

ATRAZINE

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

I. INTRODUCTION

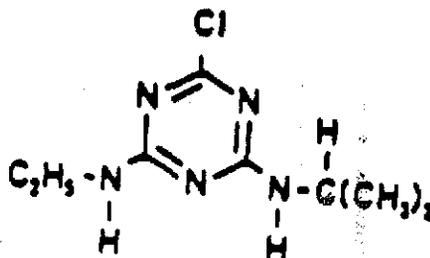
The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations 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. 1912-24-9

Structural Formula

2-Chloro-4-ethylamino-6-isopropylamino-1,3,5-triazine

Synonyms

- AAtrex; Atranex; Crisatrina; Crisazine; Farmco Atrazine; Griffex; Shell Atrazine Herbicide; Vectal SC; Gesaprim; Primatol (Meister, 1987).

Uses

- Atrazine over the past 30 years has been the most heavily used herbicide in the U.S. It is used for nonselective weed control on industrial or noncropped land and selective weed control in corn, sorghum, sugar cane, pineapple and certain other plants (Meister, 1987).

Properties (Meister, 1987; Windholz, 1976)

Chemical Formula	$C_8H_{14}ClN_5$
Molecular Weight	215.72
Physical State	White, odorless, crystalline solid
Boiling Point (25 mm Hg)	175 to 177°C
Melting Point	175 to 177°C
Density (20°)	1.187
Vapor Pressure (20°C)	3.0×10^{-7} mm Hg
Water Solubility (22°C)	70 mg/L
Log Octanol/Water Partition Coefficient	2.33 to 2.71
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- In a monitoring study of Mississippi River water, atrazine residues were found at a maximum level of 17 ppb; residues were detected throughout the year, with the highest concentrations found in June or July (Newby and Tweedy, 1976).
- Atrazine has been found in 4,123 of 10,942 surface water samples analyzed and in 343 of 3,208 ground water samples (STORET, 1988).

Samples were collected at 1,659 surface water locations and 2,510 ground water locations. The 85th percentile of all non-zero samples was 2.3 ug/L in surface water and 1.9 ug/L in ground water sources. The maximum concentration found in surface water was 2,300 ug/L and in ground water it was 700 ug/L. Atrazine was found in surface water of 31 States and in ground water in 13 States. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

- Atrazine has been found also in ground water in Pennsylvania, Iowa, Nebraska, Wisconsin and Maryland; typical positives were 0.3 to 3 ppb (Cohen et al., 1986).

Environmental Fate

- An aerobic soil metabolism study in Lakeland sandy loam, Hagerstown silty clay loam, and Wehadkee silt loam soils showed conversion of atrazine to hydroxyatrazine, after 8 weeks, to be 38, 40 and 47% of the amount applied, respectively, (Harris, 1967). Two additional degradates, deisopropylated atrazine and deethylated atrazine, were identified in a sandy loam study (Beynon et al., 1972).
- Hurle and Kibler (1976) studied the effect of water-holding capacity on the rate of degradation and found a half-life for atrazine of more than 125 days, 37 days and 36 days in sandy soil held at 4%, 35% and 70% water-holding capacity, respectively.
- In Oakley sandy loam and Nicollet clay loam, atrazine had a half-life of 101 and 167 days (Warnock and Leary, 1978).
- Carbon dioxide production was generally slow in several anaerobic soils: sandy loam, clay loam, loamy sand and silt loam (Wolf and Martin, 1975; Goswami and Green, 1971; Lavy et al., 1973).
- ¹⁴C-Atrazine was stable in aerobic ground water samples incubated for 15 months at 10 or 25°C in the dark (Weidner, 1974).
- Atrazine is moderately to highly mobile in soils ranging in texture from clay to gravelly sand as determined by soil thin layer chromatography (TLC), column leaching, and adsorption/desorption batch equilibrium studies. Atrazine on soil TLC plates was intermediately mobile in loam, sandy clay loam, clay loam, silt loam, silty clay loam, and silty clay soils, and was mobile in sandy loam soils. Hydroxyatrazine showed a low mobility in sandy loam and silty clay loam soils (Helling, 1971).

- Soil adsorption coefficients for atrazine in a variety of soils were: sandy loam (0.6), gravelly sand (1.8), silty clay (5.6), clay loam (7.9), sandy loam (8.7), silty clay loam (11.6), and peat (more than 21) (Weidner, 1974; Lavy 1974; Talbert and Fletchall, 1965).
- Soil column studies indicated atrazine was mobile in sand, fine sandy loam, silt loam and loam; intermediately mobile in sand, silty clay loam and sandy loam; low to intermediately mobile in clay loam (Weidner, 1974; Lavy, 1974; Ivey and Andrews, 1964; Ivey and Andrews, 1965).
- In a Mississippi field study, atrazine in silt loam soil had a half-life of less than 30 days (Portnoy, 1978). In a loam to silt loam soil in Minnesota, atrazine phytotoxic residues persisted for more than 1 year and were detected in the maximum-depth samples (30 to 42 inches) (Darwent and Behrens, 1969). In Nebraska, phytotoxic residues persisted in silty clay loam and loam soils 16 months after application of atrazine; they were found at depths of 12 to 24 inches. But atrazine phytotoxic residues had a half-life of about 20 days in Alabama fine sandy loam soil, although leaching may partially account for this value (Buchanan and Hiltbold, 1973).
- Under aquatic field conditions, dissipation of atrazine was due to leaching and to dilution by irrigation water, with residues persisting for 3 years in soil on the sides and bottoms of irrigation ditches, to the maximum depth sampled, 67.5 to 90 cm (Smith et al., 1975).
- Ciba-Geigy (1988) recently submitted comments on the atrazine Health Advisory. These comments included a summary of the results of its studies on the environmental fate of atrazine. This summary indicated that laboratory degradation studies showed that atrazine is relatively stable in the aquatic medium under environmental pH conditions and indicated that atrazine degraded in soil by photolysis and microbial processes. The products of degradation are dealkylated metabolites, hydroxyatrazine and nonextractable (bound) residues. Atrazine and the dealkylated metabolites are relatively mobile whereas hydroxyatrazine is immobile.
- Ciba-Geigy (1988) also indicated that field dissipation studies conducted in California, Minnesota and Tennessee show no leaching of atrazine and metabolites below 6 to 12 inches of soil. The half-lives of atrazine in soil ranged between 20 to 101 days, except in Minnesota where degradation was slow. A forestry degradation study conducted in Oregon showed no adverse effects on either terrestrial or aquatic environments. Also, Bioconcentration studies have shown low potential for bioaccumulation with a range of 15 to 77x.

III. PHARMACOKINETICS

Absorption

- Atrazine appears to be readily absorbed from the gastrointestinal tract of animals. Bakke et al. (1972) administered single 0.53-mg doses of ¹⁴C-ring-labeled atrazine to rats by gavage. Total fecal

excretion after 72 hours was 20.3% of the administered dose; the remainder was excreted in urine (65.5%) or retained in tissues (15.8%). This indicates that at least 80% of the dose was absorbed.

Distribution

- Bakke et al. (1972) administered single 0.53-mg doses of ¹⁴C-ring-labeled atrazine to rats by gavage. Liver, kidney and lung contained the largest amounts of radioactivity, while fat and muscle had lower residues than the other tissues examined.
- In a metabolism study by Ciba-Geigy (1983a), the radioactivity of ¹⁴C-atrazine dermally applied to Harlan Sprague-Dawley rats at 0.25 mg/kg was distributed to a minor extent to body tissues. The highest levels were measured in liver and muscle at all time points examined; 2.1% of the applied dose was in muscle and 0.5% in liver at 8 hours.
- Khan and Foster (1976) observed that in chickens the hydroxy metabolites of atrazine accumulate in the liver, kidney, heart and lung. Residues of both 2-chloro and 2-hydroxy moieties were found in chicken gizzard, intestine, leg muscle, breast muscle and abdominal fat.

Metabolism

- The principal reactions involved in the metabolism of atrazine are dealkylation at the C-4 and C-6 positions of the molecule. There is also some evidence of dechlorination at the C-2 position. These data were reported by several researchers as demonstrated below.
- Bakke et al. (1972) administered single 0.53-mg doses of ¹⁴C-ring-labeled atrazine to rats by gavage. Less than 0.1% of the label appeared in carbon dioxide in expired air. Most of the radioactivity was recovered in the urine (65.5% in 72 hours), including at least 19 radioactive compounds. More than 80% of the urinary radioactivity was identified as 2-hydroxyatrazine and its two mono-N-dealkylated metabolites. None of the metabolites identified contained the 2-chloro moiety (which may have been removed via hydrolysis during the isolation technique or by a dechlorinating enzyme as suggested by the in vitro studies of Foster et al. (1979), who found evidence for a dechlorinase in chicken liver homogenates incubated with atrazine).
- Bohme and Bar (1967) identified five urinary metabolites of atrazine in rats: the two monodealkylated metabolites of atrazine, their carboxy acid derivatives and the fully dealkylated derivative. All of these metabolites contained the 2-chloro group. The in vitro studies of Dauterman and Muecke (1974) also found no evidence for dechlorination of atrazine in the presence of rat liver homogenates.
- Similarly, Bradway and Moseman (1982) administered atrazine (50, 5, 0.5 or 0.005 mg/day) for 3 days to male Charles River rats and observed that the fully dealkylated derivative (2-chloro-4,6-diamino-s-triazine) was the major urinary metabolite, with lesser amounts of the two mono-N-dealkylated derivatives.

- Erickson et al. (1979) dosed Pittman-Moore miniature pigs by gavage with 0.1 g of atrazine (80W). The major compounds identified in the urine were the parent compound (atrazine) and deethylated atrazine (which contains the 2-chloro substituent).
- Hauswirth (1988) indicated that the rat metabolism studies taken together are sufficient to show that in the female rat dechlorination of the triazine ring and N-dealkylation are the major metabolic pathways. Oxidation of the alkyl substituents appears to be a minor and secondary metabolic route. The total body half-life is approximately one and one-half days. Atrazine and/or its metabolites appear to bind to red blood cells. Other tissue accumulation does not appear to occur.

Excretion

- Urine appears to be the principal route of atrazine excretion in animals. Following the administration of 0.5 mg doses of ¹⁴C-ring-labeled atrazine by gavage to rats, Bakke et al. (1972) reported that in 72 hours most of the radioactivity (65.5%) was excreted in the urine, 20.3% was excreted in the feces, and less than 0.1% appeared as carbon dioxide in expired air. About 85 to 95% of the urinary radioactivity appeared within the first 24 hours after dosing, indicating rapid clearance.
- Dauterman and Muecke (1974) have reported that atrazine metabolites are conjugated with glutathione to yield a mercapturic acid in the urine. The studies of Foster et al. (1979) in chicken liver homogenates also indicate that atrazine metabolism involves glutathione.
- Ciba-Geigy (1983b) studied the excretion rate of ¹⁴C-atrazine from Harlan Sprague-Dawley rats dermally dosed with atrazine dissolved in tetrahydrofuran at levels of 0.025, 0.25, 2.5 or 5 mg/kg. Urine and feces were collected from all animals at 24-hour intervals for 144 hours. Results indicated that atrazine was readily absorbed, and within 48 hours most of the absorbed dose was excreted, mainly in the urine and to a lesser extent in the feces. Cumulative excretion in urine and feces appeared to be directly proportional to the administered dose, ranging from 52% at the lowest dose to 80% at the highest dose.

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- A case of severe contact dermatitis was reported by Schlicher and Beat (1972) in a 40-year-old farm worker exposed to atrazine formulation. The clinical signs were red, swollen and blistered hands with hemorrhagic bullae between the fingers. Although it is noted that the exposure of this patient may have been inclusive to exposure to other chemicals in addition to atrazine, it is also noted that atrazine is a skin irritant in animal studies.

Long-term Exposure

- Yoder et al. (1973) examined chromosomes in lymphocyte cultures taken from agricultural workers exposed to herbicides including atrazine. There were more chromosomal aberrations in the workers during mid-season exposure to herbicides than during the off-season (no spraying). These aberrations included a four-fold increase in chromatid gaps and a 25-fold increase in chromatid breaks. During the off-season, the mean number of gaps and breaks was lower in this group than in controls who were in occupations unlikely to involve herbicide exposure. This observation led the authors to speculate that there is enhanced chromosomal repair during this period of time resulting in compensatory protection. However, these data may not be representative of the effect of atrazine since the exposed workers were also exposed to other herbicides.

AnimalsShort-term Exposure

- Acute oral LD₅₀ values of 3,000 mg/kg in rats and 1,750 mg/kg in mice have been reported for technical atrazine by Bashmurin (1974); the purity of the test compound was not specified.
- Acute oral studies conducted by Ciba-Geigy (1988) with atrazine (97% a.i.) reflected the following LD₅₀s: 1,869 mg/kg in rats and >3,000 mg/kg in mice.
- Molnar (1971) reported that when atrazine was administered by gavage to rats at 3,000 mg/kg, 6% of the rats died within 6 hours, and 25% of those remaining died within 24 hours. The rats that died during the first day exhibited pulmonary edema with extensive hemorrhagic foci, cardiac dilation and microscopic hemorrhages in the liver and spleen. Rats that died during the second day had hemorrhagic broncho-pneumonia and dystrophic changes of the renal tubular mucosa. Rats sacrificed after 24 hours had cerebral edema and histochemical alterations in the lungs, liver and brain. It is noted that the dose used in this study was almost 2 x the LD₅₀ (Ciba-Geigy, 1988).
- Gaines and Linder (1986) determined the oral LD₅₀ for adult male and female rats to be 737 and 672 mg/kg respectively and 2,310 mg/kg for pups. It is, therefore, noted that young animals are more sensitive to atrazine than adults. This study also reflected that the dermal LD₅₀ for adult rats was higher than 2,500 mg/kg.
- Palmer and Radeleff (1964) administered atrazine as a fluid dilution or in gelatin capsules to Delaine sheep and dairy cattle (one animal per dosage group). Two doses of 250 mg/kg atrazine caused death in both sheep and cattle. Sixteen doses of 100 mg/kg were lethal to the one sheep tested. At necropsy, degeneration and discoloration of the adrenal glands and congestion in lungs, liver and kidneys were observed.

- Palmer and Radeleff (1969) orally administered atrazine 80W (analysis of test material not provided) by capsule or by drench to sheep at 5, 10, 25, 50, 100, 250 or 400 mg/kg/day and to cows at 10, 25, 50, 100 or 250 mg/kg/day. The number of animals in each dosage group was not stated, and the use of controls was not indicated. Observed effects included muscular spasms, stilted gait and stance and anorexia at all dose levels in sheep and at 25 mg/kg in cattle. Necropsy revealed epicardial petechiae (small hemorrhagic spots on the lining of the heart) and congestion of the kidneys, liver and lungs. Effects appeared to be dose related. A Lowest-Observed-Adverse-Effect Level (LOAEL) of 5 mg/kg/day in sheep and a No-Observed-Adverse-Effect Level (NOAEL) of 10 mg/kg/day in cows can be identified from this study.
- Bashmurin (1974) reported that oral administration of 100 mg/kg of atrazine to cats had a hypotensive effect, and that a similar dose in dogs was antidiuretic and decreased serum cholinesterase (ChE) activity. No other details of this study were reported. Atrazine is not an organophosphate (OP), therefore, its effect on ChE may not be similar to the mechanism of ChE inhibition by OPs.

Dermal/Ocular Effects

- In a primary dermal irritation test in rats, atrazine at 2,800 mg/kg produced erythema but no systemic effects (Gzheyotskiy et al., 1977).
- Ciba-Geigy (1988) indicated that the studies it performed reflected dermal sensitization in rats but not irritation in rabbits' eyes.

Long-term Exposure

- Hazelton Laboratories (1961) fed atrazine to male and female rats for 2 years at dietary levels of 0, 1, 10 or 100 ppm. Based on the dietary assumptions of Lehman (1959), these levels correspond to doses of approximately 0, 0.05, 0.50 or 5.0 mg/kg/day. After 65 weeks, the 1.0-ppm dose was increased to 1,000 ppm (50 mg/kg/day) for the remainder of the study. No treatment-related pathology was found at 26 weeks, at 52 weeks, at 2 years, or in animals that died and were necropsied during the study. Results of blood and urine analyses were unremarkable. Atrazine had no effects on the general appearance or behavior of the rats. A transient roughness of the coat and piloerection were observed in some animals after 20 weeks of treatment at the 10- and 100-ppm levels but not at 52 weeks. Body weight gains, food consumption and survival were similar in all groups for 18 months, but from 18 to 24 months there was high mortality due to infections (not attributed to atrazine) in all groups, including controls, which limits the usefulness of this study in determining a NOAEL for the chronic toxicity of atrazine.
- In a 2-year study by Woodard Research Corporation (1964), atrazine (80W formulation) was fed to male and female beagle dogs for 105 weeks at dietary levels of 0, 15, 150 or 1,500 ppm. Based on the dietary assumptions of Lehman (1959), these levels correspond to doses of 0, 0.35, 3.5 or 35 mg/kg/day. Survival rates, body weight

gain, food intake, behavior, appearance, hematologic findings, urinalyses, organ weights and histologic changes were noted. The 15-ppm dosage (0.35 mg/kg/day) produced no toxicity, but the 150-ppm dosage (3.5 mg/kg/day) caused a decrease in food intake as well as increased heart and liver weight in females. In the group receiving 1,500 ppm (35 mg/kg/day) atrazine, there were decreases in food intake and body weight gain, an increase in adrenal weight, a decrease in hematocrit and occasional tremors or stiffness in the rear limbs. There were no differences among the different groups in the histology of the organs studied. Based on these results, a NOAEL of 0.35 mg/kg/day can be identified for atrazine.

- In a study by Ciba-Geigy (1987b) using technical atrazine (97% a.i.), six-month-old beagle dogs were assigned randomly to four dosage groups: 0, 15, 150 and 1,000 ppm. These doses correspond to actual average intake of 0, 0.48, 4.97 and 33.65/33.8 (male/female) mg/kg/day. Six animals/sex/group were assigned to the control and high dose groups and four animals/sex/group were assigned to the low- and mid-dose groups. One mid-dose male, one high-dose male and one high-dose female had to be sacrificed moribund during the study period. Decreased body weight gains and food consumption were noted at the high-dose level. Statistically significant ($p < 0.05$) reductions in erythroid parameters (red cell count, hemoglobin and hematocrit) in high-dose males were noted throughout the study as well as mild increases in platelet counts in both sexes. Slight decreases in total protein and albumin ($p < 0.05$) were noted in high-dose males as well as decreased calcium and chloride in males and increased sodium and glucose in females. Decrease in absolute heart weight were noted in females and increased relative liver weight in males of the high-dose group. The mid-dose females reflected an increase in the absolute heart weight and heart/brain weight ratios. The most significant effect of atrazine in this study was reflected in the high-dose animals of both sexes as discrete myocardial degeneration. Clinical signs associated with cardiac pathology such as ascites, cachexia, labored/shallow breathing and abnormal EKG were observed in the group as early as 17 weeks into the study. Gross pathology reflected severe dilation of the right atrium and occasionally of the left atrium. These findings were also noted histopathologically as degenerative atrial myocardium (atrophy and myolysis). In the mid-dose group, two males and one female appeared to be affected with the cardiac syndrome but to a much lesser degree in the intensity of the noted responses. Therefore, the LOAEL in this study is 4.97 mg/kg/day and the NOAEL is 0.48 mg/kg/day.
- A two year chronic feeding/oncogenicity study (Ciba-Geigy, 1986) was recently evaluated by the Agency. In this study, technical atrazine (98.9% a.i.) was fed to 37 to 38 days-old Sprague-Dawley rats. The dosage levels used were 0, 10, 70, 500 or 1,000 ppm, equivalent to 0, 0.5, 3.5, 25 or 50 mg/kg/day (using Lehman's conversion factor, 1959). Twenty rats per sex per group were used to measure blood parameters and clinical chemistries and urinalysis. Fifty rats per sex per group were maintained on the treated and control diets for 24 months. An additional 10 rats per sex were placed on control and high dose (1,000 ppm) diets for a twelve month interim sacrifice and

another 10 per sex (control and high dose, 1,000 ppm) for a 13 month sacrifice (the 1,000 ppm group was placed on control diet for one month prior to sacrifice). The total number of animals/sex in the control and HDT groups was 90 and 70 for the 10, 70 and 500 ppm groups. Histopathology was performed on all animals. At the mid- and high-dose, there was a decrease in mean body weights of males and females. Survival was decreased in high-dose females but increased in high-dose males. There were decreases in organ-to-body weight ratios in high-dose animals, which were probably the result of body weight decreases. Hyperplastic changes in high-dose males (mammary gland, bladder and prostate) and females (myeloid tissue of bone marrow and transitional epithelium of the kidney) were of questionable toxicologic importance. There was an increase in retinal degeneration and in centrolobular necrosis of the liver in high-dose females and an increase in degeneration of the rectus femoris muscle in high-dose males and females when compared to controls. Based on decreased body weight gain, the LOAEL for non-oncogenic activities in both sexes is 25 mg/kg/day and the NOAEL is 3.5 mg/kg/day. However, oncogenic activities were noted at 3.5 mg/kg/day (70 ppm) and above as reflected in the increased incidence of mammary gland tumors in females.

- A recent 91-week oral feeding/oncogenicity study in mice by Ciba-Geigy (1987c) has been evaluated by the Agency. In this study, atrazine (97% ai.) was fed to five-weeks-old CD-1 strain of mice, weighing 21.0/26.8 grams (female/male). The mice were randomly assigned to five experimental groups of approximately 60 animals/sex/group. The dosage tested were 0, 10, 300, 1,500 and 3,000 ppm; these dosages correspond to actual mean daily intake of 1.4, 38.4, 194.0 and 385.7 mg/kg/day for males, and 1.6, 47.9, 246.9 and 482.7 mg/kg/day for females. This study shows that there are dose-related effects at 1,500 ppm or 3,000 ppm atrazine: an increase in cardiac thrombi, a decrease in the mean body weight gain at 12 and 91 weeks during the study, and decreases in erythrocyte count, hematocrit and hemoglobin concentration. Cardiac thrombi contributed to the deaths of the group of mice that did not survive to terminal sacrifice. The LOAEL is set at 1,500 ppm based upon decreases of 23.5% and 11.0% in mean body weight gain found at 91 weeks in male and female mice, respectively. Also, an increase in the incidence of cardiac thrombi is found in female mice in the 1,500 ppm exposure group. None of the above effects are found at 300 ppm, thus the NOAEL is set at 300 ppm (corresponding to 38.4 mg/kg/day in males and 47.9 mg/kg/day for females).

Reproductive Effects

- A three-generation study on the effects of atrazine on reproduction in rats was conducted by Woodard Research Corporation (1966). Groups of 10 males and 20 females received atrazine (80W) at dietary levels of 0, 50 or 100 ppm. Based on the dietary assumptions that 1 ppm in the diet of rats is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to doses of approximately 0, 2.5 or 5 mg/kg/day. Two litters were produced per generation but parental animals were chosen from the second litter after weaning for each generation. Young rats were maintained on the test diets for approximately ten

weeks in each generation. The third generation pups were sacrificed after weaning. It is noted that the parental animals of the first generation were fed only half of the dietary atrazine levels for the first 3 weeks of exposure. There were no adverse effects of atrazine on reproduction observed during the course of the three-generation study. A NOAEL of 100 ppm (5 mg/kg/day) was identified for this study. However, the usefulness of this study is limited due to the alteration of the atrazine content of the diet during important maturation periods of the neonates.

- A recent two-generations study in rats by Ciba-Geigy (1987a) was conducted using the 97% ai. technical atrazine. Young rats, 47 to 48 days old were maintained on the control and test diets for 10 weeks before mating. The concentrations used were 0, 10, 50 and 500 ppm (equivalent to 0, 0.5, 2.5 and 25 mg/kg/day using Lehman conversion factor, 1959). Thirty animals/sex/group were used in each generation; one litter was produced per generation. The level tested had no effect on mortality in either generation. Body weight and body weight gains were significantly depressed ($p < 0.05$) at the highest dose; however, food consumption was also decreased at this high-dose level in parental males and females during the pre-mating period and for the first generation females (F_1) on days 0 to 7 of gestation. No histopathological effects were noted nor other effects were noted during gross necropsy in either parental generation with the exception of increased testes relative weight in both generations at the high dose. In pups of both generation, significant reduction ($p < 0.05$) in body weight was noted; however, this effect was only dose-related in the second generation (F_2) at both the mid- and high-dose levels on postnatal day 21. Therefore, maternal toxicity NOAEL is 2.5 mg/kg/day; the reproductive LOAEL is 2.5 mg/kg/day (reduced pup weight in F_2 generation on postnatal day 21) and the NOAEL is 0.5 mg/kg/day.

Developmental Effects

- In the three-generation reproduction study in rats conducted by Woodard Research Corporation (1966) (described above), atrazine at dietary levels of 50 or 100 ppm (2.5 or 5 mg/kg/day) resulted in no observed histologic changes in the weanlings and no effects on fetal resorption. No malformations were observed, and weanling organ weights were similar in controls and atrazine-treated animals. Therefore, a NOAEL of 100 ppm (5 mg/kg/day) was also identified for developmental effects in this study. However, the usefulness of this study is limited due to an alteration of the atrazine content of the diet during important maturation periods of the neonates.
- Atrazine was administered orally to pregnant rats on gestation days 6 to 15 at 0, 100, 500 or 1,000 mg/kg (Ciba-Geigy, 1971). The two higher doses increased the number of embryonic and fetal deaths, decreased the mean weights of the fetuses and retarded the skeletal development. No teratogenic effects were observed. The highest dose (1,000 mg/kg) resulted in 23% maternal mortality and various toxic symptoms. The 100 mg/kg dose had no effect on either dams or embryos and is therefore the maternal and fetotoxic NOAEL in this study.

- In a study by Ciba-Geigy (1984a), Charles River rats received atrazine (97%) by gavage on gestation days 6 to 15 at dose levels of 0, 10, 70, or 700 mg/kg/day. Excessive maternal mortality (21/27) was noted at 700 mg/kg/day, but no mortality was noted at the lower doses; also reduced weight gains and food consumption were noted at both 70 and 700 mg/kg/day. Developmental toxicity was also present at these dose levels. Fetal weights were severely reduced at 700 mg/kg/day; delays in skeletal development occurred at 70 mg/kg/day, and a dose-related runting was noted at 10 mg/kg/day and above. The NOAEL for maternal toxicity appears to be 10 mg/kg/day, however, this is also the LOAEL for developmental effects.
- New Zealand white rabbits received atrazine (96%) by gavage on gestation days 7 through 19 at dose levels of 0, 1, 5 or 75 mg/kg/day (Ciba-Geigy, 1984b). Maternal toxicity, evidenced by decreased body weight gains and food consumption, was present in the mid- and high-dose groups. Developmental toxicity was demonstrated only at 75 mg/kg/day by an increased resorption rate, reduced fetal weights, and delays in ossification. No teratogenic effects were indicated. The NOAEL appears to be 1 mg/kg/day.
- Peters and Cook (1973) fed atrazine to pregnant rats (four/group) at levels of 0, 50, 100, 200, 300, 400, 500 or 1,000 ppm in the diet throughout gestation. Based on an assumed body weight of 300 g and a daily food consumption of 12 g (Arrington, 1972), these levels correspond to approximately 0, 2, 4, 8, 12, 16, 20 or 40 mg/kg/day. The number of pups per litter was similar in all groups, and there were no differences in weanling weights. This study identified a NOAEL of 40 mg/kg/day for developmental effects. In another phase of this study, the authors demonstrated that subcutaneous (sc) injections of 50, 100 or 200 mg/kg atrazine on gestation days 3, 6 and 9 had no effect on the litter size, while doses of 2800 mg/kg were embryotoxic. Therefore, a NOAEL of 200 mg/kg by the sc route was identified for embryotoxicity.

Mutagenicity

- Loprieno et al. (1980) reported that single doses of atrazine (1,000 mg/kg or 2,000 mg/kg, route not specified) produced bone marrow chromosomal aberrations in the mouse. No other details of this study were provided.
- Murnik and Nash (1977) reported that feeding 0.01% atrazine to male Drosophila melanogaster larvae significantly increased the rate of both dominant and sex-linked recessive lethal mutations. They stated, however, that dominant lethal induction and genetic damage may not be directly related.
- Adler (1980) reviewed unpublished work on atrazine mutagenicity carried out by the Environmental Research Programme of the Commission of the European Communities. Mutagenic activity was not induced even when mammalian liver enzymes (S-9) were used; however, the use of plant microsomes produced positive results. Also, in in vivo studies

in mice, atrazine induced dominant lethal mutations and increased the frequency of chromatid breaks in bone marrow. Hence, the author suggested that activation of atrazine in mammals occurs independently of the liver, possibly in the acidic part of the stomach.

- As described previously, Yoder et al. (1973) studied chromosomal aberrations in the lymphocyte cultures of farm workers exposed to various pesticides including atrazine. During mid-season a 4-fold increase in chromatid gaps and a 25-fold increase in chromatid breaks was observed. During the off-season (no spraying), the number of gaps and breaks was lower than in controls, suggesting to the authors that there is enhanced chromosomal repair during the unexposed period.
- Recently, Spencer (1987) and Dearfield (1988) evaluated several in vitro and in vivo mutagenicity studies on atrazine that were recently submitted to the U.S. EPA by Ciba-Geigy. They noted that most of these studies were inadequate with the exception of the following three tests: a Salmonella assay; an E. coli reversion assay; and a Host-Mediated assay. The first two assays were negative for mutagenic effects; the results of the third assay were equivocal.
- Ciba-Geigy (1988) indicated that Brusick (1987) evaluated atrazine mutagenicity and that the weight-of-evidence analysis he used placed the chemical in a non-mutagenic status. The Agency (Dearfield, 1988) evaluated Brusick's analysis. It is noted that the use of the weight-of-evidence approach is not appropriate at the present time. The in vivo studies by Adler (1980) suggest a positive response. These findings have not been diminished by other atrazine studies. In addition, Dearfield (1988) indicated that the scheme used by Brusick in this analysis is flawed by the lack of calibration of the chemical test scores to an external standard and by the use of some studies that are considered inadequate by design to determine the mutagenic potential of atrazine.

Carcinogenicity

- Innes et al. (1969) investigated the tumorigenicity of 120 test compounds including atrazine in mice. Two F₁ hybrid stocks (C57BL/6 x Anf) F₁ and (C57BL/6 x AKR) F₁ were used. A dose of 21.5 mg/kg/day was administered by gavage to mice of both sexes from age 7 to 28 days. After weaning at 4 weeks, this dose level was maintained by feeding 82 ppm atrazine ad libitum in the diet for 18 months. The incidence of hepatomas, pulmonary tumors, lymphomas and total tumors in atrazine-treated mice was not significantly different from that in the negative controls.
- A two-year feeding/oncogenicity study in rats by Ciba-Geigy (1986) has been evaluated recently by the Agency. Atrazine (98.9% a.i.) was fed to 37 to 38 days-old Sprague-Dawley rats. The dosage levels used were 0, 10, 70, 500 or 1,000 ppm, equivalent to 0, 0.5, 3.5, 25 or 50 mg/kg/day (using Lehman's conversion factor, 1959). The total number of animals/sex in the control and HDT groups was 90; and 70 animals/sex/group for the 10, 70 and 500 ppm groups. Histopathology

was performed on all animals. In females, atrazine was associated with a statistically significant increase in mammary gland fibroadenomas at 1,000 ppm, in mammary gland adenocarcinomas (including two carcinosarcomas at the HDT) at 70, 500 and 1,000 ppm, and in total mammary gland tumor bearing animals at 1,000 ppm. Each of these increases was associated with a statistically significant dose-related trend and was outside of the high end of the historical control range. In addition, U.S. EPA (1986a) indicated that there was evidence for decreased latency for mammary gland adenocarcinomas at the 12 month interim sacrifice that was already submitted by Ciba-Geigy in 1985. This study was also reported as positive in a briefing paper by Ciba-Geigy (1987).

- ° A recent 91-week oral feeding/oncogenicity study in mice by Ciba-Geigy (1987c) has been evaluated by the Agency. In this study, atrazine (97% ai.) was fed to five-weeks-old CD-1 mice weighing 21.0/26.8 grams (female/male). The mice were randomly assigned to five experimental groups of approximately 60 animals/sex/ group. The dosage tested were 0, 10, 300, 1,500 and 3,000 ppm; these dosages correspond to actual mean daily intake of 1.4, 38.4, 194.0 and 385.7 mg/kg/day for males, and 1.6, 47.9, 246.9 and 482.7 mg/kg/day for females. The following kinds of neoplasms were noted in this study: mammary adenocarcinomas, adrenal adenomas, pulmonary adenomas and malignant lymphomas. However, no dose-related or statistically significant increases were observed in the incidences of these neoplasms. Therefore, atrazine is not considered oncogenic in this strain of mice.

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:

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

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 suitable information was found in the available literature for the determination of the One-day HA value for atrazine. It is, therefore, recommended that the Ten-day HA value calculated below for a 10-kg child of 0.1 mg/L (100 ug/L), be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

Two teratology studies by Ciba-Geigy, one in the rat (1984a) and one in the rabbit (1984b), were considered for the calculation of the Ten-day HA value. The rat study reflected a NOAEL of 10 mg/kg/day for maternal toxicity but this value was also the LOAEL for developmental toxicity while the rabbit study reflected NOAELs of 5 mg/kg/day for developmental toxicity and 1 mg/kg/day for maternal toxicity. Thus, the rabbit appears to be a more sensitive species than the rat for maternal toxicity, hence, the rabbit study with a NOAEL of 1 mg/kg/day is used in the calculations below.

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

$$\frac{(1 \text{ mg/kg/d}) \times (10\text{kg})}{(100) \times (1 \text{ L/day})} = 0.1 \text{ mg/L (100 ug/L)}$$

where:

1 mg/kg/day = NOAEL, based on maternal toxicity evidenced by decreased body weight gain and food consumption.

10 kg = assumed body weight of a child.

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

1 L/day = assumed daily consumption for a child.

Longer-term Health Advisory

No suitable information was found in the available literature for the determination of the longer-term HA value for atrazine. It is, therefore, recommended that the adjusted DWEL for a 10-kg child of 0.05 mg/L (50 ug/L) and the DWEL for a 70-kg adult of 0.2 mg/L (200 ug/L) be used at this time as conservative estimates of the Longer-term HA values.

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 esti-

mate 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, 1986b), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Three studies were considered for the development of the Lifetime HA. A two-year dog feeding study (Woodard, 1964), a one-year dog feeding study (Ciba-Geigy, 1987b) and a two-year rat oral feeding/oncogenicity study (Ciba-Geigy, 1986).

The first study in dogs (1964) reflected a NOAEL of 0.35 mg/kg/day and a LOAEL of 3.5 mg/kg/day that was associated with increased heart and liver weights in females. The new one-year dog study (1988) reflected a NOAEL of 0.48 mg/kg/day and a LOAEL of 4.97 mg/kg/day based on mild cardiac pathology intensified at the higher dose tested 33.65/33.8 (male/female) mg/kg/day. The two-year rat study (Ciba-Geigy, 1986) reflected a NOAEL at 3.5 mg/kg/day for systemic effect other than oncogenicity; however, this study indicated that atrazine caused mammary gland tumors at this dose level and above, no adverse effects were observed at the lowest dose tested, 0.5 mg/kg/day.

The 1964 dog study was initially used for the calculation of the RfD and the Lifetime HA. However, this study was partially flawed by the lack of information on the purity of the test material and by the inadequate documentation of the hematological data. Therefore, the recent one-year dog study (Ciba-Geigy, 1987b), using technical atrazine (97% ai.), is considered as a more adequate study for the calculation of the RfD and the Lifetime HA. The NOAEL in this study, 0.48 mg/kg/day, is also supported by the NOAEL of 0.5 mg/kg/day in the two-generation reproduction study (Ciba-Geigy, 1987a) and by the fact that no systemic effects or tumors were noted at this dose level in the two-year chronic feeding/oncogenicity study in rats (Ciba-Geigy, 1986). [Other studies: Woodard Research Corporation (1966) and Hazelton Laboratories (1961) identified long-term NOAEL values of 5 to 50 mg/kg/day and were not considered to be as protective as the dog studies for use in calculating the HA values for atrazine.]

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{0.48 \text{ mg/kg/day}}{(100)} = 0.005 \text{ mg/kg/day}$$

(rounded from 0.0048 mg/kg/day)

where:

0.48 mg/kg/day = NOAEL, based on the absence of cardiac pathology or any other/adverse clinical, hematological, biochemical and histopathological effects in dogs.

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

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

$$\text{DWEL} = \frac{(0.0048 \text{ mg/kg/day}) (70 \text{ kg})}{(2 \text{ L/day})} = 0.168 \text{ mg/L (200 ug/L)}$$

where:

0.0048 mg/kg/day = RfD (before rounding off to 0.005 mg/kg/day)

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

$$\text{Lifetime HA} = \frac{(0.168 \text{ mg/L}) (20\%)}{10} = 0.003 \text{ mg/L (3 ug/L)}$$

where:

0.168 mg/L = DWEL (before rounding off to 0.2 mg/L)

20% = assumed relative source contribution from water.

10 = additional uncertainty factor, according to ODW policy, to account for possible carcinogenicity.

Evaluation of Carcinogenic Potential

- A study submitted by Ciba-Geigy Corporation (1986) in support of the pesticide registration of atrazine indicated that atrazine induced an increased incidence of mammary tumors in female Sprague-Dawley rats. These findings have been further confirmed in a briefing by Ciba-Geigy (1987) on this study.
- Atrazine was not oncogenic in mice (Ciba-Geigy, 1987c).
- Three closely related analogs: propazine, terbutryn and simazine are presently classified as Group C oncogens based on an increased incidence of tumors in the same target tissue (mammary gland) and animal species (rat) as was noted for atrazine.

- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of atrazine.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986b), atrazine may be classified in Group C: possible human carcinogen. This category is used for substances with limited evidence of carcinogenicity in animals in the absence of human data.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Toxicity data on atrazine were reviewed by the National Academy of Sciences (NAS, 1977), and the study by Innes et al. (1969) was used to identify a chronic NOAEL of 21.5 mg/kg/day. Although at that time it was concluded that atrazine has low chronic toxicity, an uncertainty factor of 1,000 was employed in calculation of the ADI from that study, since only limited data were available. The resulting value (0.021 mg/kg/day) corresponds to an ADI of 0.73 mg/L in a 70-kg adult consuming 2 L of water per day.
- Tolerances for atrazine alone and the combined residues of atrazine and its metabolites in or on various raw agricultural commodities have been established (U.S. EPA, 1986c). These tolerances range from 0.02 ppm (negligible) in animal products (meat and meat by-products) to 15 ppm in various animal fodders.

VII. ANALYTICAL METHODS

- Analysis of atrazine is by a gas chromatographic (GC) method, Method No. 507, applicable to the determination of certain nitrogen-phosphorus containing pesticides in water samples (U.S. EPA, 1988). In this method, approximately 1 L of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen phosphorus detector. The method has been validated in a single Laboratory. The estimated detection limit for the analytes in this method, including atrazine, is 0.13 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Treatment technologies which will remove atrazine from water include activated carbon adsorption, ion exchange, reverse osmosis, ozone oxidation and ultraviolet irradiation. Conventional treatment methods have been found to be ineffective for the removal of atrazine from drinking water (ESE, 1984; Miltner and Fronk, 1985a). Limited data suggest that aeration would not be effective in atrazine removal (ESE, 1984; Miltner and Fronk, 1985a).
- Baker (1983) reported that a 16.5-inch GAC filter cap using F-300, which was placed upon the rapid sand filters at the Fremont, Ohio

water treatment plant, reduced atrazine levels by 30 to 64% in the water from the Sandusky River. At Jefferson Parish, Louisiana, Lykins et al. (1984) reported that an adsorber containing 30 inches of Westvaco WV-G® 12 x 40 GAC removed atrazine to levels below detectable limits for over 190 days.

- At the Bowling Green, Ohio water treatment plant, PAC in combination with conventional treatment achieved an average reduction of 41% of the atrazine in the water from the Maumee River (Baker, 1983). Miltner and Fronk (1985a) reported that in jar tests using spiked Ohio River water with the addition of 16.7 and 33.3 mg/L of PAC and 15-20 mg/L of alum, PAC removed 64 and 84%, respectively, of the atrazine. Higher percent removals reflected higher PAC dosages. Miltner and Fronk (1985b) monitored atrazine levels at water treatment plants, which utilized PAC, in Bowling Green and Tiffin, Ohio. Applied at dosages ranging from 3.6 to 33 mg/L, the PAC achieved 31 to 91% removal of atrazine, with higher percent removals again reflecting higher PAC dosages.
- Harris and Warren (1964) reported that Amberlite IR-120 cation exchange resin removed atrazine from aqueous solution to less than detectable levels. Turner and Adams (1968) studied the effect of varying pH on different cation and anion exchange resins. At a pH of 7.2, 45% removal of atrazine was achieved with Dowex® 2 anion exchange resin and with $H_2PO_4^-$ as the exchangeable ion species.
- Chian et al. (1975) reported that reverse osmosis, utilizing cellulose acetate membrane and a cross-linked polyetheleneimine (NS-100) membrane, successfully processed 40% of the test solution, removing 84 and 98%, respectively, of the atrazine in the solution.
- Miltner and Fronk (1985a) studied the oxidation of atrazine with ozone in both spiked distilled and ground water. Varying doses of ozone achieved a 70% removal of atrazine in distilled water and 49 to 76% removal of atrazine in ground water.
- Kahn et al. (1978) studied the effect of fulvic acid upon the photochemical stability of atrazine to ultraviolet irradiation. A 50% removal of atrazine was achieved much faster at higher pH conditions than at lower pH conditions. In the presence of fulvic acids, the time needed for ultraviolet irradiation to achieve 50% removal was almost triple the time required to achieve similar removals without the presence of fulvic acids. Since fulvic acids will be present in surface waters, ultraviolet irradiation may not be a cost-effective treatment alternative.

IX. REFERENCES

- Adler, I.D. 1980. A review of the coordinated research effort on the comparison of test systems for the detection of mutagenic effects, sponsored by the E.E.C. *Mutat. Res.* 74:77-93.
- Arrington, L.R. 1972. The laboratory animals. In: *Introductory laboratory animal science. The breeding, care and management of experimental animals.* Danville, IL: Interstate Printers and Publishers, Inc., pp. 9-11.
- Baker, D. 1983. Herbicide contamination in municipal water supplies in northwestern Ohio. Final Draft Report 1983. Prepared for Great Lakes National Program Office, U.S. Environmental Protection Agency. Tiffin, OH.
- Bakke, J.E., J.D. Larson and C.E. Price. 1972. Metabolism of atrazine and 2-hydroxyatrazine by the rat. *J. Agric. Food Chem.* 20:602-607.
- Bashmurin, A.F. 1974. Toxicity of atrazine for animals. *Sb. Rab. Leningrad Vet. Institute.* 36:5-7. (English abstract only)
- Beynon, K.I., G. Stoydin and A.N. Wright. 1972. A comparison of the breakdown of the triazine herbicides cyanazine, atrazine and simazine in soils and in maize. *Pestic. Biochem. Physiol.* 2:153-161.
- Bohme, E., and F. Bar. 1967. *Über den Abbau von Triazin-Herbiciden in tierischen Organismus.* *Food Cosmet. Toxicol.* 5:23-28. (English abstract only)
- Bradway, D.E., and R.F. Moseman. 1982. Determination of urinary residue levels of the n-dealkyl metabolites of triazine herbicides. *J. Agric. Food Chem.* 30:244-247.
- Brusick, D.J. 1987. An assessment of the genetic toxicity of atrazine: relevance to health and Environmental effects. A document prepared for Ciba-Geigy Corporation (submitted to EPA in 1988 as a part of Ciba-Geigy comments on the HA). December.
- Buchanan, G.A., and A.E. Hiltbold. 1973. Performance and persistence of atrazine. *Weed Sci.* 21:413-416.
- Chian, E.S.K., W.N. Bruce and H.H.P. Fang. 1975. Removal of pesticides by reverse osmosis. *Environmental Science and Technology.* 9(1):52-59.
- Ciba-Geigy. 1971. Rat reproduction study-test for teratogenic or embryotoxic effects. 10/1971; Teratology study of atrazine technical in Charles River rats 9/1984, SCDF, Sacramento.
- Ciba-Geigy. 1983a. Dermal absorption of ¹⁴C-atrazine by rats. Ciba-Geigy Corporation, Greensboro, NC. Report No. ABR-83005, May, 1983. Accession No. 255815.
- Ciba-Geigy. 1983b. Excretion rate of ¹⁴C-atrazine from dermally dosed rats. Ciba-Geigy Corporation, Greensboro, NC. Report No. ABR-83081, October, 1983. Accession No. 255815.

- Ciba-Geigy Ltd. 1984a. A teratology study of atrazine technical in Charles River Rats: Toxicology/pathology report No. 60-84. MRID 00143008.
- Ciba-Geigy Ltd. 1984b. Segment II. Teratology study in rabbits: Toxicology/pathology report No. 68-84. MRID 00143006.
- Ciba-Geigy. 1985. Atrazine chronic feeding/oncogenicity study. One-year interim report. May 17, 1985.
- Ciba-Geigy. 1986. Twenty-four month combined chronic oral toxicity and oncogenicity in rats utilizing atrazine technical by American Biogenic Corp. Study No. 410-1102. Accession Nos. 262714-262727.
- Ciba-Geigy. 1987. Briefing paper on atrazine. December, 1986. Analysis of chronic rat feeding study results. Ciba-Geigy Corp., Greensboro, NC.
- Ciba-Geigy. 1987a. Two-generation rat reproduction. Study No. 852063. MRID 404313-03.
- Ciba-Geigy. 1987b. Atrazine technical--52-week oral feeding in dogs. Study No. 852008 and Pathology Report No. 7048. MRID 40313-01.
- Ciba-Geigy. 1987c. Atrazine technical--91-week oral carcinogenicity study in mice. Study No. 842120. MRID 404313-02.
- Ciba-Geigy. 1988. Comments on the atrazine draft health advisory. A letter from Thomas Parish to U.S. EPA/ODW.
- Cohen, S.Z., C. Eiden and M.N. Lorber. 1986. Monitoring Ground Water for Pesticides in the U.S.A. In Evaluation of pesticides in ground water. American Chemical Society Symposium Series. No. 315.
- Cosmopolitan Laboratories.* 1979. CBI, Document No. 00541, EPA Accession No. 2-41725.
- Darwent, A.L., and R. Behrens. 1968. Dissipation and leaching of atrazine in a Minnesota soil after repeated applications. In Proc. North Cent. Weed Control Conf., December 3-5, 1968, Indiana. pp. 66-68.
- Dauterman, W.C., and W. Muecke. 1974. In vitro metabolism of atrazine by rat liver. Pestic. Biochem. Physiol. 4:212-219.
- Dearfield, K.L. 1988. An assessment of the genetic toxicity of atrazine; review of submitted studies and document prepared by D. Brusick for Ciba-Geigy. A memo (including an executive summary) from U.S. EPA, Office of Pesticide Programs. April 26.
- ESE. 1984. Environmental Science and Engineering. Review of treatability data for removal of 25 synthetic organic chemicals from drinking water. U.S. Environmental Protection Agency, Office of Drinking Water, Washington, DC.

- Erickson, M.D., C.W. Frank and D.P. Morgan. 1979. Determination of s-triazine herbicide residues in urine: Studies of excretion and metabolism in swine as a model to human metabolism. *J. Agric. Food Chem.* 27:743-745.
- Foster, T.S., S.U. Khan and M.H. Akhtar. 1979. Metabolism of atrazine by the soluble fraction (105,000 g) from chicken liver homogenates. *J. Agric. Food Chem.* 17:300-302.
- Gaines T.B. and R.E. Linder. 1986. Acute toxicity of pesticides in adult and weanling rats. *Fundam. Appl. Toxicol.* 7:299-308
- Goswami, K.P., and R.E. Green. 1971. Microbial degradation of the herbicide atrazine and its 2-hydroxy analog.
- Gzhegotzkiy, M.I., L.V. Shklyaruk and L.A. Dychok. 1977. Toxicological characteristics of the herbicide zeazin. *Vrach. Delo* 5:133-136. In: Pesticides Abstract 10:711-712, 1977.
- Harris, C.I., and G.F. Warren. 1964. Adsorption and desorption of herbicides by soil. *Weeds.* 12:120-126.
- Harris, C.I. 1967. Fate of 2-chloro-s-triazine herbicides in soil. *J. Agric. Food Chem.* 15:157-162.
- Hauswirth, J.W. 1988. Summary on some atrazine toxicity studies submitted Ciba-Geigy (including metabolism studies No. ABR-87116, 87048, 87087, 85104, 87115 and AG-520). M memo from U.S. EPA, Office of Pesticide Programs. May 3.
- Hayes, W.J., Jr. 1982. Pesticides studied in man. Baltimore, MD: Williams and Wilkins.
- Hazelton Laboratories.* 1961. Two-year chronic feeding study in rats. CBI, Document No. 000525, MRID 0059211.
- Helling, C.S. 1971. Pesticide mobility in soils. II. Applications of soil thin-layer chromatography. *Proc. Soil Sci. Soc. Am.* 35:737-748.
- Hurle, K., and E. Kibler. 1976. The effect of changing moisture conditions on the degradation of atrazine in soil. *Proceedings of the British Crop Protection Conference--Weeds.* 2:627-633.
- Innes, J.R.M., B.M. Ulland, and M.G. Valerio. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: A preliminary note. *J. Natl. Cancer Inst.* 42:1101-1114.
- Ivey, M.J., and H. Andrews. 1964. Leaching of simazine, atrazine, diuron, and DCPA in soil columns. Unpublished study submitted by Ciba-Geigy, Greensboro, N.C.
- Ivey, M.J., and H. Andrews. 1965. Leaching of simazine, atrazine, diuron, and DCPA in soil columns. Unpublished study prepared by University of Tennessee, submitted by American Carbonyl, Inc., Tenafly, NJ.

- Khan, S.U., and T.S. Foster. 1976. Residues of atrazine (2-chloro-4-ethyl-amino-6-isopropylamino-s-triazine) and its metabolites in chicken tissues. *J. Agric. Food Chem.* 24:768-771.
- Khan, S.U., and M. Schnitzer. 1978. "UV irradiation of atrazine in aqueous fulvic acid solution. *Environmental Science and Health.* B13:299-310.
- Lavy, T.L. 1974. Mobility and deactivation of herbicides in soil-water systems: Project A-024-NEB. Available from National Technical Information Service, Springfield, VA; PB-238-632.
- Lavy, T.L., F.W. Roeth and C.R. Fenster. 1973. Degradation of 2,4-D and atrazine at three soil depths in the field. *J. Environ. Qual.* 2:132-137.
- Lehman, A.J. 1959. Appraisal of the safety of chemicals in foods, drugs and cosmetics. *Assoc. Food and Drug Off.*
- Loprieno, N., R. Barale, L. Mariani, S. Presciuttini, A.M. Rossi, I. Shrana, L. Zaccaro, A. Abbondandolo and S. Bonatti. 1980. Results of mutagenicity tests on the herbicide atrazine. *Mutat. Res.* 74:250. Abstract.
- Lykins, Jr., B.W., E.E. Geldreich, J.Q. Adams, J.C. Ireland and R.M. Clark. 1984. Granular activated carbon for removing nontrihalomethane organics from drinking water. U.S. Environmental Protection Agency, Office of Research and Development, Municipal Environmental Research Laboratory, Cincinnati, OH.
- Meister, R.G., ed. 1987. *Farm chemicals handbook.* 3rd ed. Willoughby, OH: Meister Publishing Co.
- Miltner, R.J., and C.A. Fronk. 1985a. Treatment of synthetic organic contaminants for Phase II regulations. Progress report. U.S. Environmental Protection Agency, Drinking Water Research Division. July 1985.
- Miltner, R.J., and C.A. Fronk. 1985b. Treatment of synthetic organic contaminants for Phase II regulations. Internal report. U.S. Environmental Protection Agency, Drinking Water Research Division. December 1985.
- Molnar, V. 1971. Symptomatology and pathomorphology of experimental poisoning with atrazine. *Rev. Med.* 17:271-274. (English abstract only)
- Murnik, M.R., and C.L. Nash. 1977. Mutagenicity of the triazine herbicides atrazine, cyanazine, and simazine in Drosophila melanogaster. *J. Toxicol. Environ. Health.* 3:691-697.
- NAS. 1977. National Academy of Sciences. *Drinking Water and Health.* Washington, DC: National Academy Press. pp. 533-539.
- Newby, L., and B.G. Tweedy. 1976. Atrazine residues in major rivers and tributaries. Unpublished study submitted by Ciba-Geigy Corporation, Greensboro, N.C.

- Palmer, J.S., and R.D. Radeleff. 1964. The toxicological effects of certain fungicides and herbicides on sheep and cattle. *Ann. N.Y. Acad. Sci.* 111:729-736.
- Palmer, J.S., and R.D. Radeleff. 1969. The toxicity of some organic herbicides to cattle, sheep and chickens. Production Research Report No. 106. U.S. Department of Agriculture, Agricultural Research Service: 1-26.
- Peters, J.W., and R.M. Cook. 1973. Effects of atrazine on reproduction in rats. *Bull. Environ. Contam. Toxicol.* 9:301-304.
- Portnoy, C.E. 1978. Disappearance of bentazon and atrazine in silt loam soil. Unpublished study submitted by BASF Wyandotte Corporation, Parsippany, NJ.
- Schlicher, J.E., and V.B. Beat. 1972. Dermatitis resulting from herbicide use -- A case study. *J. Iowa Med. Soc.* 62:419-420.
- Smith, A.E., R. Grover, G.S. Emmond and H.C. Korven. 1975. Persistence and movement of atrazine, bromacil, monuron, and simazine in intermittently-tilled irrigation ditches. *Can. J. Plant Sci.* 55:809-816.
- Spencer, H. 1987. Review of several mutagenicity studies on atrazone. U.S. EPA, Office of Pesticide Programs' review of a Ciba-Geigy data submission. Accession No. 284052. MRID 402466-01.
- STORET. 1988. STORET Water Quality File. Office of Water. U.S. Environmental Protection Agency. (Data file search conducted in March, 1988).
- Talbert, R.E., and O.H. Fletchall. 1965. The adsorption of some S-triazines in soils. *Weeds.* 13:46-52.
- Turner, M.A., and R.S. Adams, Jr. 1968. The adsorption of atrazine and atratone by anion- and cation-exchange resins. *Soil Sci. Amer. Proc.* 32:62-63.
- U.S. EPA. 1986a. U.S. Environmental Protection Agency. Atrazine chronic feeding/oncogenicity study preliminary incidence table of tumors regarding possible section 6(a)(2) effect. Washington, DC: U.S. EPA Office of Pesticide Programs.
- U.S. EPA. 1986b. U.S. Environmental Protection Agency. Guideline for carcinogen risk assessment. *Fed. Reg.* 51(185):33992-34003. September 24.
- U.S. EPA. 1986c. U.S. Environmental Protection Agency. Code of Federal Regulations. Protection of the environment. Tolerances and exemptions from tolerances for pesticide chemicals in or on raw agricultural commodities. 40 CFR 180.220. p. 216.
- U.S. EPA. 1988. U.S. Environmental Protection Agency. Method #507 - Determination of nitrogen and phosphorus containing pesticides in ground water by GC/NPD. April 14, draft.

- Warnock , R.E., and J.B. Leary. 1978. Paraquat, atrazine and Bladex--dissipation in soils. Unpublished study prepared by Chevron Chemical Company, submitted by Shell Chemical Company, Washington, DC.
- Weidner, C.W. 1974. Degradation in groundwater and mobility of herbicides. Master's thesis. University of Nebraska, Department of Agronomy.
- Wolf, D.C., and J.P. Martin. 1975. Microbial decomposition of ring-14C-atrazine, cyanuric acid, and 2-chloro-4,6-diamino-S-triazine. J. Environ. Qual. 4:134-139.
- Woodard Research Corporation.* 1964. Two-year feeding study in dogs. CBI, Document No. 000525, MRID 00059213.
- Woodard Research Corporation.* 1966. Three-generation reproduction study in rats. CBI, Document No. 000525, MRID 00024471.
- Yoder, J., M. Watson and W.W. Benson. 1973. Lymphocyte chromosome analysis of agricultural workers during extensive occupational exposure to pesticides. Mutat. Res. 21:335-340.
- Windholz, M., ed. 1976. The Merck index. 9th ed. Rahway, NJ: Merck and Co., Inc.

DINOSEB

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

I. INTRODUCTION

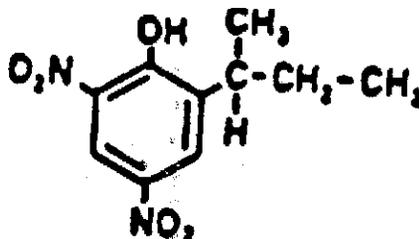
The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations 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. 88-85-7

Structural Formula

2-sec-butyl-4,6-dinitrophenol

Synonyms

- DNBP, dinitro, dinoseb (BSI, ISO, WSSA); dinosebe (France); Basanite (BASF Wyandotte); Caldon, Chemox General, Chemox PE, Chemsect DNBP, DN-289 (product discontinued), Dinitro, Dinitro-3, Dinitro General, Dynamite (Drexel Chemical); Elgetol 318, Gabutox, Hel-Fire (Helena); Kiloseb, Nitropon C, Premerge 3 (Agway); Sinox General (FMC Corp.); Subitex, Unicrop DNBP, Vertac Dinitro Weed Killer 5, Vertac General Weed Killer, Vertac Selective Weed Killer (Meister, 1984).

Uses

- Dinoseb is used as a herbicide, desiccant and dormant fruit spray (Meister, 1984).

Properties (WSSA, 1983)

Chemical Formula	C ₁₀ H ₁₂ N ₂ O ₅
Molecular Weight	240
Physical State (room temp.)	Dark amber crystals
Boiling Point	--
Melting Point	32°C
Density (°C)	1.2647 (45°C)
Vapor Pressure	(151°C) 1 mm Hg
Specific Gravity	--
Water Solubility	52 mg/L (25°C)
Log Octanol/Water Partition Coefficient	--
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Dinoseb has been found in 1 of 89 surface water samples analyzed and in none of 1,270 ground water samples (STORET, 1988). Samples were collected at 89 surface water locations and 1,184 ground water locations.

and dinoseb was found in Ohio. The 85th percentile of all nonzero samples was 1 ug/L in surface water. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

- Dinoseb has been found in New York ground water; typical positives were 1 to 5 ppb (Cohen et al., 1986).

Environmental Fate

- Dinoseb was stable to hydrolysis at pH 5, 7, and 9 at 25°C over a period of 30 days (Dzialo, 1984).
- With natural sunlight on a California sandy loam soil, dinoseb had a half-life of 14 hours; with artificial light, it had a half-life of 30 hours, indicating that dinoseb is subject to photolytic degradation (Dinoseb Task Force, 1985a).
- In water with natural sunlight, dinoseb had a half-life of 14 to 18 days; with artificial light, it had a half-life of 42 to 58 days (Dinoseb Task Force, 1985b).
- With soil thin-layer chromatography plates, dinoseb was intermediate to very mobile in silt loam, sand, sandy loam and silty clay loam (Dinoseb Task Force, 1985c).
- Soil adsorption studies gave a K_d of less than 5 for four soils: a silt loam, sand, sandy loam and silty clay loam, with organic matter content of 0.8 to 3% (Dinoseb Task Force, 1985d).

III. PHARMACOKINETICS

Absorption

- Following oral administration of dinoseb to rats (Bandal and Casida, 1972) and mice (Gibson and Rao, 1973) (specific means of administration not specified), approximately 25% of the administered dose appeared in the feces. However, following intraperitoneal (ip) administration in the mouse, approximately 40% appeared in the feces, thus suggesting to Gibson and Rao (1973) that dinoseb is initially completely absorbed following oral administration with subsequent secretion into the gut.

Distribution

- Following oral administration of dinoseb in the mouse (specific means of administration not specified), no appreciable amounts accumulated in the blood, liver or kidney (Gibson and Rao, 1973).

Metabolism

- While the metabolism of dinoseb has not been completely characterized, a number of metabolites have been identified including: 2-(2-butyric acid)-4,6-diaminophenol, 2-(2-butyric acid)-4,6-dinitrophenol, 2-sec-butyl-4-nitro-6-aminophenol, 2-sec-butyl-4-acetamido-6-nitrophenol and 2-(3-butyric acid)-4,6-dinitrophenol (Ernst and Bar, 1964; Froslic and Karlog, 1970; Bandal and Casida, 1972).

Excretion

- In mice, dinoseb is excreted in both urine (20%) and feces (30%) following oral administration (specific means of administration not specified) (Gibson and Rao, 1973).

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- While minimal data are available concerning human toxicity, at least one death has been attributed to an accidental exposure of a farm worker to sprayed dinoseb and dinitro-ortho-cresol (Heyndrickx et al., 1964).

Long-term Exposure

- No information on the long-term health effects of dinoseb in humans was found in the available literature.

Animals

Short-term Exposure

- In rats and mice, the acute oral LD₅₀ of dinoseb ranges from 20 to 40 mg/kg (Bough et al., 1965).

Dermal/Ocular Effects

- In rats, the acute dermal toxicity of dinoseb ranges from 67 to 134 mg/kg (Noakes and Sanderson, 1969).
- No other information on the dermal or ocular effects of dinoseb in animals was found in the available literature.

Long-term Exposure

- Hall et al. (1978) reported the results (abstract only) of a feeding study in male and female rats. Eight groups of rats, each group composed of 14 males and 14 females, were exposed to levels of 0, 50, 100, 150, 200, 300, 400 or 500 ppm of dinoseb (80% pure) in the diet for 153 days, respectively. Assuming that 1 ppm in the diet of rats

is equivalent to 0.05 mg/kg/day (Lehman, 1959), these levels correspond to 0, 2.5, 5.0, 7.5, 10.0, 15.0, 20.0 and 25.0 mg/kg/day. Mortality was observed at 300 ppm (15 mg/kg/day) and above, and growth was depressed at all dose levels. The LOAEL for this study was identified as 50 ppm (2.5 mg/kg/day), the lowest dose tested.

- In a 6-month dietary study by Spencer et al. (1948), groups of male rats were exposed to dinoseb (99% pure) at levels of 0 (30 animals), 1.35, 2.7, 5.4 (20 animals) and 13.5 mg/kg/day (10 animals). Based on increased mortality at the highest dose and increased liver weight at intermediate doses, the No-Observed-Adverse-Effect Level (NOAEL) for dinoseb was identified as 2.7 mg/kg/day.
- In a study submitted to EPA in support of the registration of dinoseb (Hazleton, 1977), four groups of rats (60/sex/dose) were exposed to dinoseb (purity not specified) in their diets for periods up to two years at dose levels of 0, 1, 3 and 10 mg/kg/day, respectively. Although no evidence of dose-related changes in histopathology, hematology, blood chemistry or certain other parameters were observed, a dose-related decrease in mean thyroid weight was observed in all treated males. The LOAEL in this study was identified as 1 mg/kg/day.

Reproductive Effects

- In a reproduction study by Linder et al. (1982), four groups of ten male rats each were exposed to dinoseb (97% pure) in the diet at levels of 0, 3.8, 9.1 or 15.6 mg/kg/day over an 11-week period, respectively. In addition, a group of five animals was exposed to 22.2 mg/kg/day. The fertility index was reduced to 0 at 22.2 mg/kg and to 10% at 15.6 mg/kg/day; in neither case did the fertility index improve in 104 to 112 days following treatment. A variety of other effects were seen at levels of 9.1 mg/kg/day and higher, including decreased weight of the seminal vesicles, decreased sperm count and an increased incidence of abnormal sperm. The NOAEL for dinoseb in this study was 3.8 mg/kg/day based on a decrease in sperm count and other effects at higher levels.
- In a two-generation rat reproduction study (Irvine, 1981), four groups of rats (25/sex/dose) were exposed to 0, 1, 3, and 10 mg/kg/day of dinoseb in the diet for 29 weeks. Although no reproductive effects were observed in this study per se, a decrease in pup body weight was observed at day 21 post-parturition for all dose levels. Thus, based on a compound-related depression in pup body weight at all dose levels, the LOAEL in this study was 1 mg/kg/day.

Developmental Effects

- Although dinoseb has been reported to be teratogenic (e.g., oligodactyly, imperforate anus, hydrocephalus, etc.) when administered to mice intraperitoneally (Gibson, 1973), it was not teratogenic when administered orally to mice (Gibson, 1973; Gibson and Rao, 1973) or rats (Spencer and Sing, 1982).

- Dinoseb (95% pure), administered to pregnant rats in the diet on days 6 through 15 of gestation, produced a marked reduction in fetal survival at doses of 9.2 mg/kg/day and above but not at doses of 6.9 mg/kg/day (NOAEL) and below (Spencer and Sing, 1982).
- Dinoseb (purity not specified) was without effect in a study in which pregnant mice were orally exposed to a single dose of 15 mg/kg/day (Chernoff and Kavlock, 1983).
- In a developmental toxicity study by Research and Consulting Company (1986), four groups of 16 Chinchilla rabbits were exposed to dinoseb (98% pure) by oral gavage at levels of 0, 1, 3 or 10 mg/kg/day from day 6 to 18 of gestation. At the highest dose level dinoseb produced a statistically significant increase in malformations and/or anomalies when compared to the controls, with external, internal (body cavities and cephalic viscera) and skeletal defects being observed in 11/16 litters examined. Neural tube defects, the major developmental toxic effect, included dyscrania associated with hydrocephaly, scoliosis, kyphosis, malformed or fused caudal and sacral vertebrae and encephalocele. The NOAEL for dinoseb in this study was identified as 3.0 mg/kg/day, based on the occurrence of neural tube defects at the highest dose level.
- In a study by the Dinoseb Task Force (1986), developmental toxicity was observed in Wistar/Han rats. Groups of 25 rats received dinoseb (purity 96.1%) by gavage at levels of 0, 1, 3 or 10 mg/kg/day from day 6 to 15 of gestation. Developmental toxicity was observed at the high dose as evidenced by a slight depression in fetal body weight, increased incidence of absence of skeletal ossification for a number of sites and an increase in the number of supernumerary ribs. Slight to moderate decreases in body weight gain and food consumption were observed in dams at the intermediate- and high-dose levels. Based on the occurrence of developmental effects at the highest dose level, a NOAEL of 3.0 mg/kg/day was identified.

Mutagenicity

- With the exception of an increase in DNA damage in bacteria (Waters, et al., 1982), dinoseb was not mutagenic in a number of organisms including Salmonella typhimurium, Escherichia coli, Saccharomyces cerevisiae, Drosophila melanogaster or Bacillus subtilis (Simmon et al., 1977; Waters et al., 1982; Moriya et al., 1983).

Carcinogenicity

- No evidence of a carcinogenic response was observed in a 2-year chronic feeding study in which dinoseb was administered to rats at levels as high as 10 mg/kg/day (Hazleton, 1977).

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:

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

where:

NOAEL or LOEL = 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 information was found in the available literature that was suitable for determination of the One-day HA value. It is therefore recommended that the Ten-day HA value for a 10-kg child (0.3 mg/L, calculated below) be used as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The rabbit developmental toxicity study (Research and Consulting Co., 1986) in which dinoseb produced neural tube defects at doses greater than 3 mg/kg/day (NOAEL) was selected as the basis for determination of the Ten-day HA. While it is reasonable to base a Ten-day HA for the adult on a positive developmental toxicity study, there is some question as to whether it is appropriate to base the Ten-day HA for a 10-kg child on a such a study. However, since this study is of appropriate duration and since the fetus may be more sensitive than a 10-kg child, it was judged that, while it may be overly conservative, it is reasonable to base the Ten-day HA for a 10-kg child on such a study.

Using a NOAEL of 3.0 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(3.0 \text{ mg/kg/day}) (10 \text{ kg})}{(100) (1 \text{ L/day})} = 0.3 \text{ mg/L (300 ug/L)}$$

where:

3.0 mg/kg/day = NOAEL, based on the absence of teratogenic effects in rabbits.

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 Hall et al. (1978) 153-day dietary dinoseb study in rats was originally selected to serve as the basis for determination of the Longer-term HA (decreased growth was observed at all exposure levels with a LOAEL of 2.5 mg/kg/day). Subsequently, however, a two-generation reproduction study in rats (Irvine, 1981) was identified with a LOAEL of 1 mg/kg/day (based on a decrease in pup body weight at all dose levels). Since a reproduction study is of appropriate duration, the Irvine (1981) study has been selected to serve as the basis for determination of the Longer-term HA.

Using a LOAEL of 1 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(1.0 \text{ mg/kg/day}) (10 \text{ kg})}{(1,000) (1 \text{ L/day})} = 0.010 \text{ mg/L (10 ug/L)}$$

where:

1.0 mg/kg/day = LOAEL, based on decreased pup body weight.

10 kg = assumed body weight of a child.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a LOAEL 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:

$$\text{Longer-term HA} = \frac{(1.0 \text{ mg/kg/day}) (70 \text{ kg})}{(1,000) (2 \text{ L/day})} = 0.035 \text{ mg/L (40 ug/L)}$$

where:

1.0 mg/kg/day = LOAEL, based on decreased pup body weight.

70 kg = assumed body weight of an adult.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a LOAEL 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.

The 2-year dietary rat study by Hazelton (1977) was selected to serve as the basis for determination of the Lifetime HA. In this study, a compound-related decrease in mean thyroid weights was observed in all males (LOAEL = 1 mg/kg/day) treated with dinoseb (purity not specified).

Using a LOAEL of 1 mg/kg/day, the Lifetime HA for a 70-kg adult is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(1 \text{ mg/kg/day})}{(1,000)} = 0.001 \text{ mg/kg/day}$$

where:

1 mg/kg/day = LOAEL, based on decreased thyroid weight in male rats exposed to dinoseb via the diet for up to 2 years.

1,000 = uncertainty factor, chosen in accordance with EPA or NAS/ODW guidelines for use with a LOAEL from an animal study.

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

$$\text{DWEL} = \frac{(0.001 \text{ mg/kg/day}) (70 \text{ kg})}{(2 \text{ L/day})} = 0.035 \text{ mg/L (40 ug/L)}$$

where:

0.001 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

Lifetime HA = (0.035 mg/L) (20%) = 0.007 mg/L (7 ug/L)

where:

0.035 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No evidence of carcinogenicity was found in a 2-year dietary study in which dinoseb was administered to rats at levels as high as 10 mg/kg/day (Hazleton Labs, 1977).
- The International Agency for Research on Cancer has not evaluated the carcinogenic potential of dinoseb.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), dinoseb is classified in Group D: not classified. This group is for agents with inadequate human and animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Tolerances have been established for dinoseb (CFR, 1985) at 0.1 ppm on a wide variety of agricultural commodities.
- The EPA RfD Workgroup approved a 0.001 mg/kg/day RfD for dinoseb. The EPA RfD Workgroup is an EPA wide group whose function is to ensure that consistent RfD values are used throughout the EPA.

VII. ANALYTICAL METHODS

- Analysis of dinoseb is by a gas chromatographic (GC) method applicable to the determination of certain chlorinated acid pesticides in water samples (U.S. EPA, 1985). 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 been estimated at 0.07 ug/L for dinoseb.

III. TREATMENT TECHNOLOGIES

- The treatment technologies which will remove dinoseb from water include activated carbon and ion exchange. No data were found for the removal of dinoseb from drinking water by conventional treatment or by aeration. However, limited data suggest that aeration would not be effective in the removal of dinoseb from drinking water (ESE, 1984).
- Becker and Wilson (1978) reported on the treatment of a contaminated lake water with three activated carbon columns operated in series. The columns processed about 2 million gallons of lake water and achieved a 99.98 percent removal of dinoseb. Weber and Gould (1966) performed successful isotherm tests using Columbia LC carbon, which is coconut based, and reported the following Langmuirian equilibrium constants:

$$Q = 444 \text{ mg dinoseb per g of carbon}$$

$$1/b = 1.39 \text{ mg/L}$$

Though the Langmuir equation provides a good fit over a broad concentration range, greater adsorption would probably be achieved at lower concentrations (less than 100 ug/L) than predicted by using these constants.

- Weber (1972) has classified dinoseb as an acidic pesticide; and such compounds have been readily adsorbed in large amounts by ion exchange resins. Harris and Warren (1964) studied the adsorption of dinoseb from aqueous solution by anion exchanger (Amberlite® IRA-400) and a cation exchanger (Amberlite® IR-200). The anion exchanger adsorbed dinoseb to less than detectable limits in solution.

IX. REFERENCES

- Bandal, S.K. and J.E. Casida. 1972. Metabolism and photoalteration of 2-sec-butyl-4,6-dinitrophenol (DNBP herbicide) and its isopropyl carbonate derivative (dinobuton acaricide). *J. Agr. Food Chem.* 20:1235-1245.
- Becker, D.L. and Wilson, S.C. 1978. The use of activated carbon for the treatment of pesticides and pestididal wastes. *In* Carbon Adsorption Handbook (D.H. Chermisinoff and F. Ellerbusch, Eds.). Ann Arbor Science Publishers, Ann Arbor, MI.
- Bough, R.G., E.E. Cliffe and B. Lessel. 1965. Comparative toxicity and blood level studies on binapacryl and DNBP. *Toxicol. Appl. Pharmacol.* 7:353-360.
- CFR. 1985. Code of Federal Regulations. 40 CFR 180.281. July 1, 1985.
- Chernoff, N. and R.J. Kavlock. 1983. A teratology test system which utilizes postnatal growth and viability in the mouse. *Environ. Sci. Res.* 27:417-427.
- Cohen, S.Z., C. Eiden and M.N. Lorber. 1986. Monitoring ground water for pesticides in the USA. *In*: American Chemical Society Symposium Series titled Evaluation of Pesticides in Ground Water (in press).
- Dinoseb Task Force. 1985a. Photodegradation of dinoseb on soil. Prepared by Hazleton Laboratories America, Inc. Report No. 6015-191 (Tab 3), July 19, 1985.
- Dinoseb Task Force. 1985b. Photodegradation of dinoseb in water. Prepared by Hazleton Laboratories America, Inc. Report No. 6015-190 (Tab 4), July 19, 1985.
- Dinoseb Task Force. 1985c. Determination of the mobility of dinoseb in selected soils by soil TLC. Prepared by Hazleton Laboratories America, Inc. Report No. 6015-192 (Tab 1). July 19, 1985.
- Dinoseb Task Force. 1985d. The adsorption/desorption of dinoseb on representative agricultural soils. Prepared by Hazleton Laboratories America, Inc. Report No. 6015-193 (Tab 2), July 19, 1985.
- Dinoseb Task Force. 1986. Probe embryotoxicity study with dinoseb technical grade in Wistar rats. Prepared by Research and Consulting Company. Project No. 045281. April 22, 1986.
- Dzialo, D. 1984. Hydrolysis of dinoseb: Project No. 84239. Unpublished study prepared by Uniroyal Inc.
- Environmental Science and Engineering (ESE). 1984. Review of treatability data for removal of twenty-five synthetic organic chemicals from drinking water. U.S. Environmental Protection Agency, Office of Drinking Water, Washington, DC.

- Ernst, W. and F. Bar. 1964. Die umwandlung des 2,4-dinitro-6-sec-butylphenols and seiner ester im tierischen organismus. Arzenimittel Forschung. 14:81-84.
- Froslie, A. and O. Karlog. 1970. Ruminal metabolism of DNOC and DNBP. Acta Vet. Scand. 11:31-43.
- Gibson, J.E. 1973. Teratology studies in mice with 2-sec-butyl-4,6-dinitrophenol (dinoseb). Fd. Cosmet. Toxicol. 11:31-43.
- Gibson, J.E. and K.S. Rao. 1973. Disposition of 2-sec-butyl-4,6-dinitrophenol (dinoseb) in pregnant mice. Fd. Cosmet. Toxicol. 11:45-52.
- Hall, L., R. Linder, T. Scotti, R. Bruce, R. Moseman, T. Heidersheit, D. Hinkle, T. Edgerton, S. Chaney, J. Goldstein, M. Gage, J. Farmer, L. Bennett, J. Stevens, W. Durham and A. Curley. 1978. Subchronic and reproductive toxicity of dinoseb. Toxicol. Appl. Pharmacol. 45:235-236. (abstract only)
- Harris, C.I. and G.F. Warren. 1964. Adsorption and desorption of herbicides by soil. Weeds, 12:120.
- Hazleton.* 1977. Hazleton Labs. 104-Week dietary study in rats. Dinoseb DNBP. Final Report. Unpublished study. MRID 00211
- Hayndrickx, A., R. Maes and F. Tyberghein. 1964. Fatal intoxication by man due to dinitro-ortho-cresol (DNOC) and dinitro butylphenol (DNBP). Mededel Lanhovwhoge School Opzoekingstaa Staa Gent. 29:1189-1197.
- Irvine, L.F.H.* 1981. 3-Generation reproduction study; Hazelton Laboratories Europe, Ltd.
- Lehman, A. J. 1959. Appraisal of the safety of chemicals in foods, drugs and cosmetics. Assoc. Food Drug Off. U.S., Q. Bull.
- Linder, R.E., T.M. Scotti, D.J. Svendsgaard, W.K. McElroy and A. Curley. 1982. Testicular effects of dinoseb in rats. Arch. Environ. Toxicol. 11:475-485.
- Meister, R., ed. 1984. Farm chemicals handbook. Willoughby, OH: Meister Publishing Co.
- Moriya, M., T. Ohta, T. Watanabe, K. Kato and Y. Shirasu. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat. Res. 116:185-216.
- Noakes, D.N. and D.M. Sanderson. 1969. A method for determining the dermal toxicity of pesticides. Brit. J. Ind. Med. 26:59-64.
- Research and Consulting Company. 1986. Embryotoxicity study with dinoseb technical grade in the rabbit (oral administration). Unpublished study.

- Simmon, V.F., A.D. Mitchell and T.A. Jorgenson. 1977. Evaluation of selected pesticides as chemical mutagens in vitro and in vivo studies. Research Triangle Park, NC: U.S. Environmental Protection Agency, EPA 600/1-77-028
- Spencer, F. and L.T. Sing. 1982. Reproductive toxicity in pseudopregnant and pregnant rats following postimplantational exposure: Effects of the herbicide dinoseb. *Pestic. Biochem. Physiol.* 18:150-157.
- Spencer, H.C., V.K. Rowe, E.M. Adams and D.D. Irish. 1948. Toxicological studies on laboratory animals of certain alkyldinitrophenols used in agriculture. *J. Ind. Hyg. Toxicol.* 30:10-25.
- STORET. 1988. STORET Water Quality File. Office of Water. U.S. Environmental Protection Agency (data file search conducted in May, 1988).
- U.S. EPA. 1985. U.S. EPA Method 615 - Chlorinated Phenoxy Acids. Fed. Reg. 50:50701. October 4.
- U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogen risk assessment. Fed. Reg. 51(185):33992-34003. September 24
- Waters, M.D., S. Shahbeg, S. Sandhu et al. 1982. Study of pesticide genotoxicity. *Basic Life Sci.* 21:275-326.
- Weber, J.B. 1972. Interaction of organic pesticides with particulate matter in aquatic and soil systems. In *Advances in Chemistry Series 111* (R.F. Gould, Ed.). American Chemical Society, Washington, DC.
- Weber, W.J., Jr. and J.P. Gould. 1966. Sorption of organic pesticides from aqueous solution. In *Advances in Chemistry Series 60* (R.F. Gould, Ed.). American Chemical Society, Washington, DC.
- WSSA. 1983. Weed Science Society of America. *Herbicide handbook*, 5th ed. Champaign, IL.

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

am Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Atrazine

File On-Line 09/30/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	01/01/91
Inhalation RfC Assessment (I.B.)	no data	$C_s = \left(\frac{10^{-6}}{0.72 \text{ (ms/kg-d)}'} \right) \left(\frac{70 \text{ kg}}{0.0001 \text{ kg}} \right)$ $= 3.15 \times 10^6$
Carcinogenicity Assessment (II.)	pending	$NC_s = \left(0.005 \frac{\text{mg}}{\text{kg-d}} \right) \left(\frac{16 \text{ kg}}{0.0002 \text{ kg}} \right)$ $= 400 \text{ mg/kg}$
Drinking Water Health Advisories (III.A.)	no data	$C_w = \frac{10^{-6}}{0.72 \text{ (ms/kg-d)}'} \times \frac{70 \text{ kg}}{2.3 \text{ L}}$ $= 1.6 \times 10^{-4} \text{ ms/L}$
U.S. EPA Regulatory Actions (IV.)	no data	$NC_w = \left(0.005 \frac{\text{mg}}{\text{kg-d}} \right) \left(\frac{16 \text{ kg}}{2.3 \text{ L}} \right) = 0.04 \frac{\text{mg}}{\text{L}}$
Supplementary Data (V.)	no data	

I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Atrazine
 CASRN -- 1912-24-9
 Last Revised -- 01/01/91

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file when a review of that evaluation is completed.

I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased body weights of F2 generation pups on postnatal day 21	NOEL: 10 ppm (0.5 mg/kg/day)	100	1	5E-3 mg/kg/day
2-Generation Rat Reproduction Study	LEL: 50 ppm (2.5 mg/kg/day)			
Ciba-Geigy, 1987a				

*Conversion Factors: 1 ppm = 0.05 mg/kg/day (assumed rat food consumption)

<<< Atrazine >>>

I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Ciba-Geigy Corporation. 1987a. MRID No. 40431303.
Available from EPA. Write to FOI, EPA, Washington, DC 20460.

In a 2-generation reproduction study, 120 rats/sex were randomly distributed into 4 treatment groups and fed atrazine at 0, 10, 50, or 500 ppm (0, 0.5, 2.5, and 25 mg/kg/day). Exposure to the test material began when male rats were 47 days old and females were 48 days old. They were maintained on these diets for 10 weeks prior to mating. Males and females were housed together in a 1:1 ratio and allowed 3 weeks for mating. The rats were separated following evidence of mating. One litter was produced in each generation. After weaning, 30 males and 30 females from the first generation were selected to be the second parental generation. The remaining male parental animals were sacrificed on days 133 to 134 of the study. Animals selected for the second generation were exposed to test diets for 12 weeks prior to mating. Mating was conducted in the same manner as for the first generation. Parental males were sacrificed on day 138 of the study and parental females on days 138, 139, and 152 after weaning of their litters.

The NOEL for reproductive toxicity is 10 ppm (0.5 mg/kg/day) based on statistically significantly lower F2 generation pup weights at postnatal day 21 at 50 and 500 ppm (2.5, and 25 mg/kg/day). The NOEL for parental toxicity is 50 ppm (2.5 mg/kg/day) based on statistically significantly decreased body weights, body weight gain and food consumption for males and females throughout the study at 500 ppm (25 mg/kg/day). In addition, a statistically significant increase in relative testes weights was seen in both generations.

<<< Atrazine >>>

I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 100. An uncertainty factor of 100 was used to account for the inter- and intraspecies differences.

MF = 1.

<<< Atrazine >>>

I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

Data Considered for Establishing the RfD

- 1) 2-Generation Reproduction - rat: see previous description; core grade minimum (Ciba-Geigy Corp., 1987a)
- 2) 1-Year Feeding - dog: Dietary levels tested: 0, 15, 150, and 1000 ppm (Male: 0, 0.48, 4.97, and 33.65 mg/kg/day; Female: 0, 0.48, 4.97, and 33.6 mg/kg/day). NOEL=150 ppm (4.97 mg/kg/day); LEL=1000 ppm (43 mg/kg/day) (UDTs based on death, cachexia, cavities, decreased body weight and body

- weight gain, decreased food consumption; EKG changes [irregular heart beat and increased heart rate, decrease P-II values, atrial premature complexes, atrial fibrillation]; cardiac lesions [dilation of atria, atrial degeneration]; core grade minimum (Ciba-Geigy Corp., 1987b)
- 3) 2-Year Feeding (oncogenic) - rat: Dietary levels tested: 0, 70, 500, and 1000 ppm (0, 3.5, 25, and 50 mg/kg/day). Administration of atrazine to male and female CD-1 Sprague-Dawley rats resulted in decreased mean body weights for males and females receiving 500 and 1000 ppm. Survival was decreased in high-dose females but increased in high-dose males. Red blood cell parameters (hemoglobin, hematocrit, and red cell count) were decreased in high-dose females only. The serum glucose level was decreased in high-dose females at 3, 6, and 12 months and serum triglyceride levels showed a decreasing trend in high-dose males throughout the study. There were decreases in organ-to-body weight ratios in high-dose animals, which were probably the result of body weight decreases. Hyperplastic changes in high-dose males (mammary gland, bladder, and prostate) and females (myeloid tissue of bone marrow and transitional epithelium of the kidney) were of questionable toxicologic importance. There was an increase in retinal degeneration and in centrilobular necrosis of the liver in high-dose females and an increase in degeneration of the rectus femoris muscle in high-dose males and females when compared to controls. Based on decreased body weight gain, the LEL for males and females is 500 ppm (25 mg/kg/day) and the NOEL is 70 ppm (3.5 mg/kg/day); core grade minimum (Ciba-Geigy Corp., 1986)
 - 4) Developmental toxicity - rat: Dietary levels tested: 0, 10, 70, and 700 mg/kg/day (by gavage). Administration of atrazine technical to Charles River CD rats from days 6 to 15 of gestation resulted in maternal toxicity during and after the treatment period at the high-dose. Signs of toxicity at the high-dose included death (21 of 27 dams), reduced food consumption, reduced weight gain, salivation, ptosis, swollen abdomen, oral/nasal discharge, and bloody vulva. Maternal toxicity was also found at the 70 mg/kg/day dose level. Toxicity signs in this group included reduced food consumption, reduced body weight, and reduced weight gain. No maternal toxicity was observed in the 10 mg/kg/day or control groups. Based on the above effects, the maternal toxicity NOEL is 10 mg/kg/day and the LEL is 70 mg/kg/day. At 70 mg/kg/day, there were statistically significant increases in both fetal and litter incidences for skeletal variations indicating delayed ossification. Variations included: skull not completely ossified, metacarpals not ossified, metacarpals bipartite, and phalanx not ossified. Based on these effects the NOEL and LEL for developmental toxicity are 10 and 70 mg/kg/day, respectively.; core grade minimum (Ciba-Geigy Corp., 1984a)
 - 5) Developmental toxicity - rabbit: Dietary levels tested: 0, 1, 5, 75 mg/kg/day (by gavage). Administration of atrazine technical to New Zealand White rabbits from days 7 to 19 of gestation resulted in maternal toxicity during the treatment period at doses of 5 and 75 mg/kg/day. Does in the 75 mg/kg/day group did not recover from symptoms of this toxicity during the period after dosing. Signs of maternal toxicity in the 5 mg/kg/day dose group were decreased food consumption and decreased body weight. Signs of maternal toxicity in the high-dose group included blood on vulva or in cage, decreased food consumption, abnormal stools, and decreased body weight and body weight gain. No effects were observed at the lowest dose tested, 1 mg/kg/day. Based on the above effects, the maternal toxicity NOEL is 1 mg/kg/day and the LEL 5 mg/kg/day. An increased number of resorptions in the HDT was statistically significant and was not observed at any other dose level. In the HDT, the weights of both the male and female fetuses were significantly reduced. No compound-related malformations were observed. Skeletal variations, especially delayed ossification of appendicular skeletal elements, were found more frequently in the HDT. Based on the above effects, the developmental toxicity NOEL is 5 mg/kg/day and the LEL 75 mg/kg/day; core grade minimum (Ciba-Geigy Corp., 1984b)

Other Data Reviewed:

1) Chronic Feeding - rat: Dietary levels tested: 0, 10, 300, 1500, and 3000

On oral feeding - mouse: Dietary levels tested: 0, 1.4, 38.4, 194.0, and 385.7 mg/kg/day; Female: 0, 1.6, 47.9, 246.9, and 482.7 mg/kg/day). This study shows that there are dose-related effects of atrazine in CD-1 mice fed diets containing 1500 or 3000 ppm of atrazine. The dose-related effects were the production of cardiac thrombi, decreases of 23.5% and 11.0% in the mean body weight gain at 91 weeks in males and females, respectively, and decreases in erythrocyte count, hematocrit and hemoglobin concentration. An increase in the incidence of cardiac thrombi was found in females receiving 1500 and 3000 ppm. Based on the above effects, the LEL for systemic toxicity is 1500 ppm (Male: 194.0 mg/kg/day; Female: 246.9 mg/kg/day). The NOEL for systemic toxicity is 300 ppm (Male: 38.4 mg/kg/day; Female: 47.9 mg/kg/day).; core grade guideline (Ciba-Geigy Corp., Agricultural Division, 1987c)

- 2) 2-Year Feeding - dog: Dietary levels tested: 0, 14.1, 141.5, and 1415 ppm (0, 0.35, 3.54, and 35.38 mg/kg/day). The NOEL for systemic toxicity is 14.1 ppm (0.35 mg/kg/day) based on increased heart and liver weights in females at 141.5 ppm (3.54 mg/kg/day). Effects observed at 1415 ppm (35.38 mg/kg/day) included reduced food intake, decreased body weight, and reduced hemoglobin and hematocrit values. core grade supplementary (Ciba-Geigy Corp., 1964)
- 3) Developmental toxicity - rat: Dietary levels tested: 0, 100, 500, and 1000 mg/kg/day. Administration of atrazine at 1000 mg/kg/day produced 7 deaths in the 30 dams treated. Slight weight losses in females were observed at 500 mg/kg/day. A reduction in mean fetal weights and an increase in the number of embryonic and fetal resorptions were observed in the mid- and high-dose groups. Based on the above effects, the maternal toxicity and fetotoxicity NOEL and LEL are 100 and 500 mg/kg/day, respectively; core grade minimum (Ciba-Geigy, Corp., 1971)

Data Gap(s): None

<<< Atrazine >>>

I.A.5. CONFIDENCE IN THE ORAL RfD

Study: High
Data Base: High
RfD: High

The critical study is of good quality and is given a high confidence rating. Additional studies are supportive and of good quality; therefore, the data base is given a high confidence rating. High confidence in the RfD follows.

<<< Atrazine >>>

I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

The only U.S. EPA documentation at present is on IRIS.

Pesticide Registration Standard

Pesticide Registration Files

Agency Work Group Review: 07/08/86, 12/09/86, 05/20/87, 06/22/88, 02/21/90

Verification Date: 02/21/90

I.A.7. EPA CONTACTS (ORAL RfD)

George Ghali / OPP -- (703)557-7490 / FTS 557-7490

Reto Engler / OPP -- (703)557-7491 / FTS 557-7491

_I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RFC)

Substance Name -- Atrazine
CASRN -- 1912-24-9

Not available at this time.

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Atrazine
CASRN -- 1912-24-9

This substance/agent has been evaluated by the U.S. EPA for evidence of human carcinogenic potential. This does not imply that this chemical is necessarily a carcinogen. The evaluation for this chemical is under review by an inter-office Agency work group. A risk assessment summary will be included on IRIS when the review has been completed.

_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

_III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Atrazine
CASRN -- 1912-24-9

Not available at this time.

_III.B. OTHER ASSESSMENTS

Substance Name -- Atrazine
CASRN -- 1912-24-9

Content to be determined.

_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Atrazine
CASRN -- 1912-24-9

Not available at this time.

=====

V. SUPPLEMENTARY DATA

Substance Name -- Atrazine
CASRN -- 1912-24-9

Not available at this time.

=====

VI. BIBLIOGRAPHY

Substance Name -- Atrazine
CASRN -- 1912-24-9
Last Revised -- 05/01/90

VI.A. ORAL RfD REFERENCES

Ciba-Geigy Corporation, 1964. MRID No. 00059213. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation, 1971. MRID No. 00038041. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation, 1984a. EPA Accession No. 254979. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation, 1984b. EPA Accession No. 254979. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation, 1986. EPA Accession No. 262714-262727. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation, Agricultural Division, 1987a. MRID No. 40431303. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation, 1987b. MRID No. 40431301. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation, Agricultural Division, 1987c. MRID No. 40431302. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

-----<<< Atrazine >>>-----

VI.B. INHALATION RfD REFERENCES

None

-----<<< Atrazine >>>-----

VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

None

-----<<< Atrazine >>>-----

VI.D. DRINKING WATER HA REFERENCES

None

=====

SYNONYMS

Substance Name -- Atrazine
CASRN -- 1912-24-9
Last Revised -- 09/30/87

1912-24-9
A 361
AATREX
AATREX 4L
AATREX 80W
AATREX NINE-O
2-AETHYLAMINO-4-CHLOR-6-ISOPROPYLAMINO-1,3,5-TRIAZIN
2-AETHYLAMINO-4-ISOPROPYLAMINO-6-CHLOR-1,3,5-TRIAZIN
AKTIKON
AKTIKON PK
AKTINIT A
AKTINIT PK
ARGEZIN
ATAZINAX
ATRANEX
ATRASINE
ATRATOL A
ATRAZIN
Atrazine
ATRED
ATREX
CANDEX
CEKUZINA-T
2-CHLORO-4-ETHYLAMINEISOPROPYLAMINE-s-TRIAZINE
1-CHLORO-3-ETHYLAMINO-5-ISOPROPYLAMINO-2,4,6-TRIAZINE
1-CHLORO-3-ETHYLAMINO-5-ISOPROPYLAMINO-s-TRIAZINE
2-CHLORO-4-ETHYLAMINO-6-ISOPROPYLAMINO-1,3,5-TRIAZINE
2-CHLORO-4-ETHYLAMINO-6-ISOPROPYLAMINO-s-TRIAZINE
6-CHLORO-N-ETHYL-N'-(1-METHYLETHYL)-1,3,5-TRIAZINE-2,4-DIAMINE
2-CHLORO-4-(2-PROPYLAMINO)-6-ETHYLAMINO-s-TRIAZINE
CRISATRINA
CRISAZINE
CYAZIN
FARMCO ATRAZINE
FENAMIN
FENAMINE
FENATROL
G 30027
GEIGY 30,027
GESAPRIM
GESOPRIM
GRIFFEX
HUNGAZIN
HUNGAZINE PK

INAKOR
OLEOGESAPRIM
PRIMATOL
PRIMATOL A
PRIMAZE
RADAZIN
RADIZINE
STRAZINE
TRIAZINE A 1294
s-TRIAZINE, 2-CHLORO-4-ETHYLAMINO-6-ISOPROPYLAMINO-
1,3,5-TRIAZINE-2,4-DIAMINE, 6-CHLORO-N-ETHYL-N'-(1-METHYLETHYL)-
VECTAL
VECTAL SC
WEEDEX A
WONUK
ZEAZIN
ZEAZINE

Enter keywords or Read or Scan or Mail

--

ed,
 risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Dinoseb

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	06/01/90
Inhalation RfD Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	06/01/90
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	03/01/88

I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- Dinoseb
 CASRN -- 88-85-7
 Last Revised -- 06/01/90

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file when a review of that evaluation is completed.

<<< Dinoseb >>>

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfDo)

I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
-----------------	---------------------	----	----	-----

Decreased fetal weight

NOEL: none

1000

1

1E-3 mg/kg/day

LEL: 1 mg/kg/day

$$\begin{aligned}
 NCW &= (0.001 \frac{mg}{kg \cdot d}) \left(\frac{16 kg}{2 d/d} \right) = \\
 &= 0.008 \frac{mg}{L}
 \end{aligned}$$

$$NC_s = (0.001) \left(\frac{16}{0.0002} \right) = 80 \frac{mg}{L}$$

3-Generation Rat Reproduction Study

Dow Chemical Co., 1981a

*Conversion Factors: none

<<< Dinoseb >>>

I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RFD)

Dow Chemical Company. 1981a. MRID No. 00152675. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Groups of 25 male and 25 female rats (2 littering groups/generation) received dinoseb in their diet at concentrations of 0, 1, 3, and 10 mg/kg bw/day for 29 weeks.

There was a consistent, compound-related depression in body weight gain at the high-dose in both adult males and females in the pre-mating period in all three generations, which continued in the treated males and females during mating, post-mating, etc. at the high-dose concentration. Although the mean weight gains fluctuate considerably, the males continue to exhibit a lower weight at the high dose than the controls during the period from mating to the completion of the study. There continued to be a consistent but slight decrease in female weights during the gestation period in the a and b matings in all three generations at the high dose.

Examination of the mean fetal indices indicated that fetal weights were affected by dinoseb administration, but not consistently, throughout the generations studied. Decreased weight gains appear to occur in three of the littering groups including F1a, F2b, and F3b. F0-->F1ba pup weights were diminished (combined sexes) at day 21 at all dose levels compared with controls and the percent weight increases were statistically significant lower at all dose levels (p<0.5). This was reflected by the lower pup weight gains observed in the individual sexes at day 21 and indicates an effect of dinoseb on the pups during lactation since the pup weights at birth were similar. Based on the findings for pup weights (decreased), a reproductive LEL of 1 mg/kg/day (LDT) was determined. A reproductive NOEL was not established.

<<< Dinoseb >>>

I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RFD)

UF = 1000. An uncertainty factor of 100 was used to account for the inter- and intraspecies differences. An additional UF of 10 was used to account for the lack of an established NOEL in the critical study and for the lack of chronic toxicity studies.

MF = 1.

I.A.4. ADDITIONAL COMMENTS (ORAL RFD)

A number of toxicologic issues concerning dinoseb have been raised as a result of the review of the data base for the Registration Standard including: acute toxicity, lenticular opacities, teratogenicity, immunotoxicity, contamination with nitrosamines, and testicular effects. Dinoseb is presently under Emergency Suspension and is not in use. The FIFRA Science Advisory Panel has concurred with EPA on a developmental and reproductive risk assessment produced for Special Review.

Data Considered for Establishing the RfD:

- 1) 3-Generation Reproduction - Principal study - see previous description; core grade supplementary
- 2) 2-Generation Reproduction (continuation of 3-generation study) - rat: Reproductive LEL=1 mg/kg/day [low viability index for control pups (F4 to F5), inconsistency between the increased body weight changes in this study and the previous 3-generation study, and consistent decreases in gonadal weights and gonadal weights/body weight ratios (F4a) at all dose levels]; Systemic LEL=1 mg/kg/day (based on treatment-related or dose-related reductions in relative parental body weights with significant decreases at low and high doses in F3 males); core grade supplementary (Dow Chemical Co., 1981b)
- 3) Developmental Toxicity (teratology) - rabbit: Developmental Toxicity NOEL=3 mg/kg/day [based on biological and statistically significant increases in malformations and/or anomalies at the high dose (10 mg/kg/day) with external, internal and skeletal defects observed in 11/16 litters examined; brain/spinal cord defects accounted for majority of developmental toxicity and included dyscrania associated with hydrocephaly, hydrocephaly alone, scoliosis, malformed/fused caudal or sacral vertebrae and encephalocele]; Maternal NOEL=10 mg/kg/day (based on lack of significant observable systemic toxicity); core grade minimum (American Hoechst Corp., 1986a)
- 4) Teratology - rat: Developmental Toxicity NOEL=3 mg/kg/day [based on relative increase in reported incidence of absence of ossification for a number of skeletal sites (phalangeal nuclei, cervical vertebrae, etc.) and supernumerary ribs (left or right sides of rib 14) at the high dose]; Maternal Systemic NOEL=3 mg/kg/day (based on moderate mean body weight depression); core grade supplementary (American Hoechst Corp., 1986b)

Other Data Reviewed:

- 1) 2-Year Feeding - mouse: NOEL=none; LEL=1 mg/kg/day (LDT; cystic endometrial hyperplasia and testicular atrophy/degeneration with hypospermatogenesis at all doses; lenticular opacities at 3 and 10 mg/kg/day (low-dose animals not examined)); core grade supplementary (ChE studies not performed) (Dow Chemical Co., 1981c)

Data Gap(s): Chronic Rat Feeding/Carcinogenicity Study; Chronic Dog Feeding Study; Rat Developmental Toxicity Study; Rabbit Developmental Toxicity Study

<<< Dinoseb >>>

I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Low
Data Base: Low
RfD: Low

The principal study appears to be of adequate quality, in many respects, although only rated as core supplementary data; confidence in the study is considered low. Additional studies are supportive, but many data gaps remain; therefore, the data base is given low confidence. Low confidence in the RfD follows.

I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Draft Registration Standard, June 1986

Agency RfD Work Group Review: 07/08/85, 07/22/85, 12/09/86

Verification Date: 12/09/86

___I.A.7. EPA CONTACTS (ORAL RfD)

Reto Engler / OPP -- (703)557-7491 / FTS 557-7491

George Ghali / OPP -- (703)557-7490 / FTS 557-7490

-----<<< Dinoseb >>>-----

___I.B. REFERENCE DOSE FOR CHRONIC INHALATION EXPOSURE (RfDi)

Not available at this time

=====
___II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Dinoseb

CASRN -- 88-85-7

Last Revised -- 06/01/90

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Dinoseb >>>

___II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogenicity

Basis -- Dinoseb was not observed to be carcinogenic in two inadequate studies in rats and in mice. In a third study, an increase in benign liver tumors in female mice was not considered to be treatment-related. The increase was much lower in the high-dose group than in the mid-dose group. There were no decreases in time to tumor, nor any evidence of lesions in the liver, such as hypertrophy, hyperplasia, or degeneration, which are often associated with known hepatocellular carcinogens.

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

II.A.3. ANIMAL CARCINOGENICITY DATA

Inadequate. In an unpublished report from Dow Chemical Company (1981) male and female CD-1 mice (70/sex/group) were fed diets containing dinoseb at 0, 1, 3, and 10 mg/kg/day for 100 weeks. Survival was not affected by exposure to the chemical. However, body weight gain was significantly reduced in the mid- and high-dose females indicating that an MTD was reached. At the end of the study, the body weight gain of the mid- and the high-dose females was 10 and 13% less than the controls, respectively, and no differences were found in the food consumption in the treated group as compared to the controls. Reproductive organs in males and females were also affected: cystic endometrial hyperplasia and atrophy were observed in females, and hypospermatogenesis and degeneration were seen in the testes of all the treated males. These effects indicated that an MTD had been reached.

Dinoseb induced statistically significant increases in liver adenomas in female mice at the 3 and 10 mg/kg/day doses. The incidence was 0/57, 4/59, 7/60, and 5/58 for 0, 1, 3, and 10 mg/kg/day doses, respectively. Only one carcinoma was observed (in a low-dose female). There were no decreases in latency, no dose-response and none of the hepatocytic changes commonly associated with carcinogens. The tumors were late-appearing (the first tumor appeared after 78 weeks, and the remaining ones after 100 weeks).

Adjusting for animals at risk, OPP estimated that the resulting incidences were 0/38, 4/39, 7/41, and 5/39 for the 0, 1, 3, and 10 mg/kg/day dose groups, respectively. The reanalysis failed to show a significant positive trend. Incorporating the historical control incidence of 0-10% did not change the conclusion of the report. There were no decreases in time-to-tumor, nor was there any evidence of lesions in the liver, such as hypertrophy, hyperplasia or degeneration, which are often associated with known hepatocellular carcinogens. It is thus concluded that the increase in liver adenomas may not be attributable to dinoseb.

In a separate screening study, mice failed to demonstrate significant increase in tumors (Innes et al., 1969). Two strains of mice (hybrids of female C57BL/6 and male C3H/Anf or AKR mice, 18/sex/group) were exposed to dinoseb for 18 months. The animals were first exposed via gavage at 2.15 mg/kg/day for 3 weeks beginning at 1 week of age, then they were fed a diet containing 7 ppm dinoseb (1.05 mg/kg/day) throughout the observation period of approximately 18 months. Equal numbers of mice served as controls. After 18 months of treatment, no significant increase in tumors in the mice were observed. This study is considered inadequate because of the small number of animals, the use of only one dose level, and the short observation period (18 months).

In an unpublished study from Dow Chemical Company (1977), male and female Charles River rats were fed diets containing dinoseb at levels of 0, 1, 3, and 10 mg/kg/day for 104 weeks. Dinoseb did not give positive results for carcinogenicity. However, this study was inadequate because of the limited histopathological assessment of both animals and tissues examined and a lack of individual data for several measured parameters.

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Dinoseb was not mutagenic for *Salmonella typhimurium* in three studies with or without addition of rat liver homogenate (Simmon et al., 1977; Moriya et al., 1983; Waters et al., 1982). Mixed results were obtained in DNA damage tests. Dinoseb tested positive in procaryotes without hepatic homogenates (Waters et al., 1982; Simmon et al., 1977; U.S. EPA, 1981), negative in eucaryotes (Simmon et al., 1977; Waters et al., 1982), and negative in human fibroblasts (Simmon et al., 1977).



-----<<< Dinoseb >>>-----

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

-----<<< Dinoseb >>>-----

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

-----<<< Dinoseb >>>-----

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

U.S. EPA. 1975. In vitro and in vivo studies of selected pesticides to evaluate their potential as chemical mutagens. In: Substitute Chemical Program -- the First Year of Progress. Toxicological Methods and Genetic Effects Workshop: Vol. II. EPA MRID 0043656.

U.S. EPA. 1986. Toxicology Branch Peer Review Committee memorandum on Dinoseb, June 19.

II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The Toxicology Branch Peer Review Committee reviewed data on dinoseb.

Agency Work Group Review: 01/13/88, 11/09/88, 05/03/89

Verification Date: 05/03/89

II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Julie Du / ODW -- (202)382-7583 / FTS 382-7583

Larry Anderson / ODW -- (202)382-7587 / FTS 382-7587

III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- Dinoseb
CASRN -- 88-85-7

Not available at this time

IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Dinoseb
CASRN -- 88-85-7
Last Revised -- 03/01/88

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

IV.A. CLEAN AIR ACT (CAA)

No data available

-----<<< Dinoseb >>>-----

IV.B. SAFE DRINKING WATER ACT (SDWA)

No data available

-----<<< Dinoseb >>>-----

IV.C. CLEAN WATER ACT (CWA)

No data available

-----<<< Dinoseb >>>-----

IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

IV.D.1. PESTICIDE ACTIVE INGREDIENT, Registration Standard

None

IV.D.2. PESTICIDE ACTIVE INGREDIENT, Special Review

Action -- Emergency Suspension Order/Notice of Intent to Cancel

Considers technological or economic feasibility? -- YES

Summary of regulatory action -- Dinoseb exposure was determined to pose a risk of birth defects, male sterility, and acute toxicity to agricultural workers. On 10/07/87 the Agency modified the Suspension Order and permitted

use of Dinoseb on drypeas, lentils, and chick peas in Idaho and Washington during the 1987 growing season. Dinoseb is currently in the hearing process.

Reference -- 51 FR 36634 (10/14/86)

EPA Contact -- Special Review Branch, OPP / (703)557-7400 / FTS 557-7400

-----<<< Dinoseb >>>-----

IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

-----<<< Dinoseb >>>-----

IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

-----<<< Dinoseb >>>-----

IV.G. SUPERFUND (CERCLA)

IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1000 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ is based on both aquatic toxicity and oral mammalian toxicity. The 96-Hour Median Threshold Limit for aquatic toxicity is between 12 and 100 ppm and the oral LD50 for rats is between 10 and 100 mg/kg.

Reference -- 50 FR 13456 (04/04/85)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

V. SUPPLEMENTARY DATA

Substance Name -- Dinoseb
CASRN -- 88-85-7
Last Revised -- 01/31/87

The information contained in this section (subsections A and B) has been

extracted from the EPA Chemical Profiles Database, which has been compiled from a number of secondary sources and has not undergone formal Agency review. The complete reference listings for the citations in this section are provided in Service Code 5. The user is urged to read Background Document 5 in Service Code 5 for further information on the sources and limitations of the data presented here.

<<< Dinoseb >>>

V.A. ACUTE HEALTH HAZARD INFORMATION

Toxicity -- Extremely toxic: Probable oral lethal dose is 5-50 mg/kg; between 7 drops and 1 teaspoonful for a 70-kg person (150 lb.) (Gosselin et al., 1976, p. II-197).

Medical Conditions Generally Aggravated by Exposure -- Not Found

Signs and Symptoms of Exposure -- Marked fatigue, tremendous thirst, profuse sweating, flushing of face. Nausea, vomiting, abdominal pain, occasional diarrhea. Restlessness, anxiety, excitement, occasionally leading to convulsions. Rise in body temperature, rapid heart beat, difficulty breathing, bluish skin, and sometimes muscle cramps. Loss of consciousness, cessation of breathing, and death (Gosselin et al., 1976). Skin: staining of skin and minor irritation by very small amount. Eyes: mild to moderate irritation expected. Inhalation: dusts may be irritating and may cause serious illness (Weed Science Society of America, 1979).

-----<<< Dinoseb >>>-----

V.B. PHYSICAL-CHEMICAL PROPERTIES

Chemical Formula -- C₁₀H₁₂N₂O₅

Molecular Weight -- 240.2

Boiling Point -- Not Found

Specific Gravity (H₂O=1) -- 1.2647 at 45C (Weed Science Society of America, 1979)

Vapor Pressure (mmHg) -- 1 at 151.1C (Weed Science Society of America, 1979)

Melting Point -- 100-108F, 38-42C (Merck, 1983, p. 479)

Vapor Density (AIR=1) -- 7.73 (Sax, 1984, p. 582)

Evaporation Rate (Butyl acetate=1) -- Not Found

Solubility in Water -- 0.0052 g/100 mL (Weed Science Society of America, 1979)

Flash Point (Method Used) -- 60.1F to 84.9F, 15.6C to 29.4C for 3 commercial products (Weed Science Society of America, 1979)

Flammable Limits --

LEL -- Not Found

UEL -- Not Found

Appearance and Odor -- Orange-brown viscous liquid (Merck, 1983, p. 479); pungent odor (Weed Science Society of America, 1979) or crystals (Sax, 1979); orange solid when pure; technical grade is orange-brown solid (Worthing, 1983)

Conditions and Materials to Avoid -- Appear to be stable in acid solution, but are susceptible to decomposition by ultraviolet radiation in alkaline solution

(Kearney and Kaufman, 1975).

Hazardous Decomposition or Byproducts -- On decomposition, nitro compounds such as this emit toxic fumes (Sax, 1979).

Use -- Plant growth regulator; insecticide and herbicide (Hawley, 1981, p. 374).

=====

_VI. BIBLIOGRAPHY

Substance Name -- Dinoseb
CASRN -- 88-85-7
Last Revised -- 08/01/89

__VI.A. ORAL RfD REFERENCES

Dow Chemical Company. 1981a. MRID No. 00152675. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Dow Chemical Company. 1981b. MRID No. 00152676. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

Dow Chemical Company. 1981c. MRID No. 00152674. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

American Hoechst Corporation. 1986a. MRID No. 00159363, 00163130. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

American Hoechst Corporation. 1986b. MRID No. 00161309, 00165513. Available from EPA. Write to FOI, EPA, Washington D.C. 20460.

-----<<< Dinoseb >>>-----

__VI.B. INHALATION RfD REFERENCES

None

-----<<< Dinoseb >>>-----

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Dow Chemical Company. 1977. MRID No. 00025582. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Dow Chemical Company. 1981. MRID 00152674. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Innes, J.R.M., M.G. Valerio, L. Petruceli, et al. 1969. Bioassay of pesticides and industrial chemicals for tumorigenicity in mice. A preliminary note. J. Natl. Cancer Inst. 42: 1104-1114.

Moriya, M., T. Ohta, T. Watanabe, K. Kato and Y. Shirasn. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat. Res. 116: 185-216.

Simmon, V.F., A.D. Mitchell and T.A. Jorgenson. 1977. Evaluation of selected pesticides as chemical mutagens. In vitro and in vivo studies. U.S. Environmental Protection Agency, Research Triangle Park, NC. EPA 600/1-77-028.

U.S. EPA. 1975. In vitro and in vivo studies of selected pesticides to evaluate their potential as chemical mutagens. In: Substitute Chemical Program -- the First Year of Progress. Toxicological Methods and Genetic Effects Workshop: Vol. II. EPA MRID 0043656.

U.S. EPA. 1986. Toxicology Branch Peer Review Committee memorandum on Dinoseb, June 19.

Waters, M.D., S.S. Sandhu, V.F. Simmon et al. 1982. Study of pesticide genotoxicity. Basic Life Sci. 21: 275-326.

-----<<< Dinoseb >>>-----

VI.D. DRINKING WATER HA REFERENCES

None

=====

SYNONYMS

- 88-85-7
- AATOX
- Aretit
- Basanite
- BNP 20
- BNP 30
- Butaphene
- Caldon
- Chemox General
- Chemox PE
- DBNF
- Dibutox
- Dinitrall
- Dinitrobutylphenol
- 2,4-Dinitro-6-sec-Butylphenol
- 4,6-Dinitro-2-sec-Butylphenol
- 4,6-Dinitro-o-sec-Butylphenol
- 2,4-Dinitro-6-(1-Methylpropyl)Phenol
- 4,6-Dinitro-2-(1-Methyl-n-Propyl)Phenol
- Dinitro-Ortho-Sec-Butyl Phenol
- Dinoseb
- DN 289
- DNBP
- DNOSBP
- DNSBP
- Elgetol
- Elgetol 318
- ENT 1,122
- Gebutox
- Hivertox
- Kiloseb
- Knoxweed
- Ladob
- Laseb

Toxaphene; CASRN 8001-35-2 (01/01/91)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

$$C_w = \left(\frac{10^{-6}}{1.1} \right) \left(\frac{70}{2} \right) = 3.2 \times 10^5 \text{ mg/l}$$

$$NC_w = \text{none}$$

$$C_s = \frac{10^{-6}}{1.1} \cdot \frac{70}{0.0001} = 0.6 \text{ mg/kg}$$

$$NC_s = \text{none}$$

STATUS OF DATA FOR Toxaphene

File On-Line 08/22/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	01/01/91
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	
Supplementary Data (V.)	on-line	04/01/89

I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Toxaphene
 CASRN -- 8001-35-2

Not available at this time.

Substance Name -- Toxaphene
CASRN -- 8001-35-2

Not available at this time.

=====

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Toxaphene
CASRN -- 8001-35-2
Last Revised -- 01/01/91

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Toxaphene >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- B2; probable human carcinogen.

Basis -- The classification is based on increased incidence of hepatocellular tumors in mice and thyroid tumors in rats and is supported by mutagenicity in Salmonella.

<<< Toxaphene >>>

II.A.2. HUMAN CARCINOGENICITY DATA

None.

<<< Toxaphene >>>

II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. Two long-term carcinogenicity bioassays with toxaphene have been performed in rats and mice with both species showing a carcinogenic response. Dietary toxaphene was administered for 18 months at doses of 0, 7, 20 and 50 ppm to 54 B6C3F1 mice/sex/group. Animals were observed 6 months post-treatment. An increased incidence of hepatocellular carcinomas and neoplastic nodules (adenomas) was seen in both sexes and was statistically significant in males administered 50 ppm (Litton Bionetics, 1978).

In a second study (NCI, 1979), dietary toxaphene was administered to 50

Osborne-Mendel rats/sex/group and 50 B6C3F1 mice/sex/group for 80 weeks. Rats received TWA doses of 556 and 1112 ppm for males and 540 and 1080 ppm for females. The animals were observed for 28-30 weeks post-treatment. Controls consisted of 10 matched controls/sex and 45 additional pooled controls/sex. A statistically significant dose-related increased incidence of thyroid tumors (adenomas and carcinomas) was seen in both male and female rats.

Mice received TWA doses of 99 and 198 ppm for both sexes. Controls consisted of 10 matched controls/sex and 40 additional pooled controls/sex. A statistically significantly increased incidence of liver cancer in treated animals was observed and was dose-related (NCI, 1979).

<<< Toxaphene >>>

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Toxaphene is mutagenic to Salmonella (Hill, 1977). It was negative in a modified dominant lethal assay of male ICR/Ha Swiss mice (Epstein, 1972). No significant differences were found between rates of chromosomal aberrations in leukocytes of workers occupationally exposed to toxaphene and of unexposed workers (U.S. EPA, 1978).

-----<<< Toxaphene >>>-----

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

II.B.1. SUMMARY OF RISK ESTIMATES

Oral Slope Factor -- $1.1E+0$ per (mg/kg)/day

Drinking Water Unit Risk -- $3.2E-5$ per (ug/L)

Extrapolation Method -- linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	$3E+0$ ug/L
E-5 (1 in 100,000)	$3E-1$ ug/L
E-6 (1 in 1,000,000)	$3E-2$ ug/L

<<< Toxaphene >>>

II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor Type -- hepatocellular carcinomas and neoplastic nodules

Test Animals -- Mouse/B6C3F1, males

Route -- Diet

Reference -- Litton Bionetics, 1978

Dose Administered		Human Equivalent	Tumor Incidence
ppm	mg/kg/day	mg/kg/day	
0	0.0	0	10/53
7	0.91	0.051	10/54
20	2.6	0.144	12/53
50	6.5	0.361	18/51

<<< Toxaphene >>>

II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

The Litton Bionetics (1978) study was used for derivation of a slope factor because more dose levels were used, and a positive carcinogenic response was found at a lower dose than in the NCI study (1979). Weight of the animals was assumed to be 0.03 kg, and animal lifetime was taken as 735 days, the duration of the experiment.

The unit risk should not be used if the water concentration exceeds $3E+2$ ug/L, since above this concentration the unit risk may not be appropriate.

<<< Toxaphene >>>

II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

An adequate number of animals was observed. A dose-response effect was seen in a study with 3 non-zero dose levels.

-----<<< Toxaphene >>>-----

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

II.C.1. SUMMARY OF RISK ESTIMATES

Inhalation Unit Risk -- $3.2E-4$ per (ug/cu.m)

Extrapolation Method -- linearized multistage procedure, extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	$3E-1$ ug/cu.m
E-5 (1 in 100,000)	$3E-2$ ug/cu.m
E-6 (1 in 1,000,000)	$3E-3$ ug/cu.m

<<< Toxaphene >>>

II.C.2. DOSE-RESPONSE DATA FOR CARCINOGENICITY, INHALATION EXPOSURE

The unit risk was calculated from the oral data presented in II.B.2.

<<< Toxaphene >>>

II.C.3. ADDITIONAL COMMENTS (CARCINOGENICITY, INHALATION EXPOSURE)

The unit risk should not be used if the air concentration exceeds $3.1E+1$ ug/cu.m, since above this concentration the unit risk may not be appropriate.

<<< Toxaphene >>>

II.C.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, INHALATION EXPOSURE)

This inhalation risk estimate was based on oral data.

-----<<< Toxaphene >>>-----

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

U.S. EPA. 1978. Occupational Exposure to Toxaphene. A Final Report by the Epidemiologic Studies Program, Human Effects Monitoring Branch, Benefits and Field Studies Division, OPP, OTS, EPA.

U.S. EPA. 1980. Ambient Water Quality Criteria for Toxaphene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards. Washington, DC. EPA 440/5-80-076. NTIS PB 81-117863.

Epstein, S.S. et al. 1972. Detection of chemical mutagen by the dominant lethal assay in the mouse. Toxicol. Appl. Pharmacol. 23: 288.

Hill, R.N. 1977. Memorandum to Fred Hageman. Off. Spec. Pestic. Rev., U.S. EPA. December 15.

Linton Bionetics. 1978. Carcinogenic evaluation in mice: Toxaphene. Prepared by Litton Bionetics, Inc., Kensington, MD for Hercules, Inc., Wilmington, DE.

NCI. 1979. Bioassay of Toxaphene for Possible Carcinogenicity. Carcinogenesis Testing Program. Division of Cancer Cause and Prevention. NCI, National Institute of Health, Bethesda, Maryland, 20014. U.S. Department of Health, Education and Welfare. DHEW Publication No. (NIH) 79-837.

<<< Toxaphene >>>

II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The values in the 1980 Ambient Water Quality Criteria document have received both Agency and outside review.

Agency Work Group Review: 03/05/87

Verification Date: 03/05/87

II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Charlie Hiremath / ORD -- (202)382-5725 / FTS 382-5725

William E. Pepelko / ORD -- (202)382-5904 / FTS 382-5904

=====
III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Toxaphene
CASRN -- 8001-35-2

Not available at this time.

III.B. OTHER ASSESSMENTS

Substance Name -- Toxaphene
CASRN -- 8001-35-2

Content to be determined.

=====
_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Toxaphene
CASRN -- 8001-35-2

Not available at this time.

=====
_V. SUPPLEMENTARY DATA

Substance Name -- Toxaphene
CASRN -- 8001-35-2
Last Revised -- 04/01/89

The information contained in this section (subsections A and B) has been extracted from the EPA Chemical Profiles Database, which has been compiled from a number of secondary sources and has not undergone formal Agency review. The complete reference listings for the citations in this section are provided in Service Code 5. The user is urged to read Background Document 5 in Service Code 5 for further information on the sources and limitations of the data presented here.

<<< Toxaphene >>>

_V.A. ACUTE HEALTH HAZARD INFORMATION

Toxicity -- Toxaphene is extremely toxic. The probable oral lethal dose (human) is 5-50 mg/kg or between 7 drops and 1 teaspoonful for 70 kg person (Gosselin, 1984).

Medical Conditions Generally Aggravated by Exposure -- Not Found

Signs and Symptoms of Exposure -- Acute toxicity of toxaphene is manifested as generalized convulsions preceded by cyanosis. Also reported is sudden exertional dyspnea (labored breathing), tachycardia (rapid heart rate), weakness and low blood pressure (Gosselin, 1984, p. III-387). Lethal doses of toxaphene cause respiratory failure. Hypersalivation, leg and back muscle spasms, nausea, vomiting, hyperexcitability, tremors, shivering, clonic convulsions, and tetanic muscular contractions of all skeletal muscles have also been reported (Weiss, 1980, p. 874).

-----<<< Toxaphene >>>-----

_V.B. PHYSICAL-CHEMICAL PROPERTIES

Chemical Formula -- C10H10Cl8 approximate (Hawley, 1981, p. 1034)

Molecular Weight -- Unknown

Boiling Point -- Not Found

Specific Gravity (H2O=1) -- 1.65 (Worthing, 1976)

Vapor Pressure (mmHg) -- 0.4 at 25C (Sunshine, 1969)

Melting Point -- 149-194F, 65-90C (Merck, 1983)

Vapor Density (AIR=1) -- Not Found

Evaporation Rate (Butyl acetate=1) -- Not Found

Solubility in Water -- 3 mg/l at room temperature (Worthing, 1979)

Appearance and Odor -- Yellow, waxy solid with a pleasant piney odor (Merck, 1983)

Flash Point (Method Used) -- 84F, 29C (CC) (Weiss, 1980, p. 874)

Flammable Limits:

LEL -- 1.1% (Weiss, 1980, p. 874)

UEL -- 6.4% (Weiss, 1980, p. 874)

Conditions and Materials to Avoid -- Toxaphene dehydrochlorinates in the presence of alkali, on prolonged exposure to sunlight, and at temperatures above 155C (Merck, 1983). Avoid strong oxidizers (NIOSH/OSHA, 1984, p. 62); toxaphene is corrosive to iron (Merck, 1983, p. 9384).

Hazardous Decomposition or Byproducts -- Toxaphene releases hydrochloric acid in the presence of alkali, on prolonged exposure to sunlight, and at temperatures above 155C (Merck, 1983).

Use -- Toxaphene is an insecticide, primarily for cotton and early growth stages of vegetables (Hawley, 1981, p. 1034). Toxaphene is also used on peas, soybeans, peanut, corn, and wheat. Toxaphene has not been produced commercially in the U.S. since 1982 (SRI). The chemical is only registered for scabies control on cattle in the U.S. (USEPA/Pesticide Index, 1985).

=====

VI. BIBLIOGRAPHY

Substance Name -- Toxaphene
CASRN -- 8001-35-2
Last Revised -- 06/01/90

VI.A. ORAL RfD REFERENCES

None

-----<<< Toxaphene >>>-----

VI.B. INHALATION RfD REFERENCES

None

VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Epstein, S.S. E. Arnold, J. Andrea, W. Bass and Y. Bishop. 1972. Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicol. Appl. Pharmacol. 23(2): 288-325.

Hill, R.N. 1977. Memorandum to Fred Hageman. Off. Spec. Pestic. Rev., U.S. EPA. December 15.

Litton Bionetics. 1978. Carcinogenic evaluation in mice: Toxaphene. Final report. Prepared by Litton Bionetics, Inc., Kensington, MD for Hercules, Inc., Wilmington, DE. LBI Project No. 20602.

NCI (National Cancer Institute). 1979. Bioassay of Toxaphene for Possible Carcinogenicity. Carcinogenesis Testing Program. Division of Cancer Cause and Prevention. NCI, National Institute of Health, Bethesda, Maryland, 20014. U.S. Department of Health, Education and Welfare. DHEW Publication No. (NIH) 79-837.

U.S. EPA. 1978. Occupational Exposure to Toxaphene. A Final Report by the Epidemiologic Studies Program, Human Effects Monitoring Branch, Benefits and Field Studies Division, OPP, OTS, EPA.

U.S. EPA. 1980. Ambient Water Quality Criteria for Toxaphene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards. Washington, DC. EPA 440/5-80-076. NTIS PB 81-117863.

VI.D. DRINKING WATER HA REFERENCES

None

=====

SYNONYMS

Substance Name -- Toxaphene
CASRN -- 8001-35-2
Last Revised -- 08/22/88

- 8001-35-2
- alltox
- chlorinated-camphene
- geniphene
- penphene
- phenacide
- toxadust
- toxakil
- Toxaphene

Arsenic, inorganic; CASRN 7440-38-2 (02/01/91)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Arsenic, inorganic

File On-Line 02/10/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	pending	
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	02/01/91
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	06/01/90
Supplementary Data (V.)	no data	

C_{soil} = 10⁻⁶

I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Arsenic, inorganic
CASRN -- 7440-38-2

A risk assessment for this substance/agent will be reviewed by an EPA work group.

I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RFC)

Substance Name -- Arsenic, inorganic
CASRN -- 7440-38-2

Not available at this time.

=====
II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Arsenic, inorganic
CASRN -- 7440-38-2
Last Revised -- 02/01/91

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Arsenic, inorganic >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- A; human carcinogen

Basis -- based on observation of increased lung cancer mortality in populations exposed primarily through inhalation and on increased skin cancer incidence in several populations consuming drinking water with high arsenic concentrations.

<<< Arsenic, inorganic >>>

II.A.2. HUMAN CARCINOGENICITY DATA

Studies of smelter worker populations (Tacoma, WA; Magma, UT; Anaconda, MT; Ronnskar, Sweden; Saganoseki-Machii, Japan) have all found an association between occupational arsenic exposure and lung cancer mortality (Enterline and Marsh, 1982; Lee-Feldstein, 1983; Axelson et al., 1978; Tokudome and Kuratsune, 1976; Rencher et al., 1977). Both proportionate mortality and cohort studies of pesticide manufacturing workers have shown an excess of lung cancer deaths among exposed persons (Ott et al., 1974; Mabuchi et al., 1979). One study of a population residing near a pesticide manufacturing plant revealed that these residents were also at an excess risk of lung cancer (Matanoski et al., 1981). Case reports of arsenical pesticide applicators have also demonstrated an association between arsenic exposure and lung cancer (Roth, 1958).

A cross-sectional study of 40,000 Taiwanese exposed to arsenic in drinking water found significant excess skin cancer prevalence by comparison to 7500 residents of Taiwan and Matsu who consumed relatively arsenic-free water (Tseng et al., 1968). This study design limited its usefulness in risk estimation. Arsenic-induced skin cancer has also been attributed to water supplies in Chile, Argentina and Mexico (Borgono and Greiber, 1972; Bergoglio, 1964; Cebrian et al., 1983). No excess skin cancer incidence has been observed in U.S. residents consuming relatively high levels of arsenic in drinking water (Morton et al., 1976; Southwick et al., 1981). The results of these U.S. studies, however, are not necessarily inconsistent with the existing findings from the foreign populations. The statistical powers of the U.S. studies are considered to be inadequate because of the small sample size.

A follow-up study (Tseng, 1977) of the population living in the same area of Taiwan, where arsenic contamination of the water supply was endemic, found significantly elevated standard mortality ratios for cancer of the bladder, lung, liver, kidney, skin and colon. This study of bladder, liver and lung cancer cases in the endemic area found a significant association with arsenic exposure that was dose-related. The association of arsenic ingestion and cancer of various internal organs has also been cited in a number of case reports (Chen et al., 1985, 1986). Persons treated with arsenic-containing medicinals have also been shown to be at a risk of skin cancer (Sommer and McManus, 1953).

<<< Arsenic, inorganic >>>

II.A.3. ANIMAL CARCINOGENICITY DATA

None. There has not been consistent demonstration of arsenic carcinogenicity in test animals for various chemical forms administered by different routes to several species (IARC, 1980). There are some data to indicate that arsenic may produce animal tumors if retention time in the lung can be increased (Pershagen et al., 1982, 1984).

<<< Arsenic, inorganic >>>

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Sodium arsenate has been shown to transform Syrian hamster embryo cells (Dipaolo and Casto, 1979) and to produce sister-chromatid-exchange in DON cells, CHO cells and human peripheral lymphocytes exposed in vitro (Wan et al., 1982; Ohno et al., 1982; Larramendy et al., 1981; Andersen, 1983; Crossen, 1983). While arsenic compounds have not been shown to mutate bacterial strains, it produces preferential killing of repair deficient strains (Rossman, 1981).

-----<<< Arsenic, inorganic >>>-----

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

The Risk Assessment Forum has completed a reassessment of the carcinogenicity risk associated with ingestion of inorganic arsenic. This report, which has been extensively peer-reviewed by outside reviewers (including SAB review) concluded that the most appropriate basis for an oral quantitative estimate was the study by Tseng et al. (1977), which reported increased prevalence of skin cancers in humans as a consequence of arsenic exposure in drinking water. Based on this study a unit risk of $5E-5/\mu\text{g/L}$ was proposed.

A recent memorandum by the Administrator of the EPA recommended that the above unit risk be adopted. The memorandum further counsels that "in reaching risk management decisions in a specific situation, risk managers must recognize and consider the qualities and uncertainties of risk estimates. The

uncertainties associated with ingested inorganic arsenic are such that estimates could be modified downwards as much as an order of magnitude, relative to risk estimates associated with most other carcinogens. In such instances, the management document must clearly articulate this fact and state the factors that influenced such a decision."

-----<<< Arsenic, inorganic >>>-----

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

II.C.1. SUMMARY OF RISK ESTIMATES

Inhalation Unit Risk -- $4.3E-3$ /ug/cu.m

Extrapolation Method -- absolute-risk linear model

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	$2E-2$ ug/cu.m
E-5 (1 in 100,000)	$2E-3$ ug/cu.m
E-6 (1 in 1,000,000)	$2E-4$ ug/cu.m

<<< Arsenic, inorganic >>>

II.C.2. DOSE-RESPONSE DATA FOR CARCINOGENICITY, INHALATION EXPOSURE

Tumor Type -- lung cancer

Test Animals -- human, male

Route -- inhalation, occupational exposure

Reference -- Brown and Chu, 1983a,b,c; Lee-Feldstein, 1983; Higgins, 1982;

Enterline and Marsh, 1982

Ambient Unit Risk Estimates

Exposure Source	Study	Unit Risk	Geometric Mean Unit Risk	Final Estimates Unit Risk
Anaconda smelter	Brown and Chu, 1983a,b,c	$1.25 E-3$		
	Lee-Feldstein, 1983	$2.80 E-3$	$2.56 E-3$	
	Higgins, 1982;	$4.90 E-3$		$4.29 E-3$
	Higgins et al., 1982;			
	Welch et al., 1982			
ASARCO smelter	Enterline and Marsh, 1982	$6.81 E-3$ $7.60 E-3$	$7.19 E-3$	

<<< Arsenic, inorganic >>>

II.C.3. ADDITIONAL COMMENTS (CARCINOGENICITY, INHALATION EXPOSURE)

A geometric mean was obtained for data sets obtained within distinct exposed populations (U.S. EPA, 1984). The final estimate is the geometric mean of those two values. It was assumed that the increase in age-specific mortality rate of lung cancer was a function only of cumulative exposures.

The unit risk should not be used if the air concentration exceeds 2 ug/cu.m, since above this concentration the unit risk may not be appropriate.

<<< Arsenic, inorganic >>>

II.C.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, INHALATION EXPOSURE)

Overall a large study population was observed. Exposure assessments included air measurements for the Anaconda smelter and both air measurements and urinary arsenic for the ASARCO smelter. Observed lung cancer incidence was significantly increased over expected values. The range of the estimates derived from data from two different exposure areas was within a factor of 6.

-----<<< Arsenic, inorganic >>>-----

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

U.S. EPA. 1984. Health Assessment Document for Inorganic Arsenic. Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA 600/8-83-021F.

<<< Arsenic, inorganic >>>

II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1984 Health Assessment Document for Inorganic Arsenic received Agency and external review including a review by SAB.

Agency Work Group Review: 01/13/88

Verification Date: 01/13/88

II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Herman J. Gibb / ORD -- (202)382-5898 / FTS 382-5898

Chao W. Chen / ORD -- (202)382-5898 / FTS 382-5898

=====

III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Arsenic, inorganic
CASRN -- 7440-38-2

Not available at this time.

III.B. OTHER ASSESSMENTS

Substance Name -- Arsenic, inorganic
CASRN -- 7440-38-2

Content to be determined.

=====
_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Arsenic, inorganic
CASRN -- 7440-38-2
Last Revised -- 06/01/90

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Arsenic, inorganic >>>

__IV.A. CLEAN AIR ACT (CAA)

No data available

-----<<< Arsenic, inorganic >>>-----

__IV.B. SAFE DRINKING WATER ACT (SDWA)

__IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value (status) -- 0.05 mg/L (Proposed, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 0.05 mg/L for arsenic is proposed based on the current MCL of 0.05 mg/L. Even though arsenic is potentially carcinogenic in humans by inhalation and ingestion, its potential essential nutrient value was considered in determination of an MCLG. The basis for this evaluation is nutritional requirements by NAS (NAS, 1983, Vol. 5, Drinking Water and Health, National Academy of Sciences Press, Washington, DC.)

Reference -- 50 FR 46936 Part IV (11/13/85)

EPA Contact -- Criteria and Standards Division, ODW / (202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

<<< Arsenic, inorganic >>>

__IV.B.2. MAXIMUM CONTAMINANT LEVEL (MCL) for Drinking Water

Value (status) -- 0.05 mg/L (Interim, 1980)

Considers technological or economic feasibility? -- * YES

Discussion -- As an interim measure, the U.S. EPA is using the value

previously derived by the Public Health Service.

Reference -- 45 FR 57332 (08/27/80)

EPA Contact -- Criteria and Standards Division, ODW /
(202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

-----<<< Arsenic, inorganic >>>-----

IV.C. CLEAN WATER ACT (CWA)

IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption -- 2.2E-3 ug/L

Fish Consumption Only -- 1.75E-2 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- For the maximum protection from the potential carcinogenic properties of this chemical, the ambient water concentration should be zero. However, zero may not be attainable at this time, so the recommended criteria represents a E-6 estimated incremental increase of cancer risk over a lifetime.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

<<< Arsenic, inorganic >>>

IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute -- 3.6E+2 ug/L (Arsenic III)
Chronic -- 1.9E+2 ug/L (Arsenic III)

Marine:

Acute -- 6.9E+1 ug/L (Arsenic III)
Chronic -- 3.6E+1 ug/L (Arsenic III)

Considers technological or economic feasibility? -- NO

Discussion -- The criteria given are for Arsenic III. Much less data are available on the effects of Arsenic V to aquatic organisms, but the toxicity seems to be less. A complete discussion may be found in the referenced notice.

Reference -- 50 FR 30784 (07/29/85)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

-----<<< Arsenic, inorganic >>>-----

IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

-----<<< Arsenic, inorganic >>>-----

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

-----<<< Arsenic, inorganic >>>-----

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

__IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

-----<<< Arsenic, inorganic >>>-----

__IV.G. SUPERFUND (CERCLA)

__IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1 pound (Proposed, 1987)

Considers technological or economic feasibility? -- NO

Discussion -- The proposed 1-pound RQ for arsenic is based on its potential carcinogenicity. Available data indicate a hazard ranking of high based on a potency factor of 142.31/mg/kg/day and a weight-of-evidence group A, which corresponds to an RQ of 1 pound. Evidence found in "Water-Related Environmental Fate of 129 Priority Pollutants" (EPA 440/4-79-029a) also indicates that this material, or a constituent of this material, is bioaccumulated to toxic levels in the tissue of aquatic and marine organisms, and has the potential to concentrate in the food chain.

Reference -- 52 FR 8140 (03/16/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

=====

_V. SUPPLEMENTARY DATA

Substance Name -- Arsenic, inorganic
CASRN -- 7440-38-2

Not available at this time.

=====

VI. BIBLIOGRAPHY

Substance Name -- Arsenic, inorganic
CASRN -- 7440-38-2
Last Revised -- 06/01/90

VI.A. ORAL RfD REFERENCES

None

-----<<< Arsenic, inorganic >>>-----

VI.B. INHALATION RfD REFERENCES

None

-----<<< Arsenic, inorganic >>>-----

VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Anderson, O. 1983. Effects of coal combustion products and metal compounds on sister chromatid exchange (SCE) in a macrophage cell line. Environ. Health Perspect. 47: 239-253.

Axelsson, O., E. Dahlgren, C.D. Jansson and S.O. Rehnlund. 1978. Arsenic exposure and mortality: A case referent study from a Swedish copper smelter. Br. J. Ind. Med. 35: 9-15.

Bergoglio, R.M. 1964. Mortality from cancer in regions of arsenical waters of the province of Cordoba Argentine Republic. Prensa Med. Argent. 51: 994-998.

Borgono, J.M. and R. Greiber. 1972. Epidemiological study of arsenicism in the city of Antofagasta. In: Trace Substances in Environmental Health-V. Proceed. 5th Annual Conference, University of Missouri, Columbia, MO, June 29-July 1, 1971. D.C. Hemphill, Ed., University of Missouri, Columbia, MO. p. 13-24.

Brown, C.C. and K.C. Chu. 1983a. Approaches to epidemiologic analysis of prospective and retrospective studies: Example of lung cancer and exposure to arsenic. In: Risk Assessment Proc. SIMS Conf. on Environ. Epidemiol. June 28-July 2, 1982, Alta, VT. SIAM Publication.

Brown, C.C. and K.C. Chu. 1983b. Implications of the multistage theory of carcinogenesis applied to occupational arsenic exposure. J. Natl. Cancer Inst. 70: 455-463.

Brown, C.C. and K.C. Chu. 1983c. A new method for the analysis of cohort studies. Implications of the multistage theory of carcinogenesis applied to occupational arsenic exposure. Environ. Health Perspect. 50: 293-308.

Cebrian, M.E., A. Albores, M. Aguilar and E. Blakeley. 1983. Chronic arsenic poisoning in the north of Mexico. Human Toxicol. 2: 121-133.

Crossen, B.E. 1983. Arsenic and SCE in human lymphocytes. Mutat. Res. 119: 115-119.

DiPaolo, J. and B. Casto. 1979. Quantitative studies of in vitro morphological transformation of Syrian hamster cells by inorganic metal salts. *Cancer Res.* 39: 1008-1013.

Higgins, I. 1982. Arsenic and respiratory cancer among a sample of Anaconda smelter workers. Report submitted to the Occupational Safety and Health Administration in the comments of the Kennecott Minerals Company on the inorganic arsenic rulemaking. (Exhibit 203-5)

Higgins, I., K. Welch and C. Burchfield. 1982. Mortality of Anaconda smelter workers in relation to arsenic and other exposures. University of Michigan, Dept. Epidemiology, Ann Arbor, MI.

IARC (International Agency for Research on Cancer). 1980. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Vol. 23. Some Metals and Metallic Compounds. World Health Organization, Lyon, France.

Larramendy, M.L., N.C. Popescu and J. DiPaolo. 1981. Induction by inorganic metal salts of sister chromatid exchanges and chromosome aberrations in human and Syrian hamster strains. *Environ. Mutagen.* 3: 597-606.

Lee-Feldstein, A. 1983. Arsenic and respiratory cancer in man: Follow-up of an occupational study. In: *Arsenic: Industrial, Biomedical, and Environmental Perspectives*, W. Lederer and R. Fensterheim, Ed. Van Nostrand Reinhold, New York.

Mabuchi, K., A. Lilienfeld and L. Snell. 1979. Lung cancer among pesticide workers exposed to inorganic arsenicals. *Arch. Environ. Health.* 34: 312-319.

Matanoski, G., E. Landau, J. Tonascia, C. Lazar, E. Elliot, W. McEnroe and K. King. 1981. Cancer mortality in an industrial area of Baltimore. *Environ. Res.* 25: 8-28.

Morton, W., G. Starr, D. Pohl, J. Stoner, S. Wagner and P. Weswig. 1976. Skin cancer and water arsenic in Lane County, Oregon. *Cancer.* 37: 2523-2532.

Ohno, H., F. Hanaoka and M. Yamada. 1982. Inductibility of sister chromatid exchanges by heavy-metal ions. *Mutat. Res.* 104: 141-145.

Ott, M.G., B.B. Holder and H.I. Gordon. 1974. Respiratory cancer and occupational exposure to arsenicals. *Arch. Environ. Health.* 29: 250-255.

Pershagen, G., B. Lind and N.E. Bjorkund. 1982. Lung retention and toxicity of some inorganic arsenic compounds. *Environ. Res.* 29: 425-434.

Pershagen, G., G. Nordberg and N.E. Bjorklund. 1984. Carcinomas of the respiratory tract in hamsters given arsenic trioxide and/or benzo(a)pyrene by the pulmonary route. *Environ. Res.* 34: 227-241.

Rencher, A.C., M.W. Carter and D.W. McKee. 1978. A retrospective epidemiological study of mortality at a large western copper smelter. *J. Occup. Med.* 19: 754-758.

Rossmann, T.G. 1981. Enhancement of UV-mutagenesis by low concentrations of arsenite in *E. Coli*. *Mutat. Res.* 91: 207-211.

Roth, F. 1958. Uber den Bronchialkrebs Arsengeschodigter Winzer. *Virchows Arch.* 331: 119-137.

Sommers, S.C. and R.G. McManus. 1953. Multiple arsenical cancers of the skin and internal organs. *Cancer.* 6: 347-359.

Southwick, J., A. Western, M. Beck, T. Whitley, R. Isaacs, J. Petajan and C. Hansen. 1981. Community health associated with arsenic in drinking water in Millard County, Utah. Health Effects Research Laboratory, Cincinnati, OH.

Tokudome, S. and M. Kuratsune. 1976. A cohort study on mortality from cancer and other causes among workers at a metal refinery. Int. J. Cancer. 17: 310-317.

Tseng, W.P. 1977. Effects and dose response relationships of skin cancer and blackfoot disease with arsenic. Environ. Health Perspect. 19: 109-119.

U.S. EPA. 1984. Health Assessment Document for Inorganic Arsenic. Prepared by Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA/600/8-83/021F.

Wan, B., R.T. Christian and S.W. Sookup. 1982. Studies of cytogenetic effects of sodium arsenicals on mammalian cells in vitro. Environ. Mutag. 4: 493-498.

Welch, K., I. Higgins, M. Oh and C. Burchfield. 1982. Arsenic exposure, smoking, and respiratory cancer in copper smelter workers. Arch. Environ. Health. 37: 325-335.

-----<<< Arsenic, inorganic >>>-----

VI.D. DRINKING WATER HA REFERENCES

None

=====

SYNONYMS

Substance Name -- Arsenic, inorganic
CASRN -- 7440-38-2
Last Revised -- 02/10/88

7440-38-2
Arsenic
Arsenic, inorganic
gray-arsenic

Enter keywords or Read or Scan or Mail

--

Vertac Chemical Corporation
Status Report

Process History:

Vertac Chemical Corporation currently operates an impoundment as a hazardous waste storage facility. The impoundment receives runoff from the facility as well as spills and leaks from process operations. The facility has manufactured pesticide and herbicide products containing atrazine, toxaphene and DNEP in the past. Presently dinoseb (DNEP) is the primary process contributing to the process wastewater inflow to the impoundment.

Regulatory History:

Vertac Chemical Corporation completed a Part A application in November, 1980, to operate the impoundment under the interim status (Part 265) regulations of the hazardous waste rules. However, Vertac's processes are not listed under the hazardous waste regulations as a process to be regulated. Also, the discharge of wastewater containing discarded commercial chemical products, or chemical intermediates, which are listed, is not regulated if they constitute "de minimis losses". BPC has taken the position that the facility is so sloppily operated that the wastewater entering the impoundment is considered to be a hazardous waste and not "de minimis losses". Therefore, we have continued to regulate the facility.

In August, 1983, Vertac Chemical Corporation submitted a Part B application to receive a final permit to operate the impoundment. The Part B application is not complete. The facility has changed closure plan several times and is still collecting groundwater data to characterize apparent groundwater contamination. One well near the impoundment has detected 1 ppm of DNEP.

Vertac Proposal:

Vertac Chemical Corporation has asked BPC to consider a proposal to revise process sewer drains around the DNEP process, formulating and packaging areas such that DNEP spills and water used to clean up the spills will be contained locally and not drain to the surface impoundment. Vertac would also remove contaminated sludge and soil in the impoundment to a specified level. The impoundment would then be considered closed under RCRA and groundwater monitoring/clean-up would continue under post-closure.

Problems:

The future inflow to the impoundment could be monitored to insure that concentrations are low enough to be considered "de minimis losses". However, the proposed closure of the impoundment would not fit EPA's requirement for closure as a landfill (capping) since some soil contamination will most probably be left and evidence indicates groundwater contamination may exist. The Industrial Wastewater Section believes the impoundment should be left open to treat runoff from the plant and act as an emergency spill control impoundment under NPDES.

BPC Options:

1. Withdraw interim status for the facility and obtain a Commission Order or Consent Decree allowing the facility to close the impoundment as proposed and allowing continued use of the impoundment under NPDES. Also, require groundwater assessment/clean-up.
2. Require Vertac to complete the Part B including a closure plan describing a landfill closure (capping). Then after new process sumps have been constructed, allow the facility to amend the closure plan to clean the impoundment to our satisfaction and continue operating under NPDES. Groundwater monitoring/clean-up would be covered under a RCRA post-closure permit.
3. Require Vertac to complete the Part B application ^{including a} with closure ^{plan describing a} ~~as a~~ landfill ^{closure} (capping). Within four years, require Vertac to either retrofit the impoundment (double liner and double leachate collection system) as per RCRA Reauthorization law or close the impoundment as a landfill. Closing as a landfill would mean the facility would have to construct a new NPDES impoundment which would only accept run-off from the plant.

CE:hdb

7
Cadmium; CASRN 7440-43-9 (01/01/92)

8
Vanadium pentoxide; CASRN 1314-62-1 (01/01/92)

9
Selenious acid; CASRN 7783-00-8 (01/01/92)

10
Beryllium; CASRN 7440-41-7 (01/01/92)

Enter keywords or Read or Scan or Mail

--read 4

Arsenic, inorganic; CASRN 7440-38-2 (01/01/92)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented

in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Arsenic, inorganic

File On-Line 02/10/88

Category (section)	Status	Last Revised
-----	-----	-----
Oral RfD Assessment (I.A.)	on-line	10/01/91
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	02/01/91
Drinking Water Health Advisories (III.A.)	no data	

U.S. EPA Regulatory Actions (IV.)

on-line

01/01/92

Supplementary Data (V.)

no data

I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Arsenic, inorganic

CASRN -- 7440-38-2

Last Revised -- 10/01/91

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this

file when a review of that evaluation is completed.

<<< Arsenic, inorganic >>>

NOTE: There was not a clear consensus among Agency scientists on the oral RfD. Applying the Agency's RfD methodology, strong scientific arguments can be made for various values within a factor of 2 or 3 of the currently recommended RfD value, i.e., 0.1 to 0.8 ug/kg/day. It should be noted, however, that the RfD methodology, by definition, yields a number with inherent uncertainty spanning perhaps an order of magnitude. New data that possibly impact on the recommended RfD for arsenic will be evaluated by the Work Group as it becomes available. Risk managers should recognize the considerable flexibility afforded them in formulating regulatory decisions when uncertainty and lack of clear consensus are taken into account.

 I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
-----	-----	-----	-----	-----
Hyperpigmentation, keratosis and possible vascular complications	NOAEL: 0.009 mg/L converted to 0.0008 mg/kg/day	3	1	
Human chronic oral exposure	LOAEL: 0.17 mg/L converted to 0.014 mg/kg/day			

Tseng, 1977;

Tseng et al., 1968

*Conversion Factors: NOAEL was based on an arithmetic mean of 0.009 mg/L in a range of arsenic concentration of 0.001 to 0.017 mg/L. This NOAEL also included estimation of arsenic from food. Since experimental data were missing, arsenic concentrations in sweet potatoes and rice were estimated as 0.002 mg/day. Other assumptions included consumption of 4.5 L water/day and 55 kg bw (Abernathy et al., 1989). $NOAEL = [(0.009 \text{ mg/L} \times 4.5 \text{ L/day}) + 0.002 \text{ mg/day}] / 55 \text{ kg} = 0.0008 \text{ mg/kg/day}$. The LOAEL dose was estimated using the same assumptions as the NOAEL starting with an arithmetic mean water concentration from Tseng (1977) of 0.17 mg/L. $LOAEL = [(0.17 \text{ mg/L} \times 4.5 \text{ L/day}) + 0.002 \text{ mg/day}] / 55 \text{ kg} = 0.014 \text{ mg/kg/day}$.

<<< Arsenic, inorganic >>>

I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Tseng, W.P. 1977. Effects and dose-response relationships of skin cancer and blackfoot disease with arsenic. Environ. Health Perspect. 19: 109-119.

Tseng, W.P., H.M. Chu, S.W. How, J.M. Fong, C.S. Lin and S. Yeh. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J. Natl. Cancer Inst. 40: 453-463.

The data reported in Tseng (1977) show an increased incidence of blackfoot disease that increases with age and dose. Blackfoot disease is a significant adverse effect. The prevalences (males and females combined) at the low dose are 4.6 per 1000 for the 20-39 year group, 10.5 per 1000 for the 40-59 year group, and 20.3 per 1000 for the >60 year group. Moreover, the prevalence of blackfoot disease in each age group increases with increasing dose. However, a recent report indicates that it may not be strictly due to arsenic exposure

(Lu, 1990). The data in Tseng et al. (1968) also show increased incidences of hyperpigmentation and keratosis with age. The overall prevalences of hyperpigmentation and keratosis in the exposed groups are 184 and 71 per 1000, respectively. The text states that the incidence increases with dose, but data for the individual doses are not shown. These data show that the skin lesions are the more sensitive endpoint. The low dose in the Tseng (1977) study is considered a LOAEL.

The control group described in Tseng et al. (1968; Table 3) shows no evidence of skin lesions and presumably blackfoot disease, although this latter point is not explicitly stated. This group is considered a NOAEL.

The arithmetic mean of the arsenic concentration in the wells used by the individuals in the NOAEL group is 9 ug/L (range: 1-17 ug/L) (Abernathy et al., 1989). The arithmetic mean of the arsenic concentration in the wells used by the individuals in the LOAEL group is 170 ug/L (Tseng, 1977; Figure 4). Using estimates provided by Abernathy et al. (1989), the NOAEL and LOAEL doses for both food and water are as follows: LOAEL - $[170 \text{ ug/L} \times 4.5 \text{ L/day} + 2 \text{ ug/day (contribution of food)}] \times (1/55 \text{ kg}) = 14 \text{ ug/kg/day}$; NOAEL - $[9 \text{ ug/L} \times 4.5 \text{ L/day} + 2 \text{ ug/day (contribution of food)}] \times (1/55 \text{ kg}) = 0.8 \text{ ug/kg/day}$.

Although the control group contained 2552 individuals, only 957 (approximately 38%) were older than 20, and only 431 (approximately 17%) were older than 40. The incidence of skin lesions increases sharply in individuals above 20; the incidence of blackfoot disease increases sharply in individuals above 40 (Tseng, 1968; Figures 5, 6 and 7). This study is less powerful than it appears at first glance. However, it is certainly the most powerful study available on arsenic exposure to people.

This study shows an increase in skin lesions, 22% (64/296) at the high

dose vs. 2.2% (7/318) at the low dose. The average arsenic concentration in the wells at the high dose is 410 ug/L and at the low dose is 5 ug/L (Cebrian et al., 1983; Figure 2 and Table 1) or 7 ug/L (cited in the abstract). The average water consumption is 3.5 L/day for males and 2.5 L/day for females. There were about an equal number of males and females in the study. For the dose estimates given below we therefore assume an average of 3 L/day. No data are given on the arsenic exposure from food or the body weight of the participants (we therefore assume 55 kg). The paper states that exposure times are directly related to chronological age in 75% of the cases. Approximately 35% of the participants in the study are more than 20 years old (Figure 1).

Exposure estimates (water only) are: high dose - $410 \text{ ug/L} \times 3 \text{ L/day} \times (1/55 \text{ kg}) = 22 \text{ ug/kg/day}$; low dose - $5\text{-}7 \text{ ug/L} \times 3 \text{ L/day} \times (1/55 \text{ kg}) = 0.3\text{-}0.4 \text{ ug/kg/day}$.

The high-dose group shows a clear increase in skin lesions and is therefore designated a LOAEL. There is some question whether the low dose is a NOAEL or a LOAEL since there is no way of knowing what the incidence of skin lesions would be in a group where the exposure to arsenic is zero. The 2.2% incidence of skin lesions in the low-dose group is higher than that reported in the Tseng et al. (1968) control group, but the dose is lower (0.4 vs. 0.8 ug/kg/day).

The Southwick et al. (1983) study shows a marginally increased incidence of a variety of skin lesions (palmar and plantar keratosis, diffuse palmar or plantar hyperkeratosis, diffuse pigmentation, and arterial insufficiency) in the individuals exposed to arsenic. The incidences are 2.9% (3/105) in the control group and 6.3% (9/144) in the exposed group. There is a slight, but not statistically significant increase in the percent of exposed individuals

that have abnormal nerve conduction (8/67 vs. 13/83, or 12% vs. 16% (Southwick et al., 1983; Table 8). The investigators excluded all individuals older than 47 from the nerve conduction portion of the study. These are the individuals most likely to have the longest exposure to arsenic.

Although neither the increased incidence of skin lesions nor the increase in abnormal nerve conduction is statistically significant, these effects may be biologically significant because the same abnormalities occur at higher doses in other studies. The number of subjects in this study was insufficient to establish statistical significance.

Table 3 (Southwick et al., 1983) shows the annual arsenic exposure from drinking water. No data are given on arsenic exposure from food or the body weight (assume 70 kg). Exposure times are not clearly defined, but are >5 years, and dose groups are ranges of exposure.

Exposure estimates (water only) are: dosed group - $152.4 \text{ mg/year} \times 1 \text{ year}/365 \text{ days} \times (1/70) \text{ kg} = 6 \text{ ug/kg/day}$; control group - $24.2 \text{ mg/year} \times 1 \text{ year}/365 \text{ days} \times (1/70) \text{ kg} = 0.9 \text{ ug/kg/day}$.

Again because there are no data for a group not exposed to arsenic, there is some question if the control group is a NOAEL or a LOAEL. The incidence of skin lesions in this group is about the same as in the low-dose group from the Cebrian et al. (1983) study; the incidence of abnormal nerve conduction in the control group is higher than that from the low-dose group in the Hindmarsh et al. (1977) study described below. The control dose is comparable to the dose to the control group in the Tseng et al. (1968) and Hindmarsh et al. (1977) studies. The dosed group may or may not be a LOAEL, since it does not report statistically significant effects when compared to the control.

This study shows an increased incidence of abnormal clinical findings and abnormal electromyographic findings with increasing dose of arsenic (Hindmarsh et al., 1977; Tables III and VI). However, the sample size is extremely small. Percentages of abnormal clinical signs possibly attributed to As were 10, 16, and 40% at the low, mid and high doses, respectively. Abnormal EMG were 0, 17 and 53% in the same three groups.

The exact doses are not given in the Hindmarsh et al. (1977) paper; however, some well data are reported in Table V. The arithmetic mean of the arsenic concentration in the high-dose and mid-dose wells is 680 and 70 ug/L, respectively. Figure 1 (Hindmarsh et al., 1977) shows that the average arsenic concentration of the low-dose wells is about 25 ug/L. No data are given on arsenic exposure from food. We assume daily water consumption of 2 liters and body weight of 70 kg. Exposure times are not clearly stated.

Exposure estimates (water only) are: low - $25 \text{ ug/L} \times 2 \text{ L/day} \times (1/70) \text{ kg} = 0.7 \text{ ug/kg/day}$; mid - $70 \text{ ug/L} \times 2 \text{ L/day} \times (1/70) \text{ kg} = 2 \text{ ug/kg/day}$; high - $680 \text{ ug/L} \times 2 \text{ L/day} \times (1/70) \text{ kg} = 19 \text{ ug/kg/day}$.

The low dose is a no-effect level for abnormal EMG findings. However, because there is no information on the background incidence of abnormal clinical findings in a population with zero exposure to arsenic, there is no way of knowing if the low dose is a no-effect level or another marginal effect level for abnormal clinical findings. The low dose is comparable to the dose received by the control group in the Tseng (1977) and Southwick et al. (1983) studies.

The responses at the mid dose do not show a statistically significant increase but are part of a statistically significant trend and are biologically significant. This dose is an equivocal NOAEL/LOAEL. The high

dose is a clear LOAEL for both responses.

As discussed previously there is no way of knowing whether the low doses in the Cebrian et al. (1983), Southwick et al. (1983) and Hindmarsh et al. (1977) studies are NOAELs for skin lesions and/or abnormal nerve conduction. However, because the next higher dose in the Southwick and Hindmarsh studies only shows marginal effects at doses 3-7 times higher, the Agency feels comfortable in assigning the low doses in these studies as NOAELs.

The Tseng (1977) and Tseng et al. (1968) studies are therefore considered superior for the purposes of developing an RfD and show a NOAEL for a sensitive endpoint. Even discounting the people <20 years of age, the control group consisted of 957 people that had a lengthy exposure to arsenic with no evidence of skin lesions.

The following is a summary of the defined doses in mg/kg/day from the principal and supporting studies:

- 1) Tseng (1977): NOAEL = $8E-4$; LOAEL = $1.4E-2$
- 2) Cebrian et al. (1983): NOAEL = $4E-4$; LOAEL = $2.2E-2$
- 3) Southwick et al. (1983): NOAEL = $9E-4$; LOAEL = none (equivocal effects at $6E-3$)
- 4) Hindmarsh et al., 1977: NOAEL = $7E-4$; LOAEL = $1.9E-2$ (equivocal effects at $2E-3$)

<<< Arsenic, inorganic >>>

 I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 3. The UF of 3 is to account for both the lack of data to preclude

reproductive toxicity as a critical effect and to account for some uncertainty in whether the NOAEL of the critical study accounts for all sensitive individuals.

MF = 1.

<<< Arsenic, inorganic >>>

 I.A.4. ADDITIONAL STUDIES / COMMENTS (ORAL RfD)

Ferm and Carpenter (1968) produced malformations in 15-day hamster fetuses via intravenous injections of sodium arsenate into pregnant dams on day 8 of gestation at dose levels of 15, 17.5, or 20 mg/kg bw. Exencephaly, encephaloceles, skeletal defects and genitourinary systems defects were produced. These and other terata were produced in mice and rats all at levels around 20 mg/kg bw. Minimal effects or no effects on fetal development have been observed in studies on chronic oral exposure of pregnant rats or mice to relatively low levels of arsenic via drinking water (Schroeder and Mitchner, 1971). Nadeenko et al. (1978) reported that intubation of rats with arsenic solution at a dose level of 25 ug/kg/day for a period of 7 months, including pregnancy, produced no significant embryotoxic effects and only infrequent slight expansion of ventricles of the cerebrum, renal pelves and urinary bladder. Hood et al. (1977) reported that very high single oral doses of arsenate solutions (120 mg/kg) to pregnant mice were necessary to cause prenatal fetal toxicity, while multiple doses of 60 mg/kg on 3 days had little effect.

Extensive human pharmacokinetic, metabolic, enzymic and long-term information is known about arsenic and its metabolism. Valentine et al. (1987) established that human blood arsenic levels did not increase until

daily water ingestion of arsenic exceeded approximately 250 ug/day (approximately 120 ug of arsenic/L. Methylated species of arsenic are successively 1 order of magnitude less toxic and less teratogenic. Some evidence suggests that inorganic arsenic is an essential nutrient in goats, chicks, mini pigs and rats. No comparable data are available for humans.

<<< Arsenic, inorganic >>>

___ I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Medium

Data Base: Medium

RfD: Medium

Confidence in the chosen study is considered medium. An extremely large number of people were included in the assessment (>40,000) but the doses were not well-characterized and other contaminants were present. The supporting human toxicity data base is extensive but somewhat flawed. Problems exist with all of the epidemiological studies. For example, the Tseng studies do not look at potential exposure from food or other source. A similar criticism can be made of the Cebrian et al. (1983) study. The U.S. studies are too small in number to resolve several issues. However, the data base does support the choice of NOAEL. It garners medium confidence. Medium confidence in the RfD follows.

<<< Arsenic, inorganic >>>

___ I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- The only U.S. EPA documentation for this RfD is on IRIS.

Other EPA Documentation -- U.S. EPA, 1984, 1988

Source Document Review -- This analysis has been reviewed by EPA's Risk Assessment Council on 11/15/90.

This assessment was discussed by the Risk Assessment Council of EPA on 11/15/90 and verified through a series of meetings during the 1st, 2nd and 3rd quarters of FY91.

Agency Work Group Review: 03/24/88, 05/25/88, 03/21/89, 09/19/89, 08/22/90, 09/20/90

Verification Date: 11/15/90

I.A.7. EPA CONTACTS (ORAL RfD)

Charles Abernathy / OW -- (202)260-5374 / FTS 260-5374

Michael Dourson / ORD -- (513)569-7533 / FTS 684-7533

I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Arsenic, inorganic

Not available at this time.

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Arsenic, inorganic

CASRN -- 7440-38-2

Last Revised -- 02/01/91

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for

information on long-term toxic effects other than carcinogenicity.

<<< Arsenic, inorganic >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- A; human carcinogen

Basis -- based on observation of increased lung cancer mortality in populations exposed primarily through inhalation and on increased skin cancer incidence in several populations consuming drinking water with high arsenic concentrations.

<<< Arsenic, inorganic >>>

II.A.2. HUMAN CARCINOGENICITY DATA

Studies of smelter worker populations (Tacoma, WA; Magma, UT; Anaconda, MT; Ronnskar, Sweden; Saganoseki-Machii, Japan) have all found an association between occupational arsenic exposure and lung cancer mortality (Enterline and Marsh, 1982; Lee-Feldstein, 1983; Axelson et al., 1978; Tokudome and Kuratsune, 1976; Rencher et al., 1977). Both proportionate mortality and cohort studies of pesticide manufacturing workers have shown an excess of lung cancer deaths among exposed persons (Ott et al., 1974; Mabuchi et al., 1979). One study of a population residing near a pesticide manufacturing plant revealed that these residents were also at an excess risk of lung cancer (Matanoski et al., 1981). Case reports of arsenical

pesticide applicators have also demonstrated an association between arsenic exposure and lung cancer (Roth, 1958).

A cross-sectional study of 40,000 Taiwanese exposed to arsenic in drinking water found significant excess skin cancer prevalence by comparison to 7500 residents of Taiwan and Matsu who consumed relatively arsenic-free water (Tseng et al., 1968). This study design limited its usefulness in risk estimation. Arsenic-induced skin cancer has also been attributed to water supplies in Chile, Argentina and Mexico (Borgono and Greiber, 1972; Bergoglio, 1964; Cebrian et al., 1983). No excess skin cancer incidence has been observed in U.S. residents consuming relatively high levels of arsenic in drinking water (Morton et al., 1976; Southwick et al., 1981). The results of these U.S. studies, however, are not necessarily inconsistent with the existing findings from the foreign populations. The statistical powers of the U.S. studies are considered to be inadequate because of the small sample size.

A follow-up study (Tseng, 1977) of the population living in the same area of Taiwan, where arsenic contamination of the water supply was endemic, found significantly elevated standard mortality ratios for cancer of the bladder, lung, liver, kidney, skin and colon. This study of bladder, liver and lung cancer cases in the endemic area found a significant association with arsenic exposure that was dose-related. The association of arsenic ingestion and cancer of various internal organs has also been cited in a number of case reports (Chen et al., 1985, 1986). Persons treated with arsenic-containing medicinals have also been shown to be at a risk of skin cancer (Sommers and McManus, 1953).

<<< Arsenic, inorganic >>>

None. There has not been consistent demonstration of arsenic carcinogenicity in test animals for various chemical forms administered by different routes to several species (IARC, 1980). There are some data to indicate that arsenic may produce animal tumors if retention time in the lung can be increased (Pershagen et al., 1982, 1984).

<<< Arsenic, inorganic >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Sodium arsenate has been shown to transform Syrian hamster embryo cells (Dipaolo and Casto, 1979) and to produce sister-chromatid-exchange in DON cells, CHO cells and human peripheral lymphocytes exposed in vitro (Wan et al., 1982; Ohno et al., 1982; Larramendy et al., 1981; Andersen, 1983; Crossen, 1983). While arsenic compounds have not been shown to mutate bacterial strains, it produces preferential killing of repair deficient strains (Rossman, 1981).

-----<<< Arsenic, inorganic >>>-----

___II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

The Risk Assessment Forum has completed a reassessment of the carcinogenicity risk associated with ingestion of inorganic arsenic. This report, which has been extensively peer-reviewed by outside reviewers (including SAB review) concluded that the most appropriate basis for an oral quantitative estimate was the study by Tseng et al. (1977), which reported

increased prevalence of skin cancers in humans as a consequence of arsenic exposure in drinking water. Based on this study a unit risk of $5E-5/ug/L$ was proposed.

A recent memorandum by the Administrator of the EPA recommended that the above unit risk be adopted. The memorandum further counsels that "in reaching risk management decisions in a specific situation, risk managers must recognize and consider the qualities and uncertainties of risk estimates. The uncertainties associated with ingested inorganic arsenic are such that estimates could be modified downwards as much as an order of magnitude, relative to risk estimates associated with most other carcinogens. In such instances, the management document must clearly articulate this fact and state the factors that influenced such a decision."

-----<<< Arsenic, inorganic >>>-----

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

II.C.1. SUMMARY OF RISK ESTIMATES

Inhalation Unit Risk -- $4.3E-3/ug/cu.m$

Extrapolation Method -- absolute-risk linear model

Air Concentrations at Specified Risk Levels:

Risk Level

Concentration

-----	-----
E-4 (1 in 10,000)	2E-2 ug/cu.m
E-5 (1 in 100,000)	2E-3 ug/cu.m
E-6 (1 in 1,000,000)	2E-4 ug/cu.m

<<< Arsenic, inorganic >>>

___II.C.2. DOSE-RESPONSE DATA FOR CARCINOGENICITY, INHALATION EXPOSURE

Tumor Type -- lung cancer

Test Animals -- human, male

Route -- inhalation, occupational exposure

Reference -- Brown and Chu, 1983a,b,c; Lee-Feldstein, 1983; Higgins, 1982;

Enterline and Marsh, 1982

Ambient Unit Risk Estimates

Exposure	Unit	Geometric Mean	Final Estimates
Source	Study	Risk	Unit Risk
			Unit Risk
Anaconda	Brown and Chu,	1.25 E-3	
smelter	1983a,b,c		
	Lee-Feldstein, 1983	2.80 E-3	2.56 E-3
	Higgins, 1982;	4.90 E-3	4.29 E-3
	Higgins et al., 1982;		
	Welch et al., 1982		
ASARCO	Enterline and	6.81 E-3	7.19 E-3
smelter	Marsh, 1982	7.60 E-3	

<<< Arsenic, inorganic >>>

___II.C.3. ADDITIONAL COMMENTS (CARCINOGENICITY, INHALATION EXPOSURE)

A geometric mean was obtained for data sets obtained within distinct exposed populations (U.S. EPA, 1984). The final estimate is the geometric mean of those two values. It was assumed that the increase in age-specific mortality rate of lung cancer was a function only of cumulative exposures.

The unit risk should not be used if the air concentration exceeds 2 ug/cu.m, since above this concentration the unit risk may not be appropriate.

<<< Arsenic, inorganic >>>

___II.C.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, INHALATION EXPOSURE)

Overall a large study population was observed. Exposure assessments included air measurements for the Anaconda smelter and both air measurements and urinary arsenic for the ASARCO smelter. Observed lung cancer incidence was significantly increased over expected values. The range of the estimates derived from data from two different exposure areas was within a factor of 6.

-----<<< Arsenic, inorganic >>>-----

___II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1984. Health Assessment Document for Inorganic Arsenic.
Environmental Criteria and Assessment Office, Research Triangle Park, NC.
EPA 600/8-83-021F.

<<< Arsenic, inorganic >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1984 Health Assessment Document for Inorganic Arsenic received
Agency and external review including a review by SAB.

Agency Work Group Review: 01/13/88

Verification Date: 01/13/88

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Herman J. Gibb / ORD -- (202)260-5898 / FTS 260-5898

Chao W. Chen / ORD -- (202)260-5898 / FTS 260-5898

___III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Arsenic, inorganic

CASRN -- 7440-38-2

Not available at this time.

III.B. OTHER ASSESSMENTS

Substance Name -- Arsenic, inorganic

CASRN -- 7440-38-2

Content to be determined.

IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Arsenic, inorganic

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Arsenic, inorganic >>>

IV.A. CLEAN AIR ACT (CAA)

No data available

-----<<< Arsenic, inorganic >>>-----

IV.B. SAFE DRINKING WATER ACT (SDWA)

___IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value (status) -- 0.05 mg/L (Proposed, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 0.05 mg/L for arsenic is proposed based on the current MCL of 0.05 mg/L. Even though arsenic is potentially carcinogenic in humans by inhalation and ingestion, its potential essential nutrient value was considered in determination of an MCLG. The basis for this evaluation is nutritional requirements by NAS (NAS, 1983, Vol. 5, Drinking Water and Health, National Academy of Sciences Press, Washington, DC.)

Reference -- 50 FR 46936 (11/13/85)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

<<< Arsenic, inorganic >>>

___IV.B.2. MAXIMUM CONTAMINANT LEVEL (MCL) for Drinking Water

Value (status) -- 0.05 mg/L (Interim, 1980)

Considers technological or economic feasibility? -- YES

Discussion -- As an interim measure the U.S. EPA is using the value previously derived by the Public Health Service.

Monitoring requirements -- Ground water systems every three years; surface

water systems annually.

Analytical methodology -- Atomic absorption/furnace technique (EPA 206.2; SM 304); atomic absorption/gaseous hydride (EPA 206.3; SM 303E; ASTM D-2972-78B)

Best available technology -- No data available.

Reference -- 45 FR 57332 (08/27/80); 50 FR 46936 (11/13/85)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

<<< Arsenic, inorganic >>>

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

<<< Arsenic, inorganic >>>

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

-----<<< Arsenic, inorganic >>>-----

___IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption -- 2.2E-3 ug/L

Fish Consumption Only -- 1.75E-2 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- For the maximum protection from the potential carcinogenic properties of this chemical, the ambient water concentration should be zero. However, zero may not be attainable at this time, so the recommended criteria represents a E-6 estimated incremental increase of cancer risk over a lifetime.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

<<< Arsenic, inorganic >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute -- 3.6E+2 ug/L (Arsenic III)

Chronic -- 1.9E+2 ug/L (Arsenic III)

Marine:

Acute -- 6.9E+1 ug/L (Arsenic III)

Chronic -- 3.6E+1 ug/L (Arsenic III)

Considers technological or economic feasibility? -- NO

Discussion -- The criteria given are for Arsenic III. Much less data are available on the effects of Arsenic V to aquatic organisms, but the toxicity seems to be less. A complete discussion may be found in the referenced notice.

Reference -- 50 FR 30784 (07/29/85)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

-----<<< Arsenic, inorganic >>>-----

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

___IV.D.1. PESTICIDE ACTIVE INGREDIENT, Registration Standard

Status -- Issued (1988)

Reference -- Arsenic, Chromium and Chromated Arsenical Compounds Pesticide
Registration Standard. June, 1988. [NTIS# PB89-102842]

EPA Contact -- Registration Branch / OPP

(703)557-7760 / FTS 557-7760

<<< Arsenic, inorganic >>>

___IV.D.2.a. PESTICIDE ACTIVE INGREDIENT, Special Review

Action -- Final regulatory decision - PD4 (1988) [non-wood use]

Considers technological or economic feasibility? -- NO

Summary of regulatory action -- Cancellation of specified uses. Registrant of lead arsenate voluntarily canceled 09/87. Registrant of calcium arsenate voluntarily canceled 02/14/89. Use of sodium arsenate as ant bait canceled on 07/26/89. Criterion of concern: oncogenicity, mutagenicity and teratogenicity.

Reference -- 53 FR 24787 (06/30/88)

EPA Contact -- Special Review Branch / OPP

(703)557-7400 / FTS 557-7400

<<< Arsenic, inorganic >>>

___IV.D.2.b. PESTICIDE ACTIVE INGREDIENT, Special Review

Action -- Final regulatory decision - PD4 (1984) [wood use]

Considers technological or economic feasibility? -- No

Summary of regulatory action -- Requires label changes including a restricted use classification. Criterion of concern: oncogenicity, mutagenicity and teratogenicity.

Reference -- 49 FR 28666 (07/13/84) [NTIS# PB84-241538]; 49 FR 43772 (10/31/84);
50 FR 4269 (01/30/85)

EPA Contact -- Special Review Branch / OPP
(703)557-7400 / FTS 557-7400

<<< Arsenic, inorganic >>>

IV.D.2.c. PESTICIDE ACTIVE INGREDIENT, Special Review

Action -- Voluntary Cancellation of copper arsenate (1977)

Considers technological or economic feasibility? -- NO

Summary of regulatory action -- Voluntary cancellation. Criterion of concern: oncogenicity.

Reference -- 42 FR 18422 (04/07/77)

EPA Contact -- Special Review Branch / OPP
(703)557-7400 / FTS 557-7400

<<< Arsenic, inorganic >>>

___IV.D.2.d. PESTICIDE ACTIVE INGREDIENT, Special Review

Action -- Voluntary Cancellation of sodium arsenite (1978)

Considers technological or economic feasibility? -- NO

Summary of regulatory action -- Voluntary cancellation of two products.

Criterion of concern: oncogenicity, mutagenicity and teratogenicity.

Reference -- 43 FR 48267 (10/18/78)

EPA Contact -- Special Review Branch / OPP

(703)557-7400 / FTS 557-7400

-----<<< Arsenic, inorganic >>>-----

___IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

-----<<< Arsenic, inorganic >>>-----

___IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

-----<< Arsenic, inorganic >>-----

IV.G. SUPERFUND (CERCLA)

IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1 pound (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The 1-pound RQ for arsenic is based on its potential carcinogenicity. Available data indicate a hazard ranking of high based on a potency factor of 142.31/mg/kg/day and a weight-of-evidence group A, which corresponds to an RQ of 1 pound. Evidence found in "Water-Related Environmental Fate of 129 Priority Pollutants" (EPA 440/4-79-029a) also indicates that this material, or a constituent of this material, is bioaccumulated to toxic levels in the tissue of aquatic and marine organisms, and has the potential to concentrate in the food chain. Reporting of releases of massive forms of this hazardous substance is not required if the diameter

of the pieces released exceeds 100 micrometers (0.004 inches).

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline

(800)424-9346 / (202)260-3000 / FTS 260-3000

_V. SUPPLEMENTARY DATA

Substance Name -- Arsenic, inorganic

CASRN -- 7440-38-2

Not available at this time.

_VI. BIBLIOGRAPHY

Substance Name -- Arsenic, inorganic

CASRN -- 7440-38-2

Last Revised -- 09/01/91

VI.A. ORAL RfD REFERENCES

Abernathy, C.O., W. Marcus, C. Chen, H. Gibb and P. White. 1989. Office of Drinking Water, Office of Research and Development, U.S. EPA. Memorandum to P. Cook, Office of Drinking Water, U.S. EPA and P. Preuss, Office of Regulatory Support and Scientific Management, U.S. EPA. Report on Arsenic (As) Work Group Meetings. February 23.

Cebrian, M.E., A. Albores, M. Aguilar and E. Blakely. 1983. Chronic arsenic poisoning in the north of Mexico. Human Toxicol. 2: 121-133.

Ferm, V.H. and S.J. Carpenter. 1968. Malformations induced by sodium arsenate. J. Reprod. Fert. 17: 199-201.

Hindmarsh, J.T., O.R. McLetchie, L.P.M. Heffernan et al. 1977. Electromyographic abnormalities in chronic environmental arsenicalism. J. Appl. Toxicol. 1: 270-276.

Hood, R.D., G.T. Thacker and B.L. Patterson. 1977. Effects in the mouse and rat of prenatal exposure to arsenic. Environ. Health Perspect. 19: 219-222.

Lu, F.J. 1990. Blackfoot disease. Arsenic or humic acid? The Lancet. 336: 115-116.

Nadeenko, V.G., V. Lenchenko, S.B. Genkina and T.A. Arkhipenko. 1978. The influence of t:
620-623.

- Schroeder, H.A. and H.A.M. Mitchner. 1971. Toxic effects of trace elements on the reproduction of mice and rats. Arch. Environ. Health. 23(2): 102-106.
- Southwick, J.W., A.E. Western, M.M. Beck, et al. 1983. An epidemiological study of arsenic in drinking water in Millard County, Utah. In: Arsenic: Industrial, Biomedical, Environmental Perspectives, W.H. Lederer and R.J. Fensterheim, Ed. Van Nostrand Reinhold Co., New York. p. 210-225.
- Tseng, W.P. 1977. Effects and dose-response relationships of skin cancer and blackfoot disease with arsenic. Environ. Health Perspect. 19: 109-119.
- Tseng, W.P., H.M. Chu, S.W. How, J.M. Fong, C.S. Lin and S. Yeh. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. J. Natl. Cancer. Inst. 40(3): 453-463.
- Valentine, J.L., L.S. Reisbord, H.K. Kang and M.D Schluchter. 1987. Arsenic effects on population health histories. In: Trace Elements in Man and the Environment, O. Axelson, O. 198 on sister chromatid exchange (SCE) in a macrophage cell line. Environ. Health Perspect. 47: 239-253.
- Axelson, O., E. Dahlgren, C.D. Jansson and S.O. Rehnlund. 1978. Arsenic exposure and mortality: A case referent study from a Swedish copper smelter. Br. J. Ind. Med. 35: 8-15.
- Bergoglio, R.M. 1964. Mortality from cancer in regions of arsenical waters of the province of Cordoba Argentine Republic. Prensa Med. Argent. 51: 994-998.
- Borgono, J.M. and R. Greiber. 1972. Epidemiological study of arsenicism in the city of Antofagasta. In: Trace Substances in Environmental Health-V.

Proceed. 5th Annual Conference, University of Missouri, Columbia, MO, June 29-
July 1, 1971. D.C. Hemphill, Ed., University of Missouri, Columbia, MO.
p. 13-24.

Brown, C.C. and K.C. Chu. 1983a. Approaches to epidemiologic analysis of
prospective and retrospective studies: Example of transformation of Syrian hamst
Cancer Res. 39: 1008-1013.

Higgins, I. 1982. Arsenic and respiratory cancer among a sample of Anaconda
smelter workers. Report submitted to the Occupational Safety and Health
Administration in the comments of the Kennecott Minerals Company on the
inorganic arsenic rulemaking. (Exhibit 203-5)

Higgins, I., K. Welch and C. Burchfield. 1982. Mortality of Anaconda
smelter workers in relation to arsenic and other exposures. University of
Michigan, Dept. Epidemiology, Ann Arbor, MI.

IARC (International Agency for Research on Cancer). 1980. IARC Monographs on
the Evaluation of Carcinogenic Risk of Chemicals to Man, Vol. 23. Some Metals
and Metallic Compounds. World Health Organization, Lyon, France.

Larramendy, M.L., N.C. Popescu and J. DiPaolo. 1981. Induction by inorganic
metal salts of sister chromatid exchanges and chromosome aberrations in human
and Syrian hamst

Ohno, H., F. Hanaoka and M. Yamada. 1982. Inductibility of sister chromatid
exchanges by heavy-metal ions. Mutat. Res. 104: 141-145.

Ott, M.G., B.B. Holder and H.I. Gordon. 1974. Respiratory cancer and
occupational exposure to arsenicals. Arch. Environ. Health. 29: 250-255.

Pershagen, G., B. Lind and N.E. Bjorkund. 1982. Lung retention and toxicity of some inorganic arsenic compounds. Environ. Res. 29: 425-434.

Pershagen, G., G. Nordberg and N.E. Bjorklund. 1984. Carcinomas of the respiratory tract in hamsters given arsenic trioxide and/or benzo(a)pyrene by the pulmonary route. Environ. Res. 34: 227-241.

Rencher, A.C., M.W. Carter and D.W. McKee. 1978. A retrospective epidemiological study of mortality at a large western copper smelter. J. Occup. Med. 19: 754-758.

Rossman, T.G. 1981. Enhancement of UV-mutagenesis by low concentrations of arsenite in E. Coli. Mutat. Res. 91: 207-211.

Roth, F. 1958. Uber den Bronchialk cancer and blackfoot disease with arsenic. Environ. Health Perspect. 19: 109-119.

U.S. EPA. 1984. Health Assessment Document for Inorganic Arsenic. Prepared by Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA/600/8-83/021F.

Wan, B., R.T. Christian and S.W. Sookup. 1982. Studies of cytogenetic effects of sodium arsenicals on mammalian cells in vitro. Environ. Mutag. 4: 493-498.

Welch, K., I. Higgins, M. Oh and C. Burchfield. 1982. Arsenic exposure, smoking, and respiratory cancer in copper smelter workers. Arch. Environ. Health. 37: 325-335.

-----<<< Arsenic, inorganic >>>-----

VI.D. DRINKING WATER HA REFERENCES

None

SYNONYMS

Substance Name -- Arsenic, inorganic

CASRN -- 7440-38-2

Last Revised -- 02/10/88

7440-38-2

Arsenic

Arsenic, inorganic

gray-arsenic

EPA Contact -- Drinking Water Standards Division / OGWDW /

(202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

<<< Toxaphene >>>

___ IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

<<< Toxaphene >>>

___ IV.B.4. REQUIRED MONITORING

Toxaphene; CASRN 8001-35-2 (01/01/92)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects

(e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Toxaphene

File On-Line 08/22/88

Category (section)	Status	Last Revised
-----	-----	-----
Oral RfD Assessment (I.A.)	no data	
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	01/01/91
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	01/01/92
Supplementary Data (V.)	on-line	04/01/89

I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Toxaphene

CASRN -- 8001-35-2

Not available at this time.

I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Toxaphene

CASRN -- 8001-35-2

Not available at this time.

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Toxaphene

CASRN -- 8001-35-2

Last Revised -- 01/01/91

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Toxaphene >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- B2; probable human carcinogen.

Basis -- The classification is based on increased incidence of hepatocellular tumors in mice and thyroid tumors in rats and is supported by mutagenicity in Salmonella.

<<< Toxaphene >>>

___ II.A.2. HUMAN CARCINOGENICITY DATA

None.

<<< Toxaphene >>>

___ II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. Two long-term carcinogenicity bioassays with toxaphene have been performed in rats and mice with both species showing a carcinogenic response. Dietary toxaphene was administered for 18 months at doses of 0, 7, 20 and 50 ppm to 54 B6C3F1 mice/sex/group. Animals were observed 6 months post-treatment. An increased incidence of hepatocellular carcinomas and neoplastic nodules (adenomas) was seen in both sexes and was statistically significant in males administered 50 ppm (Litton Bionetics, 1978).

In a second study (NCI, 1979), dietary toxaphene was administered to 50 Osborne-Mendel rats/sex/group and 50 B6C3F1 mice/sex/group for 80 weeks. Rats received TWA doses of 556 and 1112 ppm for males and 540 and 1080 ppm for females. The animals were observed for 28-30 weeks post-treatment. Controls consisted of 10 matched controls/sex and 45 additional pooled controls/sex. A statistically significant dose-related increased incidence

of thyroid tumors (adenomas and carcinomas) was seen in both male and female rats.

Mice received TWA doses of 99 and 198 ppm for both sexes. Controls consisted of 10 matched controls/sex and 40 additional pooled controls/sex. A statistically significantly increased incidence of liver cancer in treated animals was observed and was dose-related (NCI, 1979).

<<< Toxaphene >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Toxaphene is mutagenic to Salmonella (Hill, 1977). It was negative in a modified dominant lethal assay of male ICR/Ha Swiss mice (Epstein, 1972). No significant differences were found between rates of chromosomal aberrations in leukocytes of workers occupationally exposed to toxaphene and of unexposed workers (U.S. EPA, 1978).

-----<<< Toxaphene >>>-----

___II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

___II.B.1. SUMMARY OF RISK ESTIMATES

Oral Slope Factor -- 1.1E+0 per (mg/kg)/day

Drinking Water Unit Risk -- 3.2E-5 per (ug/L)

Extrapolation Method -- linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	3E+0 ug/L
E-5 (1 in 100,000)	3E-1 ug/L
E-6 (1 in 1,000,000)	3E-2 ug/L

<<< Toxaphene >>>

II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor Type -- hepatocellular carcinomas and neoplastic nodules

Test Animals -- Mouse/B6C3F1, males

Route -- Diet

Reference -- Litton Bionetics, 1978

----- Dose -----		Tumor
Admin-	Human	Incidence
istered	Equivalent	
-----	-----	-----
ppm	mg/kg/day	mg/kg/day
0	0.0	0
7	0.91	0.051
20	2.6	0.144
50	6.5	0.361
		10/53
		10/54
		12/53
		18/51

<<< Toxaphene >>>

___ II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

The Litton Bionetics (1978) study was used for derivation of a slope factor because more dose levels were used, and a positive carcinogenic response was found at a lower dose than in the NCI study (1979). Weight of the animals was assumed to be 0.03 kg, and animal lifetime was taken as 735 days, the duration of the experiment.

The unit risk should not be used if the water concentration exceeds $3E+2$ ug/L, since above this concentration the unit risk may not be appropriate.

<<< Toxaphene >>>

___ II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

An adequate number of animals was observed. A dose-response effect was seen in a study with 3 non-zero dose levels.

-----<<< Toxaphene >>>-----

___ II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

___ II.C.1. SUMMARY OF RISK ESTIMATES

Inhalation Unit Risk -- $3.2E-4$ per (ug/cu.m)

Extrapolation Method -- linearized multistage procedure, extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
-----	-----
E-4 (1 in 10,000)	3E-1 ug/cu.m
E-5 (1 in 100,000)	3E-2 ug/cu.m
E-6 (1 in 1,000,000)	3E-3 ug/cu.m

<<< Toxaphene >>>

___ II.C.2. DOSE-RESPONSE DATA FOR CARCINOGENICITY, INHALATION EXPOSURE

The unit risk was calculated from the oral data presented in II.B.2.

<<< Toxaphene >>>

___ II.C.3. ADDITIONAL COMMENTS (CARCINOGENICITY, INHALATION EXPOSURE)

The unit risk should not be used if the air concentration exceeds 3.1E+1 ug/cu.m, since above this concentration the unit risk may not be appropriate.

<<< Toxaphene >>>

___ II.C.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, INHALATION EXPOSURE)

This inhalation risk estimate was based on oral data.

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

U.S. EPA. 1978. Occupational Exposure to Toxaphene. A Final Report by the Epidemiologic Studies Program, Human Effects Monitoring Branch, Benefits and Field Studies Division, OPP, OTS, EPA.

U.S. EPA. 1980. Ambient Water Quality Criteria for Toxaphene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards. Washington, DC. EPA 440/5-80-076. NTIS PB 81-117863.

Epstein, S.S. et al. 1972. Detection of chemical mutagen by the dominant lethal assay in the mouse. Toxicol. Appl. Pharmacol. 23: 288.

Hill, R.N. 1977. Memorandum to Fred Hageman. Off. Spec. Pestic. Rev., U.S. EPA. December 15.

Linton Bionetics. 1978. Carcinogenic evaluation in mice: Toxaphene. Prepared by Litton Bionetics, Inc., Kensington, MD for Hercules, Inc., Wilmington, DE.

NCI. 1979. Bioassay of Toxaphene for Possible Carcinogenicity. Carcinogenesis Testing Program. Division of Cancer Cause and Prevention.

NCI, National Institute of Health, Bethesda, Maryland, 20014. U.S.
Department of Health, Education and Welfare. DHEW Publication No. (NIH)
79-837.

<<< Toxaphene >>>

___ II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The values in the 1980 Ambient Water Quality Criteria document have
received both Agency and outside review.

Agency Work Group Review: 03/05/87

Verification Date: 03/05/87

___ II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Charlie Hiremath / ORD -- (202)260-5725 / FTS 260-5725

William E. Pepelko / ORD -- (202)260-5904 / FTS 260-5904

___ III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Toxaphene

CASRN -- 8001-35-2

Not available at this time.

III.B. OTHER ASSESSMENTS

Substance Name -- Toxaphene

CASRN -- 8001-35-2

Content to be determined.

IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Toxaphene

CASRN -- 8001-35-2

Last Revised -- 01/01/92

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Toxaphene >>>

__IV.A. CLEAN AIR ACT (CAA)

No data available

-----<<< Toxaphene >>>-----

__IV.B. SAFE DRINKING WATER ACT (SDWA)

___IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value -- 0.00 mg/L (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- The final MCLG for toxaphene is zero based on the evidence of carcinogenic potential (classification B2).

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

<<< Toxaphene >>>

___IV.B.2. MAXIMUM CONTAMINANT LEVEL (MCL) for Drinking Water

Value -- 0.003 mg/L (Final, 1991)

Considers technological or economic feasibility? -- YES

Discussion -- The MCL is based on a PQL of 0.003 mg/L and is associated with a maximum lifetime individual risk of E-4.

Monitoring requirements -- All systems initially monitored for four consecutive quarters every three years; repeat monitoring dependent upon detection, vulnerability status and system size.

Analytical methodology -- Microextraction/gas chromatography (EPA 505).

PQL=0.003 mg/L.

Best available technology -- Granular activated carbon

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW /
(202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

<<< Toxaphene >>>

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

<<< Toxaphene >>>

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

-----<<< Toxaphene >>>-----

___IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

No data available

<<< Toxaphene >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute -- 7.3E-1 ug/L (1 hour average)

Chronic -- 2E-4 ug/L (4 day average)

Marine:

Acute -- 2.1E-1 ug/L (1 hour average)

Chronic -- 2E-4 ug/L (4 day average)

Considers technological or economic feasibility? -- NO

Discussion -- Criteria were derived from a minimum data base consisting of acute tests on a variety of species. Requirements and methods are covered in the reference to the Federal Register.

Reference -- 51 FR 43665 (12/03/86)

EPA Contact -- Criteria and Standards Division / OWRS

(202)260-1315 / FTS 260-1315

-----<<< Toxaphene >>>-----

___IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

___IV.D.1. PESTICIDE ACTIVE INGREDIENT, Registration Standard

Status -- Removed from list "B" pesticides/Registration canceled (1990)

Reference -- 55 FR 31166 (07/31/90)

EPA Contact -- Registration Branch / OPP

(703)557-7760 / FTS 557-7760

<<< Toxaphene >>>

___IV.D.2. PESTICIDE ACTIVE INGREDIENT, Special Review

Action -- Final Regulatory Decision - PD 4 (1982)

Considers technological or economic feasibility? -- NO

Summary of regulatory action -- Cancellation of registrations for most uses and continued registration of certain uses under specific terms and conditions.

Reference -- 47 FR 53784 (11/29/82) [NTIS# PB83-144204]

EPA Contact -- Special Review Branch / OPP

(703)557-7400 / FTS 557-7400

-----<<< Toxaphene >>>-----

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

-----<<< Toxaphene >>>-----

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

__IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 -(07/09/87)

EPA Contact -- RCRA/Superfund Hotline

(800)424-9346 / (202)260-3000 / FTS 260-3000

-----<<< Toxaphene >>>-----

__IV.G. SUPERFUND (CERCLA)

__IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1 pound (Final, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ for toxaphene is based on aquatic toxicity as established under CWA Section 311 (40 CFR 117.3). The available data indicate that the aquatic 96-Hour Median Threshold Limit is less than 0.1 ppm, which corresponds to an RQ of 1 pound.

Reference -- 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline

(800)424-9346 / (202)260-3000 / FTS 260-3000

V. SUPPLEMENTARY DATA

Substance Name -- Toxaphene

CASRN -- 8001-35-2

Last Revised -- 04/01/89

The information contained in this section (subsections A and B) has been extracted from the EPA Chemical Profiles Database, which has been compiled from a number of secondary sources and has not undergone formal Agency review. The complete reference listings for the citations in this section are provided

in Service Code 5. The user is urged to read Background Document 5 in Service Code 5 for further information on the sources and limitations of the data presented here.

<<< Toxaphene >>>

V.A. ACUTE HEALTH HAZARD INFORMATION

Toxicity -- Toxaphene is extremely toxic. The probable oral lethal dose (human) is 5-50 mg/kg or between 7 drops and 1 teaspoonful for 70 kg person (Gosselin, 1984).

Medical Conditions Generally Aggravated by Exposure -- Not Found

Signs and Symptoms of Exposure -- Acute toxicity of toxaphene is manifested as generalized convulsions preceded by cyanosis. Also reported is sudden exertional dyspnea (labored breathing), tachycardia (rapid heart rate), weakness and low blood pressure (Gosselin, 1984, p. III-387). Lethal doses of toxaphene cause respiratory failure. Hypersalivation, leg and back muscle spasms, nausea, vomiting, hyperexcitability, tremors, shivering, clonic convulsions, and tetanic muscular contractions of all skeletal muscles have also been reported (Weiss, 1980, p. 874).

-----<<< Toxaphene >>>-----

V.B. PHYSICAL-CHEMICAL PROPERTIES

Chemical Formula -- C₁₀H₁₀Cl₈ approximate (Hawley, 1981, p. 1034)

Molecular Weight -- Unknown

Boiling Point -- Not Found

Specific Gravity (H₂O=1) -- 1.65 (Worthing, 1976)

Vapor Pressure (mmHg) -- 0.4 at 25C (Sunshine, 1969)

Melting Point -- 149-194F, 65-90C (Merck, 1983)

Vapor Density (AIR=1) -- Not Found

Evaporation Rate (Butyl acetate=1) -- Not Found

Solubility in Water -- 3 mg/l at room temperature (Worthing, 1979)

Appearance and Odor -- Yellow, waxy solid with a pleasant piney odor (Merck, 1983)

Flash Point (Method Used) -- 84F, 29C (CC) (Weiss, 1980, p. 874)

Flammable Limits:

LEL -- 1.1% (Weiss, 1980, p. 874)

UEL -- 6.4% (Weiss, 1980, p. 874)

Conditions and Materials to Avoid -- Toxaphene dehydrochlorinates in the presence of alkali, on prolonged exposure to sunlight, and at temperatures above 155C (Merck, 1983). Avoid strong oxidizers (NIOSH/OSHA, 1984, p. 62);

toxaphene is corrosive to iron (Merck, 1983, p. 9384).

Hazardous Decomposition or Byproducts -- Toxaphene releases hydrochloric acid in the presence of alkali, on prolonged exposure to sunlight, and at temperatures above 155C (Merck, 1983).

Use -- Toxaphene is an insecticide, primarily for cotton and early growth stages of vegetables (Hawley, 1981, p. 1034). Toxaphene is also used on peas, soybeans, peanut, corn, and wheat. Toxaphene has not been produced commercially in the U.S. since 1982 (SRI). The chemical is only registered for scabies control on cattle in the U.S. (USEPA/Pesticide Index, 1985).

=====

VI. BIBLIOGRAPHY

Substance Name -- Toxaphene

CASRN -- 8001-35-2

Last Revised -- 06/01/90

VI.A. ORAL RfD REFERENCES

None

-----<<< Toxaphene >>>-----

VI.B. INHALATION RfD REFERENCES

None

-----<<< Toxaphene >>>

Epstein, S.S. E. Arnold, J. Andrea, W. Bass and Y. Bishop. 1972. Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicol. Appl. Pharmacol. 23(2): 288-325.

Hill, R.N. 1977. Memorandum to Fred Hageman. Off. Spec. Pestic. Rev., U.S. EPA. December 15.

Litton Bionetics. 1978. Carcinogenic evaluation in mice: Toxaphene. Final report. Prepared by Litton Bionetics, Inc., Kensington, MD for Hercules, Inc., Wilmington, DE. LBI Project No. 20602.

NCI (National Cancer Institute). 1979. Bioassay of Toxaphene for Possible Carcinogenicity. Carcinogenesis Testing Program. Division of Cancer Cause and Prevention. NCI, National Institute of Health, Bethesda, Maryland, 20014. U.S. Department of Health, Education and Welfare. DHEW Publication No. (NIH) 79-837.

U.S. EPA. 1978. Occupational Exposure to Toxaphene. A Final Report by the Epidemiologic Studies Program, Human Effects Monitoring Branch, Benefits and

Enter keywords or Read or Scan or Mail

--search

Searching - Please wait...

2 Occurrences...

Enter keywords or Read or Scan or Mail

--atrazine

Searching - Please wait...

1 Occurrences...

Enter keywords or Read or Scan or Mail

--scan

Atrazine; CASRN 1912-24-9 (01/01/92)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects

(e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Atrazine

File On-Line 09/30/87

Category (section)	Status	Last Revised
-----	-----	-----
Oral RfD Assessment (I.A.)	on-line	01/01/91
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	pending	
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	01/01/92
Supplementary Data (V.)	no data	

I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Atrazine

CASRN -- 1912-24-9

Last Revised -- 01/01/91

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file when a review of that evaluation is completed.

<<< Atrazine >>>

I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased body weights of F2 generation pups on postnatal day 21	NOEL: 10 ppm (0.5 mg/kg/day)	100	1	5E-3 mg/kg/day
2-Generation Rat Reproduction Study	LEL: 50 ppm (2.5 mg/kg/day)			

Ciba-Geigy, 1987a

*Conversion Factors: 1 ppm = 0.05 mg/kg/day (assumed rat food consumption)

<<< Atrazine >>>

I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Ciba-Geigy Corporation. 1987a. MRID No. 40431303.

Available from EPA. Write to FOI, EPA, Washington, DC 20460.

In a 2-generation reproduction study, 120 rats/sex were randomly distributed into 4 treatment groups and fed atrazine at 0, 10, 50, or 500 ppm (0, 0.5, 2.5, and 25 mg/kg/day). Exposure to the test material began when male rats were 47 days old and females were 48 days old. They were maintained on these diets for 10 weeks prior to mating. Males and females were housed together in a 1:1 ratio and allowed 3 weeks for mating. The rats were separated following evidence of mating. One litter was produced in each generation. After weaning, 30 males and 30 females from the first generation were selected to be the second parental generation. The remaining male parental animals were sacrificed on days 133 to 134 of the study. Animals

selected for the second generation were exposed to test diets for 12 weeks prior to mating. Mating was conducted in the same manner as for the first generation. Parental males were sacrificed on day 138 of the study and parental females on days 138, 139, and 152 after weaning of their litters.

The NOEL for reproductive toxicity is 10 ppm (0.5 mg/kg/day) based on statistically significantly lower F2 generation pup weights at postnatal day 21 at 50 and 500 ppm (2.5, and 25 mg/kg/day). The NOEL for parental toxicity is 50 ppm (2.5 mg/kg/day) based on statistically significantly decreased body weights, body weight gain and food consumption for males and females throughout the study at 500 ppm (25 mg/kg/day). In addition, a statistically significant increase in relative testes weights was seen in both generations.

<<< Atrazine >>>

 I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 100. An uncertainty factor of 100 was used to account for the inter- and intraspecies differences.

MF = 1.

<<< Atrazine >>>

 I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

Data Considered for Establishing the RfD

- 1) 2-Generation Reproduction - rat: see previous description; core grade minimum (Ciba-Geigy Corp., 1987a)

- 2) 1-Year Feeding - dog: Dietary levels tested: 0, 15, 150, and 1000 ppm (Male: 0, 0.48, 4.97, and 33.65 mg/kg/day; Female: 0, 0.48, 4.97, and 33.8 mg/kg/day). NOEL=150 ppm (4.97 mg/kg/day); LEL=1000 ppm (43 mg/kg/day) (HDT; based on death, cachexia, ascites, decreased body weight and body weight gain, decreased food consumption; EKG changes [irregular heart beat and increased heart rate, decrease P-II values, atrial premature complexes, atrial fibrillation]; cardiac lesions [dilation of atria, atrial degeneration]); core grade minimum (Ciba-Geigy Corp., 1987b)
- 3) 2-Year Feeding (oncogenic) - rat: Dietary levels tested: 0, 70, 500, and 1000 ppm (0, 3.5, 25, and 50 mg/kg/day). Administration of atrazine to male and female CD-1 Sprague-Dawley rats resulted in decreased mean body weights for males and females receiving 500 and 1000 ppm. Survival was decreased in high-dose females but increased in high-dose males. Red blood cell parameters (hemoglobin, hematocrit, and red cell count) were decreased in high-dose females only. The serum glucose level was decreased in high-dose females at 3, 6, and 12 months and serum triglyceride levels showed a decreasing trend in high-dose males throughout the study. There were decreases in organ-to-body weight ratios in high-dose animals, which were probably the result of body weight decreases. Hyperplastic changes in high-dose males (mammary gland, bladder, and prostate) and females (myeloid tissue of bone marrow and transitional epithelium of the kidney) were of questionable toxicologic importance. There was an increase in retinal degeneration and in centrilobular necrosis of the liver in high-dose females and an increase in degeneration of the rectus femoris muscle in high-dose males and females when compared to controls. Based on decreased body weight gain, the LEL for males and females is 500 ppm (25 mg/kg/day) and the NOEL is 70 ppm (3.5 mg/kg/day); core grade minimum (Ciba-Geigy Corp., 1986)
- 4) Developmental toxicity - rat: Dietary levels tested: 0, 10, 70, and 700 mg/kg/day (by gavage). Administration of atrazine technical to Charles

River CD rats from days 6 to 15 of gestation resulted in maternal toxicity during and after the treatment period at the high-dose. Signs of toxicity at the high-dose included death (21 of 27 dams), reduced food consumption, reduced weight gain, salivation, ptosis, swollen abdomen, oral/nasal discharge, and bloody vulva. Maternal toxicity was also found at the 70 mg/kg/day dose level. Toxicity signs in this group included reduced food consumption, reduced body weight, and reduced weight gain. No maternal toxicity was observed in the 10 mg/kg/day or control groups. Based on the above effects, the maternal toxicity NOEL is 10 mg/kg/day and the LEL is 70 mg/kg/day. At 70 mg/kg/day, there were statistically significant increases in both fetal and litter incidences for skeletal variations indicating delayed ossification. Variations included: skull not completely ossified, metacarpals not ossified, metacarpals bipartite, and phalanx not ossified. Based on these effects the NOEL and LEL for developmental toxicity are 10 and 70 mg/kg/day, respectively.; core grade minimum (Ciba-Geigy Corp., 1984a)

- 5) Developmental toxicity - rabbit: Dietary levels tested: 0, 1, 5, 75 mg/kg/day (by gavage). Administration of atrazine technical to New Zealand White rabbits from days 7 to 19 of gestation resulted in maternal toxicity during the treatment period at doses of 5 and 75 mg/kg/day. Does in the 75 mg/kg/day group did not recover from symptoms of this toxicity during the period after dosing. Signs of maternal toxicity in the 5 mg/kg/day dose group were decreased food consumption and decreased body weight. Signs of maternal toxicity in the high-dose group included blood on vulva or in cage, decreased food consumption, abnormal stools, and decreased body weight and body weight gain. No effects were observed at the lowest dose tested, 1 mg/kg/day. Based on the above effects, the maternal toxicity NOEL is 1 mg/kg/day and the LEL 5 mg/kg/day. An increased number of resorptions in the HDT was statistically significant and was not observed at any other dose level. In the HDT, the weights of both the male and

female fetuses were significantly reduced. No compound-related malformations were observed. Skeletal variations, especially delayed ossification of appendicular skeletal elements, were found more frequently in the HDT. Based on the above effects, the developmental toxicity NOEL is 5 mg/kg/day and the LEL 75 mg/kg/day; core grade minimum (Ciba-Geigy Corp., 1984b)

Other Data Reviewed:

- 1) Chronic Feeding - mouse: Dietary levels tested: 0, 10, 300, 1500, and 3000 ppm (Male: 0, 1.4, 38.4, 194.0, and 385.7 mg/kg/day; Female: 0, 1.6, 47.9, 246.9, and 482.7 mg/kg/day). This study shows that there are dose-related effects of atrazine in CD-1 mice fed diets containing 1500 or 3000 ppm of atrazine. The dose-related effects were the production of cardiac thrombi, decreases of 23.5% and 11.0% in the mean body weight gain at 91 weeks in males and females, respectively, and decreases in erythrocyte count, hematocrit and hemoglobin concentration. An increase in the incidence of cardiac thrombi was found in females receiving 1500 and 3000 ppm. Based on the above effects, the LEL for systemic toxicity is 1500 ppm (Male: 194.0 mg/kg/day; Female: 246.9 mg/kg/day). The NOEL for systemic toxicity is 300 ppm (Male: 38.4 mg/kg/day; Female: 47.9 mg/kg/day).; core grade guideline (Ciba-Geigy Corp., Agricultural Division, 1987c)
- 2) 2-Year Feeding - dog: Dietary levels tested: 0, 14.1, 141.5, and 1415 ppm (0, 0.35, 3.54, and 35.38 mg/kg/day). The NOEL for systemic toxicity is 14.1 ppm (0.35 mg/kg/day) based on increased heart and liver weights in females at 141.5 ppm (3.54 mg/kg/day). Effects observed at 1415 ppm (35.38 mg/kg/day) included reduced food intake, decreased body weight, and reduced hemoglobin and hematocrit values. core grade supplementary (Ciba-Geigy Corp., 1964)
- 3) Developmental toxicity - rat: Dietary levels tested: 0, 100, 500, and 1000

mg/kg/day. Administration of atrazine at 1000 mg/kg/day produced 7 deaths in the 30 dams treated. Slight weight losses in females were observed at 500 mg/kg/day. A reduction in mean fetal weights and an increase in the number of embryonic and fetal resorptions were observed in the mid- and high-dose groups. Based on the above effects, the maternal toxicity and fetotoxicity NOEL and LEL are 100 and 500 mg/kg/day, respectively; core grade minimum (Ciba-Geigy, Corp., 1971)

Data Gap(s): None

<<< Atrazine >>>

___ I.A.5. CONFIDENCE IN THE ORAL RfD

Study: High

Data Base: High

RfD: High

The critical study is of good quality and is given a high confidence rating. Additional studies are supportive and of good quality; therefore, the data base is given a high confidence rating. High confidence in the RfD follows.

<<< Atrazine >>>

___ I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

The only U.S. EPA documentation at present is on IRIS.

Pesticide Registration Standard

Pesticide Registration Files

Agency Work Group Review: 07/08/86, 12/09/86, 05/20/87, 06/22/88, 02/21/90

Verification Date: 02/21/90

___ I.A.7. EPA CONTACTS (ORAL RfD)

George Ghali / OPP -- (703)557-7490 / FTS 557-7490

Reto Engler / OPP -- (703)557-7491 / FTS 557-7491

___ I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Atrazine

CASRN -- 1912-24-9

Not available at this time.

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Atrazine

CASRN -- 1912-24-9

This substance/agent has been evaluated by the U.S. EPA for evidence of human carcinogenic potential. This does not imply that this agent is necessarily a carcinogen. The evaluation for this chemical is under review by an inter-office Agency work group. A risk assessment summary will be included on IRIS when the review has been completed.

III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Atrazine

CASRN -- 1912-24-9

Not available at this time.

III.B. OTHER ASSESSMENTS

Substance Name -- Atrazine

CASRN -- 1912-24-9

Content to be determined.

IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Atrazine

CASRN -- 1912-24-9

Last Revised -- 01/01/92

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or

economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Atrazine >>>

__IV.A. CLEAN AIR ACT (CAA)

No data available

-----<<< Atrazine >>>-----

__IV.B. SAFE DRINKING WATER ACT (SDWA)

___IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value -- 0.003 mg/L (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- A MCLG of 0.003 mg/L is set based on its potential adverse effects (liver and kidney damage) reported in dog and rat studies. The MCLG is based upon a DWEL of 0.2 mg/L and an assumed drinking water contribution of 20 percent.

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Health and Ecological Criteria Division / OST /
(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

<<< Atrazine >>>

___ IV.B.2. MAXIMUM CONTAMINANT LEVEL (MCL) for Drinking Water

Value -- 0.003 mg/L (Final, 1991)

Considers technological or economic feasibility? -- YES

Discussion -- EPA has set a MCL equal to the MCLG of 0.003 mg/L.

Monitoring requirements -- All systems initially monitored for four consecutive quarters every three years; repeat monitoring dependent upon detection, vulnerability status and size.

Analytical methodology -- Microextraction/gas chromatography (EPA505); liquid-solid extraction/capillary column gas chromatography/mass spectrometry (EPA 525); (EPA 507); PQL=0.001 mg/L.

Best available technology -- Granular activated carbon.

Reference -- 56 FR 3526 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW /
(202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

<<< Atrazine >>>

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

<<< Atrazine >>>

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

-----<<< Atrazine >>>-----

___IV.C. CLEAN WATER ACT (CWA)

No data available

-----<<< Atrazine >>>-----

___IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

___IV.D.1. PESTICIDE ACTIVE INGREDIENT, Registration Standard

Status -- Issued (1983). Second Round Review still in progress.

Reference -- Atrazine Pesticide Registration Standard. September, 1983
(NTIS No. PB84-149541)

EPA Contact -- Registration Branch / OPP
(703)557-7760 / FTS 557-7760

<<< Atrazine >>>

___IV.D.2. PESTICIDE ACTIVE INGREDIENT, Special Review

No data available

-----<<< Atrazine >>>-----

___IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

-----<<< Atrazine >>>-----

___IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

No data available

-----<<< Atrazine >>>-----

IV.G. SUPERFUND (CERCLA)

No data available

V. SUPPLEMENTARY DATA

Substance Name -- Atrazine

CASRN -- 1912-24-9

Not available at this time.

VI. BIBLIOGRAPHY

Substance Name -- Atrazine

CASRN -- 1912-24-9

Last Revised -- 05/01/90

VI.A. ORAL RfD REFERENCES

Ciba-Geigy Corporation. 1964. MRID No. 00059213. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1971. MRID No. 00038041. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1984a. EPA Accession No. 254979. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1984b. EPA Accession No. 254979. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1986. EPA Accession No. 262714-262727. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation, Agricultural Division, 1987a. MRID No. 40431303. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation. 1987b. MRID No. 40431301. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Ciba-Geigy Corporation, Agricultural Division, 1987c. MRID No. 40431302. Available from EPA. Write to FOI, EPA, Washington, DC 20460.

-----<<< Atrazine >>>-----

VI.B. INHALATION RfD REFERENCES

None

-----<<< Atrazine >>>-----

VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

None

-----<<< Atrazine >>>-----

VI.D. DRINKING WATER HA REFERENCES

None

SYNONYMS

Substance Name -- Atrazine

CASRN -- 1912-24-9

Last Revised -- 09/30/87

1912-24-9

A 361

AATREX

AATREX 4L

AATREX 80W

AATREX NINE-O

2-AETHYLAMINO-4-CHLOR-6-ISOPROPYLAMINO-1,3,5-TRIAZIN

2-AETHYLAMINO-4-ISOPROPYLAMINO-6-CHLOR-1,3,5-TRIAZIN

AKTIKON

AKTIKON PK

AKTINIT A

AKTINIT PK

ARGEZIN

ATAZINAX

ATRANEX

ATRASINE

ATRATOL A

ATRAZIN

Atrazine

ATRED

ATREX

CANDEX

CEKUZINA-T

2-CHLORO-4-ETHYLAMINEISOPROPYLAMINE-s-TRIAZINE
1-CHLORO-3-ETHYLAMINO-5-ISOPROPYLAMINO-2,4,6-TRIAZINE
1-CHLORO-3-ETHYLAMINO-5-ISOPROPYLAMINO-s-TRIAZINE
2-CHLORO-4-ETHYLAMINO-6-ISOPROPYLAMINO-1,3,5-TRIAZINE
2-CHLORO-4-ETHYLAMINO-6-ISOPROPYLAMINO-s-TRIAZINE
6-CHLORO-N-ETHYL-N'-(1-METHYLETHYL)-1,3,5-TRIAZINE-2,4-DIAMINE
2-CHLORO-4-(2-PROPYLAMINO)-6-ETHYLAMINO-s-TRIAZINE
CRISATRINA
CRISAZINE
CYAZIN
FARMCO ATRAZINE
FENAMIN
FENAMINE
FENATROL
G 30027
GEIGY 30,027
GESAPRIM
GESOPRIM
GRIFFEX
HUNGAZIN
HUNGAZIN PK
INAKOR
OLEOGESAPRIM
PRIMATOL
PRIMATOL A
PRIMAZE
RADAZIN
RADIZINE
STRAZINE
TRIAZINE A 1294

Dinoseb; CASRN 88-85-7 (01/01/92)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Dinoseb

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	08/01/89
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	03/01/91
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	01/01/92
Supplementary Data (V.)	on-line	01/31/87

I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Dinoseb

CASRN -- 88-85-7

Last Revised -- 08/01/89

The Reference Dose (RfD) is based on the assumption that thresholds exist for

certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file when a review of that evaluation is completed.

<<< Dinoseb >>>

 I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
-----	-----	-----	---	-----
Decreased fetal weight	NOEL: none	1000	1	1E-3
				mg/kg/day

LEL: 1 mg/kg/day

3-Generation Rat
Reproduction Study

Dow Chemical Co., 1981a

*Conversion Factors

: none

<<< Dinoseb >>>

 I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Dow Chemical Comapny. 1981a. MRID No. 00152675.

Available from EPA. Write to FOI, EPA, Washington, DC 20460.

Groups of 25 male and 25 female rats (2 littering groups/generation) received dinoseb in their diet at concentrations of 0, 1, 3, and 10 mg/kg bw/day for 29 weeks. There was a consistent, compound-related depression in parental body weight gain at the high dose in both sexes in the pre-mating period in all three generations, which persisted into later study periods. The mean fetal weights showed a high degree of variability. Decreased weights were observed or suggested in the F0 to F1b, the F1 to F2a, and the F2 to F3a littering groups with the F0 to F1b pup weights diminished (combined sexes) at day 21 at all dose levels. Since the treated pup weights at birth were similar to controls, the subsequently depressed pup weight gains indicated a reproductive effect during the lactation period. A reproductive LEL of 1 mg/kg/day was determined.

<<< Dinoseb >>>

 I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1000. The UF includes uncertainties in the extrapolation from laboratory animals to humans (factor of 100), as well as concern for the lack of a NOEL in the reproduction study (factor of 10).

MF = 1.

I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

A number of toxicologic issues concerning dinoseb have been raised as a result of the review of the data base for the Registration Standard including: acute toxicity, lenticular opacities, teratogenicity, immunotoxicity, contamination with nitrosamines, and testicular effects. Dinoseb is presently under Emergency Suspension and is not in use. The FIFRA Science Advisory Panel has concurred with EPA on a developmental and reproductive risk assessment produced for Special Review.

Data Considered for Establishing the RfD:

- 1) 3-Generation Reproduction - Principal study - see previous description; core grade supplementary
- 2) 2-Generation Reproduction (continuation of 3-generation study) - rat: Reproductive LEL=1 mg/kg/day [low viability index for control pups (F4 to F5a), inconsistency between the increased body weight changes in this study and the previous 3-generation study, and consistent decreases in gonadal weights and gonadal weights/body weight ratios (F4a) at all dose levels]; Systemic LEL=1 mg/kg/day (based on treatment-related or dose-related reductions in relative parental body weights with signifCONFIDEN

Study: Low

Data Base: Low

RfD: Low

The principal study appears to be of adequate quality, in many respects,

although only rated as core supplementary data; confidence in the study is considered low. Additional studies are supportive, but many data gaps remain; therefore, the data base is given low confidence. Low confidence in the RfD follows.

<<< Dinoseb >>>

I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Draft Registration Standard, June 1986

Agency RfD Work Group Review: 07/08/85, 07/22/85, 12/09/86

Verification Date: 12/09/86

I.A.7. EPA CONTACTS (ORAL RfD)

Reto Engler / OPP -- (703)557-7491 / FTS 557-7491

George Ghali / OPP -- (703)557-7490 / FTS 557-7490

I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Dinoseb

Not available at this time.

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Dinoseb

CASRN -- 88-85-7

Last Revised -- 03/01/91

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing indicating that end of the study, the body weight gain was 10 and 13% less than the controls of the mid- and the high-dose females, respectively, and no differences were found in the food consumption in the treated group against controls.

Reproductive organs in males and females were also affected. Cystic endometrial hyperplasia and atrophy were observed in females, and hypospermatogenesis and degeneration were seen in the testes of all the treated males. These were indications that an MTD had been reached.

Dinoseb induced statistically significant increases in liver adenomas in female mice at the 3 and 10 mg/kg/day doses. The incidence was 0/57, 4/59, 7/60, and 5/58 for control through 10 mg/kg/day doses, respectively. Only one carcinoma was observed (in a low-dose female). There were no decreases in latency, no dose-response and no hepatocytic change commonly associated with carcinogens. The tumors were late-appearing (the first tumor appeared after 78 weeks, and the remaining ones after 100 weeks).

Adjusting for animals at risk, the resulting incidences estimated by OPP were 0/38, 4/39, 7/41, and 5/39 for control through 10 mg/kg/day. Similar to the report, the reanalysis failed to show a trend. Incorporating the historical control incidence of 0-10% did not change the conclusion of the report. There were no decreases in time-to-tumor, nor evidence of any of the potentially predisposing lesions in the liver such as hypertrophy, hyperplasia or degeneration which are often associated with known hepatocellular carcinogens. It is thus concluded that the response may not be attributed to the chemical.

In a separate screening study, mice failed to demonstrate any significant increase in tumors (Innes et al., 1969). Two strains of mice (hybrids of female C57BL/6 and male C3H/Anf or AKR mice, 18/sex/group) were exposed to dinoseb for 18 months. The animals were first exposed via gavage at 2.15 mg/kg/day for 3 weeks beginning at 1 week of age, then they were fed a diet containing 7 ppm dinoseb (1.05 mg/kg/day) throughout the observation period of approximately 18 months. Equal numbers of mice served as controls. After 18

months of treatment, dinoseb did not cause any significant increase in tumors in mice.

In an unpublished study from Dow Chemical Company (1977), male and female Charles River rats were fed diets containing dinoseb at levels of 0, 1, 3, and 10 mg/kg/day for 104 weeks. Dinoseb did not give positive results for carcinogenicity. However, this study was deficient due to limited histopathological assessment of both animals and tissues examined and a lack of individual data for several measured parameters.

<<< Dinoseb >>>

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Dinoseb was not mutagenic for *Salmonella typhimurium* in three studies with or without addition of rat liver homogen (Waters et al., 1982; Simmon et al., 1977; Waters et al., 1982), and negative in human eucaryotes (Simmon et al., 1977; Waters et al., 1982), and negative in human fibroblasts (Simmon et al., 1977).

-----<<< Dinoseb >>>-----

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

-----<<< Dinoseb >>>-----

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

-----<<< Dinoseb >>>-----

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

U.S. EPA. 1975. In vitro and in vivo studies of selected pesticides to evaluate their potential as chemical mutagens. In: Substitute Chemical Program -- the First Year of Progress. Toxicological Methods and Genetic Effects Workshop: Vol. II. EPA MRID 0043656.

U.S. EPA. 1986. Toxicology Branch Peer Review Committee memorandum on Dinoseb, June 19.

<<< Dinoseb >>>

II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The Toxicology Branch Peer Review Committee reviewed data on dinoseb.

Agency Work Group Review: 01/13/88, 11/09/88, 05/03/89

Verification Date: 05/03/89

___ II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Julie Du / ODW -- (202)260-7583 / FTS 260-7583

Edward V. Ohanian / ODW -- (202)260-7587 / FTS 260-7587

=====

_ III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

___ III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Dinoseb

CASRN -- 88-85-7

Not available at this time.

=====

III.B. OTHER ASSESSMENTS

Substance Name -- Dinoseb

CASRN -- 88-85-7

Content to be determined.

=====

Substance Name -- Dinoseb

CASRN -- 88-85-7

Last Revised -- 01/01/92

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Dinoor Drinking Water

Value -- 0.007 mg/L (Proposed, 1990)

Considers technological or economic feasibility? -- YES

Discussion -- EPA is proposing an MCL equal to the proposed MCLG of 0.007 mg/L.

Monitoring requirements -- Community and non-transient water system monitoring based on state vulnerability assessment; vulnerable systems to be monitor quarterly for one year; repeat monitoring dependent upon detection and size of systems.

Analytical methodology -- Electron-capture/gas chromatography (EPA 508): PQL= 0.002 mg/L.

Best available technology -- Granular activated carbon

Reference -- 55 FR 30370 (07/25/90)

EPA Contact -- Drinking Water Standards Division / OGWDW / (202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

<<< Dinoseb >>>

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

No data available

<<< Dinoseb >>>

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTA(800) 426-4791

-----<<< Dinoseb >>>-----

___IV.C. CLEAN WATER ACT (CWA)

No data available

-----<<< Dinoseb >>>-----

___IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

___IV.D.1. PESTICIDE ACTIVE INGREDIENT, Registration Standard

No data available

<<< Dinoseb >>>

___IV.D.2. PESTICIDE ACTIVE INGREDIENT, Special Review

Action -- Emergency Suspension Order/Notice of Intent to Cancel (1986)

Considers technological or economic feasibility? -- YES

Summary of regulatory action -- Dinoseb exposure was determined to pose a risk of birth defects, male sterility, and acute toxicity to agricultural workers. On 10/07/87 the Agency modified the Suspension Order and permitted use of Dinoseb on dry peas, lentils, and chick peas in Idaho and Washington during the 1987 growing season. A district court in Oregon permitted use on green peas and snap beans in 1987 and 1988. Under a settlement agreement reached between EPA and the registrant in 5/88, use was allowed on cranberries in 1989.

Reference -- 51 FR 36634 (10/14/86)

EPA Contact -- Special Review Branch / OPP

(703)557-7400 / FTS 557-7400

-----<<< Dinoseb >>>-----

IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

-----<<< Dinoseb >>>-----

IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

-----<<< Dinoseb >>>-----

___IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1000 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ is based on both aquatic toxicity and oral mammalian toxicity. The 96-Hour Median Threshold Limit for aquatic toxicity is between 12 and 100 ppm and the oral LD50 for rats is between 10 and 100 mg/kg.

Reference -- 50 FR 13456 (04/04/85); 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline

V. SUPPLEMENTARY DATA

Substance Name -- Dinoseb

CASRN -- 88-85-7

Last Revised -- 01/31/87

The information contained in this section (subsections A and B) has been extracted from the EPA Chemical Profiles Database, which has been compiled from a number of secondary sources and has not undergone formal Agency review. The complete reference listings for the citations in this section are provided in Service Code 5. The user is urged to read Background Document 5 in Service Code 5 for further information on the sources and limitations of the data presentoss of consciousness, cessation of breathing, and death (Gosselin et al., 1976). Skin: staining of skin and minor irritation by very small amount. Eyes: mild to moderate irritation expected. Inhalation: dusts may be irritating and may cause serious illness (Weed Science Society of America, 1979).

-----<<< Dinoseb >>>-----

V.B. PHYSICAL-CHEMICAL PROPERTIES

Chemical Formula -- C₁₀H₁₂N₂O₅

Molecular Weight -- 240.2

Boiling Point -- Not Found

Specific Gravity (H₂O=1) -- 1.2647 at 45C (Weed Science Society of America, 1979)

Vapor Pressure (mmHg) -- 1 at 151.1C (Weed Science Society of America, 1979)

Melting Point -- 100-108F, 38-42C (Merck, 1983, p. 479)

Vapor Density (AIR=1) -- 7.73 (Sax, 1984, p. 582)

Evaporation Rate (Butyl acetate=1) -- Not Found

Solubility in Water -- 0.0052 g/100 mL (Weed Science Society of America, 1979)

Flash Point (Method Used) -- 60.1F to 84.9F, 15.6C to 29.4C for 3 commercial prod.

Environmental Protection Agency, Research Triangle Park, NC. EPA 600/1-77-028.

U.S. EPA. 1975. In vitro and in vivo studies of selected pesticides to evaluate their potential as chemical mutagens. In: Substitute Chemical Program -- the First Year of Progress. Toxicological Methods and Genetic Effects Workshop: Vol. II. EPA MRID 0043656.

U.S. EPA. 1986. Toxicology Branch Peer Review Committee memorandum on Dinoseb, June 19.

Waters, M.D., S.S. Sandhu, V.F. Simmon et al. 1982. Study of pesticide genotoxicity. Basic Life Sci. 21: 275-326.

-----<<< Dinoseb >>>-----

VI.D. DRINKING WATER HA REFERENCES

None

=====

SYNONYMS

Substance Name -- Dinoseb

CASRN -- 88-85-7

Last Revised -- 01/31/87

88-85-7

AATOX

Aretit

Basanite

BNP 20

BNP 30

Butaphene

Caldon

Chemox General

Chemox PE

DBNF

Dibutox

Dinitrall

Dinitrobutylphenol

2,4-Dinitro-6-sec-Butylphenol

4,6-Dinitro-2-sec-Butylphenol

4,6-Dinitro-o-sec-Butylphenol

2,4-Dinitro-6-(1-Methylpropyl)Phenol

4,6-Dinitro-2-(1-Methyl-n-Propyl)Phenol

Dinitro-Ortho-Sec-Butyl Phenol

Dinoseb

DN 289

DNBP

DNOSBP

DNSBP

Elgetol

Elgetol 318

ENT 1,122

Gebutox

Hivertox

Kiloseb

Knoxweed

Ladob

Laseb

2-(1-Methylpropyl)-4,6-Dinitrophenol

Nitropone

Phenol, 2-sec-Butyl-4,6-Dinitro-

Phenol, 2-(1-Methylpropyl)-4,6-Dinitro-

Phenol, 2-(1-Methylpropyl)-4,6-Dinitro-

Premerg

Sinox General

Subitex

12

Xylenes; CASRN 1330-20-7 (01/01/92)

13

Toluene; CASRN 108-88-3 (01/01/92)

14

Nitrogen dioxide; CASRN 10102-44-0 (01/01/92)

15

Ethylbenzene; CASRN 100-41-4 (01/01/92)

Enter keywords or Read or Scan or Mail

--read 13

Toluene; CASRN 108-88-3 (01/01/92)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented

in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Toluene

File On-Line 01/31/87

Category (section)	Status	Last Revised
-----	-----	-----
Oral RfD Assessment (I.A.)	on-line	08/01/90
Inhalation RfC Assessment (I.B.)	pending	07/01/90
Carcinogenicity Assessment (II.)	on-line	08/01/90
Drinking Water Health Advisories (III.A.)	on-line	09/01/90

U.S. EPA Regulatory Actions (IV.)

on-line

01/01/92

Supplementary Data (V.)

no data

I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Toluene

CASRN -- 108-88-3

Last Revised -- 08/01/90

The Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this

file when a review of that evaluation is completed.

<<< Toluene >>>

___ I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
-----	-----	-----	---	-----
Changes in liver and kidney weights	NOAEL: 312 mg/kg converted to 223 mg/kg/day	1000	1	2E-1 mg/kg/day
13-Week Rat Gavage Study	LOAEL: 625 mg/kg converted to 446 mg/kg/day			
NTP, 1989				

*Conversion Factors: Dose adjusted for gavage schedule of 5 days/week.

<<< Toluene >>>

___ I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

NTP (National Toxicology Program). 1989. Toxicology and Carcinogenesis Studies of toluene in F344/N rats and B6C3F1 mice. Technical Report Series No. 371. Research Triangle Park, NC.

The oral toxicity of toluene was investigated in this subchronic gavage study in F344 rats. Groups of 10 rats/sex/group were administered toluene in corn oil at dosage levels of 0, 312, 625, 1250, 2500, or 5000 mg/kg for 5 days/week for 13 weeks. All animals receiving 5000 mg/kg died within the

first week. One female and 8 males in the 2500 mg/kg group died, but 2 of these were due to gavage errors. No deaths occurred at lower doses. Several toxic effects were noted at doses greater than or equal to 2500 mg/kg, including prostration, hypoactivity, ataxia, piloerection, lacrimation, excessive salivation, and body tremors. No signs of biologic significance were seen in groups receiving less than or equal to 1250 mg/kg. The only significant change in body weight was a decrease ($p < 0.05$) for males in the 2500 mg/kg group. There were no toxicologically significant changes in hematology or urinalysis for any group of animals. Biochemical changes, including a significant increase ($p < 0.05$) in SGOT in 2500 males and a dose-related increase in cholinesterase in females receiving 2500 and 5000 mg/kg, were not considered to be biologically significant. There were several pathologic findings and organ weight changes in the liver, kidney, brain, and urinary bladder. In males, absolute and relative weights of both the liver and kidney were significantly increased ($p < 0.05$) at doses greater than or equal to 625 mg/kg. In females, absolute and relative weights of the liver, kidney, and heart were all significantly increased at doses greater than or equal to 1250 mg/kg ($p < 0.01$ for all comparisons except $p < 0.05$ for absolute kidney and heart weights at 1250 mg/kg). Histopathologic lesions in the liver consisted of hepatocellular hypertrophy, occurring at greater than or equal to 2500 mg/kg. Nephrosis was observed in rats that died, and damage to the tubular epithelia of the kidney occurred in terminally sacrificed rats. Histopathologic changes were also noted in the brain and urinary bladder. In the brain, mineralized foci and necrosis of neuronal cells were observed in males and females at 2500 mg/kg and males at 1250 mg/kg. In the bladder, hemorrhage of the muscularis was seen in males and females at 5000 mg/kg and males at 2500 mg/kg. The NOAEL for this study is 312 mg/kg/day based on liver and kidney weight changes in male rats at 625 mg/kg. The toxicologic significance of these organ weight changes is strengthened by the occurrence of histopathologic changes in both the liver and kidney at higher doses.

Because the exposure was for 5 days/week, this dose is converted to $312 \times 5/7 = 223$ mg/kg/day. The LOAEL is 625 mg/kg, which is 446 mg/kg/day when converted.

NTP (1989) also conducted a 13-week gavage study in B6C3F1 mice, following the same regimen described above. All mice receiving 5000 mg/kg died and 8/20 receiving 2500 mg/kg also died. Signs of toxicity seen in animals receiving greater than or equal to 2500 mg/kg included subconvulsive jerking, prostration, impaired grasping reflex, bradypnea, hypothermia, ataxia, and hypoactivity. By week 13, the mean body weight of 2500 mg/kg males was significantly ($p < 0.05$) lower than controls. No other significant changes were reported for any group, including macroscopic observation, organ weight means, or clinical pathology parameters. The NOAEL for mice in this study was 1250 mg/kg.

The subchronic study by Wolf et al. (1956) is supportive of the NTP studies. Groups of 10 female Wistar rats were administered gavage doses of 0, 118, 354, or 590 mg/kg toluene dissolved in olive oil. A total of 138 doses were administered over 193 days, resulting in average doses of approximately 0, 84, 253, or 422 mg/kg/day. Hematologic, behavioral, gross and histopathologic examinations were conducted with no toxic effects being reported at any dose. Therefore, the highest dose of 422 mg/kg/day is considered to be the NOAEL for this study. However, this study is not used as the basis for the RfD because the LOAEL of 446 mg/kg/day identified by NTP (1989) is too close to the NOAEL identified by Wolf et al. (1956). Also, the NTP study indicated that male rats are more sensitive to toluene and the Wolf study utilized only female rats.

<<< Toluene >>>

I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 1000. An uncertainty factor of 1000 was applied to account for inter- and intraspecies extrapolations, for subchronic-to-chronic extrapolation and for limited reproductive and developmental toxicity data.

MF = 1.

<<< Toluene >>>

 I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

Kostas and Hotchin (1981) exposed NYLAR mice pre- and post-natally to toluene provided in the drinking water at concentrations of 0, 16, 80, or 400 ppm. Effects were noted in all dosed groups on rotorod performance, measured at 45 to 55 days of age, but there was an inverse dose-response relationship. No effects of toluene exposure were seen on maternal fluid consumption, offspring mortality rate, development of eye or ear openings, or surface-righting response. This study is not suitable for use in risk assessment because only 6 to 9 pregnancies/dose group were obtained, and because the dose-response relationship was inverse.

In an abstract providing limited information, Nawrot and Staples (1979) reported an increase in embryonic lethality in mice exposed to toluene from days 6 to 15 of gestation. Pregnant CD-1 dams were administered 0.3, 0.5, or 1.0 mL/kg bw, 3 times/day (equivalent to approximately 780, 1300, or 2600 mg/kg/day). Maternal toxicity was not observed at any dose level, but toluene was shown to be teratogenic at the high dose and embryo-lethal at the low dose. These levels are higher than the NOAEL demonstrated by the NTP (1989) study.

Several subchronic and chronic inhalation studies have been performed on toluene but are not considered to be suitable for deriving an oral RfD. These studies are summarized nicely in the introduction to the 2-year inhalation bioassay by NTP, 1989. The studies identify the following potential target organs: kidney (male rat); hematologic effects (mice); central nervous system (rats, mice, primates); developmental toxicity (rats, rabbits). It is beyond the scope of this oral RfD summary sheet to describe each of these studies, but the two chronic (2 year) inhalation studies are summarized briefly below.

In a 2-year inhalation study by NTP (1989), F344 rats (60/sex/group) were exposed to 0, 600, or 1200 ppm toluene and B6C3F1 mice (60/sex/group) to 0, 120, 600, or 1200 ppm toluene for 6.5 hours/day, 5 days/week. Ten animals/group (except male mice) were removed at 15 months for toxicologic evaluation. At 15 months, there was an increased incidence and severity of nonneoplastic lesions of the nasal cavity of exposed rats. Minimal hyperplasia of the bronchial epithelium was seen in 4/10 female mice at 1200 ppm. There were no significant differences in survival among any group of animals during the 2-year study. Mean body weights were generally similar for all groups throughout the study. Nephropathy was seen in almost all rats with the severity somewhat increased in exposed rats. There were also effects on the olfactory and respiratory epithelia of exposed rats. No biologically important lesions were seen in any groups of mice. There was no evidence of carcinogenicity for any group of animals in this study.

A chronic inhalation study in rats performed by CIIT (1980) failed to produce an adverse effect. Groups of 40 F344 rats/sex were exposed to 30, 100, or 300 ppm toluene for 6 hours/day, 5 days/week for 24 months. An unexposed group of 120 rats/sex served as a control. Clinical chemistry, hematology, and urinalysis testing were conducted at 18 and 24 months. All

parameters measured at the termination of the study were normal except for a dose-related reduction in hematocrit values in females exposed to 100 and 300 ppm toluene. The highest dose of 300 ppm was considered to be a NOAEL.

<<< Toluene >>>

 I.A.5. CONFIDENCE IN THE ORAL RfD

Study: High

Data Base: Medium

RfD: Medium

Confidence in the principal study is high because a sufficient number of animals/sex were tested in each of six dose groups (including vehicle controls) and many parameters were studied. The same protocol was tested in both mice and rats, with rats being identified as the more sensitive species. The data base is rated medium because it is supported by a 6-month oral study. It is not higher than medium because there is no reproductive study. Also, the oral studies are all subchronic, with the critical study being only 13 weeks in duration. Medium confidence in the RfD follows.

<<< Toluene >>>

 I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Agency RfD Work Group Review: 05/20/85, 08/05/85, 08/05/86, 05/17/90,
06/20/90

Verification Date: 06/20/90

I.A.7. EPA CONTACTS (ORAL RfD)

Sue Velazquez / ORD -- (513)569-7571 / FTS 684-7571

Krishan Khanna / ODW -- (202)260-7588 / FTS 260-7588

I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Toluene

CASRN -- 108-88-3

A risk assessment for this substance/agent is under review by an EPA work group.

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Toluene

CASRN -- 108-88-3

Last Revised -- 08/01/90

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Toluene >>>

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classified

Basis -- No human data and inadequate animal data. Toluene did not produce positive results in the majority of genotoxic assays.

<<< Toluene >>>

___ II.A.2. HUMAN CARCINOGENICITY DATA

None.

<<< Toluene >>>

___ II.A.3. ANIMAL CARCINOGENICITY DATA

A chronic (106-week) bioassay of toluene in F344 rats of both sexes reported no carcinogenic responses (CIIT, 1980). A total of 960 rats were exposed by inhalation for 6 hours/day, 5 days/week to toluene at 0, 30, 100, or 300 ppm. Groups of 20/sex/dose were sacrificed at 18 months. Gross and microscopic examination of tissues and organs identified no increase in neoplastic tissue or tumor masses among treated rats when compared with controls. The study is considered inadequate because the highest dose administered was well below the MTD for toluene and because of the high incidence of lesions and pathological changes in the control animals.

Several studies have examined the carcinogenicity of toluene following repeated dermal applications. Toluene (dose not reported) applied to shaved interscapular skin of 54 male mice (strains A/He, C3HeB, SWR) throughout their lifetime (3 times weekly) produced no carcinogenic response (Poel, 1963). One drop of toluene (about 6 mL) applied to the dorsal skin of 20 random-bred albino mice twice weekly for 50 weeks caused no skin papillomas or carcinomas after a 1-year latency period was allowed (Coombs et al., 1973). No increase

in the incidence of skin or systemic tumors was demonstrated in male or female mice of three strains (CF, C3H, or CBaH) when toluene was applied to the back of 25 mice of each sex of each strain at 0.05-0.1 mL/mouse, twice weekly for 56 weeks (Doak et al., 1976). One skin papilloma and a single skin carcinoma were reported among a group of 30 mice treated dermally with one drop of 0.2% (w/v) solution toluene twice weekly, administered from droppers delivering 16-20 uL per drop for 72 weeks (Lijinsky and Garcia, 1972). It is not reported whether evaporation of toluene from the skin was prevented during these studies.

<<< Toluene >>>

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Toluene was found to be nonmutagenic in reverse mutation assays with *S. typhimurium* (Mortelmans and Riccio, 1980; Nestmann et al., 1980; Bos et al., 1981; Litton Bionetics, Inc., 1981; Snow et al., 1981) and *E. coli* (Mortelmans and Riccio, 1980), with and without metabolic activation. Toluene did not induce mitotic gene conversion (Litton Bionetics, Inc., 1981; Mortelmans and Riccio, 1980) or mitotic crossing over (Mortelmans and Riccio, 1980) in *S. cerevisiae*. Although Litton Bionetics, Inc. (1981) reported that toluene did not cause increased chromosomal aberrations in bone marrow cells, several Russian studies (Dobrokhotov, 1972; Lyapkalo, 1973) report toluene as effective in causing chromosomal damage in bone marrow cells of rats. There was no evidence of chromosomal aberrations in blood lymphocytes of workers exposed to toluene only (Maki-Paakkanen et al., 1980; Forni et al., 1971), although a slight increase was noted in workers exposed to toluene and benzene (Forni et al., 1971; Funes-Craviota et al., 1977). This finding is supported by studies of cultured human lymphocytes exposed to toluene in vitro; no elevation of chromosomal aberrations or sister chromatid exchanges was observed (Gerner-

Smidt and Friedrich, 1978).

-----<<< Toluene >>>-----

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

-----<<< Toluene >>>-----

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

-----<<< Toluene >>>-----

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. ECAO-CIN-408.

<<< Toluene >>>

II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The values in the 1987 Drinking Water Criteria Document for Toluene have received peer and administrative review.

Agency Work Group Review: 09/15/87

Verification Date: 09/15/87

II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Dharm V. Singh / ORD -- (202)260-5958 / FTS 260-5958

Robert E. McGaughy / ORD -- (202)260-5898 / FTS 260-5898

III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

___III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Toluene

CASRN -- 108-88-3

Last Revised -- 09/01/90

The Office of Drinking Water provides Drinking Water Health Advisories (HAs) as technical guidance for the protection of public health. HAs are not enforceable Federal standards. HAs are concentrations of a substance in drinking water estimated to have negligible deleterious effects in humans, when ingested, for a specified period of time. Exposure to the substance from other media is considered only in the derivation of the lifetime HA. Given the absence of chemical-specific data, the assumed fraction of total intake from drinking water is 20%. The lifetime HA is calculated from the Drinking Water Equivalent Level (DWEL) which, in turn, is based on the Oral Chronic Reference Dose. Lifetime HAs are not derived for compounds which are potentially carcinogenic for humans because of the difference in assumptions concerning toxic threshold for carcinogenic and noncarcinogenic effects. A more detailed description of the assumptions and methods used in the derivation of HAs is provided in Background Document 3 in Service Code 5.

<<< Toluene >>>

___III.A.1. ONE-DAY HEALTH ADVISORY FOR A CHILD

One-day HA -- 2E+1 mg/L

NOAEL -- 21.5 mg/kg/day

UF -- 10 (allows for intrahuman variability with the use of a NOAEL from a human study)

Assumptions -- 1 L/day water consumption for a 10-kg child

Principal Study -- Gamberale and Hultengren, 1972

This study reported that a 20-minute exposure to 100 ppm toluene was a no-effect level when determined by perceptual speed and reaction time tests in human volunteers. At 200 ppm, toluene was noted as clearly causing toxic effects such as incoordination, exhilaration, and prolonged reaction time. These and other data support the selection of 100 ppm (377 mg/cu.m) toluene as the NOAEL in humans exposed for up to 8 hours. Based on the conditions of exposure and an assumed absorption rate of 60%, this level is equivalent to 21.5 mg/kg/day.

<<< Toluene >>>

___ III.A.2. TEN-DAY HEALTH ADVISORY FOR A CHILD

No information was found in the available literature that was suitable for determination of a Ten-day HA value. It is, therefore, recommended that the DWEL, adjusted for a 10-kg child (3 mg/L) be used as the Ten-day HA value.

<<< Toluene >>>

___ III.A.3. LONGER-TERM HEALTH ADVISORY FOR A CHILD

No information was found in the available literature that was suitable for determination of a Longer-term HA value. It is, therefore, recommended that the DWEL, adjusted for a 10-kg child (3 mg/L) be used as the Longer-term HA

value for a child.

<<< Toluene >>>

___ III.A.4. LONGER-TERM HEALTH ADVISORY FOR AN ADULT

No information was found in the available literature that was suitable for determination of a Longer-term HA value. It is, therefore, recommended that the DWEL, adjusted for a 70-kg adult (10 mg/L) be used as the Longer-term HA value for an adult.

<<< Toluene >>>

___ III.A.5. DRINKING WATER EQUIVALENT LEVEL / LIFETIME HEALTH ADVISORY

DWEL -- 7E-0 mg/L

Assumptions -- 2 L/day water consumption for a 70-kg adult

RfD Verification Date -- 06/20/90

Lifetime HA -- 1E-0 mg/L

Assumptions -- 20% exposure by drinking water

Principal Study -- NTP, 1989 (This study was used in the derivation of the chronic oral RfD; see Section I.A.2.)

<<< Toluene >>>

___ III.A.6. ORGANOLEPTIC PROPERTIES

Taste threshold in water is reported as 0.04 and 1 mg/L. Odor threshold in water is reported as 0.04 and 1 mg/L.

<<< Toluene >>>

___ III.A.7. ANALYTICAL METHODS FOR DETECTION IN DRINKING WATER

Analysis of toluene is by a purge-and-trap gas chromatographic procedure used for the determination of volatile aromatic and unsaturated organic compounds in water.

<<< Toluene >>>

___ III.A.8. WATER TREATMENT

Treatment options for removing toluene from drinking water sources include air stripping and adsorption onto granular activated carbon.

<<< Toluene >>>

___ III.A.9. DOCUMENTATION AND REVIEW OF HAS

U.S. EPA. 1990. Final Draft of the Drinking Water Criteria Document for Toluene. Office of Drinking Water, Washington, DC.

EPA review of HAS in 1986.

Public review of HAS in 1987.

Science Advisory Board review to be determined.

Preparation date of this IRIS summary -- 08/20/90

III.A.10. EPA CONTACTS

Krishan Khanna / ODW -- (202)260-9568 / FTS 260-9568

Edward V. Ohanian / ODW -- (202)260-7571 / FTS 260-7571

III.B. OTHER ASSESSMENTS

Substance Name -- Toluene

CASRN -- 108-88-3

Content to be determined.

IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Toluene

CASRN -- 108-88-3

Last Revised -- 01/01/92

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Toluene >>>

__IV.A. CLEAN AIR ACT (CAA)

__IV.A.1. CAA REGULATORY DECISION

Action -- Decision not to regulate

Considers technological or economic feasibility? -- NO

Discussion -- The U.S. EPA concluded that current information does not indicate that toluene endangers public health at ambient concentrations (excluding emergency releases), and thus no regulation directed specifically at toluene is necessary at this time under the CAA.

Reference -- 45 FR 22195 (05/25/84)

EPA Contact -- Emissions Standards Division, OAQPS
(919)541-5571 / FTS 629-5571

-----<<< Toluene >>>-----

IV.B. SAFE DRINKING WATER ACT (SDWA)

IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value (status) -- 1 mg/L (Final, 1991)

Considers technological or economic feasibility? -- NO

Discussion -- EPA has set a MCLG for toluene based on its potential adverse effects reported in a 13-week oral study in rats. The MCLG is based upon a DWEL of 7 mg/L and an assumed drinking water contribution of 20 percent.

Reference -- 54 FR 22062 (05/22/89)

EPA Contact -- Health and Ecological Criteria Division / OST /

(202) 260-7571 / FTS 260-7571; or Safe Drinking Water Hotline / (800) 426-4791

<<< Toluene >>>

___IV.B.2. MAXIMUM CONTAMINANT LEVEL (MCL) for Drinking Water

Value -- 1 mg/L (Final, 1991)

Considers technological or economic feasibility? -- YES

Monitoring requirements -- All systems initially monitored for four consecutive quarters; repeat monitoring dependent upon detection, vulnerability status and system size.

Analytical methodology -- Gas chromatography (EPA 502.2, 503.1); gas chromatography/mass spectrometry (EPA 524.1, 524.2): PQL= 0.005 mg/L.

Best available technology -- Granular activated carbon; packed tower aeration

Reference -- 56 FR 3526 (01/30/91); 56 FR 30266 (07/01/91)

EPA Contact -- Drinking Water Standards Division / OGWDW /
(202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

<<< Toluene >>>

___IV.B.3. SECONDARY MAXIMUM CONTAMINANT LEVEL (SMCL) for Drinking Water

Value -- 0.04 mg/L (Proposed, 1989)

Considers technological or economic feasibility? -- NO

Discussion -- SMCLs are non-enforceable and establish limits for contaminants which may affect the aesthetic qualities (e.g. taste and odor) of drinking water. It is recommended that systems monitor for these contaminants every three years. More frequent monitoring for contaminants such as pH, color, odor or others may be appropriate under certain circumstances. The SCML for toluene is based on odor detection. Promulgation deferred following public comment (56 FR 3526).

Reference -- 54 FR 22062 (05/22/89); 56 FR 3526 (01/30/91)

EPA Contact -- Drinking Water Standards Division / OGWDW /
(202) 260-7575 / FTS 260-7575; or Safe Drinking Water Hotline / (800) 426-4791

<<< Toluene >>>

___IV.B.4. REQUIRED MONITORING OF "UNREGULATED" CONTAMINANTS

No data available

-----<<< Toluene >>>-----

___IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption: 1.43E+4 ug/L

Fish Consumption Only: 4.24E+5 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- The WQC of 1.43E+4 ug/L is based on consumption of contaminated aquatic organisms and water. A WQC of 4.24E+5 ug/L has also been established based on consumption of contaminated aquatic organisms alone.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

<<< Toluene >>>

IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute LEC -- 1.75E+4 ug/L

Chronic LEC -- none

Marine:

Acute LEC -- 6.3E+3 ug/L

Chronic LEC -- 5.0E+3 ug/L

Considers technological or economic feasibility? -- NO

Discussion -- The values that are indicated as "LEC" are not criteria, but are the lowest effect levels found in the literature. LEC's are given when the minimum data required to derive water quality criteria are not available.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division / OWRS
(202)260-1315 / FTS 260-1315

-----<<< Toluene >>>-----

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

-----<<< Toluene >>>-----

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

-----<<< Toluene >>>-----

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

__IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

-----<<< Toluene >>>-----

__IV.G. SUPERFUND (CERCLA)

__IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1000 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- The final RQ is based on aquatic toxicity, as established under Section 311(b)(4) of the Clean Water Act, ignitability, and chronic toxicity. Available data indicate that the aquatic 96-Hour Median Threshold Limit for Toluene is between 10 and 100 ppm. Its closed-cup flash point is less than 100F and its boiling point is >100F. RQ assignments based on chronic toxicity

reflect two primary attributes of the hazardous substance, the minimum effective dose (MED) levels for chronic exposure (mg/day for a 70-kg person) and the type of effect (liver necrosis, teratogenicity, etc). A composite score is determined from an evaluation of these two attributes. Toluene was determined to have a composite score between 6 and 20, corresponding to a chronic toxicity RQ of 1000 pounds.

Reference -- 50 FR 13456 (04/04/85); 54 FR 33418 (08/14/89)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)260-3000 / FTS 260-3000

_V. SUPPLEMENTARY DATA

Substance Name -- Toluene
CASRN -- 108-88-3

Not available at this time.

_VI. BIBLIOGRAPHY

Substance Name -- Toluene

CASRN -- 108-88-3

Last Revised -- 08/01/91

VI.A. ORAL RfD REFERENCES

CIIT (Chemical Industry Institute of Technology). 1980. A 24-month inhalation toxicology study in Fischer-344 rats exposed to atmospheric toluene. CIIT, Research Triangle Park, NC.

Kostas, J. and J. Hotchin. 1981. Behavioral effects of low-level perinatal exposure to toluene in mice. Neurobehav. Toxicol. Teratol. 3: 467-469.

Nawrot, P.S. and R.E. Staples. 1979. Embryo-fetal toxicity and teratogenicity of benzene and toluene in the mouse. Teratology. 19: 41A (abstr.)

NTP (National Toxicology Program). 1989. Toxicology and carcinogenesis studies of toluene (CAS No. 108-88-3) in F344/N rats and B5C3F1 mice (inhalation studies). Technical Report Series No. 371. Research Triangle Park, NC.

Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health. 14: 387-398.

-----<<< Toluene >>>-----

VI.B. INHALATION RfD REFERENCES

None

-----<<< Toluene >>>-----

VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Bos, R.P., R.M.E. Brouns, R. van Doorn, J.L.G. Theuws and P.Th. Henderson. 1981. Non-mutagenicity of toluene, o-, m- and p-xylene, o-methylbenzylalcohol and o-methylbenzylsulfate in the Ames assay. *Mutat. Res.* 88(3): 273-279.

CIIT (Chemical Industry Institute of Toxicology). 1980. A twenty-four-month inhalation toxicology study in Fischer-344 rats exposed to atmospheric toluene. *Executive Summary and Data Tables, October 15.* CIIT, Research Triangle Park, NC.

Coombs, M.M., T.S. Bhatt and C.J. Croft. 1973. Correlation between carcinogenicity and chemical structure in cyclopenta(a)phenanthrenes. *Cancer Res.* 33(4): 832-837.

Doak, S.M.A., B.J.E. Simpson, P.F. Hunt and D.E. Stevenson. 1976. The carcinogenic response in mice to the topical application of propane sultone to

the skin. Toxicology. 6: 139-154.

Dobrokhotov, V.B. 1972. The mutagenic influence of benzene and toluene under experimental conditions. Gig. Sanit. 37: 36-39. (Rus.) (Evaluation of workers exposed to benzene or toluene or both. Arch. Environ. Health. 22(3): 373-378.

Funes-Craviota, F., B. Kolmodin-hedman, J. Lindsten, et al. 1977. Chromosome aberrations and sister-chromatid exchange in workers in chemical laboratories and a rototyping factory and in children of women laboratory workers. Lancet. 2: 322-325.

Gerner-Smidt, P. and U. Friedrich. 1978. The mutagenic effect of benzene, toluene and xylene studied by the SCE technique. Mutat. Res. 58(2-3): 313-316.

Lijinsky, W. and H. Garcia. 1972. Skin carcinogenesis tests of hydrogenated derivatives of anthanthrene and other polynuclear hydrocarbons. Z. Krebsforsch. Klin. Onkol. 77: 226-230.

Litton Bionetics, Inc. 1981. Mutagenicity Evaluation of Toluene Mouse Dominant Lethal Assay. Final Report. Submitted to the American Petroleum Institute, Washington, DC in January, 1981. LBI Project No. 21141-05. Litton Bionetics, Inc., Kensington, MD. p. 58.

Lyapkin, S. Salmonella/mammalian-microsome assay. Mutat. Res. 79: 203-212.

Poel, W.E. 1963. Skin as a test site for the bioassay of carcinogens and carcinogen precursors. Natl. Cancer Inst. Monogr. 10: 611-625.

Snow, L., P. MacNair and B.C. Casto. 1981. Mutagenesis testing of toluene in Salmonella strains TA100 and TA98. Report prepared for the U.S. EPA by Northrup Services, Inc., Research Triangle park, NC.

U.S. EPA. 1987. Drinking Water Criteria Document for Toluene. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

-----<<< Toluene >>>-----

VI.D. DRINKING WATER HA REFERENCES

Gamberale, F. and M. Hultengren. 1972. Toluene exposure. II. Psychophysiological functions. Work Environ. Health. 9(3): 131-139. (CA 79: 950-1973).

U.S. EPA. 1990. Final Draft of the Drinking Water Criteri

Enter keywords or Read or Scan or Mail

--

VI.D. DRINKING WATER HA REFERENCES

Gamberale, F. and M. Hultengren. 1972. Toluene exposure. II. Psychophysiological functions. Work Environ. Health. 9(3): 131-139. (CA

August, 1988

METHYL PARATHION

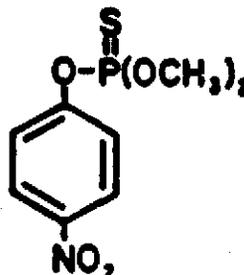
Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

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 PROPERTIESCAS No. 298-00-0Structural Formula

0,0-Dimethyl-0-(4-nitrophenyl) phosphorothioic acid

Synonyms

- Metaphos; Dimethyl parathion; Folidol M; Metocide; Penncap M; Sinafid M-48; Wofatox; Cekumethion; Devithion; Drexel Methyl Parathion 4E; E601; Fosferno M50; Gearfos; Parataf; Partron-M; Tekwaisa; Parathion-methyl (Meister, 1988).

Uses

- A restricted-use pesticide for control of various insects of economic importance; especially effective for boll weevil control (Meister, 1988)

Properties (Hawley, 1981; Meister, 1988; CHEMLAB, 1985; TDB, 1985)

Chemical Formula	$C_8H_{10}O_5NSP$
Molecular Weight	263.23
Physical State (25°C)	White crystalline solid
Boiling Point	--
Melting Point	35 to 36°C
Density	--
Vapor Pressure (20°C)	0.97×10^{-5} mm Hg
Specific Gravity	--
Water Solubility (25°C)	55 to 60 mg/L
Log Octanol/Water Partition Coefficient	3.11 (calculated)
Taste Threshold	--
Odor Threshold	--
Conversion Factor	--

Occurrence

- Methyl parathion has been found in 1,070 of 27,082 surface water samples analyzed and in 8 of 2,836 ground water samples (STORET, 1988). Samples were collected at 3,558 surface water locations and 2,111 ground water locations, and methyl parathion was found in 20 states. The 95th percentile of all nonzero samples was 1.18 ug/L in surface water and 0.05 ug/L in ground water sources. The maximum concentration found was 13 ug/L in surface water and 0.05 ug/L in ground water. This information is provided to give a general impression of the occurrence of this chemical in ground and surface waters as

reported in the STORET database. The individual data points retrieved were used as they came from STORET and have not been confirmed as to their validity. STORET data is often not valid when individual numbers are used out of the context of the entire sampling regime, as they are here. Therefore, this information can only be used to form an impression of the intensity and location of sampling for a particular chemical.

Environmental Fate

- Methyl parathion (99% pure) at 10 ppm was added to sea water and exposed to sunlight; some samples were also kept in the dark (controls). After 6 days, 57% of the parent compound had degraded but the degradates were not identified. Since only 27% of the parent compound had degraded in the dark controls, this indicates that methyl parathion is subject to photodegradation in sea water (U.S. EPA, 1981).
- The degradation rate of two formulations (EC and MCAP) of methyl parathion, applied at 0.04 ppm, was compared in a sediment/water system. Degradates were not identified; however, the parent compound had a half-life of 1 to 3 days in water. In the hydrosol plus sediment, methyl parathion applied as an emulsifiable concentrate formulation had a half-life of 1 to 3 days, whereas for the micro-encapsulated formulation, the half-life was 3 to 7 days (Agchem, 1983).
- Methyl parathion was relatively immobile in 30-cm soil columns of sandy loam, silty clay loam and silt loam soils leached with 15.7 inches of water, with no parent compound found below 10 cm or in the column leachate, which was the case for the column of sand (Pennwalt Corporation, 1977).
- Methyl parathion (MCAP or EC formulation) at 5 lb ai/A (active ingredient/acre) was detected in runoff water from field plots irrigated 4 to 5 days posttreatment. Levels found in soil and turf plots ranged from 0.13 to 21 ppm and 0.17 to 0.20 ppm, respectively (Pennwalt Corporation, 1972).
- A field dissipation study with methyl parathion (4 lb/gal EC) at 3 lb ai/A, applied alone or in combination with Curacron, dissipated to nondetectable levels (<0.05 ppm) within 30 days in silt loam and loamy sand soils (Ciba-Geigy Corporation, 1978).

III. PHARMACOKINETICS

Absorption

- Braeckman et al. (1983) administered a single oral dose of ³⁵S-methyl parathion (20 mg/kg) by stomach tube to four mongrel dogs. Peak concentrations in plasma ranged from 0.13 to 0.96 ug/mL, with peak levels occurring 2 to 9 hours after dosing. In two dogs given single oral doses of ³⁵S-methyl parathion (3 mg/kg) in this study, absorption was estimated to be 77 and 79%, based on urinary excretion of label.

The authors concluded that methyl parathion was well absorbed from the gastrointestinal tract.

- Hollingworth et al. (1967) gave a single oral dose of ^{32}P -labeled methyl parathion by gavage (3 or 17 mg/kg, dissolved in olive oil) to male Swiss mice. Recovery of label in the urine reached a maximum of about 85%, most of this occurring within 18 hours of dosing. The amount of label in the feces was low, never exceeding 10% of the dose. This indicated that absorption was at least 90% complete.

Distribution

- Ackermann and Engst (1970) administered methyl parathion to pregnant albino rats and examined the dams and fetuses for the distribution of the pesticide. The pregnant rats (weighing about 270 g each) were given 3 mg (11.1 mg/kg) of methyl parathion orally on days 1 to 3 of gestation and sacrificed 30 minutes after the last dose. Methyl parathion was detected in the maternal liver (25 ng/g), placenta (80 ng/g), and in fetal brain (35 ng/g), liver (40 ng/g) and back musculature (60 ng/g).

Metabolism

- Hollingworth et al. (1967) gave ^{32}P -labeled methyl parathion by gavage (3 or 17 mg/kg, dissolved in olive oil) to male Swiss mice. About 85% of the label appeared in the urine within 72 hours. Urinary metabolites identified 24 hours after the low dose were: dimethyl phosphoric acid (53.1%); dimethyl phosphorothioic acid (14.9%); desmethyl phosphate (14.1%); desmethyl phosphorothioate (11.7%); phosphoric acid (2.0%); methyl phosphoric acid (1.7%); and phosphate (0.6%). The radioactivity in the urine was fully accounted for by hydrolysis products and P=0 activation products. No evidence was found for reduction of the nitro group to an amine, oxidation of the ring methyl group, or hydroxylation of the ring. A generally similar pattern was observed at the high dose, except for a lower percentage of dimethyl phosphoric acid (31.9%) and higher percentages of desmethyl phosphate (23.1%) and desmethylphosphorothionate (18.8%). Based on this, the authors proposed a metabolic scheme involving oxidative desulfuration, oxidative cleavage of the phospho group from the ring and hydrolysis of the phosphomethyl esters.
- Neal and DuBois (1965) investigated the in vitro detoxification of methyl parathion and other phosphorothioates using liver microsomes prepared from adult male Sprague-Dawley rats. Metabolism was found to involve oxidative desulfuration followed by hydrolysis to yield p-nitrophenol. Extracts from livers of adult male rats exhibited higher metabolic activity than that of adult females (3.2 versus 1.9 units, where one unit equals 1 μg p-nitrophenol/50 mg liver extract) ($p < 0.01$). The activity of weanling rat liver (2.7 units) was intermediate between these two. In the case of adult CF-1 mice, the activity of female liver (3.2 units) was significantly greater ($p < 0.05$) than that of the males (2.3 units). The activity of young adult male guinea pig liver extracts was 5.6 units. The authors noted

that these differences in metabolic detoxification rates correlated with the sex and species differences in susceptibility to the acute oral toxic effects of this family of compounds.

- Nakatsugawa et al. (1968) investigated the degradation of methyl parathion using liver microsomes from adult male rats and rabbits (strains not specified). Metabolism occurred by two oxidative pathways: activation of the phosphorus-sulfur bond to the phosphorus-oxygen analog, and cleavage at the aryl phosphothioate bond to yield p-nitrophenol. These reactions occurred only in the presence of oxygen and NADPH₂. The amounts of phenol and oxygen analog formed were 3.8 and 3.7 μM in the rabbit liver extract and 2.5 and 5.4 μM in the rat liver extract, respectively.

Excretion

- Braeckman et al. (1983) administered individual doses of 3 mg/kg of ³⁵S-methyl parathion to two mongrel dogs. In each dog, the agent was given once intravenously and, 1 week later, once orally via stomach tube. This dosing pattern was repeated once in one dog. Urine was collected every 24 hours for 6 days after each treatment. Urinary excretion 6 days after oral dosing was 63% in the animal without repeated dosing and 70% and 78% in the other. Urinary excretion 6 days after intravenous dosing was 80% in the animal without repeated dosing and 95 to 96% in the other. Most of the label appeared in urine within two days. Other excretory routes were not monitored.
- Hollingworth et al. (1967) gave ³²P-labeled methyl parathion (3 or 17 mg/kg, dissolved in olive oil) by gavage to male Swiss mice. Recovery of label in the urine reached a maximum of about 85%, most of this occurring within 18 hours of dosing. The amount of label in the feces was low, never exceeding 10% of the dose. This indicated that absorption was at least 90% complete.

IV. HEALTH EFFECTS

Humans

Short-term Exposure

- Nemec et al. (1968) monitored cholinesterase (ChE) levels in two workers (entomologists) who examined plants in a cotton field after it had been sprayed with an ultra-low-volume (nonaqueous) preparation of methyl parathion (1.5 to 2 lb/acre). The men entered a cotton field to examine the plants on 3 different days over a 2-week period; two of these occasions were within 2 hours after the ultra-low-volume spraying, and the third occasion was 24 hours after a spraying. After each field trip their arms were washed with acetone and the adhering methyl parathion determined. It was found that contact with the plants 2 hours after spraying resulted in 2 to 10 mg of methyl parathion residue on the arms; exposure 24 hours after spraying resulted in a residue on the arms of 0.16 to 0.35 mg. The amount of

pesticide absorbed was not estimated. No toxic symptoms were experienced by either man, but measurement of red blood cell ChE activity immediately after the third of these exposures showed a decrease in activity to 60 to 65% of preexposure levels. These values did not increase significantly over the next 24 hours. It was concluded that workers should not enter such a field until more than 24 hours, and preferably 48 hours, have elapsed after spraying with ultra-low-volume insecticide sprays. Water emulsion sprays were not tested, but the authors cautioned that it cannot be assumed that they are less hazardous than the ultra-low-volume spray residues.

- Rider et al. (1969, 1970, 1971) studied the toxicity of technical methyl parathion (purity not specified) in human volunteers. Each phase of the study was done with different groups of seven male subjects, five of whom were test subjects and two were vehicle controls (Rider et al., 1969). Each study phase was divided into a 30-day pre-test period for establishing cholinesterase baselines, a 30-day test period when a specific dose of methyl parathion was given, and a post-test period.
- Thirty-two different dosages were evaluated by Rider et al. (1969), ranging from 1 to 19 mg/day. Early in the study, several of the groups were given more than one dose level during a single phase. The initial amount was 1.0 mg with an increase of 0.5 mg during each succeeding test period up to 15.0 mg/day. At this point, the dose was increased by 1.0 mg/day to a total dose of 19.0 mg/day. Pesticide in corn oil was given orally in capsules, once per day for each test period of 30 days. At no time during any of the studies were there any significant changes in blood counts, urinalyses, or prothrombin times, or was there any evidence of toxic side effects. Cholinesterase activity of the plasma and red blood cells (RBCs) was measured twice weekly prior to, during and after the dosing period. The authors considered a mean depression of 20 to 25% or greater in ChE activity below control levels to be indicative of the toxic threshold. At 11.0 mg/day, a depression of 15% in plasma ChE occurred, but doses up to and including 19 mg/day did not produce any significant ChE depression.
- Rider et al. (1970) studied the effects of 22, 24 and 26 mg/day technical methyl parathion. There were no effects observed at 22 mg/day. At 24 mg/day, plasma and RBC ChE depression was produced in two subjects, the maximum decreases being 24 and 23% for plasma, and 27 and 55% for RBC. The mean maximal decreases (in all five subjects) were 17% for plasma and 22% for RBC. With 26 mg/day RBC ChE depression was again produced in only two of the subjects, with maximum decreases of 25 and 37%. The mean maximum decrease was 18%. Plasma cholinesterase was not significantly altered.
- Rider et al. (1971) assessed the effects of 28 and 30 mg/day technical methyl parathion. At 28 mg/day, a significant decrease in RBC ChE was produced in three subjects (data not given), with a maximum mean decrease of 19%. With a dose of 30 mg/day, a mean maximum depression of 37% occurred. Based on their criteria of 20 to 25% average

depression of ChE activity, the authors concluded that this was the level of minimal incipient toxicity. Body weights of the test subjects were not reported, but assuming an average body weight of 70 kg, a dose of 22 mg/day corresponds to a No-Observed-Adverse-Effect Level (NOAEL) of 0.31 mg/kg/day, and the 30 mg/day dose corresponds to 0.43 mg/kg/day. The NOAEL is considered to be 22 mg/day herein because of the apparent sensitivity of some individual subjects at higher doses to have met the 20 to 25% criteria for ChE depression as an effect.

Long-term Exposure

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

Animals

Short-term Exposure

- Reported oral LD₅₀ values for methyl parathion include 14 and 24 mg/kg in male and female Sherman rats, respectively (Gaines, 1969); 14.5 and 19.5 mg/kg in male and female CD-1 mice, respectively (Haley et al., 1975); 30 mg/kg in male ddY mice (Isshiki et al., 1983); 18.0 and 8.9 mg/kg in male and female Sprague-Dawley rats, respectively (Sabol, 1985); and 9.2 mg/kg in rats of unreported strain (Galal et al., 1977).
- Galal et al. (1977) determined the subchronic median lethal dose (C-LD₅₀) of methyl parathion (purity not specified) in adult albino rats. Groups of 10 animals received an initial daily oral dose (by gavage) of 0.37 mg/kg (4% of the acute oral LD₅₀). Every 4th day the dose was increased by a factor of 1.5 (dose based on the body weight of the animals as recorded at 4-day intervals). Treatment was continued until death or termination at 36 days. Hematological and blood chemistry analyses were performed initially and on the 21st and 36th days of the study. Histopathological studies of the liver, kidneys and heart were also carried out on the 21st and 36th days of treatment. The C-LD₅₀ obtained was 13 mg/kg. The authors concluded that the most predominant hazards of subchronic exposure to methyl parathion were weight loss, hyperglycemia and macrocytic anemia, all probably secondary to hepatic toxicity. Since an increasing dose protocol was used, this study does not identify a NOAEL or a Lowest-Observed-Adverse-Effect Level (LOAEL).
- Daly et al. (1979) administered methyl parathion (technical, 93.65% active ingredient) to Charles River CD-1 mice for 4 weeks at levels of 0, 25 or 50 ppm in the diet. Assuming that 1 ppm in the diet of mice corresponds to 0.15 mg/kg/day (Lehman, 1959), this is equivalent to doses of about 0, 3.75 or 7.5 mg/kg/day. Five animals of each sex were used at each dose level. Mean body weights were lower ($p < 0.05$) than control for all treated animals throughout the test period. Mean food consumption was lower ($p < 0.05$) throughout for all test animals except females at the 25-ppm level. Mortality, physical observations, and gross postmortem examinations did not reveal any treatment-related effects. Cholinesterase measurements were not performed. Based on

body weight gain, the LOAEL for this study was identified as 25 ppm (3.75 mg/kg/day).

- Tegeris and Underwood (1977) examined the effects of feeding methyl parathion (94.32% pure) to beagle dogs (4 to 6 months of age, weighing 5 to 10 kg) for 14 days. Two animals of each sex were given doses of 0, 2.5, 5 or 10 mg/kg/day. All animals survived the 14-day test period. Mean feed consumption and weight gain were significantly ($p < 0.05$) depressed for both sexes at the 5 and 10 mg/kg/day dose levels. After the 3rd day, animals in the high-dose group began vomiting after all meals. Vomiting was observed sporadically at the lower dose levels, particularly during the 2nd week. The authors attributed this to acetylcholinesterase inhibition, but no measurements were reported. No other symptomatology was described. Based on weight loss and vomiting, this study identified a LOAEL of 2.5 mg/kg/day in the dog.
- Fan et al. (1978) investigated the immunosuppressive effects of methyl parathion administered orally to Swiss (ICR) mice. The pesticide (purity not specified) was fed in the diet at dose levels corresponding to 0, 0.08, 0.7 or 3.0 mg/kg/day for 4 weeks. Active immunity was induced by weekly injection of vaccine (acetone-killed Salmonella typhimurium) during the period of diet treatment. Defense against microbial infection was tested by intraperitoneal injection of a single LD₅₀ dose of active S. typhimurium cells. Protection by immunization was stated to be decreased in methyl parathion-treated animals, but no dose-response data were provided. The authors stated that pesticide treatment extending beyond 2 weeks was required to obtain significant increases in mortality. Increased mortality was associated with an increased number of viable bacteria in blood, decreased total gamma-globulins and specific immunoglobins in serum, and reduced splenic blast transformation in response to mitogens.
- Shtenberg and Dzhunusova (1968) studied the effect of oral exposure to methyl parathion (purity not specified) on immunity in albino rats vaccinated with NIISI polyvaccine. Three tests (six animals each) were conducted in which: (a) the vaccination was done after the animals had been on a diet supplying 1.25 mg/kg/day metaphos (methyl parathion) for 2 weeks; (b) the diet and vaccinations were initiated simultaneously; and (c) the diet was initiated 2 weeks after vaccination. The titer of agglutins in immunized control rats was 1:1,200. This titer was decreased in all exposed groups as follows: 1:46 in series (a), 1:75 in series (b) and 1:33.3 in series (c). The authors judged this to be clear evidence of inhibition of immunobiological reactivity in the exposed animals. Changes in blood protein fraction and in serum concentration of albumins were not statistically significant. Based on immune suppression, a LOAEL of 1.25 mg/kg/day was identified.

Dermal/Ocular Effects

- Gaines (1969) reported a dermal LD₅₀ of 67 mg/kg for methyl parathion in male and female Sherman rats.

- Galloway (1984a,b) studied the skin and eye irritation properties of methyl parathion (technical; purity not specified) using albino New Zealand White rabbits. In the skin irritation test, 0.5 mL undiluted pesticide was applied and the treated area occluded for 4 hours. This treatment resulted in dermal edema that persisted for 24 hours, and in erythema that lasted for 6 days. After a total observation period of 9 days, a score of 2.0 was derived, and technical methyl parathion was rated as a weak irritant. In the eye irritation test, 0.1 mL of the undiluted pesticide was applied to nine eyes. Three were washed after exposure, and six were left unwashed. Conjunctival irritation was observed starting at 1 hour and lasting up to 48 hours postexposure. Maximum average irritation scores of 11 and 10.7 were assigned for nonwashed and washed eyes, respectively, and technical methyl parathion was considered a weak irritant.
- Galloway (1985) used guinea pigs to examine the sensitizing potential of methyl parathion (technical; purity not stated). Ten doses of 0.5 mL of a 10% solution (w/v in methanol) were applied to the clipped intact skin of 10 male guinea pigs (albino Hartley strain) over a 36-day period. This corresponds to an average dose of 13.9 mg/kg/day. Another group was treated with 2,4-dinitrochlorobenzene as a positive control. No skin sensitization reaction was observed in methyl parathion-treated animals.
- Skinner and Kilgore (1982) studied the acute dermal toxicity of methyl parathion in male Swiss-Webster mice, and simultaneously determined ED₅₀ values for cholinesterase and acetylcholinesterase inhibition. Methyl parathion (analytical grade, 99% pure) was administered in acetone solution to the hind feet of the mice; the animals were muzzled to prevent oral ingestion through grooming. The dermal LD₅₀ was 1,200 mg/kg. The ED₅₀ was 950 mg/kg for cholinesterase inhibition and 550 mg/kg for acetylcholinesterase inhibition.

Long-term Exposure

- Daly and Rinehart (1980) conducted a 90-day feeding study of methyl parathion (93.65% pure) using Charles River CD-1 mice. Groups of 15 mice of each sex were given diets containing the pesticide at levels of 0, 10, 30 or 60 ppm. Assuming that 1 ppm in the diet of mice corresponds to 0.15 mg/kg/day (Lehman, 1959), this is equivalent to doses of about 0, 1.5, 4.5 or 9.0 mg/kg/day. All mice survived the test. Mean body weights were significantly ($p < 0.05$) depressed for both sexes at 60 ppm throughout the study and for males during the first 5 weeks at 30 ppm. Animals of both sexes had a slight but not significant ($p < 0.05$) increase in the mean absolute and relative brain weights at 60 ppm. There were dose-related decreases ($p < 0.05$) in the mean absolute and relative testes weights of all treated males and in the ovary weights of the females at 30 and 60 ppm. Gross and microscopic examination revealed no dose-related effects. Histological examination revealed no findings in the brain, testes or ovary to account for the observed changes in the weights of these organs. Measurements on ChE were not performed. Based on decreased testes weight, the LOAEL for this study was 10 ppm (1.5 mg/kg/day).

- Tegeris and Underwood (1978) investigated the toxicity of methyl parathion (94.32% a.i.) in beagle dogs fed the pesticide for 90 days at dose levels of 0, 0.3, 1.0 or 3.0 mg/kg/day. Four dogs (4-months old, 4.5 to 8.0 kg) of both sexes were used at each dose level. Soft stools were observed in all treatment groups throughout, and there was also occasional spontaneous vomiting. There were no persistent significant ($p < 0.05$) effects on body weight gain, feed intake, fasting blood sugar, BUN, SGPT, SGOT, hematological, or urological indices. Organ weights were within normal limits, with the exception of pituitary weights of females at 3.0 mg/kg, which were significantly ($p < 0.05$) higher than the control values. Gross and microscopic examination revealed no compound-related abnormalities. Plasma ChE was significantly ($p < 0.05$) depressed in both sexes at 6 and 13 weeks at 3 mg/kg/day, and in the males only at 1.0 mg/kg/day at 13 weeks; erythrocyte ChE was also significantly ($p < 0.05$) depressed in all animals at 6 and 13 weeks at 3 mg/kg/day, and in both sexes at 13 weeks at 1.0 mg/kg/day; brain ChE was significantly ($p < 0.05$) depressed in both sexes at 3.0 mg/kg/day. Based on ChE depression, the NOAEL and LOAEL for this study were identified as 0.3 mg/kg/day and 1.0 mg/kg/day, respectively.
- Ahmed et al. (1981) conducted a 1-year feeding study in beagle dogs. Methyl parathion (93.6% pure) was administered in the diet at ingested dose levels of 0, 0.03, 0.1 or 0.3 mg/kg/day. Eight animals of each sex were included at each dose level, with no overt signs of toxicity noted at any dose. There were no treatment-related changes in food consumption or body weight. Cholinesterase determinations in plasma, red blood cells and brain revealed marginal variations, but the changes were not consistent and were judged by the authors to be unrelated to dosing. Organ weight determinations showed changes in both males and females at 0.1 and 0.3 mg/kg/day, but the changes were neither dose-related nor consistent. It was concluded that there was no demonstrable toxicity of methyl parathion fed to the dogs at these levels. The NOAEL for this study was 0.3 mg/kg/day.
- NCI (1978) conducted a 2-year feeding study of methyl parathion (purity not specified) in F344 rats (50/sex/dose) at dose levels of 0, 20 or 40 ppm in the diet. Assuming that 1 ppm in the diet of rats corresponds to 0.05 mg/kg/day (Lehman, 1959), this is equivalent to dose levels of about 0, 1 or 2 mg/kg/day. Cholinesterase levels were not measured, but no remarkable clinical signs were noted, and no significant ($p < 0.05$) changes were observed in mortality, body weight, gross pathology or histopathology. Based on this, a NOAEL of 40 ppm (2 mg/kg/day) was identified in rats.
- NCI (1978) conducted a chronic (105-week) feeding study in B6C3F₁ mice (50/sex/dose). Animals were initially fed methyl parathion (94.6% pure) at dose levels of 62.5 or 125 ppm. Assuming that 1 ppm in the diet of mice corresponds to 0.15 mg/kg/day (Lehman, 1959), this is equivalent to doses of about 9.4 or 18.8 mg/kg/day. Because of severely depressed body weight gain in males, their doses were reduced at 37 weeks to 20 or 50 ppm, and the time-weighted averages were calculated to be 35 or 77 ppm. This corresponds to doses of

about 5.2 or 11.5 mg/kg/day, respectively. Females were fed at the original levels throughout. Mortality was significantly ($p < 0.05$) increased only in female mice at 125 ppm. Body weights were lower ($p < 0.05$) for both sexes throughout the test period and decreases were dose-related. No gross or histopathologic changes were noted, and ChE activity was not measured. Based on body weight, this study identified a LOEL of 35 ppm (5.2 mg/kg/day) in male mice.

- Daly et al. (1984) conducted a chronic feeding study of methyl parathion (93.65% active ingredient) in Sprague-Dawley (CD) rats (60/sex/dose) at dose levels of 0, 0.5, 5 or 50 ppm in the diet. Using food intake/body weight data given in the study report, these levels approximate doses of about 0, 0.025, 0.25 or 2.5 mg/kg/day. At 24 months, five animals of each sex were sacrificed for qualitative and quantitative tests for neurotoxicity. Ophthalmoscopic examinations were conducted on females at 3, 12 and 24 months and terminally. Hematology, urinalysis and clinical chemistry analyses were performed at 6, 12, 18 and 24 months. Mean body weights were reduced ($p < 0.05$) throughout the study for both sexes at 50 ppm. At this dose level, food consumption was elevated ($p < 0.05$) for males during weeks 2 to 13, but reduced for females for most of the study. Hemoglobin, hematocrit and RBC count were significantly ($p < 0.05$) reduced for females at 50 ppm at 6, 12, 18 and 24 months. For males at 5 and 50 ppm at 24 months, hematocrit and RBC count were significantly ($p < 0.05$) reduced and hemoglobin was reduced, but not significantly ($p < 0.05$). At 50 ppm, plasma and erythrocyte ChE were significantly ($p < 0.05$) depressed for both sexes during the test, and brain ChE was significantly ($p < 0.05$) decreased at termination. Slight decreases in ChE activity were also observed in animals at 5 ppm, but these changes were not statistically significant ($p > 0.05$). For males, the absolute weight and the ratio to brain weight of the testes, kidneys and the liver were reduced by 10 to 16% (not significant, $p > 0.05$) in both the 5- and 50-ppm groups, while for females absolute and organ/body weights for the brain and heart (also heart/brain weight) were found to be elevated significantly ($p < 0.05$) at the same dose levels. Overt signs of cholinergic toxicity (such as alopecia, abnormal gait and tremors) were observed in the 50-ppm animals and in one female at 5 ppm. At 24 months, 15 females were observed to have retinal degeneration. There was also a dose-related occurrence of retinal posterior subcapsular cataracts, possibly related or secondary to the retinal degeneration, since 5 of the 10 cataracts occurred in rats with retinal atrophy. The incidence of retinal atrophy was 20/55 at 50 ppm, 1/60 at 5 ppm, 3/60 at 0.5 ppm and 3/59 in the control group. Examination of the sciatic nerve and other nervous tissue from five rats per sex killed at week 106 gave evidence of peripheral neuropathy (abnormal fibers, myelin corrugation, myelin ovoids) in both sexes at 50 ppm ($p < 0.05$). Too few fibers were examined at the lower doses to perform statistical analyses, but the authors stated that nerves from both sexes in low- and mid-dose groups could not be distinguished qualitatively from controls. Slightly greater severity of nerve changes found in two males was not clearly related to treatment. No other lesions were observed that appeared to be related to ingestion of methyl parathion. Based on hematology, body weight, organ weights, 597

clinical chemistry, retinal degeneration and cholinergic signs, a NOAEL of 0.5 ppm (0.025 mg/kg/day) was identified in this study.

Reproductive Effects

- Lobdel and Johnston (1964) conducted a three-generation study in Charles River rats. Each parental dose group included 10 males and 20 females. The investigators incorporated methyl parathion (99% pure) in the diet of males and females at dose levels of 0, 10 or 30 ppm, except for reduction of each dose by 50% during the initial 3 weeks of treatment, to produce dose equivalents of 0, 1.0 and 3.0 mg/kg/day, respectively. There was no pattern with respect to stillbirths, although the 30-ppm groups had a higher total number of stillborn. Survival was reduced in weanlings of the F_{1a}, F_{1b} and F_{2a} groups at 30 ppm, and in weanlings of the F_{3a} group at 10 ppm. At 30 ppm, there was also a reduction in fertility of the F_{2b} dams at the second mating; the first mating resulted in 100% of the animals having litters, while at the second mating, only 41% had litters. Animals exposed to 10 ppm methyl parathion did not demonstrate significant deviations from the controls. A NOAEL of 10 ppm (1.0 mg/kg/day) was identified in this study.
- Daly and Hogan (1982) conducted a two-generation study of methyl parathion (93.65% pure) toxicity in Sprague-Dawley rats. Each parental dose group consisted of 15 males and 30 females. The compound was added to the diet at levels of 0, 0.5, 5.0 or 25 ppm. Using compound intake data from the study report, equivalent dose levels are about 0, 0.05, 0.5 or 2.5 mg/kg/day. Feeding of the diet was initiated 14 weeks prior to the first mating and then continued for the remainder of the study. Reduced body weight ($p < 0.05$) was observed in F₀ and F₁ dams at the 25-ppm dose level. A slight decrease in body weight was noted in F_{1a} and F_{2a} pups in the 25-ppm group, but this was not significant ($p > 0.05$). Overall, the authors concluded that there was no significant ($p > 0.05$) effect attributable to methyl parathion in the diet. Based on maternal weight gain, the NOAEL for this study was 5.0 ppm (0.5 mg/kg/day).

Developmental Effects

- Gupta et al. (1985) dosed pregnant Wistar-Furth rats (10 to 12 weeks of age) with methyl parathion (purity not specified) on days 6 to 20 of gestation. Two doses were used: 1.0 mg/kg (fed in peanut butter) or 1.5 mg/kg (administered by gavage in peanut oil). The low dose produced no effects on maternal weight gain, caused no visible signs of cholinergic toxicity and did not result in increased fetal resorptions. The high dose caused a slight but significant ($p < 0.05$) reduction in maternal weight gain (11% in exposed versus 16% in controls, by day 15) and an increase in late resorptions (25% versus 0%). The high dose also resulted in cholinergic signs (muscle fasciculation and tremors) in some dams. Acetylcholinesterase (AChE) activity, choline acetyltransferase (CAT) activity, and quinuclidinyl benzilate (QNB) binding to muscarinic receptors were determined in several brain regions of fetuses at 1, 7, 14, 21 and 28 days postnatal age,

and in maternal brain at day 19 of gestation. Exposure to 1.5 mg/kg reduced ($p < 0.05$) the AChE and increased CAT activity in all fetal brain regions at each developmental period and in the maternal brain. Exposure to 1.0 mg/kg caused a significant ($p < 0.05$) but smaller and less persistent reduction of AChE activity in offspring, but no change in brain CAT activity. Both doses reduced QNB binding in maternal frontal cortex ($p < 0.05$), but did not alter the postnatal pattern of binding in fetuses. In parallel studies, effects on behavior (cage emergence, accommodated locomotor activity, operant behavior) were observed to be impaired in rats exposed prenatally to 1.0 mg/kg, but not to the 1.5-mg/kg dose. No morphological changes were observed in hippocampus or cerebellum. It was concluded that subchronic prenatal exposure to methyl parathion altered postnatal development of cholinergic neurons and caused subtle alterations in selected behaviors of the offspring. The fetotoxic LOAEL for this study was 1.0 mg/kg.

- Gupta et al. (1984) administered oral doses of 1.0 or 1.5 mg/kg/day of methyl parathion (purity not specified) to female Wistar-Furth rats on days 6 through 15 or on days 6 through 19 of gestation. Protein synthesis in brain and other tissues was measured on day 15 or day 19 by subcutaneous injection of radioactive valine. The specific activity of this valine in the free amino acid pool and protein-bound pool (measured 0.5, 1.0 and 2.0 hours after injection) was significantly ($p < 0.05$) reduced in various regions of the maternal brain and in maternal viscera, placenta and whole embryos (day 15), and in fetal brain and viscera (day 19). The inhibitory effect of methyl parathion on protein synthesis was dose dependent, greater on day 19 than on day 15 of gestation and more pronounced in fetal than in maternal tissues. With respect to protein synthesis in both maternal and fetal tissues, the LOAEL of this study was 1.0 mg/kg.
- Fuchs et al. (1976) reported a study in which oral administration of methyl parathion to pregnant Wistar rats on either days 5 to 9, 11 to 15, or 11 to 19 of gestation resulted in growth retardation of offspring and increased resorptions at 3 mg/kg. The NOAEL was 1 mg/kg.

Mutagenicity

- Van Bao et al. (1974) examined the lymphocytes from 31 patients exposed to various organophosphate pesticides for indications of chromosome aberrations. Five of the examined patients had been exposed to methyl parathion. Blood samples were taken 3 to 6 days after exposure and again at 30 and 180 days. A temporary, but significant ($p < 0.05$) increase was found in the frequency of chromatid breaks and stable chromosome-type aberrations in acutely intoxicated persons. Two of the methyl parathion-exposed persons were in this category, having taken large doses orally in suicide attempts. The authors concluded that the results of this study strongly suggest that the organic phosphoric acid esters exert direct mutagenic effects on chromosomes.
- Shigaeva and Savitskaya (1981) reported that metophos (methyl parathion) induced visible morphological mutations and biochemical mutations

in Pseudomonas aeruginosa at concentrations between 100 and 1,000 ug/mL, and significantly ($p < 0.05$) increased the reversion rate in Salmonella typhimurium at concentrations between 5 and 500 ug/mL.

- Grover and Malhi (1985) examined the induction of micronuclei in bone marrow cells of Wistar male rats that had been injected with methyl parathion at doses between one-third and one-twelfth of the LD₅₀. The increase in micronuclei formation led the authors to conclude that methyl parathion has high mutagenic potential.
- Mohn (1973) concluded that methyl parathion was a probable mutagen, based on the ability to induce 5-methyltryptophan resistance in Escherichia coli. Similar results were obtained using the streptomycin-resistant system of E. coli and the trp-conversion system of Saccharomyces cerevisiae.
- Rashid and Mumma (1984) found methyl parathion to be mutagenic to S. typhimurium strain TA100 after activation with rat liver microsomal and cytosolic enzymes.
- Chen et al. (1981) investigated sister-chromatid exchanges (SCE) and cell-cycle delay in Chinese hamster cells (line V79) and two human cell lines (Burkitt lymphoma B35M and normal human lymphoid cell Jeff), and found methyl parathion to be the most active pesticide of eight tested with respect to its induction potential.
- Riccio et al. (1981) found methyl parathion to be negative in two yeast assay systems (diploid strains D3 and D7 of Saccharomyces cerevisiae), based on mitotic recombination (in D3), and mitotic crossing over, mitotic gene conversion, and reverse mutation (in D7).
- In a study for dominant lethality in mice by Jorgenson et al. (1976), males (20 per dose group) were given methyl parathion in the diet for 7 weeks at 3 dose levels (not reported). Positive controls given triethylene melamine and untreated controls were also studied. Following treatment, each male was mated to 2 adult females weekly for 8 weeks. Methyl parathion was ineffective in this test.

Carcinogenicity

- NCI (1978) conducted chronic (105-week) feeding studies of methyl parathion in F344 rats and B6C3F₁ mice (50/sex/dose). Rats were fed methyl parathion (94.6% pure) at dose levels of 0, 20 or 40 ppm (equivalent to doses of 0, 1 or 2 mg/kg/day). Mice were initially fed dose levels of 62.5 or 125 ppm, but because of severely depressed body weight gain in males, their doses were reduced at 37 weeks to 20 or 50 ppm, respectively. Time-weighted averages for males were calculated to be 35 or 77 ppm (about 5.2 or 11.5 mg/kg/day). Females received the original dose level throughout. Based on gross and histological examinations, no tumors were observed to occur at an incidence significantly higher than that of the control value in either the mice or rats. The authors concluded that methyl parathion was not carcinogenic in either species under the conditions of the test.

- Daly et al. (1984) fed Sprague-Dawley rats (60/sex/dose) methyl parathion (93.65%) in the diet for 2 years. Doses tested were 0, 0.5, 5 or 50 ppm, estimated as equivalent to doses of 0, 0.025, 0.25 or 2.5 mg/kg/day. There were no significant ($p > 0.05$) increases in neoplastic lesions between treated and control groups.

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 located in the available literature that were suitable for deriving a One-day HA value. It is recommended that the Ten-day HA value for the 10-kg child (0.3 mg/L calculated below) be used at this time as a conservative estimate of the One-day HA value.

Ten-day Health Advisory

The studies by Rider (1969, 1970, 1971) have been selected to serve as the basis for calculation of the Ten-day HA for methyl parathion. In these studies, human volunteers ingested methyl parathion for 30 days at doses ranging from 1 to 30 mg/day. The most sensitive indicator of effects was inhibition of plasma ChE. No effects in any subject were observed at a dose of 22 mg/day (about 0.31 mg/kg/day with assumed 70-kg body weight), and this was identified as the NOAEL. Doses of 24 mg/day inhibited ChE activity in plasma and red blood cells in two of five subjects, maximum decreases being 23 and 24% in plasma and 27 and 55% in red blood cells. Higher doses (26 to 30 mg/day) caused greater inhibition. On this basis, 24 mg/day (0.34 mg/kg/day) was identified as the LOAEL. Short-term toxicity or teratogenicity studies in animals identified LOAEL values of 1.0 to 2.5 mg/kg/day (Gupta et al., 1984, 1985; Shtenberg and Dzhunusova, 1968; Tegeris and Underwood, 1977), but did not identify a NOAEL value.

Using a NOAEL of 0.31 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(0.31 \text{ mg/kg/day}) (10 \text{ kg})}{(10) (1 \text{ L/day})} = 0.31 \text{ mg/L (300 ug/L)}$$

where:

0.31 mg/kg/day = NOAEL, based on absence of toxic effects or inhibition of ChE in humans exposed orally for 30 days.

10 kg = assumed body weight of a child.

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

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

Longer-term Health Advisory

The 90-day feeding study in dogs by Tegeris and Underwood (1978) has been selected to serve as the basis for calculation of the Longer-term HA for methyl parathion. In this study, a NOAEL of 0.3 mg/kg/day was identified, based on absence of effects on body weight, food consumption, clinical chemistry, hematology, urinalysis, organ weights, gross pathology, histopathology and ChE activity. The LOAEL, based on ChE inhibition, was 1.0 mg/kg/day. These values are supported by the results of Ahmed et al. (1981), who identified a NOAEL of 0.3 mg/kg/day in a 1-year feeding study in dogs, and by the study of Daly and Rinehart (1980), which identified a LOAEL of 1.5 mg/kg/day (based on decreased testes weight) in a 90-day feeding study in mice.

Using a NOAEL of 0.3 mg/kg/day, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.3 \text{ mg/kg/day}) (10 \text{ kg})}{(100) (1 \text{ L/day})} = 0.03 \text{ mg/L (30 ug/L)}$$

where:

0.3 mg/kg/day = NOAEL, based on absence of effects on body weight, food consumption, clinical chemistry, hematology, urinalysis, organ weights, gross pathology, histopathology and ChE activity in dogs fed methyl parathion for 90 days.

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.

Using a NOAEL of 0.3 mg/kg/day, the Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.3 \text{ mg/kg/day}) (70 \text{ kg})}{(100) (2 \text{ L/day})} = 0.10 \text{ mg/L (100 ug/L)}$$

where:

0.3 mg/kg/day = NOAEL, based on absence of effects on body weight, food consumption, clinical chemistry, hematology, urinalysis, organ weights, gross pathology, histopathology and ChE activity in dogs fed methyl parathion for 90 days.

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 by 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, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 2-year feeding study in rats by Daly et al. (1984) has been selected to serve as the basis for calculation of the Lifetime HA for methyl parathion. In this study, a NOAEL of 0.025 mg/kg/day was identified, based on the absence of effects on body weight, organ weights, hematology, clinical chemistry, retinal degeneration and cholinergic signs. A LOAEL of 0.25 mg/kg/day was identified, based on decreased hemoglobin, red blood cell counts, and hematocrit (males), changes in organ-to-body weight ratios (males and females) and one case of

visible cholinergic signs. There was increased retinal degeneration at 2.5 mg/kg/day, but this was not greater than control at 0.25 or 0.025 mg/kg/day. This LOAEL value (0.25 mg/kg/day) is lower than most other NOAEL or LOAEL values reported in other reports. For example, NOAEL values of 0.3 to 3.0 mg/kg/day have been reported in chronic studies by Ahmed et al. (1981), NCI (1978), Lobdell and Johnston (1964) and Daly and Hogan (1982).

Using a NOAEL of 0.025 mg/kg/day, the Lifetime HA for a 70-kg adult is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{RfD} = \frac{(0.025 \text{ mg/kg/day})}{(100)} = 0.00025 \text{ mg/kg/day}$$

where:

0.025 mg/kg/day = NOAEL, based on absence of cholinergic signs or other adverse effects in rats exposed to methyl parathion in the diet for 2 years.

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)

$$\text{DWEL} = \frac{(0.00025 \text{ mg/kg/day}) (70 \text{ kg})}{(2 \text{ L/day})} = 0.009 \text{ mg/L} (9 \text{ ug/L})$$

where:

0.00025 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

$$\text{Lifetime HA} = (0.009 \text{ mg/L}) (20\%) = 0.002 \text{ mg/L} (2 \text{ ug/L})$$

where:

0.009 mg/L = DWEL.

20% = relative source contribution from water.

Evaluation of Carcinogenic Potential

- No evidence of carcinogenic activity was detected in either rats or mice in a 105-week feeding study (NCI, 1978).

- Statistically significant ($p < 0.05$) increases in neoplasm frequency were not found in a 2-year feeding study in rats (Daly et al., 1984).
- The International Agency for Research on Cancer (IARC) has not evaluated the carcinogenicity of methyl parathion.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), methyl parathion may be classified in Group D: not classified. This category is for substances with inadequate animal evidence of carcinogenicity.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- NAS (1977) concluded that data were inadequate for calculation of an ADI for methyl parathion. However, using data on parathion, NAS calculated an ADI for both parathion and methyl parathion of 0.0043 mg/kg/day, using a NOAEL of 0.043 mg/kg/day in humans (Rider et al., 1969) and an uncertainty factor of 10 (NAS, 1977). From this ADI, NAS calculated a chronic Suggested-No-Adverse-Response Level (SNARL) of 0.03 mg/L, based on water consumption of 2 L/day by a 70-kg adult, and assuming a 20% RSC.
- The U.S. EPA Office of Pesticide Program (EPA/OPP) previously calculated a provisional ADI (PADI) of 0.0015 mg/kg/day, based on a NOAEL of 0.3 mg/kg/day. This is based on the 90-day dog study by Tegeris and Underwood (1978) and a 200-fold uncertainty factor. This PADI has been updated to use a value of 0.0025 mg/kg/day based on a NOAEL of 0.0250 mg/kg/day in a 2-year rat chronic feeding study and a 100-fold uncertainty factor.
- ACGIH (1984) has proposed a time-weighted average threshold limit value of 0.2 mg/m³.
- The National Institute for Occupational Safety and Health has recommended a standard for methyl parathion in air of 0.2 mg/m³ (TDB, 1985).
- The U.S. EPA has established residue tolerances for parathion and methyl parathion in or on raw agricultural commodities that range from 0.1 to 0.5 ppm (CFR, 1985). A tolerance is a derived value based on residue levels, toxicity data, food consumption levels, hazard evaluation and scientific judgment; it is the legal maximum concentration of a pesticide in or on a raw agricultural commodity or other human or animal food (Paynter et al., undated).
- The World Health Organization established an ADI of 0.02 mg/kg/day (Vettorazi and van den Hurk, 1985).

VII. ANALYTICAL METHODS

- Analysis of methyl parathion is by a gas chromatographic (GC) method applicable to the determination of certain nitrogen-phosphorus-containing pesticides in water samples (U.S. EPA, 1986b). In this 605

method, approximately 1 liter of sample is extracted with methylene chloride. The extract is concentrated and the compounds are separated using capillary column GC. Measurement is made using a nitrogen phosphorus detector. The method detection limit has not been determined for methyl parathion, but it is estimated that the detection limits for analytes included in this method are in the range of 0.1 to 2 ug/L.

VIII. TREATMENT TECHNOLOGIES

- Available data indicate that granular-activated carbon (GAC) and reverse osmosis (RO) will effectively remove methyl parathion from water.
- Whittaker (1980) experimentally determined adsorption isotherms for methyl parathion and methyl parathion diazinion bi-solute solutions. As expected, the bi-solute solution showed a lesser overall carbon capacity than that achieved by the application of pure solute solution.
- Under laboratory conditions, GAC removed 99+% of methyl parathion (Whittaker et al., 1982).
- Reverse osmosis is a promising treatment method for methyl parathion-contaminated water. Chian (1975) reported 99.5% removal efficiency for two types of membrane operating at 600 psig and a flux rate of 8 to 12 gal/ft²/day. Membrane adsorption, however, is a major concern and must be considered, as breakthrough of methyl parathion would probably occur once the adsorption potential of the membrane was exhausted.
- Oxidation with ozone and chlorine may be possible in the treatment of methyl parathion.
- Oxidation with 4.5 and 9.5 mg/L ozone reduced the methyl parathion by 95 to 99%. The same removal efficiency was achieved with 1 and 2 mg/L chlorine (Gabovich and Kurennoy, 1974).
- Ozonation with 0.32 mg ozone/mg methyl parathion reduced methyl parathion in drinking water by 90 to 95% (Shevchenko et al., 1982).
- Oxidation degradation by either ozone or chlorine produces several degradation products, whose environmental toxic impact should be evaluated prior to selecting oxidative degradation for treatment of methyl parathion-contaminated water (Shevchenko et al., 1982).
- Aeration does not seem to be a practical technique for removing methyl parathion from potable water (Saunders and Sieber, 1983).
- Treatment technologies for the removal of methyl parathion from water are available and have been reported to be effective. However, selection of individual or combinations of technologies for methyl parathion removal from water must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

IX. REFERENCES

- ACGIH. 1984. American Conference of Governmental Industrial Hygienists, Inc. Documentation of the threshold limit values for substances in workroom air, 3rd ed. Cincinnati, OH: ACGIH.
- Ackermann, H., and R. Engst. 1970. The presence of organophosphorus insecticides in the fetus. Arch. Toxikol. 26(1):17-22. (In German)
- Agchem.* 1983. Persistence and release rate of Penncap M insecticide in water and hydrosol: Project No. WT-5-82. Unpublished study.
- Ahmed, F.E., J.W. Sagartz and A.S. Tegeris.* 1981. One-year feeding study in dogs. Pharmacopathics Research Laboratories Inc., Laurel, Maryland for Monsanto Company. Unpublished study. MRID 00093895.
- Braeckman, R.A., F. Audenaert, J. L. Willems, F. M. Belpaire and M.G. Bogaert. 1983. Toxicokinetics of methyl parathion and parathion in the dog after intravenous and oral administration. Arch. Toxicol. 54:71-82.
- CFR. 1985. Code of Federal Regulations. 40 CFR 180.121. July 1, 1985. p. 484.
- CHEMLAB. 1985. The chemical information system. CIS, Inc., Bethesda, MD.
- Chen, H.H., J.L. Hsueh, S.R. Sirianni and C.C. Huang. 1981. Induction of sister-chromatid exchanges and cell cycle delay in cultured mammalian cells treated with eight organophosphorus pesticides. Mut. Res. 88:307-316.
- Chian, E.S., W.N. Bruce and H.H.P. Fang. 1975. Removal of pesticides by reverse osmosis. Environ. Sci. and Tech. 9(1):52-59.
- Ciba-Geigy Corporation.* 1978. Residue of CGA-15324 Curacron™ (R) +4E and methyl parathion 4E on soil. Compilation; unpublished study, including AG-A Nos. 4635 I, II, II, and 5023.
- Daly, I., and G. Hogan.* 1982. A two-generation reproduction study of methyl parathion in rats. Bio/Dynamics, Inc. for Monsanto Company. Unpublished study. MRID 00119087.
- Daly, I., G. Hogan and J. Jackson.* 1984. A two-year chronic feeding study of methyl parathion in rats. Bio/Dynamics, Inc. for Monsanto Company. Unpublished study. MRID 00139023.
- Daly, I.W., and W.E. Rinehart.* 1980. A three month feeding study of methyl parathion in mice. Bio/Dynamics, Inc., for Monsanto Company. Unpublished study. MRID 00072513.
- Daly, I.W., W.E. Rinehart and M. Cicco.* 1979. A four week pilot study in mice with methyl parathion. Bio/Dynamics, Inc., for Monsanto Company. Unpublished study. MRID 00072514.

- Fan, A., J.C. Street and R.M. Nelson. 1978. Immunosuppression in mice administered methyl parathion and carbofuran by diet. *Toxicol. Appl. Pharmacol.* 45(1):235.
- Fuchs, V., S. Golbs, M. Kuhnert, and F. Oswald. 1976. Studies into the prenatal toxic action of parathion methyl on Wistar rats and comparison with prenatal toxicity of cyclophosphamide and trypan blue. *Arch. Exp. Vet. Med.* 30:343-350. German, English abstract.
- Gabovich, R.D., and I.L. Kurennoy. 1974. Ozonation of water containing humic compounds, phenols and pesticides. Army Medical Intelligence and Information Agency. USAMIIA-K-4564.
- Gaines, T.B. 1969. Acute toxicity of pesticides. *Toxicol. Appl. Pharmacol.* 14:515-534.
- Galal, E.E., H.A. Samaan, S. Nour El Dien, S. Kamel, M. El Saied, M. Sadek, A. Madkour, K.H. El Saadany and A. El-Zawahry. 1977. Studies on the acute and subchronic toxicities of some commonly used anticholinesterase insecticides rats. *J. Drug Res. Egypt.* 9(1-2):1-17.
- Galloway, C.* 1984a. Rabbit skin irritation: methyl parathion technical (Cheminova). STILLMEADOW, Inc., Houston, TX. for Gowan Company. Unpublished study. MRID 00142804.
- Galloway, C.* 1984b. Rabbit eye irritation: methyl parathion technical (Cheminova). STILLMEADOW, Inc., Houston, TX. for Gowan Company. Unpublished study. MRID 00142808.
- Galloway, C.* 1985. Guinea pig skin sensitization: methyl parathion technical (Cheminova). STILLMEADOW, Inc., Houston, TX. for Gowan Company. Unpublished study. MRID 00142005.
- Grover, I.S., and P.K. Malhi. 1985. Genotoxic effects of some organophosphorus pesticides. I. Induction of micronuclei in bone marrow cells in rat. *Mutat. Res.* 155:131-134.
- Gupta, R.C., R.H. Rech, K.L. Lovell, F. Welsch and J.E. Thornburg. 1985. Brain cholinergic, behavior, and morphological development in rats exposed in utero to methyl parathion. *Toxicol. Appl. Pharmacol.* 77:405-413.
- Gupta, R.C., J.E. Thornburg, D.B. Stedman and D.B. Welsch. 1984. Effect of subchronic administration of methyl parathion on in vivo protein synthesis in pregnant rats and their conceptuses. *Toxicol. Appl. Pharmacol.* 72:457-468.
- Haley, T.J., J.H. Farmer, J.R. Harmon and K.L. Dooley. 1975. Estimation of the LD₁ and extrapolation of the LD_{0.1} for five organothiophosphate pesticides. *J. Eur. Toxicol.* 8(4):229-235.
- Hawley, G.G. 1981. *The Condensed Chemical Dictionary*, 10th ed. NY: Van Nostrand Reinhold Company.

- Hollingworth, R.M., R.L. Metcalf and I.R. Fukuto. 1967. The selectivity of sumithion compared with methyl parathion. Metabolism in the white mouse. *J. Agr. Food Chem.* 15:242-249.
- Ishiki, K., K. Miyata, S. Matsui, M. Tsutsumi and T. Watanabe. 1983. Effects of post-harvest fungicides and piperonyl butoxide on the acute toxicity of pesticides in mice. Safety evaluation for intake of food additives. III. *Shokuhin Eiseigaku Zasshi.* 24(3):268-274.
- Jorgenson, T.A., C.J. Rushbrook, and G.W. Newell. 1976. *In vivo* mutagenesis investigations of ten commercial pesticides. *Toxicol. Appl. Pharmacol.* 37: 109.
- 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.
- Lobdell, J.L., and C.D. Johnston.* 1964. Methyl parathion: three-generation reproduction study in the rat. Virginia: Woodard Research Corporation for Monsanto Company. Unpublished study. MRID 0081923.
- Meister, R., ed. 1988. Farm Chemicals Handbook. Willoughby, OH: Meister Publishing Company.
- Mohn, G. 1973. 5-Methyltryptophan resistance mutations in *Escherichia coli* K-12: Mutagenic activity of monofunctional alkylating agents including organophosphorus insecticides. *Mut. Res.* 20:7-15.
- Nakatsugawa, T., N.M. Tolman and P.A. Dahm. 1968. Degradation and activation of parathion analogs by microsomal enzymes. *Biochem. Pharmacol.* 17:1517-1528.
- NAS. 1977. National Academy of Sciences. Drinking water and health. Vol. 1. Washington, DC: National Academy Press.
- NCI. 1978. National Cancer Institute. Bioassay of methyl parathion for possible carcinogenicity. Bethesda, MD: NCI, National Institutes of Health. NCI-CG-TR-157.
- Neal, R.A., and K.P. DuBois. 1965. Studies on the mechanism of detoxification of cholinergic phosphorothioates. *J. Pharmacol. Exp. Ther.* 148(2):185-192.
- Namec, S.J., P.L. Adkisson and H.W. Dorough. 1968. Methyl parathion adsorbed on the skin and blood cholinesterase levels of persons checking cotton treated with ultra-low-volume sprays. *J. Econ. Entomol.* 61(6):1740-1742.
- Paynter, O.E., J.G. Cummings and M.H. Rogoff. Undated. United States Pesticide Tolerance System. U.S. EPA, Office of Pesticide Programs, Washington, DC. Unpublished draft report.
- Pennwalt Corporation.* 1972. Soil and water run off test for Penncap M versus methyl parathion E.C. Compilation. Unpublished study.
- 609

- Pennwalt Corporation.* 1977. Penncap-M™ (R)+ and Penncap-E™ (TM)+ insecticides--soil leaching. Unpublished study.
- Rashid, K.A., and R.O. Mumma. 1984. Genotoxicity of methyl parathion in short-term bacterial test systems. J. Environ. Sci. Health. B19(6):565-577.
- Riccio, E., G. Shepherd, A. Pomeroy, K. Mortelmans and M.D. Waters. 1981. Comparative studies between the S. cerevisiae D3 and D7 assays of eleven pesticides. Environ. Mutagen. 3(3):327.
- Rider, J.A., H.C. Moeller, E.J. Puletti and J.I. Swader. 1969. Toxicity of parathion, systox, octamethyl pyrophosphoramidate and methyl parathion in man. Toxicol. Appl. Pharmacol. 14:603-611.
- Rider, J.A., J.I. Swader and E.J. Puletti. 1970. Methyl parathion and guthion anticholinesterase effects in human subjects. Federation Proc. 29(2):349. Abstracts.
- Rider, J.A., J.I. Swader and E.J. Puletti. 1971. Anticholinesterase toxicity studies with methyl parathion, guthion and phosdrin in human subjects. Federation Proc. 30(2):443. Abstracts.
- Sabol, E.* 1985. Rat: Acute oral toxicity of methyl parathion technical (Cheminova). STILLMEADOW, Inc., Houston, TX. for Gowan Company. Unpublished study. MRID 00142806.
- Saunders, P.F. and J.N. Seiber. 1983. A chamber for measuring volatilization of pesticides from model soil and water disposal systems. Chemosphere. 12(7/8):999-1012.
- Shevchenko, M.A., P.N. Taran and P.V. Marchenko. 1982. Modern methods of purifying water from pesticides. Soviet J. Water Chem. Technol. 4(4):53-71.
- Shigaeva, M.K. and I.S. Savitskaya. 1981. Comparative study of the mutagenic activity of some organophosphorus insecticides in bacteria. Tsitol. Genet. 15(3):68-72.
- Shtenberg, A.I. and R.M. Dzhunusova. 1968. Depression of immunological reactivity in animals by some organophosphorus pesticides. Bull. Exp. Biol. Med. 65(3):317-318.
- Skinner, C.S. and W.W. Kilgore. 1982. Acute dermal toxicities of various organophosphate insecticides in mice. J. Toxicol. Environ. Health. 9(3):491-497.
- STORET. 1988. STORET Water Quality File. Office of Water. U.S. Environmental Protection Agency (data file search conducted in May, 1988).
- TDB. 1985. Toxicology Data Bank. MEDLARS II. National Library of Medicine National Interactive Retrieval Service.

- Tegeris, A.S. and P.C. Underwood.* 1977. Fourteen-day feeding study in the dog. Pharmacopathics Research Laboratories, Laurel, MD., for Monsanto Company. Unpublished study. MRID 00083109.
- Tegeris, A.S. and P.C. Underwood.* 1978. Methyl parathion: Ninety-day feeding to dogs. Pharmacopathics Research Laboratories, Inc., Laurel, Maryland. Unpublished study. MRID 00072512.
- U.S. EPA. 1981. U.S. Environmental Protection Agency. Acephate, aldicarb, carbophenothion, DEF, EPN, ethoprop, methyl parathion, and phorate: their acute and chronic toxicity, bioconcentration potential, and persistence as related to marine environment. Environmental Research Laboratory. Unpublished study. Report No. EPA-600/4-81-023.
- U.S. EPA. 1986a. U.S. Environmental Protection Agency. Guidelines for carcinogen risk assessment. Fed. Reg. 51(185):33992-34003. September 24.
- U.S. EPA. 1986b. U.S. Environmental Protection Agency. U.S. EPA Method #1 - Determination of nitrogen- and phosphorus-containing pesticides in ground water by GC/NPD, January 1986 draft. Available from U.S. EPA's Environmental Monitoring and Support Laboratory, Cincinnati, Ohio.
- Van Bao, T., I. Szabo, P. Ruzicska and A. Czeizel. 1974. Chromosome aberrations in patients suffering acute organic phosphate insecticide intoxication. Human Genetik 24(1):33-57.
- Vettorazzi, G. and G.W. van den Hurk, eds. 1985. Pesticides Reference Index. J.M.P.R., p. 41.
- Whittaker, K.F. 1980. Adsorption of selected pesticides by activated carbon using isotherm and continuous flow column systems. Ph.D. Thesis, Purdue University.
- Whittaker, K.F., J.C. Nye, R.F. Weekash, R.J. Squires, A.C. York and H.A. Razemier. 1982. Collection and treatment of wastewater generated by pesticide application. EPA-600/2-82-028, Cincinnati, Ohio.