United States
Environmental Protection
Agency

# Drinking Water Health Advisory For Dacthal and Dacthal Degradates: Tetrachloroterephthalic acid (TPA) and Monomethyl Tetrachloroterephthalic acid (MTP)

April 2008

# Drinking Water Health Advisory
# For Dacthal and Dacthal Degradates: Tetrachloroterephthalic Acid (TPA) and Monomethyl Tetrachloroterephthalic Acid (MTP)

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http://www.epa.gov/waterscience/

Document Number: 822-R-08-011
April, 2008

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## ACKNOWLEDGMENTS

This document was prepared by Oak Ridge National Laboratory, Oak Ridge, Tennessee, work assignment 2006-002-2, under the U.S. EPA IAG Number DW-89-92209701. The Lead EPA Scientist is Joyce Morrissey Donohue, Ph.D., Health and Ecological Criteria Division, Office of Science and Technology, Office of Water, U. S. Environmental Protection Agency.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| a.i. | active ingredient |
| atm | atmosphere |
| BMD | benchmark dose |
| BMDL | lower confidence bound on the Bench Mark Dose |
| CAS | Chemical Abstracts Service |
| EPA | Environmental Protection Agency |
| g | gram |
| gd | gestation day |
| Hg | mercury |
| HSDB | Hazardous Substances Data Bank |
| kg | kilogram |
| $K_{oc}$ | organic carbon partition coefficient |
| $K_{ow}$ | octanol-water partition coefficient |
| L | liter |
| LEL | lowest effect level |
| LOAEL | lowest observed adverse effect level |
| LOEL | lowest observed effect level |
| m | meter |
| $m^3$ | cubic meters |
| µg | microgram |
| mg | milligram |
| min | minute |
| mL | milliliter |
| mm | millimeter |
| mM | millimolar |
| mol | mole |
| MRL | minimum reporting level |
| NAWQA | National Water Quality Assessment |
| NOAEL | no observed adverse effect level |
| NOEL | no observed effect level |
| OPP | Office of Pesticide Programs |
| OGWDW | Office of Ground Water and Drinking Water |
| OST | Office of Science and Technology |
| OW | Office of Water |
| ppm | parts per million |
| PWS | Public Water Systems |
| RED | Reregistration Eligibility Decision |
| RfD | reference dose |
| RSC | relative source contribution |
| SDWA | Safe Drinking Water Act |
| UCM | unregulated contaminant monitoring |

## 1.0 INTRODUCTION

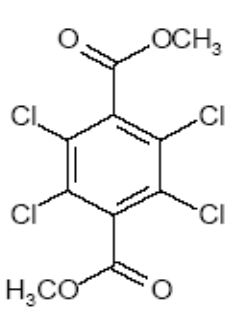
The Health Advisory (HA) Program, sponsored by the Office of Water (OW), provides information on the environmental properties, health effects, analytical methods, and treatment technologies for regulated and unregulated drinking water contaminants. HAs establish nonregulatory concentrations of drinking water contaminants at which adverse health effects are not anticipated to occur over specific exposure durations (one-day, ten-days, several years, and a lifetime). HAs serve as informal technical guidance to assist Federal, State and local officials, and managers of public or community water systems in 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.

The Registration Eligibility Decision (RED for dacthal or DCPA (U.S. EPA, 1998a: http://www.epa.gov/pesticides/reregistration/dcpa/ is the peer reviewed health risk assessment that supports the HA. A comprehensive summary of the data that support this HA is included in the OW Health Effects Support Document for Dacthal and its degradates: http://www.epa.gov/safewater/ccl/pdfs/reg_determine2/healtheffects_ccl2-reg2_dacthaldegradates.pdf

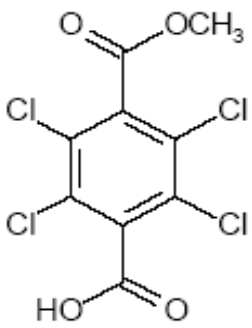
## 2.0 GENERAL INFORMATION AND PROPERTIES

### 2.1 Chemical and Physical Properties

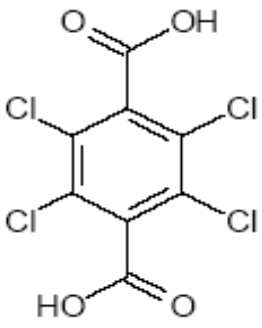
Dacthal is a pre-emergence herbicide. Tetrachloroterephthalic acid (TPA) and monomethyl tetrachloroterephthalic acid (MTP) are its environmental degradates; they are formed through hydrolysis of the methyl ester groupings in dacthal. TPA is the terminal hydrolytic dacthal degradate. The chemical structures of dacthal and of its two major metabolites, MTP and TPA are shown below. Another degradate,1,2,4,5-Tetrachlorobenzene can be formed in the environment by photolysis.




Dacthal




MTP




TPA

**Synonyms:** Dacthal (registered trade name): chlorthal-dimethyl, dimethyl tetrachloroterephthalate; 1,4-benzenedicarboxylic acid, 2,3,5,6-tetrachloro-, dimethyl ester; DAC 893; dacthalor; and DCPA (U.S. EPA, 2006a; ChemFinder 2004; HSDB, 2005).

MTP: monomethyl tetrachloroterephthalic acid; chlorthal-monomethyl; monomethyl 2,3,5,6-tetrachloroterephthalate; 1,4-benzenedicarboxylic acid, 2,3,5,6-tetrachloro-, monomethyl ester (U.S. EPA, 2006a; ChemFinder 2004; HSDB, 2005).

TPA: tetrachloroterephthalic acid; chlorothal; chlorthal; perchloroterephthalic acid; 1,4-benzenedicarboxylic acid, 2,3,5,6-tetrachloro- (U.S. EPA, 2006a; ChemFinder 2004; HSDB, 2005)

Dacthal is an odorless crystalline solid. Its physical and chemical properties are presented in Table 1. No data were found on the physical and chemical properties of the degradates. The properties of both degradates are expected to have many similarities in common with the parent dacthal. Their aqueous solubility is predicted to be higher than dacthal, because one or two of the ester functional groups have been hydrolyzed releasing methanol and increasing solubility in water. However, both compounds are still expected to be relatively insoluble in water based on the low solubility of terephthalic acid (2.8 g/L, IPCS, 1994). The vapor pressures of the acid derivatives are predicted to be lower than that of the parent (U.S. EPA 2006b).

**TABLE 1. Chemical and Physical Properties of Dacthal, TPA, and MTP**

| Property | Dacthal | TPA | MTP |
|---|---|---|---|
| CAS Registry No. | 1861-32-1 | 2136-79-0 | 887-54-7 |
| Formula | $C_{10}H_6Cl_4O_4$ | $C_8H_2Cl_4O_4$ | $C_9H_4Cl_4O_4$ |
| Molecular Weight | 331.97 | 303.91 | 317.94 |
| Color/Physical State | Colorless crystals | -- | -- |
| Odor | Odorless | -- | -- |
| Boiling point | 365°C | -- | -- |
| Melting point | 155°C | -- | -- |
| Density | 1.70 | -- | -- |
| Vapor pressure @ 25°C: | $2.5 \times 10^{-6}$ mm Hg | -- | -- |
| Solubility in Water @ (25°C):<br>in Organic Solvents@ (25°C): | 0.5 mg/L<br>70-250 mg/L | -- | -- |
| Partition coefficients:<br>Log $K_{ow}$<br>Log $K_{oc}$ | <br>4.40<br>3.77-4.28 | -- | -- |
| Conversion factors*<br>(at 25°C, 1 atm) | 1 ppm = 13.6 mg/m$^3$<br>1 mg/m$^3$ = 0.07 ppm | 1 ppm = 12.4 mg/m$^3$<br>1 mg/m$^3$ = 0.08 ppm | 1 ppm = 12.9 mg/m$^3$<br>1 mg/m$^3$ = 0.07 ppm |

Source: ChemFinder 2004; HSDB, 2005.
*Calculated as follows: ppm = mg/m$^3$ x (24.45/molecular weight); mg/m$^3$ = ppm x (molecular weight/24.45)

## 2.2 Uses

Dacthal is used as a selective, pre-emergence herbicide to control annual grasses and some annual broad-leaved weeds in turf, ornamentals, herbs, strawberries, garden vegetables, beans, and alfalfa (Meister, 1998; U.S. EPA, 1998a, U.S. EPA, 2004). Depending on crop and time of treatment, application rates generally range between 10-15 lb a.i./acre (U.S. EPA 1998a). There are many registered products with dacthal as an active ingredient. Some uses, particularly on vegetable crops, have been voluntarily terminated by the registrant in response to EPA concerns regarding the contamination of ground water with dacthal and TPA (U.S. EPA, 1998a, 2005a). Dacthal is registered for both residential and commercial use.

# 3.0 OCCURRENCE/EXPOSURE

## 3.1 Air

Dacthal is not expected to be found in air except in areas of recent application where it is likely to exist in both the vapor and particulate phases. In the vapor phase, it reacts slowly with hydroxyl radicals with an estimated half-life of 36 days (Meylan and Howard, 1993). Particulate-phase dacthal may be removed physically from air by wet and dry deposition.

There are limited data on measurements of dacthal in ambient indoor or outdoor air; no data were identified for the degradates. Indoor, outdoor, and personal air samples were collected seasonally in Jacksonville, Florida, and Springfield/Chicopee, Massachusetts by Whitmore et al. (1994), to assess non-occupational exposure to dacthal. Residents from Jacksonville had low exposures (not detected to 0.6 ng/$m^3$). The Springfield/Chicopee residents were exposed to higher levels (not detected to 2.6 ng/$m^3$). In both cases the highest concentrations were those collected by personal samplers. In 1970-1971 the arithmetic mean airborne pesticide concentration of dacthal in the United States was minimal; 0.49% of the samples were positive and the maximum dacthal concentration was 2.1 ng/$m^3$ (Lee, 1977; Kutz et al., 1976).

## 3.2 Food

Dacthal is registered and labeled for use on alfalfa, succulent and snap beans, beets, garden cress, kale, mustards, turnips, tomatoes, yams and other vegetables. Accordingly it may be present as residues in foods, especially vegetable produce. Use of dacthal on beans, peppers, squash, lettuce, soybeans, corn, and rutabagas has been terminated (U.S. EPA, 1998a, 2005a), reducing concern for these crops in the future. At present, no tolerances exist for residues of dacthal in animal commodities but tolerances have been established for a variety of vegetables, fruits, and herbs (U.S. EPA, 2004a).

When produce samples from 1989-1990 were tested for the presence of dacthal ($n$ = 6,970; approximately 80% domestic, 20% foreign), 50 samples (0.7%) were positive for dacthal at a detection limit of 0.125 ppm. In the 1991-2001 FDA Total Diet Study, dacthal residues were detected in a variety of produce. The most frequent detections were found in leafy vegetables (spinach and collard greens) and root vegetables (radish and turnip). Green beans had a low incidence of detection but relatively high mean concentrations, whereas black olives had a high

frequency of detection but a low average residue level (FDA, 2003). In market basket surveys conducted in the early 1980's, estimates of dacthal intake from foods ranged from 1.1 to 2.4 ng/kg/day (Gartrell et al., 1986a, 1986b; Gunderson, 1988). Leafy vegetables appeared to be the major source of exposure. No reissue data were identified for the dacthal degradates.

In a 1993 aquaculture survey, eight catfish samples out of 308 samples contained 10-90 µg/kg DCPA (FDA, 1993). The USGS measured the concentrations of dacthal in whole fish from 1310 sites over the period from 1992-2001 as part of the NAWQA survey described in Section 3.3. Detections were infrequent (1.9 -5% of samples) with the highest value reported for an agricultural area. The average and 95th percentile concentrations were below the method reporting limit of 5 µg/kg wet weight in tissue; the highest level reported was 33.7 µg/kg fish tissue (Nowell, 2003). The bioconcentration factor for dacthal in fish was estimated at 1,300 L/kg based on its $K_{ow}$ value (HSDB, 2005).

## 3.3 Water

Under U.S. EPA's Unregulated Contaminant Monitoring Rule (UCMR 1, 1999) monitoring for dacthal degradates (combined) was conducted by all large Public Water Systems (PWSs) and a statistical, nationally representative sample of small PWSs; there was no requirement for monitoring of dacthal. The analytical method for detection of TPA and MTP does not distinguish between the two compounds, therefore, results are reported as those for combined dacthal degradates.

Dacthal degradates were detected by 2.13% of small PWSs at a minimum reporting level of ≥1 µg/L. Among large systems 5.14% had detections. Most detections for both small and large systems were from ground water systems. The largest number of systems with detections (15.1%-42% of PWSs) were seen in Arizona, Delaware, Nebraska, New Jersey, Rhode Island, and Guam. There appeared to be a cluster of states with detections that ranged from 5% to 15% of samples in the Northeast and the states surrounding the Great Lakes. The maximum concentration detected was 39 µg/L for the large systems and 190 µg/L for small systems; median concentrations were about 2 µg/L for both small and large systems.

Occurrence data for dacthal and MTP, but not TPA, were collected from 1992 to 2001 under the United States Geological Survey's (USGS) National Water Quality Assessment (NAWQA) program. Detection limits varied, but did not exceed 0.003 µg/L for dacthal and 0.070 µg/L for MTP (Martin et al., 2003). Dacthal was found in ambient surface water at frequencies ranging from 6.34% of samples in undeveloped areas to 21.78% of samples in urban areas at 95 percentile concentrations that were less than 0.007 µg/L for all locations evaluated. In agricultural settings, 11.46% of samples were positive for dacthal along with 15.4% of samples in mixed land use settings. The highest concentration (40 µg/L) was found at an agricultural site. MTP was only detected in surface water samples ( 0.18%) from agricultural settings at a maximum concentration of 0.430 µg/L. The high frequency of detections in urban and mixed use areas may reflect applications to lawns and golf courses.

In untreated ground water, dacthal detection frequencies ranged from not detected in undeveloped settings to 1.18% in agricultural settings. Dacthal was not detected in ≥95% of the

samples from all settings. The highest ground water concentration, (10 µg/L) was found at an agricultural site (Kolpin and Martin, 2003). MTP was only detected in ground water samples from agricultural settings (0.08 %) and at maximum concentration of 1.1 µg/L (Kolpin and Martin, 2003).

### 3.4 Soil

Based on an estimated high $K_{oc}$ of 5900, dacthal is expected to bind strongly to organic matter resulting in almost complete immobility in soil. During a 21-day period, 36%-52% of the total measured dacthal loss from soil was accounted for by volatilization and 26% by breakdown in soil. Photodegradation on soil surfaces may occur with a half-life of 5 hours; reaction products include MTP, TPA, and 1,2,4,5-tetrachlorobenzene (HSDB, 2005). In soil, biodegradation of dacthal into TPA is slow. TPA is extremely mobile and persistent in the environment and will leach to ground water wherever dacthal is used, regardless of soil properties.

TPA and MTP, and to a lesser degree, dacthal, may be present in runoff and can leach to ground water (U.S. EPA, 1998a; Wettasinghe and Tinsley, 1993).

## 4.0 HEALTH EFFECTS DATA

MTP and TPA are present in the environment as degradates of the pesticide dacthal. They are also metabolites of dacthal in humans and animals. Thus, this document presents a summary of the available data on the health effects of the parent pesticide and its two degradates. Dacthal appears to be poorly absorbed from the gastrointestinal tract in humans (Tusing, 1963) and animals (Skinner and Stallard, 1963). In rat metabolism studies, the absorption of a 1 mg/kg dose was 79% but only 8 for a 1000 mg/kg (U.S. EPA, 1998a). Low solubility (0.5 mg/L) in aqueous media would contribute to its poor intestinal uptake. Metabolically, dacthal is converted first to MTP and then TPA (Hazleton and Dieterich, 1963; Skinner and Stallard, 1963; Tusing, 1963) most likely by nonspecific esterases. The solubility of the degradates is likely to be greater than that for dacthal since acids tend to be more soluble than esters.

Little is known about the distribution of dacthal or its metabolites. The target organs for dacthal suggest distributions to the liver, kidney, thyroid and lungs. Limited data from animal studies indicate that there is distribution of the metabolites to the liver and kidney; parent compound has been detected in adipose tissue. Most orally ingested dacthal is excreted in the feces, unabsorbed; TPA and MTP have been identified in the urine of humans and animals treated with dacthal (Skinner and Stallard, 1963; Tusing, 1963); the levels of MTP far exceed those of TPA. There have been no toxicokinetic studies of MTP or TPA. TPA does not degrade in living systems based on the projections of the META metabolism and biodegradation modeling program (Klopman et al., 1996).

## 4.1 Human Studies

### 4.1.1 Short-term Exposure

Pure dacthal, administered as single 25 mg or 50 mg oral dose to volunteer subjects (3 subjects at each dose), did not cause any observable effects based on assessment of hematological, serum and urinary biomarkers (Tusing, 1963). Assuming a 70 kg body weight, these amounts correspond to doses of 0.36 or 0.71 mg/kg. There are no short-term studies of TPA or MTP exposure in humans

### 4.1.2 Long-term Exposure

There are no studies in humans of long-term exposure to dacthal, TPA, or MTP.

### 4.1.3 Reproductive and Developmental Effects

No studies were identified regarding reproductive or developmental effects in humans exposed to dacthal, TPA, or MTP

### 4.1.4 Carcinogenicity

No data were located regarding the potential carcinogenicity of dacthal, TPA, or MTP in humans.

## 4.2 Animal Studies

### 4.2.1 Short-term Exposure

**Dacthal**

The oral $LD_{50}$ for dacthal is greater than 12,500 mg/kg in Spartan rats and greater than 10,000 mg/kg in beagle dogs (Wazeter et al., 1974a; 1974b).

Groups of CD Sprague-Dawley rats (5/sex/dose) were administered technical grade dacthal in the diet for 28 days at calculated doses of 0, 215, 860, or 1720 mg/kg/day for males and 0, 228, 890, or 1760 mg/kg/day for females. Food and water were available *ad libitum*. No treatment-related effects were observed on survival, clinical signs, body weight, body-weight gain, food consumption, urinalyses, hematology or clinical chemistry in either sex at any dose. A dose-related increase in absolute and relative liver weights was observed along with centrilobular hepatocyte hypertrophy. These effects were observed at the lowest dose tested, making the LOAEL 215 mg/kg/day in males and 228 mg/kg/day in females (ISK Biotech Corp., 1990a).

In an earlier 28-day study, Keller and Kundzin (1960) reported a NOAEL of 758 mg/kg/day (the highest dose evaluated) in weanling male Sprague-Dawley rats. A dose of 800 mg/kg/day given by capsule to beagle dogs (2/sex) for 28 days resulted in reduced body weight, decreased

appetite, increased liver weight, and centrilobular liver congestion and degeneration (U.S. EPA, 1989a; Keller, 1961).

**Monomethyl Tetrachloroterephthalic Acid**

Hazleton Laboratories (1961) conducted a 28-day study of 0 or 1% MTP (860 mg/kg/day based on U.S. EPA (1988) data on food intake and body weight) in the diet of male Sprague Dawley rats (n= 10/group). Nasal discharge was noted in some control and exposed rats during the study but did not appear to be treatment related. Clinical signs, body weights, liver and kidney weights were measured and the tissues subjected to gross and histological examination. No signs of toxicity were noted at the dose tested.

**Tetrachloroterephthalic Acid**

A 30-day intubation study with TPA in 0.5% methylcellulose solution at doses of 0, 100, 500 or 2000 mg/kg/day was conducted in groups of 10 male and 10 female Sprague–Dawley rats (Major, 1985). There were no treatment-related mortalities or changes in organ weights (adrenals, brain, gonads, heart, liver and kidney). Gross and histological evaluations of the organs at the high dose and selected tissues at the lower doses did not reveal any abnormalities. Soft stools (both sexes) as well as occult blood in the urine and increases in hemoglobin and hematocrit for males at the 2000 mg/kg/day dose, were originally identified as a non-adverse LOEL (U.S. EPA, 1994, 1998a) and the NOEL was 500 mg/kg/day.

The results of a 28-day study of TPA by Hazleton Laboratory (1961), comparable to the MTP study described above, did not identify any signs of toxicity at the 1% (860 mg/kg/day) dietary dose tested.

### 4.2.2 Long-term Exposure

**Dacthal**

Several subchronic (90-day) feeding studies are available for dacthal. In the study that identified the lowest response level, groups of 15 Sprague-Dawley rats/sex/dose group were administered technical dacthal in the diet at levels of 10, 50, 100, 150, or 1000 mg/kg/day for 90 days. No clinical signs were observed. Body weight was comparable among treatment groups, but body weight gain was decreased in high-dose males (92% of controls) and females (86% of controls). There were dose-related effects on the liver (increased weight and centrilobular hypertrophy), lung (increased accumulation of foamy macrophages), kidney (increased weight, epithelial hyperplasia, tubular hypertrophy, regenerative epithelium in males) and thyroid (follicular hypertrophy). Based on hepatocellular hypertrophy and microscopic findings in the liver, the LOAEL and NOAEL for dacthal in this study were set at 50 and 10 mg/kg/day, respectively (ISK Biotech Corp., 1991; U.S. EPA, 1994).

The liver was also the target organ in a 13-week study of dacthal in groups of 15 male and 15 female CD-1 mice (Fermenta Plant Protection Co., 1988). Calculated doses were 0, 100, 199, 406, and 1235 mg/kg/day for males and 0, 223, 517, 1049, and 2198 mg/kg/day for females. The

LOAELs were 1235 mg/kg/day for male mice and 1049 mg/kg/day for female mice, based on centrilobular hepatocyte hypertrophy. The NOAELs in male and female mice were 406 and 517 mg/kg/day, respectively (U.S. EPA, 1994).

There are two important studies of chronic exposures to Dacthal in rats that differ in the strain tested, the purity of the test material, the highest dose evaluated, and the number of animals per dose group. In the more recent of the two studies (ISK Biotech Corporation, 1993; U.S. EPA, 1994, 1998a), groups of Sprague-Dawley rats (70/sex/dose) were administered technical dacthal in the diet at doses of 0, 1, 10, 50, 500, or 1000 mg/kg/day for two years. The technical dacthal contained 0.13% hexachlorobenzene as an impurity (equivalent to doses of 0.0013, 0.013, 0.065, 0.65, or 1.3 mg/kg/day for the respective dacthal doses). [The NOAEL for HCB based on liver effects is 0.08 mg/kg/day with a LOAEL of 0.29 mg/kg/day in a chronic feeding study in rats (U.S. EPA, 1989b), indicating that the hexachlorobenzene exposure from dacthal exceeded its experimental LOAEL as a pure compound.] Survival in high-dose males was reduced, and animals of both sexes in the two highest dose groups showed clinical signs of poor health, including decreased body-weight gain. There was a dose-related increase in the incidence and severity of focal accumulation of foamy-appearing macrophages in the lungs in males and females. At study termination, a dose-related increase in the incidence of bilateral retinal atrophy was observed in females.

Increases in both the incidence and severity of centrilobular hepatocytic hypertrophy were observed at both interim (52-week) and terminal (104-week) sacrifices. Chronic nephropathy was increased in severity in males and in incidence in females. Thyroid-stimulating hormone (TSH) was elevated at 52 weeks in a dose-related manner. It also was increased at 104 weeks, but the increase was not dose related. Thyroxin ($T_4$) was decreased throughout the study, and triiodothyronine ($T_3$) was decreased at 52 weeks. The LOAEL for systemic toxicity was 10 mg/kg/day on the basis of effects observed in the lungs, kidneys, thyroid, and thyroid hormone levels in both sexes. The NOAEL was 1 mg/kg/day. Tumors of the thyroid and liver were also observed. The cancer findings from this study are discussed in Section 4.2.6.

Tumors were not observed in an earlier study of a purer grade of dacthal by Paynter and Kundzin/Diamond Alkali Co. (1963; U.S. EPA 1994) but one that used a lower dose range and fewer animals. Albino rats (35/sex/dose; 70/sex for controls) were fed dacthal in the diet for 2 years at 0, 100, 1000 or 10,000 ppm (approximately to 0, 5, 50 or 500 mg/kg/day). Physical appearance, behavior, hematology, biochemistry, organ weight, body weight, gross pathology and histopathology of treated and control animals were monitored. After 3 months at 500 mg/kg/day, slight hyperplasia of the thyroid was reported in both sexes. After 1 year, increased hemosiderosis of the spleen of females occurred at 500 mg/kg/day, and there were slight alterations in the centrilobular cells of the liver of both sexes. At the end of the study, kidney weight was increased significantly in males fed 500 mg/kg/day, and adrenal weight was increased significantly in females fed 500 mg/kg/day. Based on these data, a NOAEL of 50 mg/kg/day and LOAEL of 500 mg/kg/day were identified.

A 2-year study in CD-1 mice identified the liver as the critical target organ after exposure to technical grade dacthal (Fermenta Plant Protection Co., 1988). The doses were 0, 12, 123, 435 or 930 mg/kg/day in males and 0, 15, 150, 510 or 1141 mg/kg/day in females. The NOAEL for

systemic toxicity was 435 mg/kg/day in males; 510 mg/kg/day in females and the LOAEL 930 mg/kg/day for males and 1141 mg/kg/day in females based on hepatocyte enlargement increased sorbitol dehydrogenase (SDH) and ALT activities, and hepatocyte vacuolization. A dose-related increase in cholesterol was seen in females in the two highest dose groups but was not considered as a critical effect (U.S. EPA, 1994). A dose-related trend for liver tumors was also observed in females; liver tumors in males fell within the range for historic controls (U.S. EPA 1995a).

No effects were identified in beagle dogs (four/sex/dose) fed dacthal in the diet at 0, 100, 1000 or 10,000 ppm (approximately 0, 2.5, 25 or 250 mg/kg/day) for two years. Therefore, the NOEL was equal to or greater than 250 mg/kg/day (U.S. EPA, 1994, 1998a).

**Monomethyl Tetrachloroterephthalic Acid**

There were no subchronic or chronic studies of MTP.

**Tetrachloroterephthalic Acid**

A 90-day feeding study with disodium TPA was performed in Charles River CD rats (15/sex/dose group), using doses of 0, 50, 500, 1000, or 10,000 ppm (0, 2.5, 25, 50 or 500 mg/kg/day) in the diet (Goldenthal et al., 1977). The animals were evaluated for clinical signs, body weights, tissue histopathology (controls and high dose), and organ weights. Blood and urine samples were collected for analysis at 1, 2, and 3 months. There were no significant changes in clinical observations, histopathology, and other standard measures of toxicity, such as hematology and organ weights. Occasional soft stools were seen in the controls and high dose animals. A non-significant increase in thyroid: body weight ratio was observed at the highest dose. The NOAEL was set at ≥500 mg/kg/day, the highest dose tested (U.S. EPA, 1998a ).

### 4.2.3 Reproductive and Developmental Effects

**Dacthal**

In a two-generation study of dacthal with Sprague-Dawley rats, dacthal was administered in the diet at concentrations of 0, 1000, 5000 or 20,000 ppm (Male: 0, 45, 233 or 952 mg/kg-day; Female: 0, 63, 319 or 1273 mg/kg-day). In the $F_1$ generation, there was an increase in stillbirths at the highest dose level (1273 mg/kg/day), which was more pronounced in the second generation than in the first (ISK Biotech Corp., 1990b). Decreased body weight gain in the parents established the LOAELs at 319 mg/kg/day for the dams and 952 mg/kg/day for the males. The NOAELs were 63 and 233 mg/kg/day for the females and males, respectively. Based on weight decrements, the $F_1$ and $F_{2a}$ offspring LOAEL was 319 mg/kg/day, the same as that of the dams. On day 0 for the $F_{2b}$ litters, the diets for the low and mid-dose groups were changed to 18 and 47 mg/kg/day, respectively. For this generation, the offspring NOEL was set at 18 mg/kg/day and the LOEL was 47 mg/kg/day (U.S. EPA, 1994).

Developmental testing of dacthal with CD (25/group) rats exposed to gavage doses of 0, 500, 100 or 2000 mg/kg-day on gestation days (gd) 6-15 failed to identify a LOAEL; the NOAEL was

2000 mg/kg/day (SDS Biotech Corp., 1986). Similar results were seen in New Zealand White rabbits exposed by gavage at doses of 0, 125, 250 or 500 mg/kg-day during gd 7-19. The NOAEL and highest dose tested was 500 mg/kg/day (Fermenta Plant Protection Co., 1989). In a second study in New Zealand White rabbits by the same company, dacthal was given by gavage on gestation days 6-19 at doses of 0, 500, 1000 or 1500 mg/kg-day from day (Fermenta Plant Protection Co., 1989). There were four maternal deaths at the lowest dose of 500 mg/kg/day. Thirteen maternal deaths occurred at a dose of 1000 mg/kg/day and 12 maternal deaths occurred at 1500 mg/kg/day. The animals that died had signs of neurotoxicity, and the mid- and high-dose groups had higher incidences of gastric ulcerations than controls. No embryo or fetal toxicity or teratogenicity was observed. When the results of the two studies were considered, the LOAEL for maternal toxicity was 500 mg/kg/day and the NOAEL was 250 mg/kg/day. The NOAEL for developmental toxicity was set at 500 mg/kg/day (U.S. EPA, 1994, 1998a).

**Monomethyl Tetrachloroterephthalic Acid**

There were no reproductive or developmental studies of MTP.

**Tetrachloroterephthalic Acid**

Pregnant COBS CD rats (25 per dose group) were administered 0, 625, 1250, or 2500 mg of TPA per kg/day via gavage in methyl cellulose on gd 6-15 (Mizen, 1985; U.S. EPA, 1998a). The dams were observed for clinical signs, body weights, and food intake. After sacrifice, the ovaries were examined for corpora lutea, and the uterus for implantations, early and late resorptions, live and dead pups. Because no developmental effects were noted at the highest dose, the NOAEL for developmental effects was identified as 2500 mg/kg/day. Maternal toxicity, however, was noted at 2500 mg/kg/day, based on soft or liquid stools, red mucus in the feces, labored breathing, decreased body weight gain, and decreased food consumption. Excess salivation was observed at the two highest doses but was considered to be the result of the acidity of TPA. A LOAEL of 2500 mg/kg/day and a NOAEL of 1250 mg/kg/day were set for the dams. There were no reproductive studies of TPA.

### 4.2.4 Genotoxicity

**Dacthal**

Dacthal had no mutagenic activity, with or without activation, in *Salmonella* assays (Auletta et al., 1977), in *in vivo* cytogenetic tests (Kouri et al., 1977b), in DNA repair tests (Auletta and Kuzava, 1977), or in dominant lethal tests (Kouri et al., 1977a).

**Monomethyl Tetrachloroterephthalic Acid**

No genotoxicity studies of MTP were identified.

**Tetrachloroterephthalic Acid**

TPA did not induce a mutagenic response in either the Ames (Godek, 1984) or hypoxanthine guanine phosphoribosyl transferase assays with or without metabolic activation (Godek, 1985) . It did not induce a significant increase in the frequency of sister chromatid exchanges in Chinese hamster ovary cells with or without metabolic activation (San Sebastian, 1985). TPA does not appear to induce unscheduled DNA synthesis (Barfknecht, 1984). An *in vivo* mouse micronucleus assay (7/sex/group) with TPA was negative in females and equivocal in males (a weak response at the highest dose) in a study by Siou (1985). The males were given doses of 0, 1000, 5000, or 10000 mg/kg by gavage and the females 0, 500, 2500, or 5000 mg/kg, both in methylcellulose. High doses were used in most of the genotoxicity assays; limitations on solubility may have influenced the results.

### 4.2.5 Carcinogenicity

**Dacthal**

Dacthal (technical grade, purity 97.7%), at doses of 0, 1, 10, 50, 500 or 1000 mg/kg/day induced thyroid tumors in male and female rats, and liver tumors in female rats (ISK Biotech Corp., 1993). However, there was no significant increase in tumor incidence in the Paynter and Kundzin/ Diamond Alkali Co. (1963) study in albino rats (35/sex/dose and 70/sex for the controls) which used fewer animals and a lower dose range (0, 5, 50 or 500 mg/kg/day) of a purer grade of dacthal.

In the ISK Biotech Corp. (1993) study, 70 Sprague-Dawley rats/sex/dose were administered technical dacthal in the diet at doses of 0, 1, 10, 50, 500 or 1000 mg/kg/day for two years. The material used contained 0.13% hexachlorobenzene as an impurity. This is equivalent to doses of 0, 0.0013, 0.013, 0.065, 0.65, or 1.3 mg/kg/day hexachlorobenzene for the respective dacthal doses. Incidences of thyroid follicular cell adenomas in male rats for the respective dose groups were 1, 2, 2, 8, 10, and 7; thyroid follicular cell carcinomas were not increased. In females, incidences of thyroid follicular cell adenomas in the respective dose groups were 1, 1, 2, 4, 1, and 4, and incidences of thyroid follicular cell carcinomas in the respective dose groups were 0, 0, 1, 0, 1, and 4. Hepatocellular adenomas were increased in females (0, 0, 1, 1, 5, 7 in the respective dose groups) as were hepatocellular carcinomas (0, 0, 1, 0, 3, 3 in the respective dose groups). Hepatocholangiocarcinomas were increased in females in the high-dose group only (2 vs. none in all other groups) (U.S. EPA 2002).

Male and female CD-1 mice (90/sex/dose ) both developed carcinomas and adenomas in the liver after chronic exposure to dacthal in the diet at concentrations of 0, 100, 1000, 3500 or 7500 ppm (Male: 0, 12, 123, 435 or 930 mg/kg-day; Female: 0, 15, 150, 510 or 1141 mg/kg-day) for 2 years. (Fermenta Plant Protection Company, 1988). Tumors were found in the controls as well as the exposed animals. The tumors in male mice fell within the range for historical controls from 9 studies in CD-1 mice (U.S.. EPA, 1995a). The incidence of adenomas in the female mice at the high dose (11%) was slightly greater than that for the historic controls (2-8%). The same was true for combined adenomas and carcinomas (12%) when compared to the historic controls. There was also a dose-response trend for the numbers of adenomas with

incidences of 3%, 0%, 3%, 5%, and 11% for the 0, 100, 1000, 3500, and 7500 ppm doses, respectively (U. S. EPA, 1995a).

**Dacthal Degradates**

There are no carcinogenicity studies for either TPA or MTP. The short-term studies that have been conducted for TPA did not identify thyroid or liver effects at the doses tested, reducing concern that TPA might have tumorigenic properties similar to dacthal. Klopman et al. (1996) used a Multicase QSAR analytical model to predict the carcinogenicity potential of TPA. Based on the results from this QSAR model, the authors concluded "that TPA does not present any substantial carcinogenic risk."

## 4.3 Proposed Mode of Action

### 4.3.1 Noncancer Effects

There are no mode-of-action data for any of the noncancer effects of dacthal or TPA except for TPA's laxative effect. Ten- and 30-day gavage studies of TPA in adult rats were reported to cause soft or liquid stools at doses of 2000 and 2500 mg/kg/day (Major, 1985; Mizen, 1985). Gavage doses of 500 and 1250 mg/kg/day did not have an effect (Goldenthal et al., 1977; Major, 1985; Mizen, 1985). Neither did dacthal in subchronic and chronic dietary studies at doses of 1760 mg/kg/day or 1000 mg/kg/day, respectively (ISK Biotech Corp., 1990a, 1993).

TPA and dacthal are poorly absorbed in the gastrointestinal tract when high doses are administered. In the case of TPA, both studies that resulted in soft stools were studies where the compound was administered by gavage in methylcellulose, a reflection of it poor solubility. Poorly absorbed substances increase intraluminal osmotic activity, causing the retention of water within the intestine. The result is excess water in the fecal matter (soft stools) or diarrhea. The gavage administration and osmolality of TPA in the 30-day and developmental studies provides a probable mode of action that explains its laxative effect at high doses.

### 4.3.2 Cancer Effects

There are few data on the mode of action for the tumorigenic effects of dacthal. Thyroid follicular cell hyperplasia or hypertrophy occurred in the ISK Biotech Corp (1991) 90-day rat studies of dacthal, as well as in the long-term ISK Biotech Corporation (1993) and Paynter and Kundzen (1963) studies and may contribute to tumor initiation in the thyroid. Hypertrophy, eosinophilic foci, and/or centrilobular cellular vacuolization of the liver were observed in the subchronic and chronic studies of dacthal in mice and rats but none of these studies reported necrotic lesions and biomarkers of membrane damage, where observed, did not show a dose-related response.

Dacthal used in the more recent chronic rodent studies (Fermenta Plant Protection Company, 1988; ISK Biotech Corporation, 1993 ) contained 0.13% hexachlorobenzene as an impurity. The Agency has classified hexachlorobenzene as a $B_2$ (probable human) carcinogen based on significant increases of tumor incidence in rodents. Hexachlorobenzene induced tumors in the

livers of rats, hamsters and mice. Neoplasms of the thyroid and kidney have also been observed (U.S. EPA 1989b). EPA (1998a) concluded that the dacthal impurities could contribute to its tumorigenicity but could not fully explain the observed potency.

Klopman et al. (1996) examined the alkylating properties of dacthal, as reflected in its ability to react with (-4-nitrobenzylpyridine ((4-NBP). Dacthal demonstrated some ability to react with (4-NBP raising the possibility that alkylating potential, alone or in combination with the carcinogenicity of the product impurities, might explain the weak tumorigenic response.

## 5.0 QUANTIFICATION OF TOXICOLOGICAL EFFECTS

HAs describe nonregulatory concentrations of drinking water contaminants at which adverse health effects are not anticipated to occur over specific exposure durations. HAs are developed for both short-term and long-term (Longer-term and Lifetime) exposure periods based on data describing noncarcinogenic endpoints of toxicity.

Short-term exposures can include One-day and Ten-day exposure periods. One-day and Ten-day HA's use parameters that reflect exposures and effects for a 10 kg child consuming 1 liter of water per day.

A Longer-term HA covers an exposure period of approximately 7 years, or 10 percent of an individual's lifetime. Longer-term HAs can incorporate parameters for either a child (10 kg body weight consuming 1 liter per day water) or an adult (70 kg body weight consuming 2 liters per day water) parameters.

A Lifetime HA covers an individual's lifetime, approximately 70 years. A lifetime HA considers a 70 kg adult consuming 2 liters of water per day. The lifetime HA is considered protective of non-carcinogenic adverse health effects over a lifetime exposure. A relative source contribution from water is also factored into the lifetime HA calculation to account for contaminant exposures from other sources (air, food, soil, etc). For those substances that are *Carcinogenic to Humans, Likely to Be Carcinogenic to Humans* (U.S. EPA, 2005b), known (Group A), or probable (Groups $B_1$ and $B_2$) human carcinogens (U.S. EPA, 1986), the development of a Lifetime Health Advisory is not usually recommended. A Lifetime HA can be calculated for substances that are possible carcinogens (U.S. EPA, 1986) or provide "*Suggestive Evidence of Carcinogenic Potentia*l"(U.S. EPA 2005b).

The One-day, Ten-day, or Longer-term HA is derived using the following formula:

$$HA = \frac{\text{NOAEL or LOAEL} \times \text{BW}}{\text{UF} \times \text{DW}}$$

Where:

| | | |
|---|---|---|
| NOAEL or LOAEL | = | No- or Lowest-Observed-Adverse-Effect Level (in mg/kg bw/day) from a study of an appropriate duration |
| BW | = | Assumed body weight of a child (10 kg) or an adult (70 kg). |
| UF | = | Uncertainty factor in accordance with EPA guidelines |
| DWI | = | Assumed human daily water consumption for a child (1 L/day) or an adult (2 L/day) |

The Lifetime HA is calculated in a three-step process:

**Step 1**: Adopt a pre-existing Reference Dose (RfD) or calculate an RfD using the following equation:

$$RfD = \frac{\text{NOAEL, LOAEL or BMDL}}{\text{UF}}$$

Where:

| | | |
|---|---|---|
| NOAEL or LOAEL | = | No- or Lowest-Observed-Adverse-Effect Level (in mg/kg bw/day). |
| BMDL | = | Lower confidence bound on the Bench Mark Dose (BMD). The BMD and BMDL are obtained through modeling of the dose-response relationship. |
| UF | = | Uncertainty factor established in accordance with EPA guidelines. |

**Step 2:** Calculate a Drinking Water Equivalent Level (DWEL) from the RfD. The DWEL assumes that 100% of the exposure comes from drinking water.

$$DWEL = \frac{RfD \times BW}{DWI}$$

Where:

| | | |
|---|---|---|
| RfD | = | Reference Dose (in mg/kg bw/day). |
| BW | = | Assumed body weight of an adult (70 kg). |
| DWI | = | Assumed human daily water consumption for an adult (2 L/day) |

**Step 3:** The Lifetime HA is calculated by factoring in other sources of exposure (such as air, food, soil) in addition to drinking water using the RSC for the drinking water.

$$\text{Lifetime HA} = \text{DWEL} \times \text{RSC}$$

Where:

| | | |
|---|---|---|
| DWEL | = | Drinking Water Equivalent Level (calculated from step 2) |
| RSC | = | Relative source contribution |

**Note.** The procedure for establishing the RSC is described in U.S. EPA (2000a): Methodology for deriving Ambient Water Quality Criteria for the Protection of Human Health (pages 4-5 to 4-17). The methodology can be accessed at:
http://www.epa.gov/waterscience/criteria/humanhealth/method/complete.pdf

In cases where monitoring data are available for both dacthal and its degradates, and an HA is only available for dacthal, the combined degradate concentrations can be multiplied by 1.09 to convert them to dacthal equivalent estimates and added to the dacthal concentration for comparison with the dacthal HA. The 1.09 conversion factor is the ratio of the dacthal molecular weight to the formula weight for TPA.

## 5.1 One-day Health Advisory

### Dacthal

No suitable information was found for determining the One-day HA for dacthal. The study of dacthal in humans by Tusing (1963) is not appropriate since no effects were observed when low doses (0.36 or 0.71 mg/kg) were tested in few individuals. Animal data for an appropriate exposure duration are not available. Therefore, it is recommended that the Ten-day HA value for dacthal be used as conservative estimate of the One-day HA.

### Dacthal Degradates

There are no appropriate data to support derivation of a One-day health advisory for MTP or TPA. It is recommended that the Ten-day HA value for TPA be used as conservative estimate of the One-day HA.

## 5.2 Ten-day Health Advisory

### Dacthal

The 28-day rat study by ISK Biotech Corp. (1990a) was selected to serve as the basis for the Ten-day HA for dacthal. In this study, a LOAEL for increased liver weight and centrilobular hepatocyte hypertrophy of 215 mg/kg/day in males and 228 mg/kg/day in females was identified. There was no NOAEL in this study. This study was selected because it is of appropriate duration, had sufficient dose groups, and was conducted in the most sensitive of the non-primate species evaluated.

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

$$\text{Ten Day HA} = \frac{215\ \text{mg/kg/day} \times 10\ \text{Kg}}{1000 \times 1\ \text{L/day}} = 2.15\ \text{mg/L}\ \text{(rounded to 2 mg/L)}$$

Where:

| | | |
|---|---|---|
| 215 mg/kg/day | = | LOAEL for hepatotoxicity in male rats (ISK Biotech Corp., 1990a). |
| 10 kg | = | Assumed body weight of a child |
| 1000 | = | Uncertainty factor chosen for interspecies (10), intraspecies (10) differences, and a LOAEL to NOAEL (10) adjustment |
| 1 L | = | Assumed daily water consumption of a child. |

**Note.** A 10-fold adjustment was used for the LOAEL to NOAEL because the 90-day subchronic study by ISK Biotech Corp. (1991) observed similar effects in the liver at a NOAEL of 10 mg/kg/day and a LOAEL of 50 mg/kg/day, well below the LOAEL in the ISK Biotech Corp. (1990a) study.

**Monomethyl Tetrachloroterephthate**

There are no data that are appropriate for the derivation of a longer term HA for MTP. The only study identified was a 28-day single dose (860 mg/kg/day) dietary study in rats that observed no adverse effects. Although the duration of the study would support its use for a ten-day HA, the evaluation of toxicological endpoints was limited.

**Tetrachloroterephthalic Acid**

Both the 10-day developmental study with pregnant rats (Mizen, 1985) and the 30-day gavage study with male and female Sprague-Dawley rats (Major, 1985) can be considered as the basis for the 10-day HA for TPA because both studies showed that TPA has an effect on stool consistency and possibly causes intestinal irritation. There were no developmental effects in the Mizen (1985) study, but a NOAEL of 1250 and LOAEL of 2500 mg/kg/day, respectively, were determined for the dams based on soft stools, red mucus in the feces, and effects on food consumption and weight gain. In the 30-day study (Major, 1985), soft stools were observed in both sexes at 2000 mg/kg/day, but not at the next lowest dose of 500 mg/kg/day. The highest NOAEL of 1250 mg/kg/day in the study of Mizen (1985) was selected as the basis of the ten-day HA for TPA.

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

$$\text{Ten Day HA} = \frac{1{,}250\ \text{mg/kg/day} \times 10\ \text{Kg}}{100 \times 1\ \text{L/day}} = 125\,\text{mg/L}\ (\text{rounded to}\ 100\,\text{mg/L})$$

Where:

| | | |
|---|---|---|
| 1,250 mg/kg/day | = | NOAEL for soft stools (Mizen, 1985). |
| 10 kg | = | Assumed body weight of a child |
| 100 | = | Uncertainty factor chosen for interspecies (10) intraspecies (10) differences |
| 1 L | = | Assumed daily water consumption of a child. |

**Note.** A 10-fold interspecies uncertainty factor was applied because the impact of TPA on the consistency of stools may depend on the total osmolality of the diet. Human diets are far more varied than those of laboratory animals providing opportunities for additive effects if TPA were combined with a diet containing high concentrations of other osmotically active solutes.

### 5.3 Longer-term Health Advisory

**Dacthal**

The study by ISK Biotech Corp. (1991) was selected to serve as the basis for the Longer-term HA for dacthal. The NOAEL was 10 mg/kg/day based on for centrilobular hypertrophy of the liver in rats at a LOAEL of 50 mg/kg/day in a subchronic (90-day) duration study. This study was selected because it is of appropriate duration and was conducted in the most sensitive of the non-primate species evaluated.

For a 10 kg child, the Longer-term HA is calculated as follows:

$$\text{Longer - term HA} = \frac{10\,\text{mg/kg/day} \times 10\ \text{Kg}}{100 \times 1\ \text{L/day}} = 1\,\text{mg/L}$$

Where:

| | | |
|---|---|---|
| 10 mg/kg/day | = | NOAEL for hepatotoxicity (ISK Biotech Corp., 1991) |
| 10 kg | = | Assumed body weight of a child |
| 100 | = | Uncertainty factor, chosen for interspecies (10) and intraspecies (10) differences |
| 1 L | = | Assumed daily water consumption of a child. |

For an adult, the Longer-term HA is calculated as follows:

$$\text{Longer - term HA} = \frac{10\,\text{mg/kg/day} \times 70\ \text{Kg}}{100 \times 2\ \text{L/day}} = 3.5\,\text{mg/L}\ (\text{rounded to}\ 4\,\text{mg/L})$$

Where:

| | | |
|---|---|---|
| 10 mg/kg/day | = | NOAEL for hepatotoxicity (ISK Biotech Corp., 1991) |
| 70 kg | = | Assumed body weight of an adult |
| 100 | = | Uncertainty factor, chosen for interspecies (10) and intraspecies (10) differences |
| 2 L | = | Assumed daily water consumption of an adult. |

**Monomethyl Tetrachloroterephthalate.**

There are no data that are appropriate for the derivation of a longer term HA for MTP. The only study identified (Hazleton Laboratories, 1961) was a 28-day single dose study (860 mg/kg/day) in rats that does not meet the duration requirements for a longer-term HA.

**Tetrachloroterephthalic Acid.**

The data from the subchronic study (Goldenthal et al., 1977) of TPA were selected as the basis for a longer term HA. Charles River CD rats (15/sex/dose) received doses of 0, 2.5, 25, 50 or 500 mg/kg/day in their diets for 90 days. The animals were evaluated for clinical signs, body weights, organ weights and tissue histopathology for the control and high dose animals. Blood and urine were evaluated at 1, 2, and 3 months. The highest dose tested was identified as a NOAEL.

For a 10 kg child, the Longer-term HA is calculated as follows:

$$\text{Longer - term HA} = \frac{500\ \text{mg/kg/day} \times 10\ \text{Kg}}{100 \times 1\ \text{L/day}} = 50\ \text{mg/L}$$

Where:

| | | |
|---|---|---|
| 500 mg/kg/day | = | NOAEL (highest dose tested; Goldenthal et al., 1977) |
| 10 kg | = | Assumed body weight of a child |
| 100 | = | Uncertainty factor, chosen for interspecies (10) and intraspecies (10) differences |
| 1 L | = | Assumed daily water consumption of a child. |

For an adult, the Longer-term HA is calculated as follows:

$$\text{Longer - term HA} = \frac{500\ \text{mg/kg/day} \times 70\ \text{Kg}}{100 \times 2\ \text{L/day}} = 175\ \text{mg/L}\ \text{(rounded to 200 mg/L)}$$

Where:

| | | |
|---|---|---|
| 500 mg/kg/day | = | NOAEL (highest dose tested; Goldenthal et al., 1977) |
| 70 kg | = | Assumed body weight of an adult |
| 100 | = | Uncertainty factor, chosen for interspecies (10) and intraspecies (10) differences |
| 2 L | = | Assumed daily water consumption of an adult. |

## 5.4 Lifetime Health Advisory

**Dacthal**

An oral RfD of 0.01 mg/kg/day has been established for dacthal (U.S. EPA, 1994, 1998a). The RfD was derived from a NOAEL of 1 mg/kg/day in a 2-year feeding study with rats (ISK Biotech Corp., 1993). The LOAEL was 10 mg/kg/day for a decrease in $T_4$, increased thyroid follicular cell hyperplasia, and hepatic eosinophilic foci and centrilobular hypertrophy.

$$\text{RfD} = \frac{1 \text{ mg/kg/day}}{100} = 0.01 \text{ mg/kg/day}$$

Where:

| | | |
|---|---|---|
| 1 mg/kg/day | = | NOAEL for thyroid toxicity and hepatotoxicity (ISK Biotech Corp., 1993) |
| 100 | = | Uncertainty factor, chosen for interspecies (10) and intraspecies (10) differences |

A Drinking Water Equivalent Level (DWEL) can be derived from the oral RfD as follows:

$$\text{DWEL} = \frac{0.01 \text{ mg/kg/day} \times 70 \text{ Kg}}{2 \text{ L/day}} = 0.35 \text{ mg/L}$$

Where:

| | | |
|---|---|---|
| 0.01 mg/kg/day | = | Oral Reference Dose |
| 70 Kg | = | Assumed body weight of an adult |
| 2 L/day | = | Assumed daily water consumption of an adult. |

The Lifetime HA is calculated as follows:

$$\text{Lifetime HA} = 0.35 \text{ mg/L} \times 0.20 = 0.07 \text{ mg/L } (70 \mu\text{g/L})$$

Where:

| | | |
|---|---|---|
| 0.35 mg/kg/day | = | Drinking Water Equivalent Level |
| 0.20 | = | Relative source contribution (default value of 20%) |

**Note.** Because data on the relative contributions of food and air to total exposure are inadequate, the default value of 20% was used for drinking water (U.S. EPA, 2000a). There are no Total Diet Study- type data for MTP or TPA in foods that provide the national estimates needed to determine a value other than a default for the sum of dacthal and its degradates. However OPP modeled estimates for residues of dacthal and its degradates in foods and drinking water indicate that total residues are below levels of concern (U.S. EPA, 2004a); Earlier OPP concerns related to the levels of degradates in ground water were addressed by restricting use on some commodities (U.S. EPA, 2005a)

**Dacthal Degradates**

Data are inadequate to establish lifetime HAs for MTP and TPA. Based on the relative toxicities for dacthal and TPA in subchronic studies, the lifetime HA for dacthal will be protective when applied to the sum of dacthal and its degradates after molar conversion of the degradate concentrations to dacthal equivalents.

## 5.5 Evaluation of Carcinogenic Potential

**Dacthal**

The HA evaluation of carcinogenic potential includes the U.S. EPA descriptors for the weight of evidence for the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed, as well as a quantitative estimate of cancer potency (slope factor), where available. The Cancer Slope Factor (CSF) is the result of the application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day of the contaminant. In cases where a CSF has been derived, HAs include the drinking water concentrations equivalent to an upper-bound excess lifetime cancer risk of one-in-ten-thousand ($1 \times 10^{-4}$), one-in-one-hundred-thousand ($1 \times 10^{-5}$), to one-in-one-million ($1 \times 10^{-6}$).

Cancer assessments conducted before 1996 used the five-category, alpha-numeric system for classifying carcinogens established by the Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986). The EPA currently requires that all new cancer risk assessments comply with the Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005b) or, if conducted between 1996 and 2005, comply with the draft versions of the 2005 Cancer guidelines.

Dacthal has not been evaluated by the Agency using the 2005 cancer guidelines. The OPP has classified dacthal as Group C, *possible human carcinogen* (U.S. EPA, 1998a) based on evidence of an increased incidence of thyroid tumors in both sexes of rats and liver tumors in female rats and mice. The OPP used a multi-stage model to calculate a cancer slope factor ($Q_1$*) of $1.49 \times 10^{-3}$ $(mg/kg/day)^{-1}$. Concentrations equivalent to an upper-bound excess lifetime cancer risk of one-in-ten-thousand ($1 \times 10^{-4}$), one-in-one-hundred-thousand ($1 \times 10^{-5}$), and one-in-one-million ($1 \times 10^{-6}$) are 2300, 230 and 23 µg/L, respectively.

The evidence for the carcinogenicity of dacthal may reflect, at least in part, the carcinogenicity of several of the impurities of the test material although OPP concluded that neither hexachlorobenzene nor dioxin/furans can fully account for the tumorigenic response from the study of technical dacthal containing these impurities (U.S. EPA, 1998a). Hexachlorobenzene is a probable human carcinogen and, like dacthal, is associated with liver and thyroid tumors in laboratory animals.

**Dacthal Degradates**

There are no cancer data for either MTP or TPA. Accordingly, they can be described as having *inadequate information to assess carcinogenic potential*. The mutagenicity data for TPA are

negative (U.S. EPA, 1998a) as are the findings from carcinogenic structure-activity analysis (Klopman et al. 1996).

## 6.0 OTHER CRITERIA, GUIDANCE, AND STANDARDS

The states of Arizona and Florida both have drinking water guidelines for dacthal of 3500 µg/L, and the State of Wisconsin has a drinking water guideline of 4000 µg/L (HSDB, 2005).

## 7.0 ANALYTICAL METHODS

EPA Method 508 is used to detect dacthal in drinking water (U.S. EPA, 1995a) using a gas chromatographic (GC) method applicable to the determination of some chlorinated pesticides in water. 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 (ECD). The estimated detection limit for dacthal is 0.025 µg/L.

Four analytical methods are available for detecting MTP and TPA in water. EPA Methods 515.1, 515.2, 515.3, and 515.4 involve hydrolyzation, extraction, derivatization, and cleanup steps before detection by GC/ECD (U.S. EPA 1995b; 1995c; 1996b; 2000b). These methods; 515.1, 515.2, 515.3 and 515.4 do not distinguish between the two degradates and give the total degradate concentration. The parent dacthal is removed from the extract prior to analysis in all four of these methods. The method detection limit (MDL) for the mono- and diacid degradates using Method 515.1 is 0.067 µg/L, and the average recovery ranges from 74-81% (U.S. EPA 1995b). The MDL for the MTP and TPA degradates using Method 515.2 is 0.13 µg/L, and the recovery ranges from 60-118%. Using Method 515.3, the MDL for the MTP and TPA degradates ranges from 0.38 to 0.63 µg/L, and the recovery ranges from 88-123%. The MDLs for Method 515.4 are 0.113 µg/L (primary column) and 0.105 µg/L (secondary column) in reagent water; the average recoveries range from 92-100%, depending on the method option used.

## 8.0 TREATMENT TECHNOLOGIES

Potential treatment technologies for removing dacthal and its degradates from water include membrane processes, activated carbon, and advanced oxidation. High pressure technologies that use nanofiltration and reverse osmosis are capable of removing dissolved organic contaminants including dacthal and its degradates.

Granular activated charcoal treatment removes contaminants via the physical and chemical process of sorption. Contaminants with double bonds and low water solubility such as dacthal generally have a high affinity for carbon. MTP and TPA which are more water soluble than dacthal, are expected to be less amenable to activated carbon treatment.

Advanced oxidation processes using a combination of oxidants produce free hydroxyl radicals that can oxidize organic or inorganic contaminants in water. Compounds with short aerobic metabolism half-lives are expected to be amenable to treatment using advanced oxidation

processes. U.S. EPA (1998a) reports that the half-life of DCPA is between 18 to 37 days, while the half-life of MTP is shorter (2.8 days) and that of TPA is longer (virtually no degradation in 300 days). These findings suggest that advanced oxidation processes may be effective for MTP, less effective for dacthal, and not effective for TPA.

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