Public Health Goal for ENDOTHALL in Drinking Water

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Endothall in Drinking Water
California Public Health Goal (PHG)
This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. The PHG describes concentrations of contaminants at which adverse health effects would not be expected to occur, even over a lifetime of exposure. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires OEHHA to adopt PHGs that meet the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which scientific evidence indicates that no known or anticipated adverse effects on health will occur, plus an adequate margin-of-safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of scientific ambiguity, OEHHA shall use criteria most protective of public health and shall incorporate uncertainty factors of noncarcinogenic substances for which scientific research indicates a safe dose-response threshold.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed periodically and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. For this reason PHGs are only one part of the
information used by DHS for establishing drinking water standards. PHGs established by OEHHA exert no regulatory burden and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are developed for technical assistance to DHS, but may also benefit federal, state and local public health officials. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of environmental waters where additional concerns of bioaccumulation in fish and shellfish may pertain. Often environmental water contaminant criteria are more stringent than drinking water PHGs, to account for human exposures to a single chemical in multiple environmental media and from bioconcentration by plants and animals in the food chain.
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SUMMARY

A Public Health Goal (PHG) of 580 ppb for endothall in drinking water is developed based on gastric toxicity observed in dogs. The U.S. Environmental Protection Agency’s (U.S. EPA’s) Maximum Contaminant Level (MCL) is 0.1 mg/L (100 ppb). Endothall, a dibasic acid, is used primarily as a herbicide and defoliant for cotton crops. It is not volatile and has a limited life in water. Due to its acidic properties, endothall has poor gastrointestinal and dermal absorption and is primarily an irritant. Endothall primarily damages the gastrointestinal tract leading to nausea, vomiting and hemorrhaging and death. Endothall was reported to be very irritating and damaging to the skin and eyes as well. Evidence of some tumor formation in the digestive tract was noted in animals severely affected by high doses of endothall in their diet. As a result, estimation of hazard focused on determining the lowest dose at which the digestive organs or body weight are affected. A PHG for endothall of 0.586 mg/L was calculated by using the level at which no effects on the gastric tract were observed in a chronic dog study and applying uncertainty factors to account for inter-species variation and human sensitivity and exposure. As a result, a drinking water concentration at or below 0.58 mg/L (580 ppb) should present no appreciable adverse health effects to the public.

INTRODUCTION

Endothall is an organic acid effective as a contact weed killer. Major uses of endothall include the defoliation of cotton, control of algae and aquatic weeds and as a desiccant on lucerne and on potato. Its rapid breakdown to nontoxic products makes it desirable for control of aquatic weeds. It is selective enough to kill weeds and leave other desirable species such as fish and insects unaffected.

CHEMICAL PROFILE

Endothall is an herbicide and algaecide which is available in the free acid form, as the potassium, sodium, or N,N-,dialkylamine salts (U.S. EPA, 1992a). Endothall is primarily used (95%) as a defoliant in cotton production. Other uses include as an herbicide for sugar beets (4%), and the remainder in landscape maintenance or “public health pest control” (e.g., clearing of overgrown ponds) (HSDB, 1997). Endothall decomposes to an anhydride when heated, which makes it useful in desiccating vegetables, but this is a minor use (HSDB, 1997).

There are few regulations regarding endothall. No Occupational Safety and Health Administration (OSHA) standards exist. Tolerances exist for raw agricultural commodities of 0.1 ppm. An interim tolerance of 0.2 ppm was proposed for sugar beets, which is identical to the tolerance for residues in drinking water derived from ponds treated with endothall (HSDB, 1997).

Chemical name: 7-Oxabicyclo(2.2.1)heptane-2,3 dicarboxylic acid
CAS number: 145-73-3
Molecular formula: C8-H10-O5
Molecular weight: 186.18
Product names: Accelerate, Aquathol, Endothall Turf herbicide, Endothall Weed Killer, Hydrothal, Herbicide 273, Herbon Pennout, Hydout, 1,2-benzenedicarboxylic acid, 1,2-cyclohexanedicarboxylic acid, 3,6 endo-epoxy- 3,6-endooxohexahydrophalic acid.
Properties: Crystalline, white solid, odorless
Melting point: when heated rapidly melts at 144 °C
Solubilities: @20° C 10 gm/100g water
Vapor pressure: very low at room temperature

ENVIRONMENTAL OCCURRENCE

Air

No specific information is available on ambient levels of endothall. Endothall is unlikely to remain airborne for very long due to its low volatility.

Soil

Most applications of endothall are to soils for weed control and defoliation. Once released to the soil endothall is fairly stable and highly mobile in aquifers. Its half-life is reported to be four to nine days due to rapid microbial degradation under aerobic conditions (HSDB, 1997).

Water

Studies of releases to water have shown that endothall rapidly degrades. It is not expected to oxidize, chemically hydrolyze, photolyze, volatilize, bioaccumulate or adsorb to suspended solids or sediments (HSDB, 1997).

Sikka and Rice (1973) applied 14C ring-labeled endothall to a lake impoundment at 2 mg/L and followed its fate. Endothall applied to ponds was found to disappear rapidly to nondetectable levels within 36 days. If the water was sterilized, endothall would persist, indicating the importance of microbial degradation on the stability of endothall in the environment. The authors speculated that the course of endothall disappearance has three phases, adsorption to the hydrosol, followed by slower microbial metabolism, then to a faster disappearance due to microbial proliferation. Similarly, Simsiman \textit{et al.} (1976) reported that 72% of endothall (applied at a concentration of 3 mg/L) persisted for over 30 days due to the prolonged oxygen depletion following weed kill. Once oxygenated conditions were restored endothall dissipated rapidly. There are microorganisms capable of incorporating the 14C ring labeled endothall into glutamic acid via the tricarboxylic acid cycle. One such organism could use endothall as its sole carbon source (Sikka and Saxena, 1973).

Endothall was not detected in recent well water surveys conducted by the California Department of Pesticide Regulation (DPR, 1996).

Food

Based on its limited use in food crops endothall is not monitored for in surveys conducted of residues in fresh produce in California (DPR, 1993). Endothall applied to rice paddy fields was not detected in harvested rice (Maini, 1992).
METABOLISM AND PHARMACOKINETICS

There are limited data (one available older study) on the metabolism and pharmacokinetics of endothall in mammals.

Absorption, Distribution, and Excretion

Six Wistar rats (two male and four female) received unlabelled endothall in their feed at a concentration of 5 mg/kg food (equivalent to approximately 0.254 mg/kg-day for males and 0.335 mg/kg-day for females) for at least two weeks. Following this pre-treatment, these laboratory animals were administered 1 mg/kg 14C-ring-labeled endothall suspended in 20% ethanol by gavage. There were no observed signs of toxicity and 85% to 91% of endothall was recovered in the feces untransformed within 48 hours. Urinary excretion accounted for approximately 7% of the dose and 3% was excreted as carbon dioxide (Soo et al., 1967).

Soo et al. (1967) also studied the distribution of endothall in nine female rats using the dosing regimen mentioned above. After receiving the radioactive endothall, rats were sacrificed at intervals ranging from 1 to 72 hours for analysis of radioactivity in tissues. The results indicate that the majority was present in the stomach and intestine (95%) with the next highest levels detected in the liver and kidney. Very low levels were measured in other tissues. After 72 hours, all tissue levels had returned to zero and only a trace of the compound remained in the gastrointestinal tract. These results indicate relatively poor absorption of endothall.

In the same report, Soo et al. (1967) administered labeled endothall to two lactating rats to determine whether endothall was secreted in milk. The animals received a daily oral dose of 0.2 mg endothall (in 10% sucrose solution) for five consecutive days prior to delivery. After birth, dams received a daily dose of 0.4 mg endothall in 10% sucrose solution for five consecutive days. After sacrifice of the pups, no radioactivity was detected in any of the tissues or stomach contents suggesting that endothall was not secreted into the milk of lactating rats.

Metabolism

Soo et al. (1967) also studied the excretion of endothall in the urine and feces of two male and four female Wistar rats that were administered a single oral dose by stomach tube of 5 mg of 14C-endothall. Endothall was the only product detected. It was concluded that no detectable biotransformation of endothall occurred from oral administration.

Endothall appears to be completely metabolized by microorganisms, plants and some fish. Bluegills appeared to poorly absorb and not to metabolize endothall dissolved in water (Sikka et al., 1975). However, radioactive carbon was detected in all body tissues examined from goldfish and salmon that had received ring-labeled endothall (Montgomery and Freed, 1964). Microorganisms found in lakes metabolized endothall completely and released it as CO₂ (Sikka and Saxena, 1973).
**TOXICOLOGY**

**Toxicological Effects in Animals**

**Acute Effects**

In acute oral toxicity studies, endothall (technical grade) caused death following administration of a single dose of 40 mg/kg in 50% of the exposed rats and all rats died following exposure to 60 mg/kg. At lower doses, decreased activity, diarrhea, abnormal gait, abnormal stance and dyspnea were observed in several animals. Some rats had fluid-filled stomachs and intestines. One animal was reported to exhibit mottled kidneys at necropsy (Pharmakon, 1991a). In a separate study, an oral LD$_{50}$ in Sherman rats was estimated to be 57 mg/kg in males and 46 mg/kg in females (Gaines and Lindner, 1986).

Endothall (technical grade) applied dermally to five male and five female rabbits at a limit dose of 2,000 mg/kg for four hours failed to produce deaths but did cause diarrhea in one female. Slight loss in mean body weight was noted in females by day seven (Pharmakon, 1992).

Rabbits (three male and three female) were administered 100 mg endothall (technical grade powder) into their eyes. Corneal opacity, conjunctival chemosis and redness and iritis was evident within an hour. Acute systemic toxicity was observed in all animals and four died within 24 hours (Pharmakon, 1991b).

An acute inhalation study with endothall was conducted in rats (Life Science, 1988a). Rats were exposed to endothall (technical) at concentrations of 0, 0.446, 1.678 or 2.472 mg/L in air (10 rats per sex per dose) The majority of rats exposed to the two highest air concentrations died within 24 hours. Most animals died within one day of dosing at the two highest dose levels.

**Subacute/Subchronic Toxicity**

Nine male dogs were orally administered one dose of endothall per dog, from 1 to 50 mg/kg-day for six weeks. Dogs receiving 20 or 50 mg/kg-day dose died within 3 to 11 days. Clinical symptoms included vomiting and diarrhea. Significant changes found in the digestive tract included erosions, hemorrhages, edema and ulcerations at 20 mg/kg-day and higher (Pennvalt, 1953).

**Genetic Toxicity**

Several mutagenicity assays have been performed on endothall. In one test endothall was tested for mutagenicity in the *Salmonella typhimurium* and *E. Coli* B T4 bacteriophage assays. No evidence for higher mutagenic rate was found (Andersen et al., 1972). In another study endothall was applied on a direct plate assay done in triplicate with and without activation in *S. typhimurium* strains TA1535, TA1538, TA98 and TA100 at 0, 0.05, 0.15, 1.5 or 5 mg/plate. No increase in revertants was noted (Microbiological Associates, 1980a). Endothall amine salt solution was also tested in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538, with or without activation in triplicate at 0 (DMSO), 0.580, 1.93, 5.8, 19.3, 58.0, 116.0 or 193.0 acid equivalent mg/plate for 48 hours. A slight increase in reversion rate was noted only in strains TA1537 and
TA1538 (about three-fold) which was considered within normal in variation (Stankowski, 1993a). The results of these assays combined suggest limited potential for mutagenicity.

In mammalian point mutation systems, endothall was found to be negative as well. In BALB 3T3 clone A31 cells in the presence of metabolic activation, endothall was applied at concentrations of 0.01, 0.1 or 1 µg/mL plates (Microbiological Associates, 1980b). In the absence of metabolic activation, endothall was applied at concentrations of 0.5, 1.0, 23 or 10 µg/mL. In both cases, no mutagenic potential was found based on reversion to resistance to ouabain toxicity (Microbiological Associates, 1980c).

In a forward mutation assay, 0 (untreated), 0 (DMSO), 0.0116, 0.0580, 0.116, 0.580, 1.160, 2.32, 2.900, 3.480, 4.060 or 4.640 µg/mL with activation and 0 (untreated), (DMSO), 0.116, 0.580, 1.160, 5.800, 11.600, 17.400, 20.300, 21.800, 23.200, 26.100 or 29.000 µg/mL (significant figures were reported by the authors) endothall amine salt was applied to a AS52 (clone -1.3) Chinese hamster ovary cell line in duplicate. Significant cytotoxicity was observed at concentrations of 5.80 µg/mL and above without activation and 25.10 µg/mL and above with activation, but no increase in forward mutation rate was noted (Stankowski, 1993b).

Endothall failed to cause significant changes in chromosomes in several assays. In an in vivo micronucleus assay, CD-1 mice (15/sex/group) were administered a single dose of endothall amine salt solution (technical grade) 0 (deionized water), 0.464, 0.928 or 1.86 mg/kg body weight via intraperitoneal injection in a volume of 10 mg/kg. The positive control group (five animals per group) received triethylenemelamine-TEM (0.5 mg/kg) and sampled 24 hours after treatment. The animals (5/sex/group) were killed and samples collected 24, 48 and 72 hours after treatment. No increase in micronuclei from the polychromatic erythrocytes was observed (San Sebastian, 1994). In another assay, endothall technical was administered to CD-1 mice in a single treatment of 0 (saline), 2, 10 or 50 mg/kg orally by gavage. The low and mid-dose groups (five per sex/group) were killed at 24 hours after treatment and sampled; the control and high-dose groups were killed (five per sex/group) and samples collected 24, 48 and 72 hours after treatment. The positive control group was given chlorambucil (30 mg/kg) and sampled at 24 hours after treatment. No increase in micronuclei in the polychromatic erythrocytes was observed (Mackay, 1989).

Clastogenic activity was tested by administering endothall (technical) grade at concentrations of 0 (DMSO and untreated), 2.5, 10, 20, 30 or 40.0 µg/L to triplicate plates of cultured human male peripheral blood lymphocytes without activation. Similarly, an assay with activation was performed at 0 (DMSO and untreated), 15.0, 60.0, 120.0 or 240.0 µ/mL. No elevation in the number of chromosomal aberrations was observed, but an increase in polyplody was noted at the high exposure, activated and nonactivated groups (Bootman, 1989).

Disodium endothall was administered to Sprague-Dawley rats in their diet for five consecutive days at 0, 150, 300 or 600 ppm, to 10 males per group mated to two females per week for seven weeks. No toxicity was shown in the high dose and no increase in lethality was noted in this dominant lethal assay (Litton Bionetics, 1977a, b). Similarly, disodium endothall was given at the same doses to male rats (five/group) in their feed for five consecutive days. No increases in micronuclei were observed in bone marrow cells.

DNA damage was assessed by using E. Coli WP2, WP67 (uvrA and polA repair-deficient) and CM871 (uvrA, recA and lexA) repair-deficient treated with endothall (technical) with or without
metabolic activation at concentrations of 0 (DMSO), 100, 316, 1000, 3160 or 10,000 μg/mL with 2 and 18 hour incubation periods. No evidence of DNA damage was noted (Life Science, 1988b).

Developmental and Reproductive Toxicity

Endothall (technical) was administered by gavage to pregnant Sprague-Dawley rats (25/group) on days 6 to 19 of gestation at 0, 10, 20 or 30 mg/kg-day (equivalent to 0, 8, 16 or 24 mg endothall ion/kg-day). Physical and behavioral parameters were monitored in offspring. No effects on development was noted. Pivoting locomotion at 20 and 30 mg/kg dose level was normal. Two dams died at the 20 mg/kg and 10 at the 30 mg/kg dose. No clinical signs were noted, nor were lesions reported at necropsy (Science Application Inc., 1982).

In mice, endothall (technical) was mixed with blended whole egg and deionized water and administered to CD-1 mice (25/group) by gavage on days 6 to 16 of gestation at 0 (water), 5, 20 or 40 mg/kg-day. Some maternal deaths occurred at the 20 and 40 mg/kg-day dose groups. The number of animals with malformations in the high dose group was 10% of total compared with 2% in controls. This slightly increased response was attributed to maternal toxicity (IRDC 1981).

A two-generation reproduction study in rats was conducted with the disodium salt of endothall admixed with feed at concentrations of 0, 6.25, 12.5 or 25 mg/kg-day and administered for two generations to 25 male and 25 female Crl:CD:BR(Sprague-Dawley) rats per dose. The F1 generation was bred twice (with six weeks between matings). A reduced number of pregnancies was observed in control and lowest-dose groups but this outcome was not compound-related. Decreased weight gain and food consumption were noted for the highest dose mature animals, the only significant compound-attributable effects noted (Trutter, 1995a).

Chronic Effects/Carcinogenicity

In a two-year study, male and female albino rats (50/group) were administered dipotassium endothall at 600, 1,200 or 2,400 ppm in the diet. After 20 weeks, rats receiving endothall had substantially reduced their intake of food. Upon consulting with U.S. EPA, the investigators changed the use of the potassium compound to the sodium salt, with the resulting corresponding average concentrations being 400, 800 or 1,600 ppm (endothall ion equivalents). Food intakes and body weights remained depressed when compared with controls, particularly at high doses. High dose rats exhibited focal tubular dilation, which was the only significant pathological change associated with treatment (IBT, 1975).

Disodium endothall was administered in the diet for 104 weeks to 62 Crl:CD(SD)BR rats/sex/group at 0, 300, 900 or 1,800 ppm with interim necropsies of 10/sex/group (MacKenzie, 1989). In a separate phase of the study, 50 rats of both sexes of the same strain were administered 0 and 150 ppm in the diet for 104 weeks. Lesions of the glandular and non-glandular regions of the stomach were common in the higher doses. Body weight decreases were significant at 150 and 300 ppm. Original pathology reported possible stomach lesions in males at the lowest doses. At a later date the pathology was reevaluated and the original observations were reversed with a no-observed-adverse-effect-level (NOAEL) of 300 ppm for males (9 mg/kg-day) reported. The NOAEL for females based on gastric changes was 150 ppm (5 mg/kg-day).
Disodium endothall was administered to CD1 mice in the diet for 24 months at 0, 300, 600 or 1,200 ppm, 50/sex/group (Cannon Labs, 1979). Body weight decreases were noted in males. There was increased inflammation of the liver, particularly at the high dose and an increase in gastritis and duodenal epithelial hyperplasia at all treatment levels. A slight increase in mammary tumors was noted, but this observation was not determined to be dose-dependent by the author.

In another study, disodium endothall was administered in the diet at concentrations 0, 50, 100 or 300 ppm to 50 Cr1:CD-1(ICR)BR mice/sex/group for 92 weeks. Mean body weight was decreased about 6% compared with controls at 300 ppm in males. Minimal to mild multifocal mineralization was observed in male kidneys at 300 ppm. A slight increase in hepatocellular tumors was noted in the 300 ppm males (WIL, 1988). A NOAEL of 100 ppm (about 18 mg/kg-day) and a lowest-observed-adverse-effect-level (LOAEL) of 300 ppm (about 55 mg/kg-day) based on body weight changes and possible kidney effects were identified from this study.

A third mouse study was conducted with disodium endothall to approximate doses at the maximum tolerated dose (MTD), since none of the dose levels in previous studies seemed to achieve an effective MTD. Endothall was administered to 60 Cr1:CD-1(ICR)BR albino mice/sex/group at concentrations of 0, 750 or 1,500 ppm in the diet for at least 78 weeks. Significant mortality was noted, with the lowest dose group exhibiting a 20% mortality rate and the highest a 50% rate of mortality. Tumors of the duodenum and jejunum were noted for the high dose group (duodenal adenoma in one male and two females, duodenal carcinoma in one male and two females and jejunal carcinoma in female). Other significant effects included a dose-dependent increase in the number of cases of prolapse of the rectum in the 750 ppm and 1,500 ppm groups. In all treated animals there was an increase in severity of mucosal hyperplasia and dilation of the gastric glands (Trutter, 1995b).

Disodium endothall was administered in the diet of four Beagle dogs/sex/group for seven days/week for 52 weeks at 0, 150, 450 or 1,350/1,000 ppm (1,350 ppm reduced from week seven to 1,000 ppm due to anorexia and body weight loss). Epithelial hyperplasia was observed at all doses down to the lowest dose. At 150 ppm, hyperplasia was very mild and limited to the gastric mucosa. At 450 ppm and above, all tissues of the gastrointestinal tract and liver parenchymal and bile ductal cells were affected. The dogs in the highest dose group received a reduction in endothall exposure, still five out of eight were prematurely terminated because of their clinical condition. Although a NOAEL could not be identified, it appears to be very close to the 150 ppm (about 4.8 mg/kg) level identified as the lowest dose (Greenough et al., 1987). In an earlier study, disodium endothall was administered to dogs (three/sex/group) for two years at 0, 100, 300 or 800 ppm in the diet. In this study, the high dose was increased in several increments to 2,000 ppm by the 22nd month, then the study concluded at the end of the 24th month. No adverse effects or histological findings were reported (800 ppm) except for increased organ weights and organ-to-body weight ratios for the stomach and small intestine (300 and 800 ppm) (Keller, 1965). Based on the results of this study, a LOAEL of 300 ppm (about 7.5 mg/kg) and a NOAEL of 100 ppm (2.5 mg/kg) were identified.

**Toxicological Effects in Humans**

Limited information exists for the effects of endothall upon humans. A male died after swallowing two mouthfuls of 175 g/L disodium endothall. This represents a dose of approximately 100 mg/kg.
In the autopsy, widespread focal hemorrhages and edema in the lungs and gastrointestinal tract were noted (Allender, 1983).

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

Endothall has been evaluated for chronic or carcinogenic effects, with at least two studies for each of the three species tested: rat, mouse and dog. The most common effect is weight loss or decreased food intake, followed by progressive to severe injury to the digestive tract, then by effects to other organs and death. In some studies, death occurred suddenly without many intervening signs.

To determine a PHG, a study must be selected which reflects the sensitivity to effects from endothall ingestion. Suitable studies are summarized in Table 1. The most appropriate study for risk characterization appears to be the Keller (1965) study in which dogs were administered endothall at 2.5, 7.5 mg/day and 20 mg/day for two years, and effects on organ weights and small intestine were observed at the two higher doses. In this study a NOAEL can be clearly identified, unlike the other study with lower LOAEL. This NOAEL is supported by the results of other studies (MacKenzie, 1989; Greenough et al., 1987) which reported modest changes (i.e., epithelial hyperplasia of the digestive tract and stomach lesions) occurred at 5 to 9 mg/day.

Table 1. Summary of NOAEL and LOAELs for Endothall (in mg/kg-day)

<table>
<thead>
<tr>
<th>Species</th>
<th>NOAEL</th>
<th>LOAEL</th>
<th>Effect</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>5.0</td>
<td>9.0</td>
<td>body weight decrease</td>
<td>MacKenzie (1989)</td>
</tr>
<tr>
<td>Dog</td>
<td>2.5</td>
<td>7.5</td>
<td>increased organ weights and organ-to-body weight ratios for stomach and small intestine</td>
<td>Keller (1965)</td>
</tr>
<tr>
<td>Dog</td>
<td>NA</td>
<td>4.8</td>
<td>stomach lesions</td>
<td>Greenough et al. (1987)</td>
</tr>
<tr>
<td>Mouse</td>
<td>18</td>
<td>55</td>
<td>body weight decrease</td>
<td>WIL (1988)</td>
</tr>
<tr>
<td>Rat</td>
<td>8</td>
<td>16</td>
<td>maternal death</td>
<td>Science Application Inc. (1982)</td>
</tr>
</tbody>
</table>

Carcinogenic Effects

Tumors have been reported in chronic studies conducted in rats and mice, but not in the dog. In the MacKenzie (1989) rat study, endometrial tumors were reported at all doses (including control), at occurrences of less than 10% and with no apparent dose-response. No significant elevated occurrences of endometrial tumors were reported in the other lifetime rat study nor in any other species. The Trutter (1995b) study reported a few animals with digestive tumors also at the highest dose. However, this dose is greater than the MTD, since more than 50% of the animals died within 24 hours of the treatment. The majority of mutagenic assays for genetic toxicity indicate that endothall is neither mutagenic nor clastogenic. It is concluded that the evidence for endothall carcinogenicity is equivocal, however it appears that endothall has low carcinogenic.
potential. Therefore, it would be most appropriate to calculate a PHG from the demonstrated noncarcinogenic effects of endothall toxicity.

CALCULATION OF PHG

Calculations of concentrations of chemical contaminants in drinking water associated with negligible risks for carcinogens or noncarcinogens take into account the toxicity of the chemical itself, as well as the potential exposure of individuals using the water. Tap water is used directly as drinking water, in food preparation and for bathing or showering. It is also used in washing, flushing toilets and other household uses resulting in potential dermal and inhalation exposures. Based on the foregoing information, endothall is not expected to be significantly volatile or permeable by the dermal route of exposure. Therefore, it is unlikely that significant exposures will occur from inhaling or from direct contact with endothall in water, but rather the primary route of exposure will be from consuming drinking water.

The following general equation for noncarcinogenic endpoints is used for calculating a public health-protective concentration (C) for endothall (in mg/L) in drinking water:

\[
C = \frac{\text{NOAEL} \times \text{BW} \times \text{RSC}}{\text{UF} \times \text{L/day}} = \text{mg/L}
\]

where,

- **NOAEL** = No-observed-adverse-effect-level (2.5 mg/kg-day)
- **RSC** = Relative source contribution of 20% (0.2)
- **UF** = Uncertainty factor of three (3-fold for inter-species variation and 10-fold for human variability)
- **L/day** = Volume of daily water consumed for an adult (2 L/day)
- **BW** = Body weight for an adult male (70 kg).

There are two factors in these equations which incorporate consideration of exposure. The relative source contribution (RSC) is based on an estimate of the contribution of drinking water relative to other sources of exposure to the chemical contaminant. The other sources are usually food, air, and soil. U.S. EPA has selected an RSC of 20% (U.S. EPA, 1988) for endothall. This RSC is used for all organic compounds for which specific information about source contribution is not available.

The other exposure factor in the equation is the daily water intake in L/day. This factor represents the amount of tap water that it is assumed an individual consumes as drinking water, as well as mixed with beverages and used in cooking. The adult default value for this factor is 2 L/day. For children, 1 L/day is used. Since the NOAEL is from a lifetime exposure study, the water consumption factor will be based on the adult value of 2 L/day.

Another assumption used in this calculation relates to the use of an uncertainty factor (UF) of 30 (3-fold for inter-species variation and 10-fold for human variation). A UF of three for inter-species variation accounts for the possibility that humans could be three times more sensitive than animals to the toxic effects of endothall. This UF is applied to allow for increased pharmacodynamic sensitivity in response only at the site of contact. An additional UF of three to account for
differences in pharmacokinetics is not applied here because there is no pharmacokinetic component to the observed most sensitive toxicity endpoint. Endothall is a strong oxidant and would be expected to affect the site of contact. Acute and chronic animal studies demonstrate that endothall causes damage at the site of contact including eye, skin and when ingested, the gastrointestinal tract. Toxicity studies in dogs and rodents (Keller, 1968; Greenough et al., 1980) resulted in direct effects on the gastrointestinal tract, or indirect effects (when considering body weight gain reductions) at lower doses that increased in a dose-dependent manner. Likewise, gastric effects appear to be the most sensitive indicators of exposure as subtle changes occur in this area before all others. Although there are no chronic human ingestion studies, in the one report on acute human exposure, the subject's gastrointestinal tract exhibited damage consistent with a very irritating and corrosive substance (Allender, 1983). The use of a factor of three rather than the default value of 10-fold has been proposed under certain circumstances (Dourson et al., 1996).

The adult human male body default assumption of 70 kg is also used.

Therefore,

\[
C = \frac{2.5 \text{ mg/kg-day} \times 70 \text{ kg} \times 0.2}{30 \times 2 \text{ L/day}}
\]

\[
= 0.58 \text{ mg/L} = 580 \text{ ppb}
\]

The PHG calculated for endothall in drinking water is 0.58 mg/L (580 ppb).

**RISK CHARACTERIZATION**

The PHG of 0.58 mg/L (580 ppb) for endothall in drinking water is higher than U.S. EPA’s MCL. U.S. EPA’s MCL is 0.1 mg/L or 100 ppb (U.S. EPA 1992a,b). The MCL calculation was based on the same NOAEL from the same study as used in the development of the PHG. However, in its calculation of the MCL, U.S. EPA rounded the NOAEL from 2.5 to 2.0 mg/kg-day. Our practice is to not round any numbers until the final value is calculated. Therefore, we use the NOAEL of 2.5 mg/kg-day in the PHG calculation. U.S. EPA also applied a UF of 100; 10-fold for interspecies variation and 10-fold for human variability in its calculation of a reference dose (RfD). All other assumptions including body weight, RSC and water consumption were the same in the calculation of the federal MCL and the state PHG.

Although the NOAEL is derived from one study, the result and magnitude of effect is supported by evidence found in a number of chronic studies in several species. These studies indicate that the most sensitive endpoint appears to be the irritant effects on the digestive tract impacting body weight and organ weights and causing histologic changes with higher doses. These effects can be severe at high doses, progressing to death in many cases. The threshold level for these changes appears to be approximately 2.5 to 8 mg/kg-day. Therefore, selection of the 2.5 mg/kg-day is an appropriate NOAEL from a chronic study and reflects a high level of certainty. Of concern is the equivocal evidence for carcinogenicity. However, the data suggest that endothall would not likely be carcinogenic at the PHG level.

One major source of uncertainty in the computation might be the use of an RSC of 20% (0.2). The RSC assumes that major contributions of endothall would be through other sources such as air and
food. However, there is little evidence that endothall is airborne for significant periods. Endothall is also fairly unstable in the environment. Furthermore, no significant contribution of endothall from food is expected. No detectable endothall residues have been detected, and it is unlikely that residues would be detected because of the instability of endothall. However, since endothall is used on food crops and to control weeds, some contribution from these sources should be accounted for in the PHG estimation. Therefore, a factor of 20% is assumed due to the inability to estimate the contribution of these sources.
REFERENCES


Microbiological Associates (1980c). Activity of T1604 (endothall) in the in vitro mammalian cell point mutation assay in the presence of exogenous metabolic activation-final report (1, 0.1 and 0.01 ug/ml). Microbiological Associates. 5/76. DPR Rec: 13120.


Soo, A., Tinsley, I. and Fang, S.C. (1967). Metabolism of 


