and Without Renal Activation With 5-(2,4-Dicyano-3,5,6- trichlorophenyl) Glutathione (SDS-66382)". Study Number 5TX-85-0043. (Microbiological Associates, 10/22/85) This potential metabolite (97.5 purity) of chlorothalonil was tested at 100, 500, 2500, 5000, and 10000 ug/plate with and without activation; Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; renal activation system; triplicate plates; No adverse effect indicated; Supplementary study. Davis 6/9/87.

140 054954 "Salmonella/Mammalian-Microsome Plate Incorporation Mutation Assay (Ames Test) With and Without Renal Activation With 5-Chloro-2,4,6- trismercaptoisophthalonitrile (SDS-66471)". Study Number 1097-86-0037. (Microbiological Associates, 12/19/86) This potential metabolite (96.2% purity) of chlorothalonil was tested at 0, 100, 500, 2500, 5000 and 10,000 ug/plate with and without rat renal activation; Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; triplicate plates with no repeat assays; No adverse effect; supplementary study with related compound. Davis 12/28/87.

140 054955 "Salmonella/Mammalian-Microsome Plate Incorporation Mutation Assay (Ames Test) With and Without Renal Activation With S,S'-(2,4-Dicyano- 3,6-Dichlorophenyl)-Dicysteine (SDS-66474)". Study Number 1097-86-0038. (Microbiological Associates, 1/20/87) This potential metabolite (95% purity) of chlorothalonil was tested at 0, 100, 500, 2500, 5000 and 10,000 ug/plate with and without rat renal activation; Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538; triplicate plates with some repeat assays; No adverse effect; supplementary study with related compound. Davis 12/28/87.

140 054956 "Salmonella/Mammalian-Microsome Plate Incorporation Mutation Assay (Ames Test) With and Without Renal Activation With S,S',S"-(2,4- Dicyano-6-Chlorophenyl)-Tricysteine (SDS-66473)". Study Number 1097-86-0039. (Microbiological Associates, 12/19/86) This potential metabolite (> 95% purity) of chlorothalonil was tested at 0, 100, 500, 2500, 5000 and 10,000 ug/plate with and without rat renal activation; Salmonella typhimurium

strains TA98, TA100, TA1535, TA1537, TA1538; triplicate plates with no repeat assays; No adverse effect; supplementary study with related compound. Davis 12/28/87.

037 027707 (formerly 941897-2) (Microbiological Associates, 6/29/77) Somatic Cell (Chinese Hamster V79 & mouse fibroblast BALB/3T3); 4-Hydroxy-2,5,6- trichloroisophthalonitrile (DS-3701), a chlorothalonil metabolite (99% purity) at 30 ug/ml + activation; Insufficient information to assess mutagenicity. Supplementary study. Christopher 3/15/85.

CHROMOSOMAL EFFECTS

Revised summary: A number of chromosome assays have been submitted, including in vivo studies in mice, rats and hamsters, somatic cell culture assays, and a barley seed assay. Of the 14 in vivo studies, none tests for mutagenicity in females, but this has been justified in the rebuttal of 11/24/86 based on the considerable evidence from other studies that males are more sensitive to chlorothalonil. The data gap is filled by seven acceptable studies. Among these acceptable studies, in vivo chromosome aberration assays in mice, rats, and (with one exception) hamsters were negative: one acute hamster assay was marginally positive at high doses. An in vitro CHO chromosome aberration assay was positive (statistical significance only at the high dose) without activation. Thus there is some evidence for mutagenicity, which is mitigated by the following factors: 1) The in vitro assay was positive only without activation (This argument is weakened by the positive effect with and without activation in a brief NTP report-see Records 34361 and 34362), 2) The effect in the acute hamster study was marginal even at quite high doses (2500 and 5000 mg/kg), 3) metabolism studies suggest that only metabolites are absorbed through the rat gastrointestinal tract. In summary, the data gap is filled, and a possible adverse effect had previously been identified, with the caveat that the evidence is equivocal. See also the documentation for the 8/27/87 meeting with Fermenta Plant Protection Company (summary dated 9/9/87 and CDFA comments dated 1/11/88). Two recent in vivo studies (acceptable) in rats and hamsters have been reviewed with no indication of chromosomal aberrations identified. The weight of evidence, therefore, is that chlorothalonil is not genotoxic, consistent with the results of the great majority of in vivo studies. Davis, 1/88, updated by Gee, 1/11/96.

073 941895 "The Micronucleus Test in the Rat, Mouse and Hamster Using Chlorothalonil" Document No. 000-5TX-81-0024-004 (C.E.R.T.I., France, 1/21/83) Chlorothalonil (98.2% purity) at 0, 8, 40, 200, 1000 or 5000 mg/kg/day; oral gavage twice with 24 hour interval to 10 males/dose level (1 death following dosing); animals sacrificed 6 hours after second dose; Schmid protocol used; Insufficient information to assess adverse effects; Incomplete. unacceptable-Needs more sample times at longer intervals. Christopher 3/27/85.

070 & 100 941876 Brief summary of 073 941895.

EPA ONE-LINER: No induction of Wistar strain rat bone marrow erythrocyte nuclei at levels up to and including 5000 mg/kg (HDT). Positive control was MMS at 65 mg/kg. CORE GRADE = Acceptable.

073 038925 (formerly 941895-2) "The Micronucleus Test in the Rat, Mouse and Hamster Using Chlorothalonil" Document No. 000-5TX-81-0024-004 (C.E.R.T.I., France, 1/21/83) Chlorothalonil (98.2% purity) at 0, 4, 20, 100, 500 or 2500 mg/kg/day to 10 to 13 male mice/group; oral gavage twice with 24 hour interval; Schmid protocol used; mice sacrificed 6 hours after second dose; Insufficient information to assess adverse effects; Incomplete. unacceptable- Needs more sample times at longer intervals, Dose-independent mortality of 9/57 treated mice suggests technical problems. Christopher 3/27/85.

070 & 100 941876 Brief summary of 073 038925.

EPA ONE-LINER: Does not induce mouse bone marrow erythrocyte micronuclei in Swiss CFLP strain at levels up to and including 5000 mg/kg (HDT). Positive control was MMS at 65 mg/kg. CORE GRADE = Acceptable.

073 038926 (formerly 941895-3) "The Micronucleus Test in the Rat, Mouse and Hamster Using Chlorothalonil" Document No. 000-5TX-81-0024-004 (C.E.R.T.I., France, 1/21/83); Chlorothalonil (98.2% purity) at 0, 4, 20, 100, 500 or 2500 mg/kg/day to 10 male hamsters/group (2 deaths following dosing); oral gavage twice with 24 hour interval; hamsters sacrificed 6 hours after second dose; Schmid protocol used; Insufficient information to assess adverse effects; Incomplete. unacceptable.-Needs more sample times at longer intervals. Christopher 3/27/85.

070 & 100 941876 Brief summary of 073 038926. EPA ONE-LINER: No significant increase in Chinese hamster bone marrow erythrocyte micronuclei at levels up to and including 5000 mg/kg (HDT). Positive control was MMS at 65 mg/kg. CORE GRADE = Acceptable.

073 038919 (formerly 941893-2) (Brown University, 1/2/74) Mouse Micronucleus Assay; Chlorothalonil (99+% purity) at 6.5 mg/kg/day by mouth to 10 mice (sex & strain not specified) for 5 days; Sacrificed 3-4 hours post-dosing; Insufficient information to assess adverse effects; Incomplete. unacceptable; No rationale for protocol: only one dose, repeated doses with one sample time, sacrificed too soon; Too little information on test material, animals, procedures. Christopher 3/25/85.

073 941896 "The Chromosomal Aberration Test in the Rat, Mouse and Hamster Using Chlorothalonil" Document No. 000-5TX-81-0025-004 (C.E.R.T.I., France 1/2/83) Chlorothalonil (98.2% purity) at 0, 8, 40, 200, 1000 or 5000 mg/kg/day to 10 to 11 male rats/group (1 death following dosing); oral gavage twice with 24 hour interval; rats sacrificed 6 hours after second dose and bone marrow cell chromosomes examined; Insufficient information to assess adverse effects; Incomplete. unacceptable-Needs more sample times at longer intervals. Christopher 3/27/85.

EPA ONE-LINER: Significant numbers of chromosomal abnormalities not induced in Wistar rats at up to 5000 mg/kg (HDT). Positive control was MMS at 65 mg/kg/day. CORE GRADE = Acceptable.

073 038927 (formerly 941896-2) "The Chromosomal Aberration Test in the Rat, Mouse and Hamster Using Chlorothalonil" Document No. 000-5TX-81-0025-004 (C.E.R.T.I., France, 1/21/83) Chlorothalonil (98.2% purity) at 0, 4, 20, 100, 500 or 2500 mg/kg/day to 10 to 11 male Swiss CFLP mice per group (3 dose- independent deaths following dosing); oral gavage twice with 24 hour interval; mice sacrificed 6 hours after second dose and bone marrow cell chromosomes examined; Insufficient information to assess adverse effects; Incomplete. unacceptable.-Needs more sample times at longer intervals. Christopher 3/27/85.

EPA ONE-LINER: Bone Marrow chromosomal anomalies not increased at levels up to 2500 mg/kg (HDT) in Swiss CFLP strain. Positive control was urethan at 2000 mg/kg. CORE GRADE = Acceptable.

073 038928 (formerly 941896-3) "The Chromosomal Aberration Test in the Rat, Mouse and Hamster Using Chlorothalonil" Document No. 000-5TX-81-0025-004 (C.E.R.T.I., France, 1/21/83) Chlorothalonil (98.2% purity) at 0, 8, 40, 200, 1000 or 5000 mg/kg/day to 10 to 13 male Chinese hamsters/group; oral gavage twice with 24 hour interval; hamsters sacrificed 6 hours after second dose and bone marrow cell chromosomes examined; Insufficient information to assess adverse effects; Incomplete. unacceptable-Needs more sample times at longer intervals. Christopher 3/27/85.

070 25234 Brief summary of 073 941896, 073 38927 and 073 38928.

EPA ONE-LINER: Bone marrow chromosomal anomalies not increased at up to 1000 (sic)mg/kg (HDT) in Chinese hamster. Positive control was MMS at 65mg/kg. CORE GRADE = Acceptable.

**109, 133, 100, 034401-4, 034412, 050905, 034359 "In vivo Bone Marrow Chromosomal Aberration Assay in Mice with a Single Dose of Technical Chlorothalonil" (C.E.R.T.I., France 6/20/85) Chlorothalonil (98.2% purity) at 0, 250, 1250, or 2500 mg/kg by single dose oral gavage to 10 male mice/group; Mice sacrificed 6, 24, or 48 hours after treatment and bone marrow cell chromosomes examined; No adverse effect; Complete. acceptable. 34359 is a summary. Previously reviewed as unacceptable (J. Remsen (Gee) 9/23/85); additional data (133 50905) and rebuttal (11/24/86) make study acceptable. Davis 6/4/87.

**109, 133, 100 034405-8, 050904, 034358 "In vivo Bone Marrow Chromosomal Aberration Assay in Rats with a Single Dose of Technical Chlorothalonil" (C.E.R.T.I., France 3/18/85) Chlorothalonil (98.2% purity) at 0, 500, 2500 or 5000 mg/kg by single dose oral gavage to 10-14 male rats/group; Rats sacrificed 6, 24, or 48 hours after treatment and bone marrow cell chromosomes examined; Mitotic indexes of treatment groups unchanged from negative control value; No adverse effect. Complete, acceptable. 34358 is a summary. Previously reviewed as unacceptable (J. Remsen (Gee) 9/23/85); additional data (133 50904) and rebuttal (11/24/86) make the study acceptable. Davis 6/4/87.

**109, 133, 100 034409, 034410, 034412, 050906, 034360 "Acute In Vivo Bone Marrow Chromosomal Aberration Assay in Chinese Hamsters with T-117-11". Study Number 5TX-83-0014. (C.E.R.T.I., France 6/17/85) Chlorothalonil (98.2% purity) at 0, 500, 2500, or 5000 mg/kg by single dose oral gavage to 10-13 male hamsters/group; Hamsters sacrificed 6, 24, or 48 hours after treatment and bone marrow cell chromosomes examined; 9 deaths in treated groups; dose- related decrease in mitotic index; Possible adverse effect-marginally increased aberration frequencies at 48 hours for 2500 and 5000 mg/kg; Statistically significant trend. Complete, acceptable. 34409 and 34412 are sponsor reports; 34360 is a summary. Previously reviewed as unacceptable (J. Remsen (Gee) 9/23/85); additional data (133 50906) and rebuttal (11/24/86) make study acceptable. Davis 6/5/87.

**109, 133, 100 034409, 034411, 034412, 050906, 034360 "Subchronic in Vivo Bone Marrow Chromosomal Aberration Assay in Chinese Hamsters with T-117-11". Study Number 5TX-83-0014. (C.E.R.T.I., France 6/17/85) Chlorothalonil (98.2% purity) at 0, 50, 125, or 250 mg/kg/day for 5 days by single dose oral gavage to 10-11 male hamsters/group; Hamsters sacrificed 6 hours after the final dose and bone marrow cell chromosomes examined; 1 death/treated group; mitotic indices were elevated in all treated groups with statistical significance at 50 and 250 mg/kg/day; No adverse effect; Complete, acceptable. 34409 and 34412 are sponsor reports; 34360 is a summary. Previously reviewed as unacceptable (J. Remsen (Gee) 9/23/85); additional data (133 50906) and rebuttal (11/24/86) make the study acceptable. Davis 6/5/87.

**133 050910 "In Vitro Chromosomal Aberration Assay in Chinese Hamster Ovary (CHO) Cells with Technical Chlorothalonil. Study Number 85-0082. (Microbiological Associates, 5/29/86) Chlorothalonil (98.8% purity) was tested at 0, 0.6, 1.5, 3.0, and 6.0 ug/ml with activation and 0, 0.03, 0.08, 0.15 and 0.30 ug/ml without activation; Numerical and structural aberrations scored; Possible adverse effect-increased structural aberrations without activation; Complete; acceptable; Davis 6/10/87.

100 034361, 034362 In vitro Aberrations and SCE's (Chinese hamster ovary cells), (National Toxicology. Program, 2/84) Chlorothalonil (no purity stated) positive for chromosome aberrations with and without activation and positive

for sister chromatid exchange with activation; Incomplete. unacceptable: No dose levels stated; a one paragraph summary for the Annual Plan NTP-84-023. Apostolou 9/18/85.

073 941891 (formerly 941893-3) (Brown University, 1/16/74) Dominant Lethal Assay; Chlorothalonil (99+% purity) by gavage to 10 male mice for 5 days; Dosing stated to be : 1) 6.5 mg/kg/day on the Diamond Shamrock summary and page 8, 2) 6.7 mg/kg per day on page 3, and 3) three unspecified concentrations on page 2; Treated males mated to two different females each week for 8 weeks; Corpora lutea, total implantations, and dead implantations counted; Insufficient information to assess mutagenicity; Incomplete. unacceptable; Contradictory dose information leaves doses unknown; Too few pregnant females; No individual data; Too little information on animals used. Christopher 3/25/85.

100 034357 No date; Summary of 073 941891.

073 941894 (Tennessee State Univ., 1979) Chromosome Aberration Assay in Barley Seed; Chlorothalonil (75%) at 0, 250, 500 or 1000 ppm; 300 cells/group; Journal article; Incomplete. unacceptable; Not a guideline study; Too little information. Christopher 3/26/85.

070 941876 No date; Summary of micronucleus (941895, 38925, 38926) and chromosomal aberration (941896, 38927, 38928) tests in volume 073. See one- liners above.

** 275-257 143364 "Five-day repeated-dose chromosomal aberration test in vivo with SB-341 using rats." (Y. Kajiwara et. al., Hita Research Laboratories, Chemical Biotesting Center, Japan, 9/7/94, study code K12-0001) SB-341 (chlorothalonil, 98.85%) was given by oral gavage to male rats [Crj:CD(SD)] on five consecutive days at 0 (olive oil), 500, 1000 or 2000 mg/kg. Five per dose were sacrificed at 6 and 24 hours after the last dosing. Mitomycin C was the positive control at 15 mg/kg with sacrifice at 18 hours. Two slides were prepared per animal and a total of 50 cells scored for aberrations. In a preliminary study, body weights were decreased at 500 mg/kg and above. No evidence of the induction of chromosomal aberrations following in vivo exposure of male rats was reported. Justification for using only males has been addressed in previous submissions. Acceptable. (Gee, 1/2/96)

** 275-258 143365 "In vivo bone marrow chromosomal analysis in Chinese hamsters following multiple dose administration of technical chlorothalonil." (M. Mizens and J. Laveglia, Huntingdon Research Centre, England, study number 94-0047, document number 6005-94-0047-TX-003, 6/2/95) Chlorothalonil technical (98.3%) was given by oral gavage to male Chinese hamsters at 0 (1% aqueous methylcellulose), 187.5, 375 or 750 mg/kg b. wt for 5 daily consecutive doses. There were 10 males per sacrifice time per dose. Cyclophosphamide was the positive control and gave the expected results. There were 4 mortalities at the high dose without the cause of death identified. Ten per group were sacrificed at 6 and at 24 hours after the final treatment for the vehicle and chlorothalonil groups; only 24 hours after a single dose for cyclophosphamide. Body weights were decreased at 375 and 750 mg/kg with some clinical signs, indicating the adequacy of the dose selection. No evidence of an increase in chromosomal aberrations due to treatment was reported. Use of only males was justified in earlier submissions. Acceptable. (Gee, 1/3/96)

DNA DAMAGE

Four studies with chlorothalonil and two with metabolites have been submitted in this category. Three of the chlorothalonil studies are acceptable. The acceptable Salmonella DNA repair assay shows a compelling positive result. The data from an unacceptable Bacillus subtilis study with the same test system also indicate mutagenicity though the study conclusions dismiss it. However, the other two acceptable studies (cell transformation and DNA

binding) were both negative. The DNA binding assay is the most relevant study, since it was done in vivo and in a mammal (the rat) and organ (the kidney) which has been shown to be a target for both chronic toxicity and oncogenicity. Other studies have shed considerable light on the metabolism of chlorothalonil in mammals and it seems unlikely that bacterial systems would approach the same biochemistry, even in the presence of mammalian activating enzymes. Therefore, we consider there to be no adverse effect in this category. See also the documentation for the 8/27/87 meeting with Fermenta Plant Protection Company (summary dated 9/9/87 and CDFA comments dated 1/11/88). Davis, 1/88.

**073 941897 "Activity of Chlorothalonil in a Test for Differential Inhibition of Repair Deficient and Repair Competent Strains of Salmonella typhimurium: Repair Test" Document No. 000-5TX-77-0033-001 (Microbiological Associates, 6/29/77) Chlorothalonil (97.8% purity) at 0, 2, 10 or 20 ug/plate + activation to matched S. typhimurium strains TA1978 (repair competent) and TA1538 (repair deficient) in a disc diffusion assay with agar overlay; Possible adverse effect; Three independent assays produced significant differences in growth inhibition between the strains at all dose levels of chlorothalonil with and without activation, suggesting DNA damage; NOEL < 2 ug/plate; Complete; acceptable. Christopher 3/25/85.

100 034363 No date; Summary of 073 941897. EPA ONE-LINER: Interferes with DNA repair in TA-1538. Tested at 2-20 ug/plate. CORE GRADE = Not stated

073, 037, 100 941888, 027708, 034364 "Mutagenicity Testing on Daconil in Microbial Systems" Document No. 000-5TX-61-0002-001 (Institute of Environmental Toxicology, Japan, 10/19/77) Chlorothalonil (99.3% purity) at 0, 2, 5, 10, 20, 100 or 200 ug/plate to matched Bacillus subtilis strains H17 (repair competent) and M45 (repair deficient) in a disc diffusion streak assay; Possible adverse effect-greater inhibition in M45 in treated plates; Incomplete. unacceptable: no activation; only one plate per dose level; no data analysis. 27708 and 34364 contain excerpts. Christopher 3/26/85, Davis 6/15/87. EPA ONE-LINER: Negative for DNA repair synthesis in B. subtilis #M44 (sic). CORE GRADE = Not stated

**073, 037 941892, 028258 "Cell Transformation Assay with Chlorothalonil" Document No. 041-5TX-79-0021-004 (Microbiological Associates, 1/14/80) Chlorothalonil (96% purity) at 0.001, 0.0001, or 0.00001 ug/ml of medium, incubated for 7 days with two rat cell lines (F1706 P95 & H4536 P+2 [infected with RLV]); each culture subcultured 12 times and assayed for foci after two weeks; subcultures 3, 6, 10, and 12 screened for ability to form macroscopic colonies in semisolid agar; high dose subculture 9 tested for ability to form tumors in newborn Fischer rats; No adverse effect; Complete, acceptable. 28258 contains pages ii and 4 of the report. Christopher 3/26/85, Davis 6/15/87.

EPA ONE-LINER: Negative for phenotypic transformations in F1706 and H4536p+2 cell lines. CORE GRADE = Not stated

**146 059035 "Determination of the Covalent Binding of Radiolabel to DNA in the Kidneys of Male Rats Administered C-Chlorothalonil (C-SDS-2787)" (Microbiological Associates, Inc., 7/9/87) Mixture of nonlabelled analytical grade chlorothalonil (98.9% purity) and C-labeled chlorothalonil (radiochemical purity of 99%) by gavage to 4 male rats with appropriate negative and positive controls; sacrificed after 6 hours; protein and DNA extracted from kidney tissue and analyzed by LSC; radiolabel was bound to protein but not DNA of kidneys from chlorothalonil-treated rats; No adverse effect; acceptable; Davis 10/14/87.

037 027706 (formerly 941897-1) (Microbiological Associates, 6/29/77) 4- Hydroxy-2,5,6-trichloroisophthalonitrile (DS-3700, a chlorothalonil metabolite, 99% purity) at 0, 2, 10 or 20 ug/plate + activation to matched S. typhimurium

strains TA1978 (repair competent) and TA1538 (repair deficient) in a disc diffusion DNA damage assay with agar overlay; Insufficient information to assess mutagenicity: no data are included; Supplementary study; This report consists of a few pages from a full study. Davis 12/17/86.

070 025238 Document No. 041-5TX-80-0015-003; Lab & Report Date not stated; 4-Hydroxy-2,5,6-trichloroisophthalonitrile (DS-3700, chlorothalonil metabolite) in a cell transformation assay with F1705 and H4536 cells; no in vitro transformation; treated cells injected into newborn Fischer rats; No tumors observed from H4536 cells; Late tumors observed in rats injected with F1705 considered to be spontaneous transformation, characteristic of this cell line; Very brief summary of a supplementary study. Davis 12/3/86.

METABOLISM STUDIES

275-165 086554 Savides, M. C., J. P. Marciniszyn, and Killeen, J. C., "Study to evaluate the urinary metabolites of Chlorothalonil from male Rhesus monkeys". Animal Metabolism Laboratory, Ricerca, Inc., 4/16/90. (In-life phase of study was conducted at White Sands Research Institute, Alamogordo, NM). Four male monkeys were administered 50 mg/kg Chlorothalonil (analytical grade, 98.8%), to which was added 14C- chlorothalonil (uniformly labeled in the benzene ring, 142.5 mCi/mmole specific activity). A single oral dosing was done using 0.75% methylcellulose aqueous suspension. Urine and feces were collected over four days. Urine samples were assayed for thiol content following derivatization with diazomethane. Half-life in blood was variable, ranging from 7 to 35 hr. From 2 to 4% of dose was excreted in urine: this compared to 52 to 92% which was excreted in feces, during the collection period of 4 days. Methyl-derivatized thiol metabolites were quantitated in urine: assays were capable of measuring monomethylthio-isophthalonitrile, as well as bis(methylthio) and tris(methylthio) derivative metabolites. Only the latter two could be detected, and the tri-thiol was the most abundant. Nevertheless, only about 0.001 to 0.01% of administered dose was recovered as tri-thiol and di- thiol isophthalonitriles, suggesting that this was a very minor pathway in monkeys. Aldous, 6/5/90.

275-165 086555 Savides, M. C., J. P. Marciniszyn, and Killeen, J. C., "Study of the urinary excretion of radio label by catheterized dogs following oral administration of 14C-Chlorothalonil by gavage". Animal Metabolism Laboratory, Ricerca, Inc., 4/17/90. Three male beagles were administered nominal doses of 50 mg/kg 14C-Chlorothalonil in single gavage administrations. Urine was collected for up to 24 hr by catheters (inserted into the bladders) to eliminate contamination by feces. Urine and feces were collected for a subsequent period (total of 8 days) with catheters removed. Total urinary excretion was estimated to be 0.7 to 1.9% of estimated actual dose: most of this was collected during the first 24 hr. Fecal elimination was estimated to be 83 to 99% of estimated actual dose. Analyses of urine for mono-, di-, and tri-thiols did not detect any of these metabolites. Aldous, 6/5/90.

275-165 086556 Magee, T. A., M.C. Savides, J. P. Marciniszyn, and Killeen, J. C., "Study to evaluate the metabolic pathway of Chlorothalonil (14C-ASC-2787) in germ-free rats". Ricerca, Inc., Department of Toxicology and Animal Metabolism, 4/18/90. "Germ-free" (lacking in intestinal flora) CD Sprague-Dawley male rats from U. Wisconsin Medical School, Madison, were dosed with 0.75% methylcellulose vehicle by gavage (single dose, 50 mg/kg Chlorothalonil). Daily urine samples were extracted for evaluation of thiol content (see methods in dog and monkey studies, this volume). Three of 9 rats had measurable levels of di- and/or tri- thiols from the 24 hr or 48 hr urine collection. Investigators noted that urine of non germ-free rats contains more than 50-fold more of these thiols as urine of germ-free rats evaluated in this study. Thus intestinal microflora are presumed to be responsible for the metabolites which are associated with kidney toxicity in non germ-free rats. This was stated to be particularly important, because the “The population of microflora in the upper gastrointestinal tract of man is much less than that in the non germ-free rat” (p. 36). Aldous, 6/5/90.

275-165 086557 Detailed report on in-life phase of 275-165:086556, above.

275-191 133333 Barrowman, J.A. (Study Director), "Recirculation of radioactivity in rat bile following intraduodenal administration of bile containing 14C-Chlorothalonil label", Memorial University of Newfoundland, SDS Biotech Study No. 4AM-79-0004. Uniformly-labeled chlorothalonil was administered into the duodena of Sprague-Dawley rats. Bile was collected via cannula. About 1 to 6% of administered label was excreted in bile. Bile collected during the first 6 hr after dosing was administered to recipient rats. About 19% of this label was excreted by the recipient rats within 24 hr. This suggests significant enterohepatic recirculation. Aldous, no worksheet, 6/20/95.

275-192 133334 Pollock, G.A., "Levels of radioactivity in blood following oral administration of 14C-Chlorothalonil (14C-DS-2787) to male rats", SDS Biotech Corp., 8/22/83. Principal finding was that very high dose levels led to delays in peak blood concentrations (5-6 hr for dose level of 5 mg/kg, 9 hr for 50 mg/kg, and about 16 hr for 200 mg/kg). Aldous, 6/21/95, no worksheet.

275-193 133337 Savides, M.C., "Pilot study for the determination of the effects of probenecid pretreatment on urinary metabolites and excretion of 14C-SDS-2787 following oral administration to male Sprague-Dawley rats", SDS Biotech Corp., 12/20/85. Probenecid is widely used to competitively inhibit active secretion of anionic metabolites from the proximal tubules of the kidney. In this study, probenecid led to (1) reduced urinary excretion of radiolabel, (2) increase in plasma radiolabel, and (3) reduction of kidney radiolabel. The first two observations were consistent with inhibition of the anionic transport system. It is not clear why there should be a reduction in radiolabel in kidney, since one would expect net accumulation of labeled anionic metabolites in the kidney. Aldous, 6/21/95, no worksheet.

275-195 133339 Savides, M.C., J. P. Marciniszyn, and Killeen, J. C., "Pilot study of the effect of the gamma-glutamyl transpeptidase inhibitor, AT-125, on the metabolism of ^{14}C- Chlorothalonil", Ricerca, Inc., Painesville, OH, 3/15/88. AT-125 would be expected to inhibit metabolism of glutathione conjugates of chlorothalonil, so that one would expect reduced overall excretion of acidified urine samples into ethyl acetate, and far less excretion of thiol metabolites. Some SD rats were pretreated with AT-125, then all received 50 mg/kg chlorothalonil by gavage. Urine was collected at 6, 12, and 24 hr post dosing, then acidified to pH 2, and extracted with ethyl acetate. During the first 12 hr, the AT-125-pretreated rats excreted only about 15% extractable label, compared to about 75% in non-pretreated rats. Total excretion of radiolabel was not changed by AT-125 treatment. The major non-extractable components were evidently di- and triglutathione metabolites of chlorothalonil. Extractable components were not identified. Aldous, 6/21/95, no worksheet.

275-196 133340 Savides, M.C., J. P. Marciniszyn, and Killeen, J. C., "A study to evaluate the effects of sulfur-containing analogs of chlorothalonil on mitochondrial function", Ricerca Animal Metabolism Laboratory, 2/29/88. Rat liver or kidney mitochondrial preparations were incubated with ADP in a medium which would allow respiration to take place, with consumption of oxygen. Oxygen consumption was assayed in the presence and absence of chlorothalonil analogs (mono- and dithiol analogs, and mono- and di-glutathione analogs). Remarkable inhibition of mitochondrial respiration occurred primarily with the dithiol analog, and to a lesser extent with the monothiol analog. This implicates these products (particularly the dithiol in this study) as causative agents of kidney toxicity by disturbing mitochondrial respiration. Aldous, 6/20/95, no worksheet.

275-197 133342 Andre, J. C., J. P. Marciniszyn, and Killeen, J. C., "Evaluation of mitochondrial function in the presence and absence of sulfur-containing analogs of chlorothalonil", Ricerca, Inc., Painesville, OH, May 10, 1991. Project ID 88-0107. Kidney cortical mitochondrial preparations were made from CD* rats. Effects on respiration were studied in presence of chlorothalonil analogs (mono-, di-, and tri-thiol analogs, and mono-, di-, and tri-glutathione analogs). Each analog was tested in the presence of either succinate or glutamate (to identify, if possible, the stage of oxidative respiration which might be affected). Both di-, and tri-thiol analogs inhibited respiration (measured by effects on oxygen consumption) in the presence of succinate, but not glutamate. Investigators concluded that these analogs inhibited mitochondrial respiration at the level of electron transfer from succinate to Coenzyme Q. This was proposed as a possible basis of nephrotoxicity of chlorothalonil, which forms glutathione metabolites and subsequently corresponding thiol metabolites, which are found in rat urine. Aldous, 6/20/95, no worksheet.

275-316 159183 Rosner, E., C. Klos, and W. Dekant, "Biotransformation of the fungicide chlorothalonil by glutathione conjugation", Dept. of Toxicology, University of Würzburg, Germany, *in* Fundam. Appl. Toxicol. **33**, 229-234 (1996). When chlorothalonil was incubated in rat liver cytosol in the presence of GSH, 4,6-bis(glutathion-*S*-yl)-2,5-dichloroisophthalonitril was the primary product. Using very brief incubation time (30 seconds), some 4-(glutathion-*S*-yl)-2,5, 6-trichloroisophthalonitril was detected [a presumed intermediate]. Male SD rats were administered acivicin (to inhibit γ-glutamyltranspeptidase) and had bile ducts cannulated prior to administration of single oral doses of 0.66 or 2.64 mmol/kg chlorothalonil. Bile was analyzed for chlorothalonil and metabolites. The only biliary product reported was a small amount of 4,6-bis(glutathion-*S*-yl)-2,5-dichloroisophthalonitril (chlorothalonil was not detected). Other male and female SD rats were dosed with chlorothalonil for urinary metabolite evaluation

(presumably without acivicin pre-treatment. The only identified product was 4,6-bis(*N*-acetylcystein-*S*-yl)-2,5-dichloroisophthalonitril, which was found in only minor amounts, with no sex difference in amount detected. The major part of orally administered chlorothalonil was excreted in feces unchanged in all *in vivo* studies. Evidently the only other metabolite assayed was 4-(*N*-acetylcystein-*S*-yl)-2,5-trichloroisophthalonitril, hence there is no report of possible mono- di- or tri-thiol compounds in excreta. The study does not address any standard data requirements, but provides some useful data. Methods and results are too sparsely reported for a more thorough evaluation. Aldous, 2/17/98.

275-253 143353 Savides, M. C. *et al.*, "Study to determine the extent and nature of biliary excretion of chlorothalonil and/or metabolites in the dog. Part I." Ricerca, Inc., 4/10/95. Document No. 5521-93-0319-AM-001, Project ID 93-0319. [No DPR worksheet: the following is mainly from the report abstract]. Four male beagles had bile ducts cannulated one day before receiving a single oral dose of 50 mg/kg [^{14}C]-chlorothalonil by gavage (0.75% CMC suspension, 2.5 ml/kg body weight). Bile was collected hourly for 48 hr. Urine and feces were also collected. About 5.1% of administered dose was collected in bile, with peak excretion at 10-14 hr post -dosing. On average, 1.4% of administered dose was collected in urine. Total absorbed dose (all routes) was calculated to average 7.7% of administered dose. Bile sample label was highly polar (only 2% was extractable into diethyl ether). Preliminary evaluation of cationic fraction of bile residues revealed a complex pattern of constituents. Urinary sample extracts were also complex, however "No radioactivity was present at HPLC retention times corresponding to dithiol, trithiol, or mono, di, and tri-S-methyl derivatives of chlorothalonil." Aldous, 2/2/98.

275-254 143354 Magee, T. A. *et al.*, "Study of the urinary excretion of radiolabel by dogs following administration of [^{14}C]-chlorothalonil by gavage". Ricerca, Inc., 12/6/91. Document No. 3086-90-0229-AM-001, Project ID 90-0229. [No DPR worksheet: the following is from the report abstract]. Three male beagles were administered a single oral dose of 50 mg/kg [^{14}C]-chlorothalonil by gavage (0.75% CMC suspension). Urine was collected at 2 hr intervals for the first 24 hr. Feces were collected after each defecation for 24 hr. Subsequently, urine and feces were collected at 24-hr intervals for a total of 72 hr. Recovery of label was 95.3% (1.4% in urine and 93.8% in feces). Urinary residues were evaluated. No mono- or di- (methylthio) metabolites were found. One sample contained 0.00012% of administered dose as tri- (methylthio) metabolite. This was noted to be a very low yield of thiol metabolites compared to that of rats. Aldous, 2/2/98.

275-255 143355 Magee, T. A. *et al.*, "Study in dogs to evaluate the pharmacokinetics of [^{14}C]-chlorothalonil. Ricerca, Inc., 6/18/92. Document No. 3421-89-0325-AM-001, Project ID 89-0325. [No DPR worksheet: the following is from the report abstract]. Four male beagles were administered a single oral dose of 50 mg/kg [^{14}C]-chlorothalonil by gavage (0.75% CMC suspension). One dog was sacrificed at each of the following intervals (2, 9, 24, and 96 hr). Urine, feces, and blood were collected at intervals, and selected tissues were collected at termination. Most label was present in feces and intestinal contents. Urine contained < 1% of radiolabel. Gallbladder contained the highest tissue level of radiolabel, followed by kidney. Only about 1% of label was still present in stomach and small intestine by 9 hr, indicating comparatively rapid passage. Thiols and similarly reactive moieties in extracts were methylated with diazomethane. In urine, there were no mono-(methylthio) residues. Six samples contained di-(methylthio) residues, and 13 samples contained tri-(methylthio) residues (about 1 x 10^{-5} and 1 x 10^{-4} % of administered dose, respectively. This was noted to be a very low yield of thiol metabolites compared to that of rats. Investigators considered results to account for the comparatively lower kidney toxicity of chlorothalonil in dogs compared to rats. Aldous, 2/2/98.

275-276 146573 "Study to evaluate the urinary metabolites of chlorothalonil following dermal application to male rhesus monkeys". This document is under review by Worker Health and Safety Branch as of 2/5/98 (Aldous).

MISCELLANEOUS

112, 113 No record # No date Not chronic; FYI.

"105 to 108 No record # 6/24/83 Not chronic; FYI.

114 034400 7/3/85 Not chronic; FYI.

100, 114 034365 No date Not chronic; FYI.

100, 114 034461 No date Not chronic; FYI.

100, 114 034460 No date Not chronic; FYI.

122 046244 9/84 Guidance For The Reregistration Of Pesticide Products Containing Chlorothalonil As the Active Ingredient; EPA Registration Standard.

069 028411 8/17/82 Summary of Data Reported and Evaluation, Experimental data (N. A. C. A.): FYI; not a study; no review necessary. Davis.

APPENDIX C

CALCULATIONS

Calculation equations:

1. Dosage estimation for animals from an inhalation study (exposure level in ppm):

$$mg/kg/day = mg/m^3 \; x \; respiration\ rate(m^3/kg/day) \; x \; \frac{hours\ exposed}{24\ hours} \; x \; \frac{days\ exposed/week}{7\ days} \; x \; AF$$

For this equation, 1 *u*g/L in air is equivalent to 1 mg/m^3. The term for number of days exposed per week/7 days is used in the calculation only for studies when the animals were not dosed every day. The dosage was not corrected for absorption (absorption factor, AF).

The default respiration rates used are: 0.96 m^3/kg/day for rats, 0.54 m^3/kg/day for rabbits, and 1.80 m^3/kg/day for mice (Zielhuis and van der Kreek, 1979).

For example: Using the LOAEL of 2 *u*g/L from Holbert (1993a) where rats were exposed to chlorothalonil for 4 hours by inhalation:

$$\frac{2\ mg}{m^3} \; x \; \frac{0.96\ m^3}{kg/day} \; x \; \frac{4\ hours}{24\ hours} = 0.32\ mg/kg/day$$

2. Dosage estimation for animals in a dietary study (exposure level expressed as ppm in the diet):

$$ug/kg/day = ppm\ (ug/g) \; x \; FR\ (g/day) \; x \; \frac{1}{body\ weight\ (kg)} \; x \; \frac{days\ exposed/week}{7days}$$

The food consumption rate (FR) is derived either from the reports or the standard default is used. The standard default is based on body weight, 15% for mouse, 5% for rat, and 3% for rabbit.

3. Margin of Exposure:

$$Margin\ of\ Exposure = \frac{NOEL}{exposure\ level}$$

4. Human equivalency in potency from animal (A) to human (H) is calculated based on the body weight (BW) to the 3/4 power (Davidson *et al.*, 1986; Travis and White, 1988) with human = 70 kg and rat =0.35 kg.

$$\frac{Dose_A}{Dose_H} x \frac{BW_H}{BW_A} = \frac{BW_A^{3/4}}{BW_H^{3/4}}$$

$$Dose_H = Dose_A x \left(\frac{BW_A}{BW_H}\right)^{1/4}$$

$$Q_1^* H = Q_1^* A x \left(\frac{BW_H}{BW_A}\right)^{1/4}$$

APPENDIX D
ONCOGENICITY POTENCY CALCULATIONS

DATE: 04/13/2004 TIME: 14:06:07

GLOBAL 86 (MAY 1986)

BY RICHARD B. HOWE AND CYNTHIA VAN LANDINGHAM
CLEMENT ASSOCIATES 1201 GAINES STREET RUSTON, LA 71270 (318) 255-4800

Renal tumors in male rats fed chlorothalonil (administered doses)

POLYNOMIAL DEGREE SELECTED BY PROGRAM, (POLY-DEGREE=0)
MONTE CARLO TEST USED IN SELECTION

GROUP	DOSE	#RESPONSES OBSERVED/#ANIMALS	#RESPONSES PREDICTED
1	.000000	1/ 55	1.16
2	1.80000	1/ 54	1.31
3	3.80000	1/ 54	1.49
4	15.2000	4/ 54	2.53
5	40.0000	7/ 60	5.25
6	80.0000	7/ 58	8.71
7	175.000	18/ 60	20.82
8	183.000	23/ 55	20.64

CHI-SQUARE GOODNESS OF FIT STATISTIC IS 3.2081
P-VALUE FOR THE MONTE CARLO TEST IS .6900000000
FORM OF PROBABILITY FUNCTION:
P(DOSE) = 1 - exp(-Q0 - Q1 * D - Q2 * D^2 - ... - Q 6 * D^ 6)

MAXIMUM LIKELIHOOD ESTIMATES OF DOSE COEFFICIENTS

Q(0) = 2.131636159740E-02
Q(1) = 1.757356232788E-03
Q(2) = .000000000000
Q(3) = .000000000000
Q(4) = .000000000000
Q(5) = .000000000000
Q(6) = 3.392305329732E-15

MAXIMUM VALUE OF THE LOG-LIKELIHOOD IS -147.769407611
CALCULATIONS ARE BASED UPON EXTRA RISK
GLOBAL 86 LOWER CONFIDENCE LIMITS ON DOSE FOR FIXED RISK
****

RISK	MLE DOSE	LOWER BOUND ON DOSE	CONFIDENCE LIMIT SIZE	COEFFICIENTS FOR CONFIDENCE LIMIT
1.00000E-06	5.69037E-04	3.63411E-04	95.0%	Q(0)= 1.29226E-02
				Q(1)= 2.75170E-03
				Q(2)= .00000
				Q(3)= .00000
				Q(4)= .00000

Renal tumors in female rats fed chlorothalonil (administered doses)

POLYNOMIAL DEGREE SELECTED BY PROGRAM, (POLY-DEGREE=0)
MONTE CARLO TEST USED IN SELECTION

GROUP	DOSE	#RESPONSES OBSERVED/#ANIMALS	#RESPONSES PREDICTED
1	.000000	0/ 55	.00
2	1.80000	0/ 54	.05
3	3.80000	0/ 55	.12
4	15.2000	0/ 53	.63
5	40.0000	4/ 60	2.91
6	80.0000	10/ 59	8.61
7	175.000	23/ 60	28.62
8	183.000	32/ 55	27.81

CHI-SQUARE GOODNESS OF FIT STATISTIC IS 4.8938

P-VALUE FOR THE MONTE CARLO TEST IS .2600000000

FORM OF PROBABILITY FUNCTION:
P(DOSE) = 1 - exp(-Q0 - Q1 * D - Q2 * D^2)

MAXIMUM LIKELIHOOD ESTIMATES OF DOSE COEFFICIENTS

Q(0) = .000000000000
Q(1) = 5.140918602094E-04
Q(2) = 1.822902553951E-05

MAXIMUM VALUE OF THE LOG-LIKELIHOOD IS -121.709287854
CALCULATIONS ARE BASED UPON EXTRA RISK

GLOBAL 86 LOWER CONFIDENCE LIMITS ON DOSE FOR FIXED RISK

RISK	MLE DOSE	LOWER BOUND ON DOSE	CONFIDENCE LIMIT SIZE	COEFFICIENTS FOR CONFIDENCE LIMIT
1.00000E-06	1.94504E-03	5.43831E-04	95.0%	Q(0) = .00000
				Q(1) = 1.83880E-03
				Q(2) = 9.62615E-06

DATE: 04/13/2004 TIME: 14:05:12

GLOBAL 86 (MAY 1986)

BY RICHARD B. HOWE AND CYNTHIA VAN LANDINGHAM
CLEMENT ASSOCIATES 1201 GAINES STREET RUSTON, LA 71270 (318) 255-4800

Renal tumors in male rats fed chlorothalonil (absorbed doses)

POLYNOMIAL DEGREE SELECTED BY PROGRAM, (POLY-DEGREE=0)
MONTE CARLO TEST USED IN SELECTION

GROUP	DOSE	#RESPONSES OBSERVED/#ANIMALS	#RESPONSES PREDICTED
1	.000000	1/ 55	1.16
2	.610000	1/ 54	1.30
3	1.29000	1/ 54	1.49
4	5.18000	4/ 54	2.54
5	13.6000	7/ 60	5.25
6	27.2000	7/ 58	8.72
7	59.5000	18/ 60	20.83
8	62.2000	23/ 55	20.63

CHI-SQUARE GOODNESS OF FIT STATISTIC IS 3.2071
P-VALUE FOR THE MONTE CARLO TEST IS .6400000000
FORM OF PROBABILITY FUNCTION:
P(DOSE) = 1 - exp(-Q0 - Q1 * D - Q2 * D^2 - ... - Q 6 * D^ 6)

MAXIMUM LIKELIHOOD ESTIMATES OF DOSE COEFFICIENTS

Q(0) = 2.129923604015E-02
Q(1) = 5.170985367135E-03
Q(2) = .000000000000
Q(3) = .000000000000
Q(4) = .000000000000
Q(5) = .000000000000
Q(6) = 2.196126400119E-12

MAXIMUM VALUE OF THE LOG-LIKELIHOOD IS -147.769357021
CALCULATIONS ARE BASED UPON EXTRA RISK
GLOBAL 86 LOWER CONFIDENCE LIMITS ON DOSE FOR FIXED RISK

RISK	MLE DOSE	LOWER BOUND ON DOSE	CONFIDENCE LIMIT SIZE	COEFFICIENTS FOR CONFIDENCE LIMIT
1.00000E-06	1.93387E-04	1.23538E-04	95.0%	Q(0) = 1.29165E-02
				Q(1) = 8.09468E-03
				Q(2) = .00000
				Q(3) = .00000
				Q(4) = .00000

Renal tumors in female rats fed chlorothalonil (adsorbed doses)

POLYNOMIAL DEGREE SELECTED BY PROGRAM, (POLY-DEGREE=0)
MONTE CARLO TEST USED IN SELECTION

GROUP	DOSE	#RESPONSES OBSERVED/#ANIMALS	#RESPONSES PREDICTED
1	.000000	0/ 55	.00
2	.610000	0/ 54	.05
3	1.29000	0/ 55	.12
4	5.18000	0/ 53	.64
5	13.6000	4/ 60	2.91
6	27.2000	10/ 59	8.61
7	59.6000	23/ 60	28.65
8	62.2000	32/ 55	27.77

CHI-SQUARE GOODNESS OF FIT STATISTIC IS 4.9463
P-VALUE FOR THE MONTE CARLO TEST IS .2950000000

FORM OF PROBABILITY FUNCTION:
P(DOSE) = 1 - exp(-Q0 - Q1 * D - Q2 * D^2)

MAXIMUM LIKELIHOOD ESTIMATES OF DOSE COEFFICIENTS

Q(0) = .000000000000
Q(1) = 1.522879649470E-03
Q(2) = 1.572299427604E-04

MAXIMUM VALUE OF THE LOG-LIKELIHOOD IS -121.738354468

CALCULATIONS ARE BASED UPON EXTRA RISK

GLOBAL 86 LOWER CONFIDENCE LIMITS ON DOSE FOR FIXED RISK

RISK	MLE DOSE	LOWER BOUND ON DOSE	CONFIDENCE LIMIT SIZE	COEFFICIENTS FOR CONFIDENCE LIMIT
1.00000E-06	6.56607E-04	1.84491E-04	95.0%	Q(0) = .00000
				Q(1) = 5.42030E-03
				Q(2) = 8.28539E-05

APPENDIX E

ACUTE DIETARY EXPOSURE ASSESSMENT

California Department of Pesticide Regulation Ver. 7.87
DEEM ACUTE Analysis for CHLOROTHALONIL (1994-98 data)
Residue file: Acute Tier2.RS7 Adjustment factor #2 NOT used.
Analysis Date: 04-02-2004/13:02:43 Residue file dated: 04-02-2004/12:59:33/14
NOEL (Acute) = 15.000000 mg/kg body-wt/day
Daily totals for food and foodform consumption used.
Run Comment: "Tier 2 PDP and DPR monitoring data, and tolerances"

U.S. Population	Daily Exposure Analysis /a (mg/kg body-weight/day) per Capita	per User
Mean	0.000863	0.000866
Standard Deviation	0.002453	0.002455
Standard Error of mean	0.000012	0.000012
Margin of Exposure 2/	17,371	17,327
Percent of aRfD	0.58	0.58

Percent of Person-Days that are User-Days = 99.75%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000120	0.08	125,069	90.00	0.001765	1.18	8,497
20.00	0.000182	0.12	82,221	95.00	0.002879	1.92	5,210
30.00	0.000243	0.16	61,683	97.50	0.004396	2.93	3,412
40.00	0.000311	0.21	48,303	99.00	0.007166	4.78	2,093
50.00	0.000400	0.27	37,473	99.50	0.010618	7.08	1,412
60.00	0.000525	0.35	28,588	99.75	0.015592	10.39	962
70.00	0.000707	0.47	21,217	99.90	0.025323	16.88	592
80.00	0.001015	0.68	14,774				

Western region

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000908	0.000911
Standard Deviation	0.003382	0.003387
Standard Error of mean	0.000034	0.000034
Margin of Exposure	16,521	16,466
Percent of aRfD	0.61	0.61

Percent of Person-Days that are User-Days = 99.67%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000127	0.08	118,068	90.00	0.001693	1.13	8,858
20.00	0.000198	0.13	75,918	95.00	0.002728	1.82	5,497
30.00	0.000258	0.17	58,121	97.50	0.004374	2.92	3,428
40.00	0.000332	0.22	45,184	99.00	0.006958	4.64	2,155
50.00	0.000429	0.29	34,958	99.50	0.010836	7.22	1,384
60.00	0.000555	0.37	27,047	99.75	0.016115	10.74	930
70.00	0.000731	0.49	20,532	99.90	0.033030	22.02	454
80.00	0.001033	0.69	14,523				

Hispanics

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000990	0.000993
Standard Deviation	0.004694	0.004702
Standard Error of mean	0.000063	0.000064
Margin of Exposure	15,146	15,098
Percent of aRfD	0.66	0.66

Percent of Person-Days that are User-Days = 99.68%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000122	0.08	123,163	90.00	0.001637	1.09	9,164
20.00	0.000197	0.13	76,106	95.00	0.002659	1.77	5,641
30.00	0.000260	0.17	57,633	97.50	0.004027	2.68	3,725
40.00	0.000339	0.23	44,226	99.00	0.006668	4.45	2,249
50.00	0.000445	0.30	33,703	99.50	0.012311	8.21	1,218
60.00	0.000568	0.38	26,426	99.75	0.033317	22.21	450
70.00	0.000753	0.50	19,908	99.90	0.113334	75.56	132
80.00	0.001037	0.69	14,460				

Non-hispanic whites — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000854	0.000856
Standard Deviation	0.002099	0.002101
Standard Error of mean	0.000012	0.000013
Margin of Exposure	17,569	17,531
Percent of aRfD	0.57	0.57

Percent of Person-Days that are User-Days = 99.78%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000124	0.08	120,823	90.00	0.001763	1.18	8,506
20.00	0.000186	0.12	80,658	95.00	0.002902	1.93	5,169
30.00	0.000246	0.16	61,052	97.50	0.004412	2.94	3,400
40.00	0.000311	0.21	48,304	99.00	0.007311	4.87	2,051
50.00	0.000394	0.26	38,072	99.50	0.010787	7.19	1,390
60.00	0.000515	0.34	29,135	99.75	0.015882	10.59	944
70.00	0.000694	0.46	21,605	99.90	0.022722	15.15	660
80.00	0.001012	0.67	14,827				

Non-hispanic blacks — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000804	0.000807
Standard Deviation	0.001546	0.001548
Standard Error of mean	0.000021	0.000021
Margin of Exposure	18,658	18,592
Percent of aRfD	0.54	0.54

Percent of Person-Days that are User-Days = 99.65%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000096	0.06	157,055	90.00	0.001839	1.23	8,156
20.00	0.000146	0.10	103,041	95.00	0.002904	1.94	5,165
30.00	0.000210	0.14	71,359	97.50	0.004495	3.00	3,337
40.00	0.000277	0.18	54,173	99.00	0.007044	4.70	2,129
50.00	0.000376	0.25	39,903	99.50	0.009468	6.31	1,584
60.00	0.000515	0.34	29,120	99.75	0.014037	9.36	1,068
70.00	0.000693	0.46	21,638	99.90	0.018228	12.15	822
80.00	0.000979	0.65	15,323				

Non-hisp/non-white/non-black

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.000890	0.000892
Standard Deviation	0.002087	0.002090
Standard Error of mean	0.000047	0.000047
Margin of Exposure	16,862	16,810
Percent of aRfD	0.59	0.59

Percent of Person-Days that are User-Days = 99.69%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000131	0.09	114,619	90.00	0.002048	1.37	7,323
20.00	0.000198	0.13	75,893	95.00	0.002934	1.96	5,112
30.00	0.000273	0.18	55,015	97.50	0.004696	3.13	3,194
40.00	0.000357	0.24	42,062	99.00	0.006936	4.62	2,162
50.00	0.000458	0.31	32,726	99.50	0.009815	6.54	1,528
60.00	0.000599	0.40	25,035	99.75	0.011023	7.35	1,360
70.00	0.000788	0.53	19,044	99.90	0.013737	9.16	1,091
80.00	0.001105	0.74	13,572				

All infants

Daily Exposure Analysis
(mg/kg body-weight/day)

	per Capita	per User
Mean	0.001499	0.001675
Standard Deviation	0.002681	0.002782
Standard Error of mean	0.000049	0.000054
Margin of Exposure	10,007	8,956
Percent of aRfD	1.00	1.12

Percent of Person-Days that are User-Days = 89.50%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000283	0.19	53,041	90.00	0.003862	2.57	3,883
20.00	0.000435	0.29	34,486	95.00	0.007141	4.76	2,100
30.00	0.000540	0.36	27,782	97.50	0.010751	7.17	1,395
40.00	0.000676	0.45	22,193	99.00	0.014716	9.81	1,019
50.00	0.000826	0.55	18,162	99.50	0.017878	11.92	839
60.00	0.001009	0.67	14,873	99.75	0.019638	13.09	763
70.00	0.001234	0.82	12,158	99.90	0.022398	14.93	669
80.00	0.001740	1.16	8,622				

Nursing infants (<1 yr old)

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000908	0.001467
Standard Deviation	0.002539	0.003098
Standard Error of mean	0.000088	0.000132
Margin of Exposure	16,521	10,224
Percent of aRfD	0.61	0.98

Percent of Person-Days that are User-Days = 61.89%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000040	0.03	378,136	90.00	0.004270	2.85	3,513
20.00	0.000096	0.06	156,171	95.00	0.007514	5.01	1,996
30.00	0.000175	0.12	85,857	97.50	0.012385	8.26	1,211
40.00	0.000271	0.18	55,274	99.00	0.016522	11.01	907
50.00	0.000432	0.29	34,696	99.50	0.017658	11.77	849
60.00	0.000619	0.41	24,249	99.75	0.018225	12.15	823
70.00	0.000841	0.56	17,826	99.90	0.018344	12.23	817
80.00	0.001451	0.97	10,339				

Non-nursing infants (<1 yr old)

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.001723	0.001724
Standard Deviation	0.002699	0.002700
Standard Error of mean	0.000058	0.000059
Margin of Exposure	8,705	8,703
Percent of aRfD	1.15	1.15

Percent of Person-Days that are User-Days = 99.98%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000398	0.27	37,733	90.00	0.003780	2.52	3,967
20.00	0.000506	0.34	29,626	95.00	0.007118	4.75	2,107
30.00	0.000614	0.41	24,425	97.50	0.010328	6.89	1,452
40.00	0.000751	0.50	19,977	99.00	0.014191	9.46	1,057
50.00	0.000898	0.60	16,704	99.50	0.018136	12.09	827
60.00	0.001071	0.71	14,009	99.75	0.019856	13.24	755
70.00	0.001285	0.86	11,669	99.90	0.022385	14.92	670
80.00	0.001766	1.18	8,492				

Children 1-6 yrs

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.001841	0.001842
Standard Deviation	0.004801	0.004802
Standard Error of mean	0.000040	0.000040
Margin of Exposure	8,145	8,143
Percent of aRfD	1.23	1.23

Percent of Person-Days that are User-Days = 99.98%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000352	0.23	42,607	90.00	0.003743	2.50	4,007
20.00	0.000489	0.33	30,702	95.00	0.005981	3.99	2,508
30.00	0.000605	0.40	24,783	97.50	0.009066	6.04	1,654
40.00	0.000743	0.50	20,180	99.00	0.014713	9.81	1,019
50.00	0.000904	0.60	16,592	99.50	0.019700	13.13	761
60.00	0.001117	0.74	13,426	99.75	0.027885	18.59	537
70.00	0.001430	0.95	10,487	99.90	0.053717	35.81	279
80.00	0.002066	1.38	7,260				

Children 7-12 yrs

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.001054	0.001054
Standard Deviation	0.002569	0.002569
Standard Error of mean	0.000047	0.000047
Margin of Exposure	14,229	14,227
Percent of aRfD	0.70	0.70

Percent of Person-Days that are User-Days = 99.98%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000213	0.14	70,339	90.00	0.002126	1.42	7,053
20.00	0.000309	0.21	48,615	95.00	0.003259	2.17	4,602
30.00	0.000384	0.26	39,026	97.50	0.004680	3.12	3,205
40.00	0.000475	0.32	31,576	99.00	0.007596	5.06	1,974
50.00	0.000563	0.38	26,632	99.50	0.010936	7.29	1,371
60.00	0.000691	0.46	21,721	99.75	0.013831	9.22	1,084
70.00	0.000874	0.58	17,155	99.90	0.032196	21.46	465
80.00	0.001227	0.82	12,226				

Females 13+ (preg/not lactating)

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000613	0.000616
Standard Deviation	0.000882	0.000883
Standard Error of mean	0.000075	0.000075
Margin of Exposure	24,453	24,333
Percent of aRfD	0.41	0.41

Percent of Person-Days that are User-Days = 99.51%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000131	0.09	114,159	90.00	0.001361	0.91	11,022
20.00	0.000187	0.12	80,383	95.00	0.002025	1.35	7,407
30.00	0.000230	0.15	65,357	97.50	0.002954	1.97	5,077
40.00	0.000281	0.19	53,447	99.00	0.005914	3.94	2,536
50.00	0.000334	0.22	44,855	99.50	0.007358	4.91	2,038
60.00	0.000441	0.29	33,981	99.75	0.007371	4.91	2,035
70.00	0.000522	0.35	28,762	99.90	0.007379	4.92	2,032
80.00	0.000837	0.56	17,919				

Females 13+ (lactating)

	Daily Exposure Analysis (mg/kg body-weight/day) per Capita	per User
Mean	0.000764	0.000764
Standard Deviation	0.001580	0.001580
Standard Error of mean	0.000172	0.000172
Margin of Exposure	19,644	19,644
Percent of aRfD	0.51	0.51

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000166	0.11	90,410	90.00	0.001312	0.87	11,429
20.00	0.000197	0.13	76,259	95.00	0.002943	1.96	5,096
30.00	0.000233	0.16	64,359	97.50	0.003351	2.23	4,476
40.00	0.000290	0.19	51,651	99.00	0.011903	7.94	1,260
50.00	0.000334	0.22	44,965	99.50	0.011911	7.94	1,259
60.00	0.000430	0.29	34,923	99.75	0.011915	7.94	1,258
70.00	0.000487	0.32	30,814	99.90	0.011917	7.94	1,258
80.00	0.000803	0.54	18,678				

Females 13-19 (not preg or lactating)

Daily Exposure Analysis

	(mg/kg body-weight/day) per Capita	per User
Mean	0.000618	0.000620
Standard Deviation	0.001249	0.001250
Standard Error of mean	0.000036	0.000036
Margin of Exposure	24,256	24,209
Percent of aRfD	0.41	0.41

Percent of Person-Days that are User-Days = 99.80%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000110	0.07	136,750	90.00	0.001116	0.74	13,437
20.00	0.000172	0.11	87,368	95.00	0.001924	1.28	7,794
30.00	0.000217	0.14	69,212	97.50	0.002874	1.92	5,218
40.00	0.000271	0.18	55,287	99.00	0.005561	3.71	2,697
50.00	0.000331	0.22	45,324	99.50	0.008273	5.52	1,813
60.00	0.000411	0.27	36,495	99.75	0.009739	6.49	1,540
70.00	0.000538	0.36	27,868	99.90	0.015881	10.59	944
80.00	0.000720	0.48	20,828				

Females 20+ (not preg or lactating)

Daily Exposure Analysis

	(mg/kg body-weight/day) per Capita	per User
Mean	0.000703	0.000704
Standard Deviation	0.001432	0.001433
Standard Error of mean	0.000015	0.000015
Margin of Exposure	21,350	21,320
Percent of aRfD	0.47	0.47

Percent of Person-Days that are User-Days = 99.86%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000098	0.07	152,926	90.00	0.001571	1.05	9,546
20.00	0.000147	0.10	102,181	95.00	0.002613	1.74	5,740
30.00	0.000197	0.13	76,296	97.50	0.003723	2.48	4,029
40.00	0.000251	0.17	59,785	99.00	0.005930	3.95	2,529
50.00	0.000314	0.21	47,763	99.50	0.007223	4.82	2,076
60.00	0.000415	0.28	36,180	99.75	0.009809	6.54	1,529
70.00	0.000573	0.38	26,160	99.90	0.018883	12.59	794
80.00	0.000854	0.57	17,569				

Females 13-50 yrs — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000662	0.000663
Standard Deviation	0.001407	0.001408
Standard Error of mean	0.000018	0.000018
Margin of Exposure	22,653	22,609
Percent of aRfD	0.44	0.44

Percent of Person-Days that are User-Days = 99.80%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000102	0.07	147,727	90.00	0.001345	0.90	11,149
20.00	0.000153	0.10	97,904	95.00	0.002319	1.55	6,469
30.00	0.000203	0.14	73,932	97.50	0.003409	2.27	4,399
40.00	0.000255	0.17	58,804	99.00	0.005852	3.90	2,563
50.00	0.000313	0.21	47,857	99.50	0.007771	5.18	1,930
60.00	0.000400	0.27	37,519	99.75	0.010207	6.80	1,469
70.00	0.000533	0.36	28,156	99.90	0.020578	13.72	728
80.00	0.000767	0.51	19,559				

Males 13-19 yrs — Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000741	0.000741
Standard Deviation	0.002419	0.002419
Standard Error of mean	0.000070	0.000070
Margin of Exposure	20,251	20,251
Percent of aRfD	0.49	0.49

Percent of Person-Days that are User-Days =100.00%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000148	0.10	101,152	90.00	0.001248	0.83	12,021
20.00	0.000220	0.15	68,305	95.00	0.002013	1.34	7,450
30.00	0.000272	0.18	55,206	97.50	0.002892	1.93	5,186
40.00	0.000327	0.22	45,849	99.00	0.005972	3.98	2,511
50.00	0.000414	0.28	36,199	99.50	0.010180	6.79	1,473
60.00	0.000503	0.34	29,833	99.75	0.012477	8.32	1,202
70.00	0.000622	0.41	24,126	99.90	0.020859	13.91	719
80.00	0.000815	0.54	18,415				

Males 20+ yrs

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000743	0.000744
Standard Deviation	0.002388	0.002389
Standard Error of mean	0.000024	0.000025
Margin of Exposure	20,190	20,172
Percent of aRfD	0.50	0.50

Percent of Person-Days that are User-Days = 99.91%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000117	0.08	127,669	90.00	0.001454	0.97	10,316
20.00	0.000173	0.12	86,939	95.00	0.002326	1.55	6,447
30.00	0.000228	0.15	65,737	97.50	0.003379	2.25	4,439
40.00	0.000279	0.19	53,694	99.00	0.005602	3.73	2,677
50.00	0.000353	0.24	42,532	99.50	0.008330	5.55	1,800
60.00	0.000449	0.30	33,408	99.75	0.012120	8.08	1,237
70.00	0.000609	0.41	24,643	99.90	0.022767	15.18	658
80.00	0.000866	0.58	17,329				

Seniors 55+

Daily Exposure Analysis (mg/kg body-weight/day)

	per Capita	per User
Mean	0.000762	0.000762
Standard Deviation	0.001451	0.001451
Standard Error of mean	0.000017	0.000017
Margin of Exposure	19,682	19,672
Percent of aRfD	0.51	0.51

Percent of Person-Days that are User-Days = 99.95%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE) and Percent of aRfD

Perc.	Exposure	% aRfD	MOE	Perc.	Exposure	% aRfD	MOE
10.00	0.000101	0.07	148,700	90.00	0.001772	1.18	8,463
20.00	0.000151	0.10	99,019	95.00	0.002737	1.82	5,481
30.00	0.000204	0.14	73,670	97.50	0.003876	2.58	3,870
40.00	0.000260	0.17	57,705	99.00	0.006281	4.19	2,388
50.00	0.000335	0.22	44,826	99.50	0.007929	5.29	1,891
60.00	0.000463	0.31	32,427	99.75	0.010854	7.24	1,381
70.00	0.000669	0.45	22,410	99.90	0.015609	10.41	961
80.00	0.001016	0.68	14,769				

APPENDIX F

CHRONIC DIETARY EXPOSURE ASSESSMENT

California Department of Pesticide Regulation Ver. 7.87
DEEM Chronic analysis for CHLOROTHALONIL (1994-98 data)
Residue file name: H:\DEEM\DEEM Chlorothalonil\ChronicTier2 with meat and milk cran res.RS7
Adjustment factor #2 NOT used.
Analysis Date 03-25-2004/14:13:52 Residue file dated: 03-25-2004/14:13:14/14
NOEL (Chronic) = 1.8 mg/kg bw/day
COMMENT 1: Tier 2 PDP and DPR monitoring data, and tolerances, with meat and milk, cranberry at residue

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Total Exposure Percent of NOEL	Total Exposure Margin of Exposr 1/
U.S. Population (total)	0.000164	0.01%	10,950
Northeast region	0.000156	0.01%	11,511
Midwest region	0.000178	0.01%	10,121
Southern region	0.000150	0.01%	12,025
Western region	0.000180	0.01%	9,978
Hispanics	0.000195	0.01%	9,252
Non-hispanic whites	0.000160	0.01%	11,229
Non-hispanic blacks	0.000163	0.01%	11,036
Non-hisp/non-white/non-black	0.000163	0.01%	11,070
All infants (< 1 year)	0.000337	0.02%	5,344
Nursing infants	0.000122	0.01%	14,711
Non-nursing infants	0.000418	0.02%	4,304
Children 1-6 yrs	0.000355	0.02%	5,069
Children 7-12 yrs	0.000249	0.01%	7,236
Females 13-19 (not preg or nursing)	0.000137	0.01%	13,160
Females 20+ (not preg or nursing)	0.000114	0.01%	15,732
Females 13-50 yrs	0.000121	0.01%	14,916
Females 13+ (preg/not nursing)	0.000124	0.01%	14,574
Females 13+ (nursing)	0.000242	0.01%	7,430
Males 13-19 yrs	0.000200	0.01%	9,000
Males 20+ yrs	0.000133	0.01%	13,549
Seniors 55+	0.000119	0.01%	15,183

California Department of Pesticide Regulation Ver. 7.87
DEEM Chronic analysis for CHLOROTHALONIL (1994-98 data)
Residue file name: H:\DEEM\DEEM Chlorothalonil\ChronicTier2 no meat or milk cranb res.RS7
Adjustment factor #2 NOT used.
Analysis Date 03-25-2004/10:38:10 Residue file dated: 03-25-2004/10:37:22/14
NOEL (Chronic) = 1.8 mg/kg bw/day
COMMENT 1: Tier 2 PDP and DPR monitoring data, and tolerances, no meat or milk, cranberry at detected residue

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Total Exposure Percent of NOEL	Total Exposure Margin of Exposr 1/
U.S. Population (total)	0.000124	0.01%	14,534
Northeast region	0.000118	0.01%	15,243
Midwest region	0.000134	0.01%	13,450
Southern region	0.000110	0.01%	16,309
Western region	0.000140	0.01%	12,889
Hispanics	0.000148	0.01%	12,189
Non-hispanic whites	0.000122	0.01%	14,748
Non-hispanic blacks	0.000117	0.01%	15,431
Non-hisp/non-white/non-black	0.000117	0.01%	15,424
All infants (< 1 year)	0.000309	0.02%	5,827
Nursing infants	0.000114	0.01%	15,853
Non-nursing infants	0.000383	0.02%	4,699
Children 1-6 yrs	0.000255	0.01%	7,054
Children 7-12 yrs	0.000187	0.01%	9,636
Females 13-19 (not preg or nursing)	0.000104	0.01%	17,356
Females 20+ (not preg or nursing)	0.000090	0.00%	20,060
Females 13-50 yrs	0.000093	0.01%	19,319
Females 13+ (preg/not nursing)	0.000088	0.00%	20,516
Females 13+ (nursing)	0.000209	0.01%	8,619
Males 13-19 yrs	0.000151	0.01%	11,884
Males 20+ yrs	0.000097	0.01%	18,527
Seniors 55+	0.000093	0.01%	19,370

APPENDIX G

RESPONSES AND COMMENTS FROM THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Department of Pesticide Regulation

Mary-Ann Warmerdam
Director

M E M O R A N D U M

Arnold Schwarzenegger
Governor

TO: Gary Patterson, Ph.D.
Supervising Toxicologist
Medical Toxicology Branch

VIA: Keith Pfeifer, Ph.D., D.A.B.T. *[original signed by Keith Pfeifer]*
Senior Toxicologist

FROM: Lori O. Lim, Ph.D., D.A.B.T. *[original signed by Lori Lim]*
Staff Toxicologist
(916) 324-3515

DATE: December 8, 2004

SUBJECT: RESPONSE TO COMMENTS FROM THE OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT ON THE DRAFT DIETARY RISK CHARACTERIZATION DOCUMENT FOR CHLOROTHALONIL

This memorandum addresses the comment from the Office of Environmental Health Hazard Assessment (OEHHA; December 2, 2004) on the draft Dietary Risk Characterization Document for Chlorothalonil (RCD; September 8, 2004). The only concern was that subchronic/seasonal exposures were not evaluated.

Comment: The rationale provided in the RCD was insufficient support in light of the similar magnitude between the subchronic (1.5 mg/kg/day) and chronic (1.8 mg/kg/day) critical NOELs, and the potentially higher exposures during seasonal exposure compared to chronic exposure.

Response:

In a subchronic exposure scenario, individuals in a population subgroup could potentially have higher than chronic (average) exposure depending on the consumption pattern and residues on the seasonal commodities. The overall exposure for the group is, however, expected to be closer to the chronic than acute exposure because it is highly unlikely that individuals would consume commodities containing residue levels at the highest detected residues (under the acute exposure scenario) for the entire season. Using the chronic exposure estimates in the RCD (Table 23) and the critical subchronic NOEL of 1.5 mg/kg/day based on kidney effects in the rats, the margins of exposure ranged from 3571 (nonnursing infants) to 16667 (seniors, 55+ years old). Even if assuming seasonal exposure at the unlikely acute exposure level at the 95th percentile, the margins of exposure would be above the benchmark of 100 for health concern, ranging from 200 (nursing infants) to 789 (females 13 to 19 years old). Therefore, there is no additional concern with subchronic/seasonal exposure. The RCD will be revised to include this additional discussion for clarification.

Office of Environmental Health Hazard Assessment

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MEMORANDUM

Terry Tamminen
Agency Secretary

Arnold Schwarzenegger
Governor

TO: Gary Patterson, Ph.D., Chief
Medical Toxicology Branch
Department of Pesticide Regulation
P.O. Box 4015
Sacramento, California 95812-4015

FROM: Anna M. Fan, Ph.D., Chief
Pesticide and Environmental Toxicology Section
1515 Clay Street, 16th Floor
Oakland, California 946122

DATE: December 2, 2004

SUBJECT: COMMENTS ON THE DRAFT DIETARY RISK CHARACTERIZATION DOCUMENT FOR THE ACTIVE INGREDIENT CHLOROTHALONIL PREPARED BY THE DEPARTMENT OF PESTICIDE REGULATION

Thank you for the opportunity to review the draft risk characterization document (RCD) for chlorothalonil prepared by the Department of Pesticide Regulation (DPR). The Office of Environmental Health Hazard Assessment (OEHHA) reviews risk assessments prepared by DPR under the general authority of the Health and Safety Code, Section 59004, and also under the Food and Agricultural Code (FAC), Section 13129, in which OEHHA has the authority to provide advice, consultation, and recommendations to DPR concerning the risks to human health associated with exposure to pesticide active ingredients.

In addition, pursuant to Food and Agricultural Code sections 14022 and 14023, OEHHA provides review, consultation and comments to DPR on the evaluation of the health effects of candidate toxic air contaminants (TAC) included in the RCD/TAC documents. As part of its statutory responsibility, OEHHA also prepares findings on the health effects of the candidate toxic air contaminants. This documentation is to be included as part of the DPR report.

Chlorothalonil is a broad-spectrum fungicide used on fruits, vegetables, ornamentals, turf grass, paints and wood. The mechanism of action in yeast is inhibition of glycolytic and respiratory enzymes. Chlorothalonil is listed by the State of California under Proposition 65 as a chemical known to cause cancer. Approximately 630,000 pounds of chlorothalonil was applied in California in 2002.

DPR initiated this risk assessment under the mandate of California Assembly Bill 2161, known as the Food Safety Act as adverse effects were identified in acute toxicity, chronic toxicity, oncogenicity, and chromosomal effects studies with chlorothalonil. The RCD also addressed the potential risk associated with dietary exposure to SDS-3701 (a metabolite) and hexachlorobenzene (HCB, a contaminant). This version of the RCD evaluates only dietary exposures to the general public. Upon completion of the exposure assessment document, DPR plans to prepare an addendum that addresses occupational and residential exposures. OEHHA assumes that chlorothalonil will be considered in the addendum as a potential Toxic Air Contaminant (TAC). If this is indeed the case, OEHHA's subsequent review of the addendum will encompass a reevaluation of the toxicity database, taking into consideration inhalation studies that were not considered for this risk assessment since the route of human exposure under the current assessment was oral (dietary).

Our sole substantive concern with the dietary RCD is that subchronic/seasonal exposures to chlorothalonil were not evaluated in the document. The rationale provided was that "Seasonal exposure was not estimated since almost all commodities could be consumed throughout the year." We assume this to mean that because exposure to chlorothalonil does not, on average, vary appreciably over the course of a year; it is not necessary to evaluate seasonal exposures. OEHHA disagrees since seasonal exposures occur differently (exposure to food with consistently high residue levels are more likely over a short period of time than over a longer period) and are estimated differently than acute and chronic exposures (e.g., different assumptions regarding chemical concentrations in food – use of maximum residue concentrations versus mean concentrations, for example), it is important that subchronic exposure is characterized and evaluated. This is particularly relevant for chlorothalonil since the critical subchronic and chronic NOAELs are quite similar, 1.5 mg/kg-day and 1.8 mg/kg-day, respectively. The subchronic NOAEL of 1.5 mg/kg-day was based on increased kidney weights and the appearance of inclusion bodies in the kidneys of rats at the next higher dose of 3.0 mg/kg-day following a 13-week dietary exposure, and significantly increased labeling indices in rat stomach and kidney at the next higher dose of 15 mg/kg-day following a 28-day dietary exposure. The chronic NOAEL was 1.8 mg/kg-day based on kidney and fore stomach lesions in rats at the next higher dose of 3.8 mg/kg-day following a 111-week dietary exposure. Exposure sufficient to have a potential human health impact could occur in a subchronic time frame, but would be averaged out over the course of a year (or lifetime) and would therefore appear acceptable if evaluated on a chronic basis. Accordingly, OEHHA recommends adding this evaluation to the RCD.

Other than our concern with seasonal exposures noted above, OEHHA finds the dietary RCD to be appropriate, comprehensive and well written. We agree with the critical studies identified in the RCD, their respective NOAELs and the justification provided for the selection of the endpoints. We also note that under the conditions of this RCD and the assumptions made

in the document that acute and chronic dietary exposures to chlorothalonil do not appear to pose unreasonable risks to the general public.

Again, thank you for the opportunity to review this document and we hope that you find our comments useful. We look forward to our review of the addendums to this document that evaluate occupational exposure and aggregate exposures that include residues in ambient air as a source of exposure to propargite. Should you have any questions regarding OEHHA's review of this RCD, please contact Dr. David Rice at (916) 324-1277 (primary reviewer), Mr. Robert Schlag at (916) 323-2624, or me at (510) 622-3165.

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