

## ACIFLUORFEN

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

I. INTRODUCTION

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

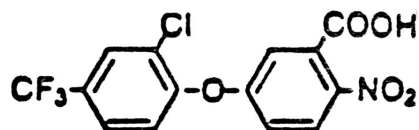
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The Has are subject to change as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

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

II. GENERAL INFORMATION AND PROPERTIES

CAS No. 50 94-66-6 (acid)

62476-59-9 (sodium salt)

Structural Formula

Sodium 5-(2-chloro-4-(trifluoromethyl)-phenoxy)-2-nitrobenzoate

Synonyms

- Blazer®; Carbofluorfen; RH-6201, Tackle\*; Sodium acifluorfen (Meister, 1983).

Uses.

- Acifluorfen is used as a selective pre- and post-emergence herbicide to control weeds and grasses in large-seeded legumes including soybeans and peanuts (Meister, 1983).

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

Chemical Formula	C <sub>14</sub> H <sub>7</sub> ClF <sub>3</sub> NO <sub>5</sub> (acid) C <sub>14</sub> H <sub>6</sub> ClF <sub>3</sub> N <sup>***</sup> (sodium salt)
Molecular Weight	361.66 (acid) 383.65 (sodium salt)
Physical State (25°C)	Off-white solid (acid), brown crystalline powder/white powder (sodium salt)
Boiling Point	--
Melting Point	124-125°C (sodium salt) 151.5-157°C (acid)
Density	--
Vapor Pressure (25°C)	24 mm Hg (45% H <sub>2</sub> O solution)
Specific Gravity	--
Water Solubility (25°C)	>25% (sodium salt) (dimensions not specified)
Log Octanol/Water Partition Coefficient	-4.85 (acid) (calculated)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- No information was found in the available literature on the occurrence of acifluorfen.

Environmental Fate

- Acifluorfen is stable to hydrolysis; no degradation was observed in solutions at pH 3, 6 or 9 within a 28-day interval. Varying temperatures (18 to 40°C) did not alter this stability. The half-life of the parent compound is 9 hours under continuous exposure to light approximating natural sunlight. The decarboxy derivative of acifluorfen was the primary degradate found in solution. It is suspected that a substantial percentage of the photodegradate parent is lost from solution (through volatilization or other mechanisms) (Registration Standard Science Chapter for Acifluorfen).
- The half-life of acifluorfen in an aerobically incubated soil was found to be about 170 days; anaerobic degradation was more rapid (half-life about 1 month). The dominant residue compounds after 6-months aerobic incubation were the parent compound and bound materials. After 2 months under anaerobic conditions, the acetamide of amino acifluorfen was the major degradate extracted from soil; the amino analog itself was also significant, and denitro acifluorfen was also formed (Registration Standard Science Chapter for Acifluorfen).
- Acifluorfen applied at 0.75 lb ai/A to a silt loam in Mississippi dissipated with a tentative half-life of 59 days. Leaching of the parent compound below 3 inches in the soil was negligible during the 179-day study. The dissipation of acifluorfen in two silt loam soils in Illinois receiving multi-residue treatments was somewhat slower; half-lives were 101 to 235 days (Registration Standard Science Chapter for Acifluorfen).

- Acifluorfen applied to soil columns at highly excessive rates indicative of spills (682 lb ai/A) is very mobile. Acifluorfen leached from the columns with 10 inches of water accounted for 79 to 93% of the acifluorfen applied. Aerobic aging of the residues in the column substantially reduced the mobility and pesticide movement was inversely proportional to the soil CEC. Results from soil TLC (un-aged residues only) predict mobility to be intermediate to mobile. Supplementary data from a batch adsorption study indicate that un-aged acifluorfen is weakly and reversibly adsorbed (Registration Standard Science Chapter for Acifluorfen).
- Greenhouse studies have demonstrated that the uptake of acifluorfen by rotational crops decreases with aging of residues in soil (Registration Standard Science Chapter for Acifluorfen).

### III. PHARMACOKINETICS

#### Absorption

- No information was found in the available literature on the absorption of acifluorfen.

#### Distribution

- No information was found in the available literature on the distribution. of acifluorfen.

#### Metabolism

- No information was found in the available literature on the metabolism of acifluorfen.

#### Excretion

- No information was found in the available literature on the excretion. of acifluorfen.

### IV. HEALTH EFFECTS

#### Humans

- No information was found in the available literature on the health effects of acifluorfen in humans.

#### Animals

##### Short-term Exposure

- The Whittaker Corporation (no date, a) reported that the oral LD<sub>50</sub> of Tackle 2S (a formulation containing 20.2% sodium acifluorfen) in the rat (strain not specified ) was 2,025 mg/kg for males and 1,370 mg/kg for females.
- Meister (1983) reported that the acute dermal LD<sub>50</sub> of Blazer® (technical grade, purity unspecified) in the rabbit is 450 mg/kg. The acute dermal LD<sub>50</sub> of Tackle® (purity unspecified) in the rabbit is 2,000 mg/kg.
- Goldenthal et al. (1978a) presented the results of a two-week rangefinding study in which RH 6201 (a formulation containing 39.4% sodium acifluorfen) was administered to Charles River CD-1 mice (10/sex/dose) at dietary concentrations of 0, 625, 1,250, 2,500, 5,000 or 10,000 ppm. Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day (Lehman,

1959), these doses correspond to about 0, 93.8, 187.5, 375.0, 750.0 or 1,500 mg/kg/day. No changes in general behavior or appearance were reported at any dose level. During the second week of the study, there was a decrease in body weight and food consumption in animals receiving 10,000 ppm (1,500 mg/kg/day). Gross pathological findings included pale kidneys, yellowish livers and reddish foci of hyperemia in the stomachs of several mice at the 5,000- and 10,000-ppm (750 and 1,500 mg/kg/day) dose levels. Absolute liver weight was increased in all test groups dosed at levels of 2,500 ppm (375 mg/kg/day) or greater. The increases were statistically significant ( $p < 0.01$ ). A statistically significant ( $p < 0.01$ ) increase in relative liver weight was reported at all dose levels. Based on the results of this study, a Lowest-Observed-Adverse-Effect Level (LOAEL) of 625 ppm (93.8 mg/kg/day) was identified.

- Piccirillo and Robbins (1976) administered RH 6201 (a formulation containing 39.8% sodium acifluorfen) to Wistar rats (5/sex/dose) for 4 weeks at dietary concentrations of 0, 5, 50, 500 or 5,000 ppm (reported to be equivalent to 0, 0.7, 7.6, 55.4 or 506.4 mg/kg/day for males and 0, 0.8, 8.3, 60.6 or 528.2 mg/kg/day for females). Assuming that these dietary levels reflect the concentration of the test compound and not the active ingredient, corresponding levels of sodium acifluorfen are 0, 0.3, 3.0, 22.1 and 201.6 mg/kg/day for males and 0, 0.3, 3.3, 24.0 and 210.2 mg/kg/day for females (Lehman, 1959). Results of the study indicated that body weight was decreased in males at 22.1 and 201.6 mg/kg/day, and food consumption was decreased in both males at 201.6 mg/kg/day and females at 210.2 mg/kg/day. Biochemical analyses revealed that serum glutamic pyruvic transaminase (SGPT) levels were increased in males at 22.1 and 201.6 mg/kg/day; in males that received 201.6 mg/kg/day, blood urea nitrogen (BUN) was increased and glucose levels were decreased. Changes in organ weights included increased: absolute liver and kidney weights in males at 201.6 mg/kg/day, increased relative liver and kidney weights in males at 201.6 mg/kg/day and females at 210.2 mg/kg/day and increased relative liver weight in males only at 22.1 mg/kg/day. Based on the results of this study, a No-Observed-Adverse-Effect Level (NOAEL) of 3.0 mg/kg/day was identified.

#### Dermal/ocular Effects

- In a dermal irritation study (Whittaker Corp., no date, b), Tackle 2S (a formulation containing 20.2% sodium acifluorfen) was applied occlusively (dose not specified) to the intact and abraded skin of rabbits. Effects observed included slight erythema, slight edema, blanching of the skin, and eschar formation. Signs of dermal irritation at intact and abraded sites were absent by 8 days post-application. The test substance was considered to be a moderate dermal irritant at 72 hours.
- In a dermal irritation study, Weatherholtz et al. (1979b) applied RH 6201 (sodium acifluorfen) to the skin of New Zealand White rabbits (five/sex/dose; ten/sex/control). Three different formulations of RH 6201 were used in the study and each formulation was tested at 1.0 or 4.0 mL/kg/day. The authors indicated that for all RH 6201 formulations tested, the dose levels correspond to 50 or 200 mg/kg/day of the active ingredient. The test material was applied once daily for 5 days, followed by 2 days with no applications, over a 4-week period (total of 20 applications). At both dose levels, two of the formulations produced slight to well-defined irritation. At 200 mg/kg/day, central nervous system depression and a statistically significant decrease in body weight gain and food consumption were noted. The third formulation produced essentially the same effects, with the addition of “thinness,” ataxia, slight tremors and mortality (2/5 males). Microscopic evaluations revealed chronic dermatitis, acanthosis and hyperkeratosis at both dose levels for all formulations
- Madison et al. (1981) presented the results of the Buhler test for dermal sensitization in Hartley-derived albino guinea pigs. In this study, Tackle® (sodium acifluorfen; purity not

specified) was not found to be a sensitizer when applied topically at a dose of 0.25 mL under occlusive binding.

- In an ocular irritation study (Whittaker Corp., no date, c), Tackle 25 (a formulation containing 20.3% sodium acifluorfen) was instilled into the eyes of rabbits. Signs of ocular irritation and lesions included opacities of the cornea, iritis, redness and chemosis of the conjunctiva and discharges from both washed and unwashed eyes. Four of six unwashed eyes and one of three washed eyes exhibited blistering of the conjunctiva. Three of six unwashed and one of three washed eyes exhibited pannus where corneal opacity had been.
- In an ocular irritation study (Weatherholtz et al., 1979a), 0.1 mL of Blazer 2S (purity not specified) was applied to the corneal surface of the eyes of rhesus monkeys. Corneal opacity and conjunctival redness, swelling and discharge were observed in both washed and unwashed eyes. All treated eyes were free of signs of irritation by 14 days posttreatment.

#### Long-term Exposure

- Harris et al. (1978) administered RH 6201 (a formulation containing 39.4% sodium acifluorfen) in the diet to Sprague-Dawley rats (15/sex/dose) for 3 months at dose levels of 0, 75, 150 or 300 mg/kg/day. Assuming that these doses reflect levels of the test compound and not the active ingredient, corresponding levels of sodium acifluorfen would be 0, 29.6, 59.1 or 118.2 mg/kg/day. At the highest dose level (118.2 mg/kg/day), a number of effects were observed in male rats. These effects included decreased body weight (13%) and decreased food consumption (8%). Biochemical analyses of blood revealed increased alkaline phosphatase levels (32%), decreased total protein (8%) and decreased albumin (14%). No such effects were reported for female rats. (These biochemical analyses were performed on control and highdose animals only.) Increased liver weight and microscopic liver changes (enlarged hepatocytes) were observed in male rats that received 59.1 or 118.2 mg/kg/day. In terms of the active ingredient, a NOAEL of 29.6 mg/kg/day was identified.
- Barnett (1982) administered Tackle 2S (a formulation containing 20.4 to 23.6% sodium acifluorfen) to Fischer 344 rats (30/sex/dose) for 90 days at dietary concentrations of 0, 20, 80, 320, 1,250, 2,500 or 5,000 ppm. The author indicated that these dietary levels correspond to average compound intake levels of 0, 1.5, 6.1, 23.7, 92.5, 191.8 or 401.7 mg/kg/day for males and 0, 1.8, 7.4, 29.7, 116.0, 237.1 or 441.8 mg/kg/day for females. Assuming that these levels reflect test compound and not active ingredient intake, corresponding levels of sodium acifluorfen intake are approximately 0, 0.4, 1.4, 5.6, 21.8, 45.3 or 94.8 mg/kg/day for males and 0, 0.4, 1.8, 7.0, 27.4, 56.0 or 114.3 mg/kg/day for females (based on 23.6% active ingredient in test compound). At 5,000 ppm the following effects were observed: decreased body weight and food consumption in both sexes; decreased red blood cell (RBC) count, hemoglobin and hematocrit in both sexes; increased serum cholesterol and serum calcium, and decreased serum phosphorous in both sexes; increased alkaline phosphatase, SGPT and BUN levels in males; elevated urobilinogen in both sexes; increased liver size and discolored liver and kidneys in both sexes; and liver cell hypertrophy and increases in mitotic figures and individual cell deaths in both sexes. At 2,500 ppm the following effects were observed: decreased body weight in males; decreased RBC count, hemoglobin and hematocrit in both sexes; increased BUN levels in males; elevated urobilinogen in both sexes; increased liver size in both sexes; and liver cell hypertrophy and increases in mitotic figures and individual cell deaths in both sexes. At 1,250 ppm, the following effects were observed: increased liver size in males and liver cell hypertrophy in both sexes. The author identified 320 ppm as the NOAEL in this study. In terms of active ingredient concentration, this corresponds to a NOAEL of 5.6 mg/kg/day for males and 7.0 mg/kg/day for females.

- Mobil (1981) presented the 6-month interim results of a longer-term study in which Tackle 2S (a formulation containing approximately 75% sodium acifluorfen) was administered to beagle dogs (eight/sex/dose) at dietary concentrations of 0, 20, 320 or 4,500 ppm. These dietary levels were reported to be equivalent to 0, 0.7, 9.0 or 160 mg/kg/day. Assuming that these levels reflect test compound and not active ingredient intake, corresponding levels of sodium acifluorfen intake are 0, 0.5, 6.8 or 120.0 mg/kg/day (based on 75% active ingredient in the test compound). Following six months of compound administration, two animals/sex/dose were sacrificed. The study reported a number of effects at the highest dose tested. These effects included decreased body weight and food consumption and increased liver weight in both sexes. Additionally, RBC count and hemoglobin concentration were decreased in both sexes. Clinical chemistry analyses revealed depressed serum cholesterol, increased alkaline phosphatase, and transient elevation of BUN in both sexes. Males only showed increased levels of lactic dehydrogenase. No histopathological examinations were conducted. The NOAEL reported in this study was 320 ppm. In terms of the active ingredient, this corresponds to a NOAEL of 6.8 mg/kg/day.
- Barnett et al. (1982b) administered Tackle 2S (a formulation containing 19.1 to 25.6% sodium acifluorfen) to Fischer 344 rats (73/sex/dose) for 1 year at dietary levels of 0, 25, 150, 500, 2,500 or 5,000 ppm. Assuming that these dietary levels reflect the concentrations of the test compound and not the active ingredient, corresponding levels of sodium acifluorfen are 0, 6.4, 38.4, 128.0, 640.0 or 1,280 ppm (based on 25.6% active ingredient in the test compound). Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day, these levels correspond approximately to 0, 0.3, 1.9, 6.4, 32.0 or 64.0 mg/kg/day (Lehman, 1959). No excess morbidity or mortality was associated with the ingestion of the test substance. At 5,000 ppm, the following effects were observed: decreased mean body weight in both sexes; increased absolute and relative liver weight in both sexes; decreased protein production, decreased serum glucose, decreased triglyceride levels, increased alkaline phosphatase and creatine phosphokinase levels, and sporadic increases in SGOT and SGPT in both sexes; a slight increase in the excretion of urobilinogen in both sexes; and the presence of acidophilic cells that were considered to be evidence of cytotoxic changes in the livers of both sexes. At 2,500 ppm, male rats showed increased absolute and relative liver weights. Based on the information presented in this study, a NOAEL of 500 ppm was identified for the test compound. In terms of the active ingredient, this corresponds to a NOAEL of 6.4 mg/kg/day.
- Spicer et al. (1983) administered Tackle 2S (a formulation containing 74.5 to 82.8% sodium acifluorfen) to beagle dogs (eight/sex/dose) for 2 years at dietary concentrations of 0, 20, 300 or 4,500 ppm, reported to be equivalent to 0, 0.5, 7.3 or 121 mg/kg/day for males and 0, 0.5, 8.3 or 154 mg/kg/day for females. Assuming that these dietary levels reflect the concentration of the test compound and not the active ingredient, corresponding levels of sodium acifluorfen are 0, 0.4, 6.0 or 100.2 mg/kg/day for males and 0, 0.4, 6.9 or 127.5 mg/kg/day for females (based on 82.8% active ingredient in the test compound). At the highest dose, body weight was decreased (not statistically significant), and a corresponding (statistically significant) decrease in food consumption was also reported. Physical examination revealed heart anomalies in the high- and mid-dose groups. At the high dose, irregular heart rhythms and rapid or slow heart rates were reported in one male and four females. Also at this dose level, one male was found to have a systolic murmur. At the mid-dose level, one animal of each sex had an irregular heart rhythm (accompanied by rapid heart rate in the male). At the highest dose tested, a number of changes were reported, including a statistically significant decrease in erythrocyte count, hemoglobin and hematocrit in both sexes; reductions in albumin and cholesterol; increased absolute and relative liver and kidney weights; and histopathological liver changes including centrilobular hepatocellular fatty vacuolation, bilirubin pigmentation and minimal foci of alteration. Renal tubules showed bilirubin pigmentation at all dose levels (most pronounced at the high dose). The authors concluded that this study showed clear

evidence of target organ toxicity affecting the liver and possibly the kidney at the highest dose level. The authors identified 300 ppm (of test compound) as the NOAEL. In terms of the active ingredient, this corresponds to a NOAEL of 6.0 mg/kg/day.

- Goldenthal (1979) administered RH 6201 (a formulation containing 39.4 to 40.5% sodium acifluorfen) to Charles River CD-1 mice (80/sex/dose) for two years in the diet at concentrations that provided dosage levels of 0, 1.25, 7.5 or 45.0 ppm of the active ingredient. After 16 weeks of administration, the 1.25 ppm dose was increased to 270 ppm. Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day, these levels correspond to about 0, 0.19 (increased to 40.5), 1.13 and 6.8 mg/kg/day (Lehman, 1959). Two control groups were used in this study. One group received acetone in the diet (control 1), and the other received water in the diet (control 2). At the 40.5 mg/kg/day dose level, the following effects were observed: slight to marked elevations in alkaline phosphatase and SGPT levels, in both sexes, beginning after one year of exposure; increased absolute and relative liver weight in males; increased absolute liver weight in females; increased relative kidney weight in males; decreased absolute heart weight in males; cellular alterations in the livers of males consisting of focal pigmentation, focal hepatocytic necrosis, focal cellular alteration, nodular hepatocellular proliferation and hepatocellular carcinoma (the only statistically significant change was the focal cellular alteration); and focal pigmentation in the livers of females. At the 6.8 mg/kg/day dose level, the following effects were observed: occasional increases in alkaline phosphatase and SGPT levels in both sexes; decreased absolute heart weight in males; and focal pigmentation in the livers of females. The author indicated that changes with an apparent dose-related distribution included focal pigmentation, hepatocellular vacuolation, focal hepatocytic necrosis and nodular hepatocellular proliferation. The incidence of hepatocellular carcinoma in males of all treatment groups was approximately the same. A NOAEL of 7.5 ppm (1.13 mg/kg/day) was identified by the author.

#### Reproductive Effects

- In a three-generation reproduction study, Goldenthal et al. (1978b) administered RH 6201 (a formulation containing sodium acifluorfen) in the diet to Charles River CD rats. During the course of the study, the test compound was administered at various levels depending on the age of the animals. The F<sub>1</sub> generation received dose levels of 2.9, 17.3 or 104 ppm during the first 2 weeks of the study, and 5, 30 and 180 ppm for the remaining weeks of the generation (study weeks 3 to 17) (Time-Weighted Average (TWA) dosage levels 4.8, 28.5 or 171.1 ppm). The F<sub>2</sub> and F<sub>3</sub> generations received dosage levels of 180, 10 or 60 ppm during the first and second weeks of the generation; 312, 17.3 or 104 ppm during the third, fourth and fifth weeks of the generation; and 540, 30 or 180 ppm for the remaining weeks of the generation (TWA for F<sub>2</sub> generation 486.0, 27.0 or 162.0 ppm; TWA for F<sub>3</sub> generation 483.8, 26.7 or 161.3 ppm). The highest dietary TWA dose tested in this study was 486 ppm of active ingredient. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day, this corresponds to a dose of 24.3 mg/kg/day (Lehman, 1959). No effects related to compound administration were observed in parents or pups in terms of general behavior, appearance or survival. Parental and pup body weights and food consumption were similar to controls. Fertility, gestation and viability indices were comparable for controls and treated groups. There were no biologically meaningful teratogenic effects in the second or third generation, based on mean number of viable fetuses, post-implantation losses, total implantations and corpora lutea per dam, mean fetal body weight, number of fetal anomalies and sex-ratio variations. No compound-related gross lesions were noted in third-generation pups necropsied. Based on the information presented, a NOAEL of 486 ppm (24.3 mg/kg/day) was identified. This NOAEL represents the highest dose tested.

- In a two-generation reproduction study, Lochry et al. (1986) administered technical grade Tackle (sodium acifluorfen) of unspecified purity to rats at levels of 0, 25, 500 and 2,500 ppm. The compound was administered in the diet ad libitum to groups of 35 rats/sex/dose beginning at 47 days of age and continuing until sacrifice. In addition, the compound was also administered to groups of 40 rats/sex/dose from weaning until sacrifice. Reproductive parameters, mortality, body weight and a number of other end points were measured; in addition, both gross and histopathological examinations were conducted. The NOAEL for toxicity to both the parents and offspring was 25 ppm, based on mortality and kidney lesions at higher doses. Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day, the NOAEL of 25 ppm in this study corresponds to 1.25 mg/kg/day (Lehman, 1959).

#### Developmental Effects

- Lightkep et al. (1980) administered Tackle 2S (a formulation containing 22.4% sodium acifluorfen) by oral intubation at doses of 0, 3, 12 or 36 mg/kg/day to New Zealand White rabbits (16/dose) on days 6 to 29 of gestation. The authors indicated that the administered doses were in terms of the active ingredient. At 36 mg/kg/day, there was a slight (nonsignificant) inhibition of maternal body weight gain and a marked (significant) inhibition of maternal food consumption. At this dose level, there was also possible interference with implantation and a slight decrease in average fetal body weight; neither of these changes was statistically significant. No gross, soft-tissue or skeletal malformations were observed in pups, fetuses or late resorptions at any dose level. Based on the information presented in this study, a NOAEL of 36 mg/kg/day was identified for maternal toxicity, fetal toxicity and teratogenicity. This NOAEL represents the highest dose tested.
- Florek et al. (1981) administered Tackle 2S (a formulation containing 22.4% sodium acifluorfen) by gavage at doses of 0, 20, 90 or 180 mg/kg/day to Sprague-Dawley rats (25/dose) on days 6 to 19 of gestation. The authors indicated that the administered doses were in terms of active ingredient. At 180 mg/kg/day, dams gained significantly less weight than controls. At 90 and 180 mg/kg/day, lower average fetal body weight and significantly delayed ossification of metacarpals and forepaw and hindpaw phalanges were noted. At 180 mg/kg/day, there was delayed ossification of caudal vertebrae, sternbrae and metatarsals. Additionally, at the highest dose level there was a significantly increased incidence of slight dilation of the lateral ventricle of the brain. The authors stated that the fetal effects were indicative of delayed fetal development. Based on the results of this study, a NOAEL of 90 mg/kg/day for maternal toxicity, a NOAEL of 20 mg/kg/day for fetotoxicity and a NOAEL of 180 mg/kg/day (the highest dose tested) for teratogenic effects were identified.
- Weatherholtz and Piccirillo (1979) administered RH 6201 (a formulation containing 39.8% sodium acifluorfen) by gavage at doses of 0, 20, 60 or 180 mg/kg/day to New Zealand White rabbits on days 7 to 19 of gestation. Maternal toxicity at 180 mg/kg/day included statistically significant weight loss and mortality. At 180 mg/kg/day, there was also evidence of fetal toxicity (mortality). Due to embryotoxicity and maternal toxicity at 180 mg/kg/day, teratogenic evaluations could not be performed at this dose level. At lower doses, no teratogenic effects were observed. Based on the results of this study, NOAELs of 60 mg/kg/day were identified for teratogenic effects, maternal toxicity and fetal toxicity.

#### Mutagenicity

- Schreiner et al. (1980) tested Tackle 2S (purity unspecified) in an Ames assay using Salmonella typhimurium strains TA 98, 100, 1535, 1537 and 1538. The test compound was not found to be mutagenic, with or without metabolic activation, at concentrations up to 1.8 mg/plate.



- Brusick (1976) tested RH 6201 (purity not specified) in a mutagenicity assay using Saccharomyces cerevisiae strain D4 and S. typhimurium strains TA 1535, 1537, 1538, 98 and 100. The compound was not found to be mutagenic, with or without metabolic activation, at concentrations up to 500 ug/plate.
- Putnam et al. (1981) tested Tackle 2S (purity not specified) in a dominant lethal assay using Sprague-Dawley rats. The compound was administered by gavage at doses of 0, 80, 360 or 800 mg/kg/day for 5 consecutive days. No detectable mutagenic activity, as defined by induction of fetal death, was reported.
- Myhr and McKeon (1981) conducted a primary rat (Fischer 344) hepatocyte unscheduled DNA synthesis (UDS) assay using Tackle 2S (purity not specified). The test compound did not induce a detectable level of UDS over a concentration range of 0.10 to 25 ug/mL. Treatment of hepatocytes with 50 ug/mL was almost completely lethal to the cells.
- Schreiner et al. (1981) tested Tackle 2S (purity not specified) in a bone marrow metaphase analysis using Sprague-Dawley rats. The animals were given the test compound by intubation at doses of 0, 0.37, 1.11 or 1.87 g/kg/day for 5 days. The test compound did not significantly increase clastogenic events in the bone marrow cells.
- Schreiner et al. (1980) tested Tackle 2S (purity not specified) in a murine lymphoma assay. The compound was tested without metabolic activation at 0.11 to 1.7 ug/mL, and with metabolic activation at 0.08 to 0.56 ug/mL. No detectable mutagenic activity was detected either with or without activation.
- Jagannath (1981) tested Tackle 2S (29.7% purity) in a mitotic recombination assay using Saccharomyces cerevisiae strain D5. The compound was tested at 0, 2.5, 5.0 or 7.5 uL/plate without metabolic activation, and at 7.5, 10.0 and 25.0 uL/plate with metabolic activation. In the absence of metabolic activation, the compound induced a dose-related increase in recombination events (significant at 5.0 uL/plate). With metabolic activation, a dose of 10.0 uL/plate induced an increase in recombination events. The authors reported that very few survivors were observed at 25.0 uL/plate.
- Bowman et al. (1981) tested Tackle 2S (purity not specified) in mutagenicity assays using Drosophila melanogaster. Assays included the Biothorax test of Lewis, a dominant lethal assay, an assay for Y-chromosome loss, and a White Ivory reversion assay. In all cases, the test compound was tested at concentrations of 15 mg/mL. Results of these assays were negative for somatic reversions of White Ivory and the Biothorax test of Lewis and positive for Y-chromosome loss and dominant lethal mutations.

#### Carcinogenicity

- Barnett et al. (1982b) administered Tackle 2S (a formulation containing 19.1 to 25.6% sodium acifluorfen) to Fischer 344 rats (73/sex/dose) for one year at dietary levels of 0, 25, 150, 500, 2,500 or 5,000 ppm. Assuming that these dietary levels reflect the concentrations of the test compound and not the active ingredient, corresponding levels of sodium acifluorfen are 0, 6.4, 38.4, 128.0, 640.0 or 1,280 ppm (based on 25.6% active ingredient in the test compound). Assuming that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day, these doses correspond to approximately 0, 0.3, 1.9, 6.4, 32.0 or 64.0 mg/kg/day (Lehman, 1959). Histopathological examinations revealed no evidence of carcinogenicity at any dose level.

- Barnett et al. (1982a) administered Tackle® (a formulation containing 24% sodium acifluorfen) to B6C3F<sub>1</sub> mice (60/sex/dose) for 18 months at dietary concentrations of 0, 625, 1,250 or 2,500 ppm. (The high dose was reported to be the maximum tolerated dose.) The authors reported that the dietary levels corresponded to average compound intake values of 0, 118.96, 258.73 or 655.15 mg/kg/day for males, and 0, 142.50, 312.65 or 710.54 mg/kg/day for females. Assuming that these levels reflect test compound and not active ingredient intake, corresponding levels of sodium acifluorfen intake are 0, 28.55, 62.10 or 157.24 mg/kg/day for males and 0, 34.20, 75.04 or 170.53 mg/kg/day for females. An obvious dose-related depression of body weight was reported for all doses. Beginning in week 52 of the study and continuing with increasing frequency was the appearance of palpable abdominal masses. Gross necropsy revealed a dose-related increase in liver masses in both sexes. Histopathological examinations conducted at the 52-week interval revealed that the livers of six animals per sex of high-dose animals (157.24 mg/kg/day for males; 170.53 mg/kg/day for females) showed evidence of acidophilic cells. Males receiving this dose displayed a statistically significant increase in the frequency of hepatocellular adenomas. After 18 months of treatment, all 40 high-dose males and 27/47 high-dose females sacrificed were found to have a single benign hepatoma, multiple benign hepatomas or hepatocellular carcinomas. In the males, the incidence of single benign hepatoma and hepatocellular carcinomas was statistically significant. In the females, the incidence of single hepatomas was statistically significant.
- Goldenthal (1979) administered RH 6201 (a formulation containing 39.4 to 40.5% sodium acifluorfen) to Charles River CD-1 mice (80/sex/dose) for two years in the diet at concentrations that provided dose levels of 0, 1.25, 7.5 or 45.0 ppm of the active ingredient. After 16 weeks of administration, the 1.25 ppm dose was increased to 270 ppm. Assuming that 1 ppm in the diet of mice is equivalent to 0.15 mg/kg/day, these doses correspond to approximately 0, 0.19 (increased to 40.5), 1.13 or 6.8 mg/kg/day (Lehman, 1959). Two control groups were used in this study. One group received acetone in the diet (control 1) and the other received water in the diet (control 2). In males receiving the highest dose there was a nonstatistically significant increase in the incidence of nodular hepatocellular proliferation and hepatocellular carcinoma, which indicated to the authors that these changes were dose-related.
- Coleman et al. (1978) administered RH 6201 (a formulation containing 39.8% sodium acifluorfen) to Charles River Outbred albino CD COBS rats (approximately 75/sex/dose) for 2 years at changing dietary concentrations. Mean sodium acifluorfen intake values over the course of the study were 0, 1.25, 7.54 and 17.56 mg/kg/day for males and 0, 1.64, 9.84 and 25.03 mg/kg/day for females.
- Acifluorfen is structurally similar to nitrofen [2,4-dichloro-1-(4 - nitrophenoxy) benzene; CAS No. 1836-75-7]. Nitrofen has been shown to be carcinogenic in Osborne-Mendel rats and B6C3F<sub>1</sub> mice (NCI, 1978, 1979; both as cited in NAS, 1985).

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

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

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

where:

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

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

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

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

#### One-day Health Advisory

No data were found in the available literature that were suitable for determination of a One-day HA value for acifluorfen. It is therefore recommended that the Ten-day HA value for a 10-kg child (2 mg/L, calculated below) be used at this time as a conservative estimate of the One-day HA value.

#### Ten-day Health Advisory

The study by Florek et al. (1981) has been selected to serve as the basis for determination of the Ten-day HA for a 10-kg child. In this study, Tackle 2S (a formulation containing 22.4% sodium acifluorfen) was administered by gavage at doses of 0, 20, 90 or 180 mg/kg/day to Sprague-Dawley rats (25/dose) on days 6 to 19 of gestation. The authors indicated that the administered doses were in terms of active ingredient. At 180 mg/kg/day, dams reportedly gained significantly less weight than controls. At 90 and 180 mg/kg/day, lower average fetal body weight and significantly delayed ossification of metacarpals and forepaw and hindpaw phalanges were noted. At 180 mg/kg/day, there was delayed ossification of caudal vertebrae, sternbrae and metatarsals. Additionally, at the highest dose level there was a significantly increased incidence of slight dilation of the lateral ventricle of the brain. The authors stated that the fetal effects were indicative of delayed fetal development. No effects on implantations, litter size, fetal viability, resorption or fetal sex ratio were reported. Based on the results of this study, a NOAEL of 20 mg/kg/day for fetotoxicity was identified.

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

$$\text{Ten-day HA} = \frac{(60 \text{ mg/kg/day}) (10 \text{ kg})}{(100) (1 \text{ L/day}) (7)} = 2 \text{ mg/L (2,000 ug/L)}$$

where:

20 mg/kg/day = NOAEL, based on absence of fetal toxicity in rats exposed to acifluorfen via gavage during days 6 to 19 of gestation.

10 kg = assumed body weight of a child.

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

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

#### Longer-term Health Advisory

The study by Barnett (1982) had been selected to serve as the basis for determination of the Longer-term HA. In this study, the NOAEL was 5.6 mg/kg/day based on an increase in the size of the liver in male rats. However, a lower NOAEL, 1.25 mg/kg/day, was recently identified in a two-

generation rat reproduction study by Lochry et al. (1986). Since the NOAEL in the Lochry et al. (1986) study is numerically identical to the value on which the DWEL is based and since a two-generation reproduction study is suitable for calculating a Longer-term HA, it was determined that it is appropriate to base the Longer-term HA on the DWEL.

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

$$\text{Longer-term HA} = \frac{(1.25 \text{ mg/kg/day}) (10 \text{ kg})}{(100) (1 \text{ L/day})} = 0.13 \text{ mg/L (100 ug/L)}$$

Where:

1.25 mg/kg/day = NOAEL (see Lifetime Health Advisory below).

10 kg = assumed body weight of a child.

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

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

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

$$\text{Longer-term HA} = \frac{(1.25 \text{ mg/kg/day}) (70 \text{ kg})}{(100) (2 \text{ L/day})} = 0.44 \text{ mg/L (400 ug/L)}$$

Where:

1.25 mg/kg/day = NOAEL (see Lifetime Health Advisory below).

70 kg = assumed body weight of an adult.

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

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

### Lifetime Health Advisory

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

the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

A 2-year Charles River CD-1 mouse dietary study by Goldenthal (1979) was originally selected to serve as the basis for determination of the DWEL for acifluorfen. In this study, a NOAEL of 1.13 mg/kg/day was identified. more recently, however, a two-generation rat reproduction study by Lochry et al. (1986) was identified that strongly supports the results of the Goldenthal (1979) study and identifies a NOAEL of 1.25 mg/kg/day.

Using the NOAEL of 1.25 mg/kg/day, the DWEL for acifluorfen is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(1.25 \text{ mg/kg/day})}{(100)} = 0.013 \text{ mg/kg/day}$$

where:

1.25 mg/kg/day = NOAEL, based on the absence of mortality and kidney lesions in rats.

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

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

$$\text{DWEL} = \frac{(0.013 \text{ mg/kg/day}) (70 \text{ kg})}{(2 \text{ L/day})} = 0.437 \text{ mg/L (400 ug/L)}$$

where:

0.013 mg/kg/day = RfD.

70 kg = assumed body weight of an adult

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

Step 3: Determination of the Lifetime Health Advisory

Acifluorfen may be classified in Group B2: probable human carcinogen. A Lifetime HA is not recommended for acifluorfen. The estimated excess cancer risk associated with lifetime exposure to drinking water containing acifluorfen at 437 ug/L is approximately  $4 \times 10^{-4}$  ( $4.4 \times 10^{-4}$ ). This estimate represents the upper 95% confidence limit from extrapolations (U.S. EPA, 1988) prepared by using the Weibull 82 multistage model (time to death).

#### Evaluation of Carcinogenic Potential

- Four studies that evaluated the carcinogenic potential of sodium acifluorfen were identified. The results of one of these studies (Barnett et al., 1982a) indicated that sodium acifluorfen was carcinogenic in B6C3F1 mice. The results of the other three studies (Goldenthal, 1979; Coleman et al., 1978; Barnett et al., 1982b) provided no evidence of carcinogenicity in two strains of rats and one strain of mice. However, due to deficiencies in the three negative studies, the results of these studies are not sufficient to contradict the results of the positive study. Each of these studies is discussed briefly below.

- In the positive study (Barnett et al., 1982a), B6C3F1 mice received sodium acifluorfen in the diet for 18 months. At the end of the study, the high-dose (157.24 mg/kg/day) male mice displayed a statistically significant increase in the incidence of single benign hepatomas and hepatocellular carcinomas. A statistically significant increase in the incidence of single hepatomas was observed in high-dose (170.53 mg/kg/day) females.
  - In one of the studies with negative results (Goldenthal, 1979) Charles River CD-1 mice received sodium acifluorfen in the diet for two years at doses of 0, 0.19 (increased to 40.5 after 16 weeks), 1.13 or 6.8 mg/kg/day. Although no evidence of carcinogenicity was observed in this study, the dose levels tested were considerably lower than the level that produced positive results in the 18-month mouse feeding study (157.24 mg/kg/day) (Barnett et al., 1982a).
  - In the second study with negative results (Coleman et al., 1978), Charles River outbred albino CD COBS rats received sodium acifluorfen for two years at dietary levels up to 25.03 mg/kg/day (females) or 17.56 mg/kg/day (males). Although it is difficult to make cross-species comparisons, these levels are considerably lower than the level that produced positive results in the 18-month mouse feeding study (157.24 mg/kg/day) (Barnett et al., 1982a). In addition, no adverse effects were observed at any dose level used in this study, indicating that the maximum tolerated dose was not used.
  - In the third study with negative results (Barnett et al., 1982b), Fischer 344 rats received sodium acifluorfen for 1 year at dietary concentrations of 0, 0.3, 1.9, 6.4, 32.0 or 64.0 mg/kg/day. Although the results of this study were negative, a study duration of 1 year is not sufficient for assessing carcinogenic potential.
- Acifluorfen is structurally similar to nitrofen [2,4-dichloro-1-(4-nitrophenoxy) benzene; CAS No. 1836-75-7]. Nitrofen has been shown to be carcinogenic in Osborne-Mendel rats and B6C3F<sub>1</sub> mice [NCI, 1978, 1979; both as cited in NAS (1985)]. Although data on nitrofen cannot be used to conclude that sodium acifluorfen is carcinogenic, these data do, to some extent, support the positive results of Barnett et al. (1982a).
  - The International Agency for Research on Cancer has not evaluated the carcinogenic potential of acifluorfen.
  - Evidence has been presented in one carcinogenicity study (Barnett et al., 1982a) showing that acifluorfen is carcinogenic to mice. Using the Weibull 82 increased multistage time-to-death with tumor model (since there is a survival disparity for male mice), the U.S. EPA (1988) reported a unit risk,  $q_1^*$ , estimated in human equivalent (surface area conversion) as  $3.55 \times 10^{-2} \text{ (mg/kg/day)}^{-1} [B_2]$ . It was noted that  $q_1^*$  is an estimate of upper (95%) bound on risk and the true value of risk is unknown and may be as low as zero.
  - Using this  $q_1^*$  value and assuming that a 70-kg human adult consumes 2 liters of water a day over a 70-year lifespan, the Weibull 82 multistage model estimates that concentrations of 100, 10 and 1 ug acifluorfen per liter may result in excess cancer risk of  $10^{-4}$ ,  $10^{-5}$  and  $10^{-6}$ , respectively.
  - For comparison purposes drinking water concentrations associated with an excess risk of  $10^{-6}$  were 0.2 ug/L, 0.7 ug/L, 7 ug/L, <0.002 ug/L and <0.002 ug/L for the multihit, one-hit, probit, logit and Weibull models, respectively.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), acifluorfen is classified in Group B2: probable human carcinogen.

#### VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The U.S. EPA has established residue tolerances for sodium acifluorfen in or on raw agricultural commodities that range from 0.01 to 0.1 ppm (CFR, 1985).
- The EPA RfD Workgroup has concluded that an RfD of 0.013 mg/kg/day is appropriate for; acifluorfen.

#### VII. ANALYTICAL METHODS

- Analysis of acifluorfen is by a gas chromatographic (GC) method applicable to the determination of certain chlorinated acid pesticides in water samples (U.S. EPA, 1986b). In this method, approximately 1 liter of sample is acidified. The compounds are extracted with ethyl ether using a separatory funnel. The derivatives are hydrolyzed with potassium hydroxide, and extraneous organic material is removed by a solvent wash. After acidification, the acids are extracted and converted to their methyl esters using diazomethane as the derivatizing agent. Excess reagent is removed, and the esters are determined by electron capture GC. The method detection limit has not been determined for this compound, but it is estimated that the detection limits for analytes included in this method are in the range of 0.5 to 2 ug/L.

#### VIII. TREATMENT TECHNOLOGIES

- Reverse osmosis (RO) is a promising treatment method for pesticide-contaminated water. As a general rule, organic compounds with molecular weights greater than 100 are candidates for removal by RO. Larson et al. (1980) report 99% removal efficiency of chlorinated pesticides by a thin-film composite polyamide membrane operating at a maximum pressure of 1,000 psi and at a maximum temperature of 113°F. More operational data are required, however, to specifically determine the effectiveness and feasibility of applying RO for the removal of acifluorfen from water. Also, membrane adsorption must be considered when evaluating RO performance in the treatment of acifluorfen-contaminated drinking water supplies.

IX. REFERENCES

- Barnett, J.\* 1982. Evaluation of ninety-day subchronic toxicity of Tackle® in Fischer 344 rats. GSRI Project No. 413-971-40. Rhone-Poulenc Agrochimie No. 372-80. Unpublished study. MRID 0122730.
- Barnett, J., L. Jenkins and R. Parent.\* 1982a. Evaluation of the potential oncogenic and toxicological effects of long-term dietary administration of Tackle® to B6C3FI mice. GSRI Project No. 413-984-41. Final Report. Unpublished Study. MRID 00122732.
- Barnett, J., L. Jenkins and R. Parent.\* 1982b. Evaluation of the potential oncogenic and toxicological effects of long-term dietary administration of Tackle® to Fischer 344 rats: GSRI Project No. 413-985-41. Interim report. Unpublished study. MRID 00122735.
- Bowman, J., C. Mackerer, S. Bowman, D.C. Jessup, R.C. Geil and B.W. Benson.\* 1981. Drosophila mutagenicity assays of Mobil Chemical Company compound MC 10109 (MRI 533). Study No. 009-275-533-9. Unpublished study. MRID 00122737.
- Brusick, D.\* 1976. Mutagenicity evaluation of RH-6201. LBI Project No. 2547. Unpublished study. MRID 00083057.
- CFR. 1985. Code of Federal Regulations. July 1, 1985. 40 CFR 180.383. p. 336.
- CHEMLAB. 1985. The Chemical Information System, CIS, Inc. Baltimore, MD.
- Coleman, M.E., T.E. Murchison, P.S. Sahota et al.\* 1978. Three and twenty-four month oral safety evaluation study of RH-6201 in rats. DRC 5800. Final Report. Unpublished study. MRID 00087478.
- Florek, M., M. Christian, G. Christian and E.M. Johnson.\* 1981. Terato- genicity study of TACU 06238001 in pregnant rats. Argus Project 113-004. Unpublished study. MRID 00122743.
- Goldenthal, E.I., D.C. Jessup, R.G. Geil and B.W. Benson.\* 1978a. Two week range finding study in mice: 285-016. Unpublished study. MRID 00080568.
- Goldenthal, E.I., D.C. Jessup and D. Rodwell.\* 1978b. Three generation reproduction study in rats: RH-6201, 285-014a. Unpublished study. MRID 001107486.
- Goldenthal, E.I., D.C. Jessup, R.G. Geil and B.W. Benson.\* 1979. Lifetime dietary feeding study in mice: 285-013a. Unpublished study. MRID 00082897.
- Harris, J.C., G. Cruzan and W.R. Brown.\* 1978. Three month subchronic rat study. RH-6201. TRD-76P-30. Unpublished study. MRID 00080569.
- Jagannath, D.\* 1981. Mutagenicity of 06238001 lot LCM 266830-7 in the mitotic recombination assay with the yeast strain D5. Genetics Assay No. 5374. Final Report. Unpublished study. MRID 00122740.
- Larson, R.E., P.S. Cartwright, P.K. Eriksson and R.J. Petersen. 1982. Applications of the FT-30 reverse osmosis membrane in metal finishing operations. Paper presented at Tokohama, Japan.
- Lehman, A.J. 1959. Appraisal of the safety of chemicals in foods, drugs and cosmetics. Association of Food and Drug Officials of the United States.



- Lightkep, G., G. Christian et al.\* 1980. Teratogenic potential of TACU 06238001 in New Zealand white rabbits (Segment II Evaluation). Argus Project 113-003. Unpublished study. MRID 00122744.
- Lochry, E.A., Hoberman, A.M. and Christian, M.S.\* 1986. Two-generation Rat Reproduction Study, Argus Research Laboratories, Inc. Study No.218-002
- Madison, P., R. Becci and R. Parent.\* 1981. Guinea pig sensitization study. Buhler test for Mobil Corporation. Tackle 2S. FDRL Study No. 6738. Unpublished study. MRID 00122729.
- Meister, R., ed. 1983. Farm chemicals handbook. Willoughby, OH: Meister Publishing Company.
- Mobil Environmental and Health Science Laboratory.\* 1981. A study of the oral toxicity of Tackle 2S in the dog. Mobil Study No. 1091-80. Six-month status report. Unpublished study. MRID 00122733.
- Myhr, B., and M. McKeon.\* 1981. Evaluation of 06238001 in the primary rat hepatocyte unscheduled DNA synthesis assay. MEHSL Study 1022-80. Final Report. Unpublished study. MRID 00122742.
- NAS. 1985. National Academy of Sciences. Drinking Water and Health. Vol. 6. Chapter 9: Toxicity of Selected Contaminants. Washington, DC. National Academy Press.
- NCI. 1978. National Cancer Institute. Bioassay of nitrofen for possible carcinogenicity. Technical Report Series No. 26. DHEW Publication No. (NIH) 78-826. U.S. Department of Health, Education and Welfare. Washington, DC. 101 pp. Cited in: NAS. 1985. National Academy of Sciences. Drinking Water and Health. Vol. 6. Chapter 9: Toxicity of Selected Contaminants. Washington, DC. National Academy Press.
- NCI. 1979. National Cancer Institute. Bioassay of nitrofen for possible carcinogenicity. Technical Report Series No. 184. DHEW Publication No. (NIH) 79-1740. U.S. Department of Health, Education and Welfare. Washington, DC. 57 pp. Cited in: NAS. 1985. National Academy of Sciences. Drinking Water and Health. Vol. 6. Chapter 9: Toxicity of Selected Contaminants. Washington, DC. National Academy Press.
- Piccirillo, V.J., and T.L. Robbins.\* 1976. Four week oral range finding study in rats. RII-6201. Unpublished study. MRID 00071892.
- Putnam, D., L. Schechtman and W. Moore.\* 1981. Activity of T1689 in the dominant lethal assay in rodents. MA Project No. T1689.116. Final Report. Unpublished study. MRID 00122738.
- Schreiner, C.A., M.A. McKenzie and M.A. Mehlman.\* 1980. An Ames Salmonella/ mammalian microsome mutagenesis assay for determination of potential mutagenicity of Tackle 2S MCI0978. Study No. 511-80. Unpublished study. MRID 00061622.
- Schreiner, C., M. Skinner and M. Mehlman.\* 1981. Metaphase analysis of rat bone marrow cells treated in vivo with Tackle 2S. Study No. 1041-80. Unpublished study. MRID 00122741.
- Spicer, E., L. Griggs, F. Marroquin, N.D. Jefferson and M. Blair.\* 1983. Two year dietary toxicity study in dogs. (Tackle®) 450-0395. Unpublished study. MRID 00131162.

- U.S. EPA. 1986a. U.S. Environmental Protection Agency. Guidelines for carcinogenic risk assessment. Fed. Reg. 51(185):33992-34003. September 24.
- U.S. EPA. 1986b. U.S. Environmental Protection Agency. U.S. EPA Method #3 - Determination of Chlorinated Acids in Ground Water by GC/ECD, January 1986 draft. Available from U.S. EPA's Environmental Monitoring and Support Laboratory. Cincinnati, OH.
- U.S. EPA. 1988. U.S. Environmental Protection Agency. CRAVE carcinogenicity assessment for lifetime exposure. OPP. June 30.
- Weatherholtz, W., S. Moore and G. Wolfe.\* 1979a. Eye irritation study in monkeys. Blazer 2S. Project No. 417-396. Final Report. Unpublished study. MRID 00140887.
- Weatherholtz, W., K. Peterson, M. Koka and R.W. Kapp.\* 1979b. Four-week repeated dermal study in rabbits. RH-6201 formulations. Project No. 417-386. Final Report. Unpublished study. MRID 00140889.
- Weatherholtz, W., and V. Piccirillo.\* 1979. Teratology study in rabbits (RH-6201 LC). Final Report. Project No. 417-374. Unpublished study. MRID 00107485.
- Whittaker Corporation.\* No date, a. Acute oral LD50 rats. Study No. 410-0249. Unpublished study. MRID 00061625.
- Whittaker Corporation.\* No date, b. Primary dermal irritation -- rabbit: Study No. 410-0286. Unpublished study. MRID 00061629.
- Whittaker Corporation.\* No date, c. Primary eye irritation -- rabbits. Study No. 410-0252. Unpublished study. MRID 00061628.
- Windholz, M., S. Budavari, R.F. Blumetti and E.S. Otterbein, eds. 1983. The Merck Index, 10th ed. Rahway, NJ: Merck and Co., Inc.
- WSSA. 1983. Herbicide Handbook, 5th Ed. Weed Science Society of America Champaign, IL.

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\* Confidential Business Information submitted to the Office of Pesticide Programs.

