

Dinoseb

Guideline

The maximum acceptable concentration (MAC) for dinoseb in drinking water is 0.01 mg/L (10 µg/L).

Identity, Use and Sources in the Environment

Dinoseb, or 2,4-dinitro-6-*sec*-butylphenol, is a selective non-systemic herbicide and desiccant with moderate use in Canada (50 000 to 300 000 kg active ingredient per year).^{1,2} It is marketed as an oil formulation or ammonium salt. Dinoseb is effective in the control of many broadleaf weeds in such crops as cereals, seedling alfalfa and peas and is also used for pre-emergence control of annual weeds in beans, peas and potatoes and for control of runners and suckers in raspberries and strawberries.³

Technical dinoseb has a melting point between 38 and 42°C and is therefore a solid or liquid, depending on the ambient temperature. The pure compound is very soluble in water (52 g/L at 20°C) and is soluble in most organic solvents.⁴ Dinoseb has a vapour pressure of 10 Pa at 20°C.⁵

Dinoseb is considered to be of intermediate to high mobility in silt loam, sandy soils, sandy loam and silty clay loam soils.⁶ It is considered by Agriculture Canada to have a high potential for leaching based on its soil half-life and its soil organic carbon partition coefficient,^{1,2} although in some experiments dinoseb could not be leached from the top 30 cm of soil in the first year after application.⁷ It has been reported to persist for about two to four weeks after application.^{7,8}

Dinoseb was degraded by three strains of *Azotobacter* to 6-acetamido-2-*sec*-butyl-4-nitrophenol.⁹ Less than 1% of dinoseb applied to bean leaves exposed to full sunlight for 20 hours in three days was degraded.¹⁰ Dinoseb was photodegraded when applied to a sandy loam soil under natural sunlight in California (half-life 14 hours) and under artificial light (half-life 30 hours).¹¹

In aqueous media, dinoseb was found to be relatively stable at pH 5, 7 and 9 at 25°C over a 30-day period.¹² In surface water under natural sunlight, dinoseb had a half-life of 14 to 18 days; with artificial light, the half-life was 42 to 58 days.¹³

Exposure

Dinoseb was detected in 14 of 406 samples taken from municipal and private water supplies in Prince Edward Island (11/40), Ontario (3/7), Manitoba and Alberta between 1978 and 1987 (detection limits 0.05 to 1.3 µg/L). The highest concentration recorded was 16.2 µg/L, observed in a well in P.E.I.¹⁴ None of over 900 samples of 115 municipal drinking water supplies in Alberta had detectable levels of dinoseb (detection limit 0.15 µg/L) during 1984 to 1990.¹⁵ Of 45 well water samples from farms in New Brunswick where dinoseb had been used in the two years prior to sampling (1988), 15% had detectable dinoseb residues ranging from 0.4 to 12.4 µg/L.¹⁶ Twenty-three of 102 samples from farm wells (some duplicates) contained dinoseb at trace levels or above (detection limit 0.4 µg/L); 12 of the 23 were from one farm, where high levels (up to 200 µg/L) were suspected to be due to contamination at the well head, whereas most of the remainder contained dinoseb at or below 10 µg/L.¹⁷ A total of 596 Ontario farm wells suspected of contamination with dinoseb were sampled during two periods between 1969 and 1984; positive results (detection limits 0.01 to 0.05 µg/L) were found in approximately 1% of samples, with concentrations ranging from 0.01 µg/L (mainly due to drift during spraying) to 1000 µg/L (due to spills nearby).^{18,19}

In the United States, dinoseb was found in one of 79 surface water samples at a maximum concentration of 1 µg/L. Groundwater samples were positive in 29 of 819 cases; the 85th percentile of all non-zero samples was 10 µg/L, with a maximum of 100 µg/L.²⁰

Few data are available pertaining to residues of dinoseb in consumer food products. Crops treated with dinoseb showed no detectable residues; therefore, no maximum limits other than the general value of 100 µg/L have been assigned.²¹ The U.S. Food and Drug

Administration examined 70 food items in 1985 and 1986 for dinoseb residues and found positive results for only one cotton meal sample. No residues were detected in shelled or unshelled peanuts or in sweet, red or white potatoes from three different areas of the United States.²²

Based on negligible residue limits for dinoseb of 100 µg/L established by the Department of National Health and Welfare for crops treated with dinoseb, the theoretical maximum daily intake of dinoseb from food is 0.042 mg/d, or 0.0006 mg/kg bw per day.²¹

Analytical Methods and Treatment Technology

A gas chromatographic method with electron capture detection is used for the analysis of dinoseb in water, following extraction of the sample with ethyl ether, hydrolysis with potassium hydroxide and conversion to the methyl ester using diazomethane. The detection limit of this method is approximately 0.07 µg/L.²³

Methods for removal of dinoseb from drinking water include activated carbon and ion exchange.²⁴ Almost total (99.98%) removal from contaminated lake water was achieved with three activated carbon columns operated in series.²⁵ Anion exchange (Amberlite IRA-400) was found to adsorb dinoseb to less than the detection limit.²⁶ Point-of-use water devices based on activated carbon are expected to be effective for removal of dinoseb from individual supplies.

Health Effects

Dinoseb is well absorbed by both oral and dermal routes. A study with rabbits showed that 66% of a single oral dose of 3 mg/kg bw was absorbed. Dermal application resulted in 68% absorption after one week.²¹ Penetration through the skin was found to be age-related, being more absorbed in the adult female rat (86 to 93%) than in young rats.²⁷

Dinoseb was about 50% metabolized after 24 hours in adult mice after both oral and intraperitoneal routes of administration, but only 15 and 43% were metabolized in the embryo after oral and intraperitoneal administration, respectively. No appreciable amounts of dinoseb were shown to accumulate in the blood, liver or kidney. Tissue levels in the embryo never exceeded 2.5% of maternal plasma levels regardless of route of administration.²⁸ The products of metabolism include nitroamino-, diamino- and dinitrophenols.²⁴ In Sherman strain rats fed a diet of dinoseb for 60 days (0 to 500 ppm), residue levels were found to be dose-dependent and decreased as follows: blood > faeces > urine > adipose tissue > brain > liver.²⁹

A number of poisoning incidents including fatalities have been reported for people ingesting concentrated dinoseb or exposed dermally in occupational settings.

Symptoms of acute poisoning include vomiting, pain and swelling of the eyes, deteriorated vision, headache, malaise, lassitude, sweating, anorexia, pain in the chest and abdomen, excessive thirst, insomnia, loss of weight, generalized yellow staining of the skin and shortness of breath. Personality changes in affected individuals have also been documented. Dinitrophenol compounds used as weight-reducing agents in the 1930s induced cataracts.³⁰ Dinoseb is very toxic to humans and is believed to act by uncoupling oxidative phosphorylation.^{4,21}

The acute toxicity of dinoseb is high, with oral LD₅₀s of 37 to 58 mg/kg bw for rats and 25 mg/kg bw for guinea pigs. The acute percutaneous LD₅₀ is 50 mg/kg for rats, 80 to 200 mg/kg for rabbits and 500 mg/kg for guinea pigs. Mild skin and eye irritations have also been observed in rabbits. In male rats (strain not given) given dinoseb (99% purity) at dietary concentrations of 0, 1.35, 2.7, 5.4 or 13.5 mg/kg per day for six months, increased liver weight was observed at 5.4 mg/kg per day, as was increased mortality at the highest dose level.³¹ In a 90-day dog study conducted in 1967 in which dinoseb was administered in the diet at 0, 50, 100 or 200 ppm, effects on the heart (endocarditis) were noted at the highest dose level; the no-observed-adverse-effect level (NOAEL) was 100 ppm, or approximately 3.8 mg/kg bw.²¹

Four groups of rats (60 per sex per dose, strain not given) were fed dinoseb (purity unspecified) in the diet for up to two years at concentrations equivalent to 0, 1, 3 or 10 mg/kg bw per day. No dose-related changes in histopathology, haematology, blood chemistry or other parameters were found, but there was a dose-related decrease in mean thyroid weight in all treated males. The lowest-observed-adverse-effect level (LOAEL) established for this study was 1 mg/kg bw per day.³² Insufficient details are available to evaluate the significance of the reported effects.

In an oncogenicity study conducted in CD-1 mice (50 per sex per dose) administered doses of 0, 1, 3 or 10 mg/kg bw per day in the diet for 100 weeks, the most noteworthy finding was the occurrence of cataracts in both sexes at 3 and 10 mg/kg bw per day dose levels. All dose levels were shown to have adverse effects on male reproductive organs, including hypospermatogenesis and degeneration of the testes, but in a non-dose-related manner. It was also reported that dinoseb induced changes in the appearance of the thymus.²² In high-dose males, treatment-related increases in focal hepatocellular necrosis and hyperplasia of the bone marrow were noted. A NOAEL of 1 mg/kg bw per day was observed based on cataractogenesis in both sexes at 3 and 10 mg/kg bw per day.^{21,33}

Determination of the carcinogenicity of dinoseb from older studies is difficult because of trace contamination by the carcinogen N-nitrosodiethanolamine in certain formulations, especially the amine formulations, which are no longer used. No evidence of carcinogenicity was observed in the above-cited dietary study on rats fed dinoseb at 0, 1, 3 or 10 mg/kg bw per day over a period of two years.³² In the 100-week feeding study cited above, performed on CD-1 mice at levels of 0, 1, 3 or 10 mg/kg bw per day, dinoseb induced hepatocellular tumours at a slightly greater incidence than in the controls, but the increase was not found to be dose-related in either sex, nor was it statistically significant. No historical control data were provided. There was no evidence of potentially predisposing lesions such as hypertrophy of the liver.²¹ Although there is no strong evidence for the carcinogenicity of dinoseb, available data are inadequate for assessment of its carcinogenicity, and an adequate dietary oncogenicity study is required.

Dinoseb did not induce point mutations in tests on four different microbial systems. No metabolic activation tests were carried out.³⁴ Dinoseb caused DNA damage in *Escherichia coli*, *Bacillus subtilis* and *Salmonella typhimurium* at levels toxic to the organisms³⁵ but was not found to be mutagenic in other tests on a number of organisms, including *S. typhimurium*, *E. coli*, *B. subtilis*, *Saccharomyces cerevisiae* and *Drosophila melanogaster*.³⁵⁻³⁹ Dinoseb was found negative in the *S. cerevisiae* recombination assay and the unscheduled DNA synthesis test using human lung fibroblasts.³⁵ Dinoseb showed positive results in the SOS chromotest, a recently validated genotoxicity test for DNA adducts in *E. coli* cells. However, the addition of rat liver S9 mix significantly decreased the inducing ability of the herbicide.⁴⁰ No *in vivo* studies were found. Based on these studies, there is no strong evidence of the mutagenic potential of dinoseb.

In a three-generation (later extended to five generations) rat reproduction study,^{21,24} four groups (25 per sex per group) of Charles River Sprague-Dawley derived rats of the CD strain were exposed to dinoseb in the diet at doses of 0, 1, 3 or 10 mg/kg bw per day for 29 weeks. No reproductive effects were observed other than a slight non-significant reduction in the number of progeny in the F₁ generation, although a statistically significant decrease in pup weight was observed 21 days post-partum at the highest dose level. The NOAEL for male reproductive toxicity in this study was 10 mg/kg bw per day. The NOAEL based on decreased body weight gain was 3 mg/kg bw per day.

Dinoseb (97% pure) was fed *ad libitum* at dietary concentrations of 0, 75, 150 or 225 ppm (0, 3.8, 9.1 or 15.6 mg/kg bw per day) for 11 weeks to four groups of 10 adult Sherman strain male rats, which were then bred to untreated virgin females. Another group of five animals was fed 300 ppm (22.2 mg/kg bw per day). Diets of 225 or 300 ppm dinoseb resulted in marked oligospermia (reduction in the number of spermatozoa in the semen), extensive damage to the seminiferous tissues of surviving rats and irreversible reproductive failure. In rats fed 150 ppm, decreased epididymal sperm counts, abnormal epididymal spermatozoa and histologic changes in the testes were observed; reproduction was unaffected, and the anomalies appeared to be reversible in the 16 weeks following treatment. There were no detectable effects in rats fed 75 ppm. Mating behaviour and libido appeared to be unaffected at all concentrations. The NOAEL observed for this study was 75 ppm (3.8 mg/kg bw per day).⁴¹ Adverse effects on testes, spermatozoa and sperm motility have also been reported in other experiments on rats, at dose levels of 7.5 mg/kg bw and higher.^{29,42}

In a developmental toxicity study,⁴³ four groups of 25 Wistar/Han rats were administered dinoseb (96.1% purity) orally by gavage at levels of 0, 1, 3 or 10 mg/kg bw per day on days 6 through 15 of gestation. Food consumption and body weight gain of highest-dose females were slightly depressed during the dosing interval but were comparable to those of other groups at the end of the experiment. No other effects were observed in females. Foetuses at the highest dose showed a slight decrease in body weight, increased incidence of skeletal ossification at a number of sites and an increase in the number of supernumerary ribs and absence of thoracic vertebrae; the latter were also absent at 3 mg/kg bw per day.²⁴ A NOAEL of 1 mg/kg bw per day was identified for foetal effects, based on absence of thoracic vertebrae at the next highest dose of 3 mg/kg bw per day.²¹

In an oral rabbit teratology study,⁴⁴ four groups of 16 Chinchilla rabbits were exposed by oral gavage to dinoseb (98% purity) at levels of 0, 1, 3 or 10 mg/kg bw per day on days 6 through 18 of gestation. In the highest dose group, statistically significant increases in malformations and anomalies were observed in 11 of 16 litters examined. The major developmental toxic effects were neural tube defects, including dyscrania associated with hydrocephaly, scoliosis, kyphosis, malformed or fused caudal or sacral vertebrae and encephalocele. Also observed were visceral and skeletal anomalies. The NOAEL for foetal effects was 3 mg/kg bw per day based on the occurrence of neural tube defects at the highest dose level of 10 mg/kg bw per day. There was no evidence of maternal effects at any dose level.^{21,24}

In pregnant Sprague-Dawley rats fed dinoseb on days 6 to 15 of pregnancy, a decline was observed in foetal survival rates at 150 ppm and neonatal body weights at 200 ppm. Maternal body weight was also adversely affected at the 150 ppm dose level and above. A malformation (abnormally small tail) was observed at the 200 ppm level in eight of 62 fetuses, or two of six litters. The NOAEL for toxicity (body weight reduction) and foetal toxicity (survival rate) was considered to be 100 ppm, or 4.9 mg/kg bw per day.⁴⁵

Dinoseb did not influence implantation or embryoletality in a series of experiments in which pregnant CD rats were administered dinoseb on days 6 to 15 of pregnancy by gastric intubation at doses up to 15 mg/kg bw or in the diet at 200 ppm, equivalent to 15 mg/kg bw. A significant increase in skeletal anomalies was noticed in the groups treated by gavage at 10 and 15 mg/kg bw and in the group given 200 ppm (15 mg/kg bw) via the diet. The NOAEL was 5 mg/kg bw for both maternal and foetal effects.⁴⁶

Dinoseb did not appear to produce any significant change in pup weight, maternal weight, litter size or pup survival in CD-1 mice administered dinoseb by gavage at a dose of 15 mg/kg bw per day on days 8 to 12 of gestation.⁴⁷ This may indicate that mice are less sensitive than rats to the reproductive and teratogenic effects of dinoseb.

In a dermal developmental toxicity test, dinoseb was applied to the clipped dorsum of pregnant New Zealand white rabbits on days 7 through 19 of pregnancy at 0, 1, 3 or 9 mg/kg bw per day (18 mg/kg bw per day dose discontinued due to premature deaths). A dose-related reduction in feeding in the first week of treatment was accompanied by an overall large maternal weight loss and an elevated body temperature. The mean number of implantations was not affected by treatment, but the number of live fetuses was reduced at 9 mg/kg bw per day. The body weight of the fetuses was not affected, except for a tendency to higher body weight in the highest dose group. Cleft palate, microcephaly, hydrocephaly, microphthalmia and anophthalmia were observed in the fetuses of the highest-dose mothers, and at least two of these effects (i.e., hydrocephaly and anophthalmia) were present in the fetuses of mothers receiving 3 mg/kg bw per day. The authors suggested a NOAEL of 1 mg/kg bw per day.⁴⁸

Effects on the immune system were investigated in inbred male hamsters (strain LHC/LAK, five to eight weeks old) in which dinoseb was found to depress both the humeral and cellular response to fluorescein-labelled ovalbumin in hamsters administered dinoseb intragastrically at one-half the LD₅₀.⁴⁹

Rationale

Based on the above information, there is no strong evidence of the carcinogenic potential of dinoseb; however, a two-year chronic feeding and oncogenicity study in rats is required to clarify its status.

The principal toxic effects of dinoseb that are of concern are its teratogenic and foetotoxic effects at doses below those that cause maternal toxicity and its potential as a cataract-inducing agent. In a recent rat study in which dinoseb was administered by gavage, skeletal anomalies were observed at 3 mg/kg bw per day and higher; the NOAEL was 1 mg/kg bw per day.⁴³ This finding was supported by an oral teratology study in rabbits in which the NOAEL for neural tube defects was 3 mg/kg bw per day;⁴⁴ a dermal teratology study in rabbits with a NOAEL of 1 mg/kg bw per day;⁴⁸ and a 100-week dietary study in mice in which the NOAEL for cataract formation was 1 mg/kg bw per day.³³

The acceptable daily intake (ADI) is derived as follows:

$$\text{ADI} = \frac{1 \text{ mg/kg bw per day}}{1000} = 0.001 \text{ mg/kg bw per day}$$

where:

- 1 mg/kg bw per day is the NOAEL for the rat reproduction study⁴³
- 1000 is the uncertainty factor (×10 for intraspecies variation; ×10 for interspecies variation; and ×10 for teratogenicity, considered to be a serious effect; in addition, there are limitations in the toxicity data base—i.e., other toxicological studies are needed).

Because of the significant toxic effects (i.e., foetotoxicity) and the probability that dinoseb will be withdrawn from the market, it was decided that a maximum acceptable concentration (MAC) should be set rather than an interim MAC. Based on the above ADI, the MAC for dinoseb in drinking water is calculated as follows:

$$\text{MAC} = \frac{0.001 \text{ mg/kg bw per day} \times 70 \text{ kg bw} \times 0.20}{1.5 \text{ L/d}} \approx 0.01 \text{ mg/L}$$

where:

- 0.001 mg/kg bw per day is the ADI, as derived above
- 70 kg bw is the average body weight of an adult
- 0.20 is the proportion of daily intake of dinoseb allocated to drinking water (the theoretical maximum daily intake is 0.6 µg/kg bw,²¹ or 60% of the ADI)
- 1.5 L/d is the average daily consumption of drinking water for an adult.

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