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CHLOROTHALONIL

DRAFT

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

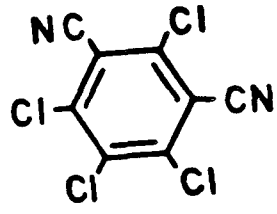
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for one-day, ten-day, longer-term (approximately 7 years, or 10% of an individual's lifetime) and lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 1897-45-6

Structural Formula




2,4,5,6-Tetrachloro-1,3-benzenedicarbonitrile

Synonyms

- Tetrachloroisophthalonitrile; Bravo; Chloroalonil; Chlorthalonil; Daconil; Exothern; Forturf; Nopcocide N96; Sweep; Termil; TPN; DAC-2787.

Uses (Meister, 1986)

- Broad-spectrum fungicide.

Properties (Meister, 1986; CHEMLAB, 1985; Meister, 1983; Windholz et al., 1983)

| | |
|---|---|
| Chemical Formula | $C_8N_2Cl_4$ |
| Molecular Weight | 265.89 |
| Physical State (25°C) | White, crystalline solid |
| Boiling Point | 350°C |
| Melting Point | 250 to 251°C |
| Density | -- |
| Vapor Pressure (40°C) | <0.01 mm Hg |
| Specific Gravity | -- |
| Water Solubility (25°C) | 0.6 mg/L |
| Octanol/Water Partition Coefficient | 1.32 (calculated) |
| Taste Threshold | -- |
| Odor Threshold | -- |
| Conversion Factor | -- |

Occurrence

- Chlorothalonil has been found in the 1 surface water sample analyzed and in none of the 560 ground water samples (STORET, 1987). Samples were collected at 1 surface water location and 556 ground water locations; and the 1 location where it was found in Michigan, the concentration was 6,500 ug/L.

Environmental Fate

- Ring-labeled $^{14}C$-chlorothalonil, at 0.5 to 1.5 ppm, was stable to hydrolysis for up to 72 days in aqueous solutions buffered at pH 5 and 7 (Szalkowski, 1976b). At pH 9, chlorothalonil hydrolyzed with half-lives of 33 to 43 days and 28 to 72 days in solutions to which ring-labeled $^{14}C$-chlorothalonil was added at 0.52 and 1.5 ppm, respectively. After 72 days of incubation, pH 9-buffered solutions treated with chlorothalonil at 1.5 ppm contained 36.4% chlorothalonil, 48.9% 3-cyano-2,4,5,6-tetrachlorobenzamide (DS-19211) and 11.3% 4-hydroxy-2,5,6-trichloroisophthalonitrile (DAC-3701).

- The degradate $^{14}C$-DAC-3701, at 1000 ppm, was not hydrolysed in aqueous solutions buffered at pH 5, 7, and 9 after 72 days of incubation (Szalkowski, 1976b).

- Ring-labeled $^{14}C$-chlorothalonil and its major degradate, ring-labeled $^{14}C$-DAC-3701, were stable to photolysis on two silt loam and three silty clay loam soils, after UV irradiation for the equivalent of 168 12-hour days of sunlight (Szalkowski, 19??).

- $^{14}C$-Chlorothalonil is degraded with half-lives of 1 to 16, 8 to 31, and 7 to 16 days in nonsterile aerobic sandy loam, silt loam and peat loam soils, respectively, at 77 to 95°F and 80% of field moisture capacity (Szalkowski, 1976a). When chlorothalonil (WP) was applied to nonsterile soils ranging in texture from sand to silty clay loam, at 76 to 100°F and 6% soil moisture, it was degraded with half-lives of 4 to more than 40 days; increasing either soil moisture content (0.6 to 8.9%) or incubation temperature (76 to 100°F) enhanced chlorothalonil degradation (Stallard and Wolfe, 1967). Soil pH (6.5 to 8) does not appear to influence or only negligibly influences the degradation rate of chlorothalonil; however, soil sterilization greatly reduced the degradation rate. The major degradate identified in nonsterile aerobic soil was DAC-3701, representing up to 69% of the applied radioactivity. Other identified degradates included DS-19221, trichloro-3-carboxybenzamide, 3-cyanotrichlorohydroxybenzamide, and 3-cyanotrichlorobenzamide (Stallard and Wolfe, 1967; Szalkowski, 1976a; Szalkowski et al., 1979).

- $^{14}C$-Chlorothalonil was immobile ($R_f$ 0.0) and the degradate $^{14}C$-DAC-3701 was found to have low to intermediate mobility ($R_f$ 0.25 to 0.43) in two silt loam and three silty clay loam soils, as evaluated using soil thin-layer chromotography (TLC) (Szalkowski, 19??). Based on batch equilibrium tests, chlorothalonil has a relatively low mobility (high adsorption) in silty clay loam (K = 26), silt (K = 29), and sandy loam (K = 20) soils but is intermediately mobile (low adsorption) in a sand (K = 3) (Capps et al., 1982). Soil organic matter content did not appear to influence the mobility of chlorothalonil in soil.

- The chlorothalonil degradate DAC-3701 is mobile in sand, loam, silty clay loam and clay soils (Wolfe and Stallard, 1968a). After eluting a 6-in soil column with the equivalent of 5 inches of water, approximately 57, 84, 10 and 84% of the applied DAC-3701 was recovered in

the leachate of the sand, loam, silty clay loam and clay soil columns, respectively.

- Chlorothalonil (4.17 lb/gal FlC) was degraded with a half-life of 1 to 3 months in sandy loam and silt loam soils when applied alone at 8.34 lb ai/A or in combination with benomyl (50% wettable powder) at 1.35 lb ai/A (Johnston, 1981). The treated soils were maintained at 80% of moisture capacity in a greenhouse.

- Under field conditions, the half-life of chlorothalonil (75% wettable powder) in a sandy loam soil was between 1 and 2 months following the last of five consecutive weekly applications totaling 15 lb ai/A (Stallard et al., 1972). Little movement of chlorothalonil (0.01 to 0.17 ppm) below the 0- to 3-inch depth occurred throughout the 8-month study. Small amounts (0.01 to 0.21 ppm) of the degradate DAC-3701 were found in soil samples collected up to 5 months post-treatment. No chlorothalonil or DAC-3701 was detected (less than 1 ppb) in a nearby stream up to 7 months post-treatment, or in ground water samples (10-foot depth) up to 8 months post-treatment. Cumulative rainfall over the study period was 26.22 inches.

## III. PHARMACOKINETICS

### Absorption

- Ryer (1966) administered $^{14}C$-chlorothalonil (dose not specified) orally to albino rats (3/sex; strain not specified). In 48 hours post-treatment, 60.21% of the radioactivity was detected in the feces, indicating that at least 40% of the oral dose was absorbed.

- Skinner and Stallard (1967) reported that rats receiving 1.54 mg of $^{14}C$-chlorothalonil in a 500 mg/kg dose (route not specified) eliminated 88% of the administered dose unchanged in the feces over 264 hours, indicating that 12% was absorbed.

- Skinner and Stallard (1967) reported that mongrel dogs receiving a single oral dose (by capsule) of 500 mg/kg of chlorothalonil, eliminated 85% of the administered dose as the parent compound within 24 hours post-treatment, indicating that 15% was absorbed.

### Distribution

- Ryer (1966) administered $^{14}C$-chlorothalonil (dose not specified) to albino rats (3/sex; strain not specified) by oral intubation. After 11 days, the carcasses retained 0.44% of the dose while 0.05% of the dose remained in the gastrointestinal tract. The highest residues occurred in the kidneys, which averaged 0.01% of the dose for the six rats. Lesser amounts were detected in the eyes, brain, heart, lungs, liver, thyroid and spleen.

- Ribovich et al. (1983) administered single doses of $^{14}C$-chlorothalonil by oral intubation to CD-1 mice at levels of 0, 1.5, 15 or 105 mg/kg.

Twenty-four hours post-treatment, the stomach, liver, kidneys, fat, small intestine, large intestine, lungs and heart accounted for less than 3% of the administered dose. The stomach and kidneys had the highest concentration at all doses tested. The compound was eliminated from the stomach and kidneys by 168 hours post-treatment.

- Wolfe and Stallard (1968b) reported a study in which dogs and rats received chlorothalonil in the diet for 2 years at 1,500 to 30,000 ppm. The amount of the 4-hydroxy-2,5,6-trichloroisophthalonitrile metabolite that was detected in the kidney tissue of dogs was less than 1.5 ppm; less than 3.0 ppm was detected in liver tissue from dogs and rats. The authors concluded that the metabolite was not stored in animal tissue.

Metabolism

- In the Wolfe and Stallard (1968b) study, only a small amount of the 4-hydroxy-2,5,6-trichloroisophthalonitrile metabolite was detected in the kidney tissue of dogs (<1.5 ppm) and in liver tissue from dogs and rats (<3 ppm).

- Marciniszyn et al. (1983) reported that when Osborne-Mendel rats were administered single oral doses of $^{14}C$-chlorothalonil by intubation at levels of 0, 5, 50, 200 or 500 mg/kg, no metabolites of chlorothalonil were unequivocally identified in urine.

Excretion

- The Ryer study (1966) revealed that, at the end of 11 days, an average of 88.45% of the administered dose was excreted in the feces, 5.14% in the urine and 0.32% in expired gases as $CO_2$.

- The Skinner and Stallard study (1967) presented results that demonstrated that 88% of a dose (route unspecified) of chlorothalonil was eliminated unchanged in the feces. Only 5.2% was eliminated via the urine and negligible amounts were detected in expired air.

- Ribovich et al. (1983) administered single doses of $^{14}C$-chlorothalonil by oral intubation to CD-1 mice at levels of 0, 1.5, 15 or 105 mg/kg. The total recoveries of radioactivity 24 hours post-treatment were 93% for the low dose, 81% for the mid dose and 62% for the high dose. The major route of elimination was the feces and was complete at 24 hours post-treatment for the low- and mid-dose animals, and by 96 hours for the high dose animals.

- Marciniszyn et al. (1981) reported a study in which single doses of $^{14}C$-chlorothalonil were administered intraduodenally to male Sprague-Dawley rats at 0.5, 5, 10, 50, 100 or 200 mg/kg. Biliary excretion of radioactivity was monitored for 24 hours. Percent recovery of radioactivity was 27.8, 20.7, 16.8, 6.4, 7.8 and 6% for each dose level, respectively.

- Marciniszyn et al. (1983a) administered $^{14}$C-chlorothalonil intraduodenally to male Sprague-Dawley rats (donor animals) at a dose of 5 mg/kg. Bile was collected for 24 hours following administration. Some of the collected bile was administered intraduodenally to recipient rats; bile was also collected from these animals for 24 hours. Data from the donor rats indicated that 1 to 6% of the administered radioactivity was excreted in the bile within 24 hours after dosing. Approximately 19% of the radioactivity in bile administered to recipient rats was excreted within 24 hours after dosing. These data suggest that enterohepatic recirculation plays a role in the metabolism of chlorothalonil in rats.

- Pollock et al. (1983) administered $^{14}$C-chlorothalonil by gavage to male Sprague-Dawley rats at dose levels of 5, 50 or 200 mg/kg. They subsequently determined blood concentrations of radioactivity. The authors hypothesized that, at 200 mg/kg, an elimination mechanism (urinary, biliary and/or metabolism) was saturated, since the kinetics were nonlinear at this dose.

## IV. HEALTH EFFECTS

- The purity of the administered chlorothalonil is assumed to be >90% for all studies described below, unless otherwise noted.

### Humans

- Johnsson et al. (1983) reported that chlorothalonil exposure resulted in contact dermatitis in 14 of 20 workers involved in woodenware preservation. The wood preservative used by the workers consisted mainly of "white spirit," with 0.5% chlorothalonil as a fungicide. Workers exhibited erythema and edema of the eyelids, especially the upper eyelids, and eruptions on the wrist and forearms. Results of a patch test conducted with 0.1% chlorothalonil in acetone were positive in 7 of 14 subjects. Reactions ranged from a few erythematous papules to marked papular erythema with a brownish hue without infiltration.

### Animals

#### Short-term Exposure

- Powers (1965) reported that the acute oral $LD_{50}$ of chlorothalonil (75% wettable powder) in Sprague-Dawley rats was >10 g/kg.

- Doyle and Elsea (1963) reported that the acute oral $LD_{50}$ of chlorothalonil in Sprague-Dawley rats was >10 g/kg.

- Rittenhouse and Narcisse (1974) reported that the acute oral $LD_{50}$ of chlorothalonil in Sprague-Dawley rats was >17.4 g/kg.

Dermal/Ocular Effects

- Doyle and Elsea (1963) reported that the dermal $LD_{50}$ of DAC-2787 (technical chlorothalonil) in albino rabbits was >10 g/kg. At dermal concentrations of 1, 2.15, 4.64 or 10 g/kg (24-hour exposure), the compound produced mild to moderate skin irritation characterized by erythema, edema, atonia and desquamation.

- Doyle and Elsea (1963) reported that when 3 mg of DAC-2787 (technical chlorothalonil) was applied to the eyes of albino rabbits, eye irritation was limited to mild conjunctivitis that subsided largely or completely within 7 days.

- Auletta and Rubin (1981) reported the results of eye irritation studies in cynomologus monkeys and New Zealand White rabbits using a formulation containing 96% chlorothalonil. In both species, 0.1 mL of the test substance was instilled into the conjunctival sac of one eye. Each species displayed mild and transient ocular irritation as evidenced by corneal opacities that were reversed by 4 days post-instillation. The animals also showed slight to moderate iridial and conjunctival effects which were also reversible. Rinsing reduced conjunctival and iridial effects and prevented formation of corneal opacities.

Long-term Exposure

- Blackmore and Shott (1968) administered technical grade DAC 2787 (chlorothalonil) to Charles River rats for 90 days at dietary levels of 0, 4, 10, 20, 30, 40 or 60 ppm (approximately 0, 0.2, 0.5, 1.0, 1.5, 2.0 or 3.0 mg/kg/day; Lehman, 1959). No compound-related effects were reported regarding physical appearance, growth, survival, terminal clinical values, organ weights or organ-to-body weight ratios. Microscopically, the kidneys exhibited occasional vacuolation and swelling of the epithelial cells lining the deeper proximal convoluted tubules. These changes were more numerous and more severe in the two highest dose groups. The authors stated that the difference between the two highest dose groups (2.0 and 3.0 mg/kg/day) and the controls was distinct, but the difference between the lower dose groups and controls was not clear. Based on this information, a NOAEL of 30 ppm (1.5 mg/kg/day) is identified.

- Wilson et al. (1981) administered chlorothalonil in the diet to Charles River CD rats (20/sex/dose) for 90 days at doses of 0, 40, 80, 175, 375, 750 or 1,500 mg/kg/day. At doses of 375 mg/kg/day or higher, significant decreases in body weight were reported. Decreases in glucose levels, blood urea nitrogen and serum thyroxine were attributed by the investigators to body weight effects. A dose-related decrease in serum glutamic-pyruvic transaminase (SGPT) was noted in all test groups. Significant increases in kidney weights were also noted in males at 40, 80, 175 and 375 mg/kg, while in females increased kidney weights were noted at 80, 175 and 750 mg/kg. These were dose-related increases in kidney-to-body weight ratios in both sexes at all doses. Focal acute gastritis occurred in some rats of both

sexes at all doses and this effect was inversely related to dose. A LOAEL of 40 mg/kg/day (the lowest dose tested) is identified in this study.

- Colley et al. (1983) administered technical-grade chlorothalonil in the diet to Charles River rats (27 males and 28 females per dose) for 13 weeks at concentrations of 0, 1.5, 3.0, 10 or 40 mg/kg/day. Histopathological examination revealed that at a dose of 3.0 mg/kg/day or greater, all males displayed an increased number of irregular intracytoplasmic inclusion bodies in the renal proximal convoluted tubules. A NOAEL of 1.5 mg/kg/day is identified in this study.

- Shults et al. (1983) administered technical-grade chlorothalonil to CD-1 mice for 90 days at dietary concentrations of 0, 7.5, 15, 50, 275 or 750 ppm (approximately 0, 1.1, 2.3, 7.5, 33.8 or 112.5 mg/kg/day; Lehman, 1959). No treatment-related effects were noted on survival, physical condition, body weight, food consumption or gross pathology. At 750 ppm (112.5 mg/kg/day), an increase in alkaline phosphatase levels was observed in females only. Increased kidney weight was reported in males dosed at 750 ppm (112.5 mg/kg/day) and in females dosed at 275 and 750 ppm (33.8 and 112.5 mg/kg/day). Histopathologically, dose-related changes in the forestomach of mice were characterized by hyperplasia and hyperkeratosis of squamous epithelial cells. These changes were observed in the 50-, 275- and 750-ppm dose groups. No other treatment-related histopathological changes were reported. A NOAEL of 15 ppm (2.3 mg/kg/day) is identified in this study.

- Paynter and Murphy (1967) administered DAC 2787 (chlorothalonil) to beagle dogs (4/sex/dose) for 16 weeks at dietary concentrations of 0, 250, 500 or 750 ppm (approximately to 0, 6.3. 12.5 or 18.8 mg/kg/day; Lehman, 1959). No effects attributable to chlorothalonil were noted in terms of appearance, behavior, appetite, elimination, body weight changes, gross pathology or organ weights. Hematological, biochemical and urinalysis values were generally within accepted limits in treated and control animals, except for slightly elevated protein-bound iodine values in treated dogs (especially high-dose females). No compound-related histopathology was noted. Based on this, a minimum NOAEL of 750 ppm (18.8 mg/kg/day) is identified.

- Hastings et al. (1975) administered chlorothalonil to Wistar albino rats (15/sex/dose for treatment groups, 30/sex for controls) for four months at dietary concentrations of 0, 1, 2, 4, 15, 30, 60 or 120 ppm (approximately 0, 0.05, 0.1, 0.2, 0.8, 1.5, 3 or 6 mg/kg/day; Lehman, 1959). No significant differences between treated and control groups were seen in body weight, food consumption, mortality or gross pathological changes. Histopathological examination of the kidneys revealed no demonstrable effects at any dose level. A minimum NOAEL of 120 ppm (6 mg/kg/day) is identified.

- Blackmore et al. (1968) administered DAC 2787 (chlorothalonil) to Charles River rats (35/sex/dose) for 22 weeks at dietary concentrations of 0, 250, 500, 750 or 1,500 ppm (approximately 0, 12.5, 25, 37.5 or

75 mg/kg/day; Lehman, 1959). At all dose levels, male rats gained less weight from weeks 11 to 22. Females gained less weight from weeks 9 to 22 at 750 and 1,500 ppm (37.5 or 75 mg/kg/day). Food consumption values were similar for all groups. No differences between control and test animals were reported for various hematological parameters, urinalysis and plasma and urine electrolytes. Results of gross necropsy revealed that livers and kidneys of males treated at 750 or 1,500 ppm (37.5 or 75 mg/kg/day) were larger than controls. Microscopic examinations demonstrated dose-related compound-induced alterations in the kidneys of both sexes at all doses. These changes were characterized by irregular swelling of the tubular epithelium, epithelial degeneration and tubular dilatation. There was a significant increase in renal tubular diameter in males at all dose levels. Accordingly, a LOAEL of 250 ppm (12.5 mg/kg/day) is identified.

° Blackmore and Kundzin (1969) administered technical-grade DAC 2787 (chlorothalonil) to rats (strain not specified) (35/sex/dose) for 1 year at dietary concentrations of 0, 4, 10, 20, 30, 40 or 60 ppm. The authors indicated that these dietary levels correspond to 0, 0.2, 0.5, 1.0, 1.5, 2.0 or 3.0 mg/kg/day. No compound-related effects on physical appearance, behavior, growth, food consumption, survival, clinical laboratory values, organ weights or gross pathology were noted. Microscopically, there were kidney alterations in both sexes at 40 and 60 ppm (2.0 and 3.0 mg/kg/day). These alterations occurred primarily in the deeper cortical tubules and consisted of increased vacuolation of epithelial cells accompanied by swelling or hypertrophy of the affected cells, often with the deposition of an eosinophilic droplet material in the cytoplasm of the vacuole. Statistical significance was not addressed. A NOAEL of 30 ppm (1.5 mg/kg/day) is identified.

° Holsing and Voelker (1970) administered technical-grade chlorothalonil to beagle dogs (eight/sex/dose) for 104 weeks at dietary concentrations of 0, 60 or 120 ppm (approximately 0, 1.5 or 3 mg/kg/day; Lehman, 1959). After 2 years of administration, compound-related histopathological changes were observed in the kidneys of males fed 120 ppm (3 mg/kg/day). Males fed 60 ppm (1.5 mg/kg/day) and females fed both dose levels were comparable to controls. The observed changes included increased vacuolation of the epithelium in both the convoluted and collecting tubules and increased pigment in the convoluted tubular epithelium. Clinical findings, terminal body weight, organ-to-body weight ratios and gross pathology revealed no conclusive compound-related trends. A NOAEL of 60 ppm (1.5 mg/kg/day) is identified.

° Tierney et al. (1983) administered technical grade chlorothalonil to Charles River CD-1 mice (60/sex/dose) for 2 years at dietary concentrations of 0, 750, 1,500 or 3,000 ppm. The authors indicated that these dietary levels were approximately 0, 119.4, 251.1 or 517.4 mg/kg/day for males and 0, 133.6, 278.5 or 585.0 mg/kg/day for females. No treatment-related effects on body weight, food consumption, physical condition or hematological parameters were noted. A slightly increased mortality rate was noted in males receiving 3,000 ppm (517.4 mg/kg/day). Also, kidney-to-body weight ratios and

kidney-to-brain weight ratios were increased significantly in all test groups. Gross necropsy revealed a number of renal effects including kidney enlargement, discoloration, surface irregularities, pelvic dilation, cysts, nodules and masses. Effects on the stomach included an increased incidence in masses or nodules. In the stomach and esophagus, nonneoplastic histopathological effects were noted at all dose levels, and included hyperplasia and hyperkeratosis of the squamous mucosa. This was considered to be indicative of mucosal irritation. Other changes in the stomach included mucosal and submucosal inflammation, focal necrosis or ulcers of mucosa and hyperplasia of glandular mucosa. Reported histopathological effects on the kidney included an increase in the incidence and severity of glomerulonephritis, cortical tubular degeneration and cortical cysts. These changes were not dose-related, but they did occur at higher incidences in treated animals. Based on the information presented in this study, a LOAEL of 750 ppm (119.4 mg/kg/day-males; 133.6 mg/kg/day-females) is identified.

Reproductive Effects

- In a three-generation reproduction study, Paynter and Kundzin (1967) administered a mixture containing 93.6% chlorothalonil to Charles River rats (10 males and 20 females per dose) at dietary concentrations of 0 or 5,000 ppm (approximately 0 or 250 mg/kg/day; Lehman, 1959). At the dose tested, the test material produced significant growth suppression in the nursing litters of each generation. Reproductive performance was not affected and pups showed no malformations attributable to the test substance. Body weight gains for exposed male and female rats of each generation were lower than controls.

Developmental Effects

- Rodwell et al. (1983) administered technical grade chlorothalonil by gavage at doses of 0, 25, 100 or 400 mg/kg/day to Sprague-Dawley rats (25/dose level) on days 6 to 15 of gestation. No compound-related external, internal or skeletal malformations were observed in fetuses. At 400 mg/kg/day, maternal toxicity was noted (as evidenced by changes in appearance, three deaths, decreased body weight gain and food consumption). A slight increase in the number of early embryonic deaths was associated with this maternal toxicity. This study identifies a NOAEL of 400 mg/kg/day for teratogenic effects and a NOAEL of 100 mg/kg/day for maternal toxicity.

- Wazeter et al. (1976) administered DTX-75-0016 (chlorothalonil; purity not specified) by oral intubation at doses of 0, 1, 2.5 or 5 mg/kg to Dutch Belted rabbits (10/dose) on days 6 to 18 of gestation. No compound-related changes in general behavior or appearance were reported at the 1 or 2.5 mg/kg dose level. Occasional hypothermia and hyperactivity were noted at a dose of 5 mg/kg. Maternal body weight was not affected at any dose. No signs of toxicity were reported regarding the number of implantation sites, numbers of live or dead fetuses, live fetal weight, sex ratio or structural development. However, an increase in the number of females with dead or resorbed

fetuses (nine) and in the number of females aborting (four, two died during the study) were seen at 5 mg/kg. Based on this information, this study identifies a NOAEL of 2.5 mg/kg/day for maternal/fetal toxicity and a NOAEL of 5 mg/kg/day for teratogenic effects.

- Shirasu and Teramoto (1975) administered chlorothalonil by gavage to Japanese white rabbits (eight controls, nine per dose) at doses of 0, 5 or 50 mg/kg/day on days 6 to 18 of gestation. At 50 mg/kg/day, four of the nine does aborted. No compound-related growth retardation or malformations were noted in offspring in any test group. This study identifies a NOAEL of 50 mg/kg/day for teratogenic effects and a NOAEL of 5 mg/kg/day for maternal toxicity.

Mutagenicity

- Quinto et al. (1981) reported that chlorothalonil (concentrations not specified) was not mutagenic, with or without metabolic activation, in five tester strains of Salmonella typhimurium.

- Wei (1982) reported that chlorothalonil, at concentrations up to 764 ug/plate, was not mutagenic in S. typhimurium strains TA 1535, 1537, 1538, 100 or 98, with or without liver or kidney activation systems.

- Kouri et al. (1977c) reported that DTX-77-0035 (chlorothalonil) at concentrations up to 6.6 ug/plate did not induce point mutations in S. typhimurium strains TA 1535, 100, 1537, 1538 or 98, with or without S-9 activation.

- Shirasu et al. (1975) reported the results of a reverse mutation test using S. typhimurium strains TA 1535, 1537, 1538, 98 and 100 and Escherichia coli WP2 $hcr^+$ and WP2 $hcr^-$. Chlorothalonil failed to produce an effect without activation at concentrations up to 500 pg/plate; negative results also were obtained with activation at chlorothalonil concentrations up to 100 pg/plate.

- Kouri et al. (1977b) reported the results of a DNA repair assay using S. typhimurium strains TA 1978 and 1538. Chlorothalonil, dissolved in dimethylsulfoxide at 1 mg/mL and tested at 2, 10 and 20 uL of the stock solution per plate, was found to be active in both strains with or without metabolic activation.

- DeBertoldi et al. (1978) reported that chlorothalonil (2,500 ppm) did not induce mitotic gene conversions in Saccharomyces cerevisiae in the presence or absence of metabolic activation systems. In tests on Aspergillus nidulans using both resting and germinating conidia, chlorothalonil (up to 200 ppm) did not induce mitotic gene conversions.

- Shirasu et al. (1975) reported that, at concentrations up to 200 ug/disk, chlorothalonil was negative in a rec-assay using Bacillus subtilis strains H17 and M45.

- Kouri et al. (1977a) exposed Chinese hamster cells (V-79) and mouse fibroblast cells (BALB/3T3) in vitro to chlorothalonil at concentrations of 0.3 ug/mL (for V-79 cells) or 0.03 ug/mL (for mouse fibroblast cells). The V-79 cells were tested without metabolic activation; the BALB/3T3 cells were tested with and without metabolic activation. Chlorothalonil was not mutagenic in either cell type.

- Mizens et al. (1983a) reported the results of a micronucleus test in Wistar rats, Swiss CFLP mice and Chinese hamsters. Rats were dosed at 0, 8, 40, 200, 1,000 or 5,000 mg/kg; mice and hamsters received 0, 4, 20, 100, 500 or 2,500 mg/kg. All animals were dosed by gavage and all received two doses, 24 hours apart. Chlorothalonil did not induce bone marrow erythrocyte micronuclei in any of the species tested.

- Legator (1974) reported the results of an in vivo cytogenetic test on chlorothalonil in mice (strain not specified) using the micronuclei procedure. The test compound was administered by gavage for 5 days at a concentration of 6.5 mg/kg/day. At this concentration, chlorothalonil did not increase the number of cells with micronuclei.

- Legator (1974) presented the results of a host-mediated assay using male Swiss albino mice and S. typhimurium strains G-46, TA1530, C-207, TA1531, C-3076, TA1700, D-3056 and TA1724. Mice (10/dose) received chlorothalonil by gavage for 5 days at 6.5 mg/kg/day. The compound did not produce any measurable mutagenic response when initially evaluated in vitro against the eight tester strains of S. typhimurium. When the tester strains were inoculated into treated mice, no increase in mutation frequency was observed.

- Legator (1974) presented the results of a dominant lethal assay in which male mice (strain not specified) were dosed with chlorothalonil for five days at 6.5 mg/kg/day. These mice were mated with untreated females, and the number of early fetal deaths and preimplantation losses were measured. There was no significant difference in the fertility rates between test and control animals during weeks 1 to 7. At week 8, there was a significant decrease in fertility in the test group.

- Mizens et al. (1983b) presented the results of a chromosomal aberration test in Chinese hamsters. The test animals received two doses of chlorothalonil, 24 hours apart, by gavage at concentrations of 0, 8, 40, 200, 1,000 or 5,000 mg/kg. At 5,000 mg/kg, a statistically significant increase in bone marrow chromosomal abnormalities was observed. However, the authors concluded that this effect could not be attributed to chlorothalonil because the animals exhibited toxic responses to dosing.

Carcinogenicity

- NCI (1980) reported the results of a study in which technical-grade chlorothalonil was administered to Osborne-Mendel rats (50/sex/dose) for 80 weeks at Time-Weighted Average (TWA) dietary doses for both males and females of 5,063 or 10,126 ppm, respectively. These dietary

doses have been calculated to correspond to approximately 253 and 506 mg/kg/day (Lehman, 1959). Matched controls consisted of groups of 10 untreated rats of each sex; pooled controls consisted of the matched controls combined with 55 untreated male or female rats from other bioassays. An observation period of 30 to 31 weeks followed dosing. Clinical signs that appeared with increased frequency in dosed rats included hematuria and, from week 72 on, bright yellow urine. Adenomas and carcinomas of renal tubular epithelium occurred with a significant ($p = 0.03$, males; $p = 0.007$, females) dose-related trend. The frequency of renal tumors was statistically greater in the high-dose males ($p = 0.035$) and high-dose females ($p = 0.016$) than in corresponding controls (males: pooled controls, 0/62; low dose, 3/46; high dose, 4/49; females: pooled controls, 0/62; low dose, 1/48; high dose, 5/50). The observed adenomas and carcinomas were considered to be histogenically related. Results of this study were interpreted as sufficient evidence of carcinogenicity in Osborne-Mendel rats.

- NCI (1980) also reported a study in which technical-grade chlorothalonil was administered to B6C3F1 mice (50/sex/dose) for 80 weeks at TWA dietary doses of 2,688 or 5,375 ppm for males and 3,000 or 6,000 ppm for females. These dietary doses have been calculated to correspond to approximately 403.2 or 806.3 mg/kg for males and 450 or 900 mg/kg for females (Lehman, 1959). Matched controls consisted of 10 untreated mice of each sex; pooled controls consisted of the matched controls combined with 50 untreated male or female mice from other bioassays. An observation period of 11 to 12 weeks followed dosing. Since the dosed female mice did not show depression in mean body weights or decreased survival compared with the controls, they may have been able to tolerate a higher dose. No tumors were found to occur at a greater incidence among dosed animals than among controls. It was concluded that, under the conditions of this bioassay, chlorothalonil was not carcinogenic in $B6C3F_1$ mice.

- Tierney et al. (1983) administered technical-grade chlorothalonil (97.7% pure) to Charles River CD-1 mice (60/sex/control and dose groups) for 2 years at dietary concentrations of 0, 750, 1,500 or 3,000 ppm. The authors indicated that these dietary levels were equivalent to 0, 119, 251 or 517 mg/kg/day for males and 0, 133, 278 or 585 mg/kg/day for females. Increased incidences of squamous cell tumors of the forestomach were noted in all treatment groups. These tumors consisted principally of carcinomas, although papillomas were also seen. This increased incidence was statistically significant in females dosed at 1,500 ppm (279 mg/kg/day). No clear dose-related trend in the incidence of these tumors was observed. A slight increase in the incidence of tumors of the glandular epithelium of the fundic stomach was observed in dosed animals; this increase was neither statistically significant nor dose-related. When the numbers of animals with epithelial tumors of the fundic or forestomach were combined, the incidence of these tumors showed a statistically significant increase in the 1,500- and 3,000-ppm female dose groups (279 and 585 mg/kg/day). No treatment-related renal neoplasms were seen in any female dose group. Increased incidences of adenomas and carcinomas in renal

cortical tubules were noted in all treated groups of male mice. These changes did not show a dose-response relationship; the increased incidence was statistically significant only in the 750 ppm (251 mg/kg/day) group. The authors concluded that the administration of chlorothalonil caused an increase in the incidence of primary gastric tumors and an increase in the incidence of renal tubular neoplasms.

- Wilson et al. (1985) gave chlorothalonil (98.1% pure with less than 0.03% hexachlorobenzene) to Fischer 344 rats (60/sex/dose) in their diet at dose levels of 0, 40, 80 or 175 mg/kg/day. Males were treated for 116 weeks, while females received the chemical for 129 weeks. Survival among the various groups was comparable. In both sexes, at the high-dose level, there were significant decreases in body weights. In addition, there were also significant increases in blood urea nitrogen and creatinine, while there were decreases in serum glucose and albumin levels. In both sexes, there were dose-dependent increases in kidney carcinomas and adenomas at doses above 40 mg/kg/day. In the high-dose females, there was also a significant increase in stomach papillomas. The data show that, in the Fischer 344 rat, chlorothalonil is a carcinogen.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for one-day, ten-day, longer-term (approximately 7 years) and lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

### One-day Health Advisory

No information was found in the available literature that was suitable for determination of a One-day HA for chlorothalonil. Accordingly, it is recommended that the Ten-day HA value (250 ug/L, calculated below) for a 10-kg child be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The rabbit teratology study by Wazeter et al. (1976) has been chosen to serve as the basis for the calculation of the Ten-day HA. Animals received 0, 1, 2.5 or 5 mg/kg chlorothalonil by gavage on days 6 through 18 of gestation. No adverse effects were observed at either of the two lower treatment doses. At 5 mg/kg, an increase in the number of females with dead or resorbed fetuses and in the number of females aborting was observed. The NOAEL for maternal/fetal toxicity is 2.5 mg/kg/day.

The Ten-day HA for the 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(2.5 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.25 \text{ mg/L } (250 \text{ ug/L})$$

where:

2.5 mg/kg/day = NOAEL, based on absence of maternal or fetal toxicity in rabbits exposed to chlorothalonil via gavage on days 6 to 18 of gestation.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The studies by Colley et al. (1983), Blackmore and Kundzin (1969) and Blackmore and Shott (1968) have been selected to serve as the basis for the Longer-term HA for chlorothalonil. In the study by Colley et al., technical-grade chlorothalonil was administered in the diet to Charles River rats for 13 weeks at concentrations of 0, 1.5, 3.0, 10 or 40 mg/kg/day. Histopathological examinations revealed that at doses of 3.0 mg/kg/day or greater, male rats displayed an increased number of intracytoplasmic inclusion bodies in the proximal convoluted renal tubules. Blackmore and Shott (1968), gave technical-grade chlorothalonil in the diet to Charles River rats for 90 days at doses of 0, 0.2, 0.5, 1.0, 1.5, 2.0 or 3.0 mg/kg/day. At the two highest dose levels, the kidneys exhibited occasional vacuolation and swelling of the epithelial cells lining the deeper proximal convoluted tubules. In the Blackmore and Kundzin (1969) study, technical-grade chlorothalonil was administered in the diet to rats for 1 year at doses of 0, 0.2, 0.5, 1.0, 1.5, 2.0 or 3.0 mg/kg/day. At the 2 higher doses, there were alterations in the deeper convoluted renal tubules in both sexes. Each of the studies identified a NOAEL of 1.5 mg/kg/day.

The Longer-term HA for a 10 kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(1.5 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.15 \text{ mg/L } (150 \text{ ug/L})$$

where:

1.5 mg/kg/day = NOAEL, based on absence of kidney effects in rats exposed to chlorothalonil in the diet for 13 weeks.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(1.5 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 0.525 \text{ mg/L } (525 \text{ ug/L})$$

where:

1.5 mg/kg/day = NOAEL, based on absence of kidney effects in rats exposed to chlorothalonil in the diet for 13 weeks.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Holsing and Voelker (1970) has been selected to serve as the basis for the Lifetime HA for chlorothalonil. In this study, technical-grade chlorothalonil was administered to beagle dogs (eight/sex/dose) for 104 weeks at dietary concentrations of 0, 60 or 120 ppm (0, 1.5 or 3.0 mg/kg/day). The results following 2 years of administration revealed compound-related histopathological changes in the kidneys of males fed 120 ppm (3 mg/kg/day). Males fed 60 ppm (1.5 mg/kg/day) and females fed both dose levels were comparable to controls. The observed changes included increased vacuolation of the epithelium in both the convoluted and collecting tubules and increased pigment in the convoluted tubule epithelium. From these results, a NOAEL of 1.5 mg/kg was identified.

Using this NOAEL, the Lifetime HA is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(1.5 \text{ mg/kg/day})}{(100)} = 0.015 \text{ mg/kg/day}$$

where:

1.5 mg/kg/day = NOAEL, based on absence of histopathological changes in dogs fed chlorothalonil for one year.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.015 \text{ mg/kg/day})\ (70 \text{ kg})}{2 \text{ L/day}} = 0.525 \text{ mg/L } (525 \text{ ug/L})$$

where:

0.015 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

The estimated excess cancer risk associated with lifetime exposure to drinking water containing chlorothalonil at 525 ug/L (the DWEL) is $3.5 \times 10^{-4}$. This estimate represents the upper 95% confidence limit from extrapolations prepared by OPP and ODW using the linearized, multistage model. The actual risk is unlikely to exceed this value, but there is considerable uncertainty as to the accuracy of risks calculated by this methodology.

Evaluation of Carcinogenic Potential

- In an NCI bioassay (1980), technical grade chlorothalonil was administered in the diet at 253 or 506 mg/kg/day to Osborne-Mendel

rats for 80 weeks. A statistically significant increase in the frequency of renal tumors was observed in high-dose males and females.

- NCI (1980) reported that chorothalonil was not carcinogenic in $B6C3F_1$ mice when administered in the diet, at 403 or 806 mg/kg and 450 or 900 mg/kg for males and females, respectively, for 80 weeks. However, Tierney et al. (1983) concluded that chlorothalonil was carcinogenic in Charles River CD-1 which received the compound (0, 119, 251 or 517 mg/kg/day for males and 0, 134, 279 or 585 mg/kg/day for females) in the diet for 2 years. Increased incidences of squamous cell papilloma and carcinoma of the forestomach were noted in all treatment groups. This increase was statistically significant only in the mid-dose females. Increased incidences of adenoma and carcinoma of the renal cortical tubules were observed in all treatment groups. Again, no dose-response was noted, since these increases were statistically significant only in the mid-dose males.

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of chlorothalonil.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), chlorothalonil is classified in Group B2: probable human carcinogen. This category is for chemicals for which there is inadequate evidence from human studies and sufficient evidence from animal studies.

- From the Wilson et al. (1985) data, OPP calculated a $q_1^*$ of $2.4 \times 10^{-2}$ $(mg/kg/day)^{-1}$. The 95% upper limit lifetime dose in drinking water associated with a $10^{-6}$ excess risk level is 1.5 ug/L. Corresponding levels for $10^{-5}$ and $10^{-4}$ are 15 and 150 ug/L, respectively. While recognized as statistically alternative approaches, the range of risks described by using any of these modelling approaches has little biological significance unless data can be used to support the selection of one model over another. In the interest of consistency of approach and in providing an upper bound on the potential cancer risk, the Agency has recommended use of the linearized multistage approach. However, for completeness, the $10^{-6}$ risk numbers for other models will be given. These values, at the $10^{-6}$ level, are: multihit - 9 ug/L; one hit - 2 ug/L; probit - 51 ug/L; logit - 0.8 ug/L; and Weibel - 0.6 ug/L.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- WHO Temporary Acceptable Daily Intake = 0.005 mg/kg/day (Vettorazzi and Van den Hurk, 1985).

- EPA/OPP has calculated a PADI of 0.015 mg/kg/day based on the NOAEL of 1.5 mg/kg/day identified in the 2-year dog study (Holsing and and Voelker, 1970) and an uncertainty factor of 100 (U.S. EPA, 1984a).

- U.S. EPA established tolerances in or on raw agricultural commodities residue levels of 0.1 to 5 ppm (40 CFR 180.275, 1985).

## VII. ANALYTICAL METHODS

- Analysis of chlorothalonil is by a gas chromatographic (GC) method applicable to the determination of certain chlorinated pesticides in water samples (U.S. EPA, 1986b). In this method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using an electron capture detector. The method detection limit has not been determined for chlorothalonil, but it is estimated that the detection limits for analytes included in this method are in the range of 0.01 to 0.1 ug/L.

## VIII. TREATMENT TECHNOLOGIES

- Reverse osmosis (RO) is a promising treatment method for pesticide-contaminated water. As a general rule, organic compounds with molecular weights greater than 100 are candidates for removal by RO. *Larson et al. (1982) reported* 99% removal efficiency of chlorinated pesticides by a thin-film composite polyamide membrane operating at a maximum pressure of 1,000 psi and a maximum temperature of 113°F. More operational data are required, however, to specifically determine the effectiveness and feasibility of applying RO for the removal of chlorothalonil from water. Also, membrane adsorption must be considered when evaluating RO performance in the treatment of chlorothalonil-contaminated drinking water supplies.

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