## B3-1.0 DINOSEB

### B3-1.1 Background Information

**DINOSEB:** 4,6-Dinitro-2-sec-butylphenol **Dow General**

**Synonyms:** 2,4-Dinitro-6-sec-butylphenol; 2-sec-Butyl-4,6-dinitrophenol; 4,6-dinitro-2-(1-methyl-n-propyl)phenol; 4,6-Dinitro-2-sec-butylphenol; Basanite; Dinitrax; Dinitro; Dinitro-o-sec-butylphenol; Dinitro-3; Dinitrobutyl phenol; Dinitro General; Dinoseb; Dinoseb; Dinoseb Phenol; BNP 30; butaphene; Caldon; Chemox General & PE; Chemox PE; Chemsect; DNBP; DNOSBP; DNPB; DNSBP; Dow General; dow general weed killer; dow selective weed killer; Drexel Dynamite 3; Dynamite; Dynanap; Elgetol 318; F-ISO; Hel-Fire; Kiloseb; Klean Krop; nitropone; Nitropone C; phenotan; pnosbp; Premerge; Premerge Plus, with Dinitro; Sinox general; sparic; spurge; Subitex; unicorp dnbp; Unicrop DNBP; vertac dinitro weed killer; Vertac Dinitro Weed Killer 5; Vertac General and Selective Weed Killer Vertac General Weed Killer; and, WSX-8365.

**IUPAC:** (RS)-2-sec-butyl-4,6-dinitrophenol

**CAS:** 2-(1-methylpropyl)-4,6-dinitrophenol

**CASRN:** 88-85-7

**DINOSEB USAGE**

Dinoseb is an agricultural herbicide which was registered for use in Canada in 1947. Historically dinoseb was registered for the control of seedling weeds in a variety of crops, in orchards prior to the appearance of foliage, and preharvest desiccation of potatoes and other crops (Health Canada, 1989). Dinoseb was banned from use in Canada as of December 21, 2001.

Dinoseb was sprayed at CFB Gagetown on designated plots during the U.S. 1967 Trial only (Table B3-1).

**Table B3-1 Dinoseb Usage at CFB Gagetown[a]**

| Year | Total DinosebApplied (kg) | Total Area Treated (ha) |
|---|---|---|
| 1967 | 1.6E+01 | 2.4E+00 |

[a] Adapted from Demaree and Haws, 1968

## B3-2.0 CHEMICAL AND PHYSICAL PROPERTIES

**Formula:** $C_{10}H_{12}N_2O_5$

**Activity:** Herbicides (dinitrophenol herbicides)

**Notes:** When this substance is used as an ester or a salt, its identity should be stated, for example dinoseb acetate [2813-95-8], dinoseb-ammonium [6365-83-9], dinoseb-diolamine [53404-43-6], dinoseb-sodium [35040-03-0], dinoseb-trolamine [6420-47-9].

**Structure:**

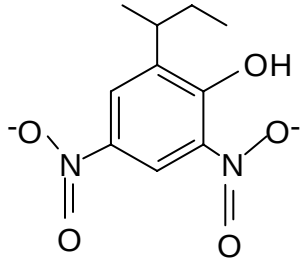


**Figure B3-1 Dinoseb CASRN 88-85-7**

**Table B3-2 Chemical and Physical Properties**

| Chemical/Physical Property | Result | Reference |
|---|---|---|
| Colour/Form | Yellow, Orange Crystals | Hartley and Kidd, 1983; Worthing and Walker, 1983 |
| Dissociation Constant (pKa) | 4.62 | Worthing and Walker, 1983; JW, 2006 |
| Henry's Law constant | $4.56 \times 10^{-7}$ atm·m$^3$/mol (25°C) | JW, 2006 |
| | $5.04 \times 10^{-4}$ atm·m$^3$/mol | Sunito *et al*., 1988 |
| Log $K_{ow}$ | 2.29-3.69 | JW, 2006 |
| Melting Point | 38-42°C | Budavari, 1989 |
| Molecular Weight | 240.21 | JW, 2006 |
| Odour | Pungent | Weed Science Society of America, 1979 |
| Specific Gravity | 1.2647 at 45°C/4°C | Hartley and Kidd, 1983 |
| Vapour Pressure | $7.44 \times 10^{-5}$ mm Hg at 25°C | JW, 2006 |
| | $8.5 \times 10^{-2}$ mm Hg at 20°C | Sunito *et al*., 1988 |
| | 1 mm Hg at 151.1°C | Weed Science Society of America, 1979 |
| Water Solubility | 52 mg/L at 25°C | Weed Science Society of America, 1979; Kearney and Kaufman, 1975; JW, 2006 |

## B3-3.0 PMRA EVALUATION

Dinoseb (2-*sec*-butyl-4,6-dinitrophenol) was developed in 1945 as a herbicide with additional uses as an insecticide, and was used on numerous food and forage crops. Dinoseb was found responsible for male sterility as well as tumors in humans (Takahashi *et al*., 2004).

On October 7, 1986 the U.S. EPA instituted a ban on the use of dinoseb following a report from Hoechst AG that showed evidence of irreversible neurological and skeletal malformations in the offspring of rabbits that received exposures to dinoseb during pregnancy (Crawford, 1986). Neurological and skeletal defects were found in 11 of 16 litters of Chinchilla rabbits that received doses of 1,3 and 10 mg/kg/day of dinoseb in the diet from day 6 to 18 of gestation. These changes were considered biologically and statistically significant increases in malformations at the highest dose tested (10 mg/kg/day) when compared to animals in a control group (Crawford, 1986). Reproductive toxicity of DNBP has also been reported in male rats as

the occurrence of reduced fertility, atrophied testes, and increased abnormal sperm in experimental animals (Linder *et al*., 1982).

The U.S. EPA also concluded that inhalation and dermal exposure to dinoseb could pose a health threat to unborn children of pregnant women, and such exposures also had the potential to produce sterility in men (Crawford, 1986).

In 1989, dinoseb applicators were found to be exposed to significant health risks through handling dinoseb products. Therefore, in 1990 dinoseb was listed as a restricted class herbicide and all non-essential uses were banned. Dinoseb continued to be used for early cane control in raspberries in British Columbia and weed control in peas and beans in the Atlantic Provinces and British Columbia. In 1994, the use of Dinoseb on raspberries was no longer deemed an essential use (PMRA, 1994).

In 2000, PMRA discontinued the use of dinoseb for all uses; however, a one year temporary registration was permitted for the control of black nightshade in peas in British Columbia. Dinoseb was banned for use in Canada as of December 21, 2001 (PMRA, 2000).

## B3-4.0 TOXICOLOGY SUMMARY

### B3-4.1 Human Health Effects

**Table B3-3 Human Health Effects from Acute and Chronic Exposure to Dinoseb[a,b]**

| Exposure | Effects | Response |
|---|---|---|
| Acute | Vital Signs | Elevated respiratory rate and blood pressure; fever with diaphoresis; tachycardia. |
| | HEENT | Severe irritation and permanent corneal damage in rabbit eyes; sclera may be stained yellow. |
| | Cardiovascular | Tachycardia; cardia dysrhythmias may occur. |
| | Respiratory | Intermittent chest pain; shortness of breath and hemoptysis; decreased FEV1 and FVC; bronchospasm, chemical pneumonitis; noncardiogenic pulmonary edema; tachypnea, laboured breathing; and, cyanosis. |
| | Neurologic | Personality changes; toxic psychosis; night sweats; lethargy; headache; lassitude; confusion; apprehension; manic behaviour; coma; seizures; and, ataxia. |
| | Gastrointestinal | Intermittent abdominal pain; nausea; vomiting; excessive thirst; stools may be a bright yellow colour; and, esophageal or gastrointestinal tract irritation if ingested. |
| | Hepatic | Impairment of liver function; liver injury with jaundice. |
| | Genitourinary | Yellowish discolouration of the urine; elevated BUN; renal tubular injury or kidney failure. |
| | Acid-Base | Acidosis |
| | Dermatologic | Yellow staining of the skin, hair and nails; profuse sweating or shivering; facial flushing. |
| | Musculoskeletal | Muscular cramping; pronounced muscle weakness |
| | Endocrine | Glucose intolerance |
| | Metabolism | Increased oxygen uptake; increased permeability of mitochondrial membranes to hydrogen ions; diverting of energy available from metabolism into heat production which raises body temperature. |

**Table B3-3 Human Health Effects from Acute and Chronic Exposure to Dinoseb[a,b]**

| Exposure | Effects | Response |
|---|---|---|
| Chronic | HEENT | Development of cataracts |
| | Hematologic | Neutropenia |
| | General Effects | Weight loss |

[a] Rumack and Hall, 2006.
[b] MEDITEXT®, 2006.

Cataracts were induced in people as a result of the former use of dinitrophenol compounds as a weight reducing aid in the 1930s (Hayes, 1982; Gosselin *et al*., 1981).

Many poisoning incidents have resulted from the use of dinitrophenol herbicides, 99% of which contain dinoseb (Health Canada, 1989). The greatest hazard occurs during ground boom application of dinitrophenols. Between 1981 to 1985 dinitrophenol was the ninth most common source of systemic poisoning with 38 reported cases (Health Canada, 1989). One human fatality was reported in Texas in 1983 due to dermal exposure to an alkanolamine salt formulation of dinoseb from a leaking backpack sprayer (Health Canada, 1989).

## B3-4.2 Health Effects by Route of Exposure

### *B3-4.2.1 Oral Exposure*

B3-4.2.1.1 Death

**Table B3-4 Mammalian $LD_{50}$ Values Resulting from Oral Exposure to Dinoseb**

| Test Organism (Species/Sex) | Exposure | $LD_{50}$ (mg/kg) | Reference |
|---|---|---|---|
| Rat (Adult male) | Oral | 27 | Budavari, 1989 |
| Rat (Adult female) | Oral | 28 | Budavari, 1989 |

**Table B3-5 Acute Mortality Resulting from Oral Exposure to Dinoseb**

| Test Organism (Species) | Exposure | Dose (Duration) | Response | eference |
|---|---|---|---|---|
| Mice (Swiss)(male) | Oral | 40 mg/kg | Resulted in 10% mortality | Mitchell *et al*., 1989 |
| Rat | Oral | 60 mg/kg | Mortality | Spencer, 1982 |
| Rat (Sherman) | Diet | 300-500 ppm (21 days) | Mortality | Hall *et al*., 1978 |

**Table B3-6 Dinoseb Oral Exposure Mortality NOEL Values**

| Test Organism (Species) | NOEL | Effect | Reference |
|---|---|---|---|
| Rat | 0.01% diet for 6 months | No ill effects | Spencer, 1982 |
| Dog | 0.01% diet for 90 days | No ill effects | Spencer, 1982 |

B3-4.2.1.2 General Toxicity

**Table B3-7 Toxic Effects Resulting from Oral Exposure to Dinoseb**

| Test Organism (Species) | Dose (Duration) | Response | eference |
|---|---|---|---|
| **Acute** | | | |
| Mice | 24-48 mg/kg in 10 doses (30 days) | Significantly lower mean total cellularity in the spleen, lymph nodes and thymus in treated mice. Decreased erythrocytes after 30 days of treatment | Springer *et al*., 1979 |
| Rat | 0.05% in diet (5-13 days) | Rapid emaciation, slight kidney and liver effects and death | Weed Science Society of America, 1983 |
| Rat | $LD_{50}$ | Liver cytochrome p450 activity decreased (50%) | DukYanchuk *et al*., 1983. |
| **Chronic** | | | |
| Mice | 3 mg/kg/day | Lenticular opacities | Dow Chemical Co., 1981a |

B3-4.2.1.3 Neurological Effects

**Table B3-8 Neurological Effects Resulting from Dinoseb Oral Exposure**

| Test Organism (Species) | Exposure | Dose (Duration) | Response | Reference |
|---|---|---|---|---|
| Mice (Swiss)(male) | Oral | 0-40 mg/kg | Significant decreases in saccharine intake (taste aversion); total activity increased by over vehicle controls | Mitchell *et al*., 1989 |

B3-4.2.1.4 Reproductive/Developmental Effects

**Developmental effects of exposure**

Lumbar supernumerary ribs (SNR), lateral to the twenty-first vertebra, are a common finding in rodent fetuses during developmental toxicity studies (Rogers *et al*., 2004). The high background incidence of SNR in many strains of rats and mice, the large number of maternal chemical and physical insults that have been shown to increase the incidence of SNR. There is some question of whether SNR have any adverse effects on health, making the interpretation of the significance of SNR problematic.

When administered by oral gavage dinoseb has been shown to induce SNR in CD-1 mice (Kavlock *et al*., 1985). Rogers *et al*. (2004) administered pregnant CD-1 mice with doses of dinoseb of 30 and 50 mg/kg/day during gestational days 7 and 8. These exposures resulted in no changes in the number of implants or live fetuses per litter. There was a slight but non-significant increase in extrauterine weight with dose (Rogers *et al*., 2004). Skeletal examinations revealed treatment-related malformations in the high dosage groups for dinoseb (sternum and vertebral centrum defects; fused ribs) that were significantly different from controls (p. 0.05). Skeletal anomalies included fused ribs at the highest dose rate.

Evidence for embryotoxic and teratogenic effects of dinoseb in mice were dependent on the route of administration and dose (Gibson, 1973). Such effects were induced when dinoseb was administered ip but not subcutaneously or orally. Teratogenic doses were also toxic to the dams

and were in the lethal range. Teratological anomalies produced from oral exposures differed from those produced by ip injection. The anomalies ranged in severity from imperforate anus and acaudia (with ip administration) to non-ossification of bone (associated with all routes).

An apparent no-effect dose level for teratogenicity and embryotoxicity for dinoseb administered orally throughout organogenesis (days 8 to 16) is 20 mg/kg/day (Gibson, 1973).

**Table B3-9 Reproductive and Developmental Effects Resulting from Oral Exposure to Dinoseb**

| Test Organism (Species) | Dose (Duration) | Response | Reference |
|---|---|---|---|
| Mice (pregnant) | Max dose: 20 mg/kg/day (dosing occurred several times during organogenesis) | Dam toxicity (>17.1 mg/kg) | Shepard, 1986 |
| Mice (pregnant) | Max dose: 20 mg/kg/day (dosing occurred several times during organogenesis) | No gross or soft tissue defects, but some skeletal defects were seen at maternally toxic levels | Shepard, 1986 |
| Mice (Swiss-Webster) (Dams) | 20 and 32 mg/kg/day | Maternal toxicity only at higher doses; NOAEL for oral administration during organogenesis: 20 mg/kg/day. | Gibson, 1973 |
| Rat (Sherman) | 0 -200 ppm (153 day parental exposure) | Fetal effects– depressed growth, decreased organ weight; increased alkaline phosphatase; alanine aminotransferase, potassium and BUN; depressed LDH; and, cholinesterase. | Hall *et al*., 1978 |
| | | Parental effects- diffuse tubular atrophy of testes (200 ppm); depressed fecundity; neonatal survival; weight gain; viability; and, lactation. | |
| Rat (CD) (pregnant) | a) 2.5-15 mg/kg in corn oil once per day<br>b) 7.5-10 mg/kg in corn oil twice a day<br>c) 15 mg/kg in 1N NaOH (pH 7) once a day (days 6-15 of gestation) | Induced maternal toxicity and embryotoxicity (reduced fetal weight and increased frequency of extra ribs) at highest doses. | Giavini *et al*., 1986 |
| Rat (Charles River CD)(pregnant) | 15 mg/kg (through day 21 of pregnancy) | Lethal (4/15 and 3/9 for two diets) to dams; Induced microphthalmia (5/77); decreased fetal weight. | Giavini *et al*., 1989 |
| Rats (decidualized pseudopregnant) | 100-750 ppm (days 6 to 9 of pseduopregnancy) | Reduced uterine wet weight. | Spencer, 1982 |
| Rat (Sherman) (Adult male) | 150 ppm (11 weeks) | Decreased epididymal sperm counts; atypical epididymal spermatozoa and minimal testicular changes; and, anomalies were reversible. | Linder *et al*, 1982 |
| Rat (pregnant) | 200-750 ppm (days 6 to 15 of pregnancy) | Diminished placental protein and glycogen concentration (>200 ppm); Reduction in embryonic survival rates (>200 ppm); and, fetal survival rates at birth (>150 ppm). | Spencer and Sing, 1982 |
| Rat (CD) (pregnant) | 200 ppm | Maternal toxicity and teratogenic effects (microphthalmia). | Giavini *et al*., 1986 |
| Rat (Sherman) (Adult male) | 225 and 300 ppm (11 weeks) | Reproductive failure; no remission of effects during 16 wk post-treatment period. | Linder *et al*, 1982 |

**Table B3-9 Reproductive and Developmental Effects Resulting from Oral Exposure to Dinoseb**

| Test Organism (Species) | Dose (Duration) | Response | Reference |
|---|---|---|---|
| Rat (Sherman) (Adult male) | 300 ppm (11 weeks) | 90% of the spermatozoa from the cauda epididymis were atypical (20 days); bizarre and amorphous forms were observed and epididymal sperm counts decreased (30 days); abnormal spermatozoa, spermatids and multinucleated spermatogenic cells (20 and 30 days); severe damage to spermatogenic cells (50 days); and, reproductive failure. | Linder *et al*, 1982 |

B3-4.2.1.5 No Observed Adverse Effect Levels

**Table B3-10 NOAELs and LOAELs for Oral Exposure to Dinoseb[a]**

| Test Type | Test Organism (Species) | Effect | Value (mg/kg/day) | Endpoint | Reference |
|---|---|---|---|---|---|
| Acute | Dog | NOAEL | ~3.8 | Mural endocarditis | Health Canada, 1989 |
| Chronic | Mouse | LOAEL | 1 | Cystic endometrial hyperplasia; testicular atrophy/degeneration with hypospermatogenesis | Dow Chemical Co., 1981a |

[a] Obtained from U.S. EPA, 1993.

**Table B3-11 Dinoseb Reproductive and Developmental NOAEL and LOAEL Values[a]**

| Test Organism (Species) | Effect | Value (mg/kg/day) | Endpoint | Reference |
|---|---|---|---|---|
| Rat (Sherman) (Adult male) | NOAEL | 75 ppm (11 weeks) | Reproductive toxicity | Linder *et al*, 1982 |
| Rat | LOAEL | 1 | Reproductive toxicity (low viability index for control pups; inconsistency between body weight changes; consistent decreased in gonadal weights; and, gonadal weights/body weight ratios). | Dow Chemical Co., 1981b |
| Rat | LOAEL | 1 | Systemic maternal toxicity (decreased parental body weights). | Dow Chemical Co., 1981b |
| Rat | LOAEL | 3 | Developmental toxicity (increased malformations and/or anomalies; and, brain/spinal cord defects). | American Hoechst Crop., 1986a |
| Rat | LOAEL | 3 | Developmental toxicity (increased incidence of absence of ossification for a number of skeletal sites). | American Hoechst Corp., 1986b |
| Rat | LOAEL | 3 | Maternal toxicity (mean body weight depression). | American Hoechst Corp., 1986b |
| Rat | LOAEL | 10 | Maternal systemic toxicity. | American Hoechst Crop., 1986a |

[a] Obtained from HSDB, 2003; U.S. EPA, 1993.

### *B3-4.2.2 Dermal Exposure*

B3-4.2.2.1 Death

**Table B3-12 Mammalian $LD_{50}$ Value Resulting from Dermal Exposure to Dinoseb**

| Test Organism (Species/Sex) | $LD_{50}$ (mg/kg) | Reference |
|---|---|---|
| Guinea Pig | 100-200 | Verschueren, 1983 |

B3-4.2.2.2 Neurological Effects

**Table B3-14 Neurological Effects Resulting from Dermal Exposure to Dinoseb**

| Test Organism (Species) | Dose (Duration) | Response | Reference |
|---|---|---|---|
| Mice (Swiss)(male) | 0-2,000 mg/kg | Significant decreases in saccharine intake (taste aversion); and, increased group activity. | Mitchell *et al*., 1989 |

## B3-4.3 Carcinogenicity

Dinoseb is not classifiable as to human carcinogenicity (U.S. EPA, 1993).

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 than the mid-dose, there was no decrease in time to tumour occurrence, and no evidence of any potentially predisposing lesions in the liver often associated with hepatocellular carcinogens (Table B3-15).

Dinoseb was not mutagenic for Salmonella typhimurium in three studies with or without the addition of rat liver homogenate (Simmon *et al.*, 1977; Moriya *et al*., 1983; Waters *et al*., 1982). Various results were obtained during DNA damage tests. Dinoseb tested position in prokaryotes without hepatic homogenates (Waters *et al*., 1982; Simmon *et al*., 1977), negative in eukaryotes (Simmon *et al*., 1977; Waters *et al*., 1982) and negative in human fibroblasts (Simmon *et al*, 1977). In the Ames *Salmonella*/mammalian microsomes assay no increase over background findings was noted for Dinoseb, as both a dilute or full strength solution (Eisenbeis *et al*., 1981).

**Table B3-15 Animal Carcinogenicity Data[a]**

| Test Subjects | Exposure | Dose | ,Response | ,Reference |
|---|---|---|---|---|
| Mice (Male and Female, CD-1) | Diet | 0,1,3 and 10 mg/kg/day for 100 weeks | Statistically significant increases in liver adenomas in female mice at the 3 and 10 mg/kg/day doses. Only one carcinoma was observed (low-dose female). No decrease in latency, no dose-response and no hepatocytic change | Dow Chemical Company, 1981c |
| Mice (AKR) | Gavage/Diet | 2.15 mg/kg/day for 3 weeks; 1.05 mg/kg/day up to 18 months | No significant increase in tumours | Innes *et al*., 1969 |

**Table B3-15 Animal Carcinogenicity Data[a]**

| Test Subjects | Exposure | Dose | ,Response | ,Reference |
|---|---|---|---|---|
| Rat (Male and Female, Charles River) | Diet | 0,1,3 and 10 mg/kg/day for 104 weeks | No positive results for carcinogenicity | Dow Chemical Company, 1977 |

[a] Obtained from U.S. EPA, 1993.

### B3-4.4 Populations at Special Risk

The most severe poisonings from absorption of dinoseb have occurred in workers who were concurrently exposed to hot environments (Morgan, 1982).

### B3-4.5 Toxicokinetics

#### *B3-4.5.1 Absorption*

Dinoseb was administered to pregnant mice through oral intubation (po) or intraperitoneal injection (i.p.). The rate of absorption was 40 times greater after intraperitoneal injection than oral administration (Gibson and Rao, 1973). Teratogenic and embryotoxic effects of ip-administered dinoseb in the mouse were considered due to the rapid and relatively extensive uptake of dinoseb by the embryo. By contrast, the slower uptake after oral intake resulted in protection of the embryos (Gibson and Rao, 1973). Similar differences in embryotoxicity were noted between oral and subcutaneous injection of dinoseb (Gibson, 1973).

Most nitrophenols (including dinoseb) are well absorbed from the gastrointestinal tract, across the skin and by the lungs when very find droplets are inhaled (Morgan, 1982). Gross differences in maternal absorption and/or elimination of dinoseb from different routes of administration did not account for the route-dependent teratogenic responses.

Dermal Absorption

Dermal penetration of dinoseb into adult rats exposed for 72 hours ranged between 86 to 93% depending on the dose (Shah *et al*., 1987). In the rabbit, over 68% of technical dinoseb applied dermal and left *in situ* for 7 days, was absorbed (Health Canada, 1989). Dinoseb displayed a constant fractional penetration following classical diffusional behaviour (Health Canada, 1989).

#### *B3-4.5.2 Distribution*

**Table B3-16 Distribution of Dinoseb and its Metabolites in Mammals**

| Test Organism | Route of Exposure | Location of Compounds | Reference |
|---|---|---|---|
| Rat | Oral Inhalation Dermal | Liver; kidney; spleen; blood | Menzie, 1969 |
| Mice (pregnant) | Oral Intraperitoneal injection | Embryonic levels ≤2.5% of maternal plasma. All maternal tissues; maternal liver and kidney; embryo brain as well as all tissues. ip admin resulted in dose 40 times faster than po. | Gibson and Rao, 1973; Gibson, 1973. |
| Mice (pregnant) | Oral Intraperitoneal injection | Embryo | The Chemical Society, 1975 |

### *B3-4.5.3 Metabolism*

**Table B3-17 Metabolites of Dinoseb**

| Test Organism | Route of Exposure | Reactions | Metabolites | Location of Metabolites | Reference |
|---|---|---|---|---|---|
| Rat and Rabbit | | | 2-(2-Hydroxy-1-Methylpropyl)-4,6-Dinitrophenol; 2-Methyl-2-)2-Hydroxy-3,5-Dintrophenyl)Propionic acid; 2-Amino-6-1(1-Methylpropyl)-4-Nitrophenol; and, Glucuronide. | Urine | The Chemical Society, 1970 |
| Rat | Inhalation Dermal Oral | Enzymatic reduction | Primary amines | Liver | Menzie, 1969 |
| Rabbit | Oral | Side chain oxidation; nitrogen reduction | Dinoseb; 2-Amino-4-Nitro-6-*sec*-Butylphenol and its glucuronide; Beta-methyl-beta-(2-hydroxyl-3,5-dinitrophenyl)propionic acid; and, one unidentified compound. | Urine | Menzie, 1969 |
| Cow | | | 6-Amino-2-butyl-4-nitrophenol; and, 2-Sec-butyl-4,6-diaminophenol. | | Menzie, 1969 |

Following the incubation of dinoseb with rumen fluid 6-Amino-2-butyl-4-nitrophenol (ABNP) was observed. With increased incubation time the concentration of ABNP diminished while 2-*sec*-butyl-4,6-diaminophenol increased. When administered to cows, the same metabolites were observed (Table B3-17). Rabbits but not rate reduced one nitro group resulting in the formation of 6-aminoderivative conjugated as the *O*-glucoside. A carboxylic acid was also formed by oxidation of the terminal carbon of the secondary side chain in rats as well as rabbits. It was postulated that metabolism of dinoseb took place in the microbial contents of the gut. Only unmetabolized dinoseb (no metabolites) was reported in the embryonic mouse or in the maternal mouse after absorption.

**Cytotoxicity *in vitro***

Dinoseb was found to exhibit a powerful cytotoxic effect on cultures of isolated primary rat hepatocytes (Palmeira *et al*., 1995). Treatment of liver cells *in vitro* only slightly altered the ratio of reduced glutathione to oxidized glutathione (GSH/GSSG ratio). Herbicides such as 2,4-D and paraquat, by contrast, rapidly altered this ratio, increased lipid peroxidation and depleted protein thiols (Palmeira *et al*., 1995). It was concluded that dinoseb cytotoxicity likely results from the uncoupling of oxidative phosphorylation in liver mitochondria (Palmeira *et al*., 1995). Very low concentrations of dinoseb decreased intracellular ATP suggesting rapid impairment of energetic processes in cells.

### *B3-4.5.4 Elimination and Excretion*

Elimination of dinoseb was first order and was dependent on the route of administration. Following oral administration dinoseb was distributed to the total body water, .i.p. injection resulted in only extracellular volume.

Dinoseb and its metabolites were excreted in urine and faeces of mice regardless of the route of administration (Gibson and Rao, 1973). Phenolic pesticides appear to be readily assimilated by animals; however, they are excreted slowly over a period of many weeks (Kearney and Kaufman, 1975). In rabbits and rats exposed to dinoseb through inhalation, skin contact or ingestion, both the parent compound as well as metabolites have been excreted in urine (Menzie, 1969; The Chemical Society, 1970). In mice, 67 to 78% of the administered dose was recovered within 64 hours (Gibson and Rao, 1973). Distribution of dinoseb to the fetus was smaller after oral exposure in the dam.

Different factors may affect the rate of dinoseb elimination from animals. For instance, food deprivation for 24 hours increased the rate of disappearance of dinoseb from plasma. However, food deprivation for 48 hours did not change the rate of disappearance from plasma. Instead an increase in the rate of disappearance from the liver was observed (Preache and Gibson, 1975).

## B3-4.6 Exposure Limits

### Table B3-18 Existing RfD Values for Dinoseb Exposures

| Reference Dose (mg/kg/ day) | Reference | Endpoint | Study | Reference | NOAEL (mg/kg/day) | Uncertainty Factor | Study Classification |
|---|---|---|---|---|---|---|---|
| **Acute/Short-term (1-7 days)** | | | | | | | |
| No information found | | | | | | | |
| **Intermediate-term (7 days- Several months)** | | | | | | | |
| No information found | | | | | | | |
| **Long-term (6 months to lifetime)** | | | | | | | |
| 0.001 | U.S. EPA, 1989a | Decreased fetal weight | 3 generation Rat Reproduction Study | Dow Chemical Co., 1981c | 1[a] | 1,000 | Acceptable, confidence in the RfD is Medium |
| 0.001[b] | Health Canada, 1991; 2004 | Skeletal abnormalities | Rat Reproduction Study | Dinoseb Task Force, 1986 | 1 | 1,000 | |

[a] Lowest-observed effect level (LEL) was used to establish the oral RfD.

[b] Acceptable Daily Intake (ADI) - The amount of a chemical a person can be exposed to on a daily basis over an extended period of time (usually a lifetime) without suffering deleterious effects.

A chronic Rfd value of 0.001 mg/kg/day was selected for dinoseb for the purpose of this risk assessment (Health Canada, 2004).

## B3-5.0 ENVIRONMENTAL FATE AND EXPOSURE

### B3-5.1 Air

#### *B3-5.1.1 Transport and Partitioning*

Based on its vapour pressure (Table B3-19), dinoseb may exist entirely in the vapour phase in the atmosphere (Eisenreich *et al*., 1981). However, due to its water solubility (Table B3-20) some of the atmospheric dinoseb may be removed by wet deposition.

#### *B3-5.1.2 Transformation and Degradation*

**Table B3-19 Half-life in Air**

| Half-life | Reference |
|---|---|
| 4.1 days[a] | Atkinson, 1985 |

[a] half-life for the reaction of vapour phase dinoseb with photochemically generated hydroxyl radicals.

### B3-5.2 Water

#### *B3-5.2.1 Transport and Partitioning*

Based on its water solubility (Table B3-20), dinoseb may be removed from the atmosphere by wet deposition and is readily transported by surface and groundwater. The estimated Henry's law constant of dinoseb suggests that volatilization of dinoseb will be slow (Lyman *et al*., 1982).

#### *B3-5.2.2 Transformation and Degradation*

Dinoseb may photodegrade as its absorption maximum in water is 375 nm (U.S. EPA, 1989b). However, hydrolysis and biodegradation are not expected to occur in most natural waters (U.S. EPA, 1989b). The compound did not undergo hydrolysis in water in the pH range of 5 to 9 at 25°C over a period of 30 days (U.S. EPA, 1989b). Dinoseb is stable at a pH of 5, 7 and 9.

**Table B3-20 Half-life in Water**

| Conditions | Half-life | Reference |
|---|---|---|
| Exposed to natural sunlight | 14-18 days | U.S. EPA, 1989b |
| | 16 days | JW, 2006 |

### B3-5.3 Sediment and Soil

#### *B3-5.3.1 Transport and Partitioning*

The water soluble salts of dinoseb leach readily into soil. However, oil-soluble or water-miscible formulations move much less than water-soluble formulations (Kearney and Kaufman, 1975).

Measured soil-sorption coefficients ($K_{oc}$) of dinoseb are 120 and 124 (Kenaga, 1980; JW, 2006). Therefore, the compound will be highly mobile in soil and may leach into groundwater (Stevens *et al*., 1989). Experiments with soil thin layer chromatography showed that dinoseb was intermediate to very mobile in silt loam, sand loam and silty loam soils (U.S. EPA, 1989b). However, sorption appears to be pH dependent as a $K_{oc}$ value of 6,607 was obtained at a buffered pH of 3 (Hodson and Williams, 1988). Therefore, at a low pH adsorption may be stronger. Dinoseb may also adsorb more strongly to clay soils as p-nitrophenol absorbs strongly to clays through an interaction between the nitro group and the water molecules or metallic cations in the clay (Saltzman and Yariv, 1974).

Volatilization of dinoseb from soil is not expected to be significant (Stevens *et al*., 1989). However, some losses may occur under specific conditions of soil acidity, high temperatures and surface soil moisture by codistillation (Weed Science Society of America, 1979; Kearney and Kaufman, 1975). Photodegradation and microbial breakdown may play a role in the breakdown of dinoseb in soil (JW, 2006).

### *B3-5.3.2 Transformation and Degradation*

Dinoseb is expected to biodegrade slowly in soil (Stevens *et al*., 1989) (Table B3-21). The half life of dinoseb in soil drastically decreased when exposed to natural sunlight suggesting that photolytic degradation from the soil surface may be an important degradation pathway (Stevens *et al*., 1989; U.S. EPA, 1989b). Dinoseb mineralization was reported in soils at normal application concentrations without apparent accumulation in fields receiving repeated applications (Stevens *et al*., 1990). On the other hand, at spill sites or where higher concentrations have been accidentally applied dinoseb has been found to persist. Disoseb soil contamination is easily visible due to its intense yellow color, even at concentrations as low as 10 ppm (10 µg/g) (Stevens *et al*., 1990).

Microbial breakdown of dinoseb in soil has been demonstrated (Weed Science Society of America, 1979). At very high application rates of 5 tons/acre biodegradation did not occur (Stojanovie *et al*., 1972). At typical application rates dinoseb degrades in soil. *Psuedomonas aeroginosa* and *P. putida* grew readily with dinoseb as their sole carbon source (Kearney and Kaufman, 1975). In addition, 5 ppm of dinoseb incubated in soil for 60 days (25°C) resulted in the evolution of 36% of the applied $^{14}C$ as $CO_2$ (Doyle *et al*., 1978).

**Table B3-21 Half-life in Soil**

| Conditions | Half-life | Reference |
|---|---|---|
| Sandy loam soil; exposed to natural sunlight | 14 hours | U.S. EPA, 1989b; JW, 2006 |
| | 26 days[a] | Morrill *et al*., 1985 |
| | 30 days[b] | Gustafson, 1989 |
| Vadose sandy loam soil | 100 days | Stevens *et al*., 1989 |

[a] Laboratory measured evapouration half-life.
[b] Hydrolysis half-life.

Models of dinoseb biodegradation. The factors which appeared to be most significant to biodegradation of dinoseb in soil were bacterial numbers, nitrate concentration, and soil sorption. No other measured parameters reduced the total variability in biodegradation rates (Stevens *et al*., 1990). Sorption of dinoseb to silt-loam soil was sufficient to have a significant effect on dinoseb degradation rates (Stevens *et al*., 1990). The great difference in sorption activity

between the sandy soil and the silt-loam was expected based on the known dependence of these factors on the lack of clays and organic matter in sandy soils. Soil pH has a profound effect on dinoseb sorption. At pH 4.5, sorption was greatly increased in the sandy soil. The pKa of dinoseb (4.7) enhances protonation of the dinoseb phenolic group at low pH.

Soils form areas previously treated with dinoseb did not necessarily experience more rapid rates of elimination. Biodegradation of dinoseb can occur in soils and is not dependent on long-term acclimation to dinoseb. The most important environmental parameters affecting dinoseb degradation at concentrations near 25 ppm were the presence of degradative microorganisms which are necessary to the process. The presence of nitrate in soil, and organic material which promotes sorption of dinoseb to soil surfaces contribute to the inhibition of the process of biodegradation (Stevens *et al*., 1990).

## B3-5.4 Other Environmental Media

### *B3-5.4.1 Transport and Partitioning*

Dinoseb has a bioconcentration factor (BCF) of 3.162. A BCF of this magnitude suggests that dinoseb will not bioconcentrate.

## B3-6.0 SUMMARY

Dinoseb belongs to the dinitro-phenol family of herbicides, and can be used either as an ester or a salt. As an agricultural herbicide, dinoseb was registered for use to control seedling weeds in a variety of crops such as apples and potatoes (Health Canada, 1989). However, dinoseb was banned from use in Canada as of December 21, 2001. In 1967, approximately 16 kg of dinoseb was sprayed at CFB Gagetown on 2.4 ha of designated plots (JW, 2006).

Many intoxication incidents have resulted from the use of dinitrophenol herbicides, 99% of which contain dinoseb (Health Canada, 1989). The most severe intoxications from dinoseb have occurred in workers who were concurrently exposed to high temperature environments (Morgan, 1982). Between 1981 and 1985, dinitrophenol herbicides was the ninth most common source of occupational intoxicant within 38 reported cases (Health Canada, 1989). One human fatality was reported in Texas in 1983 due to dermal exposure to an alkanolamine salt formulation of dinoseb from a leaking backpack sprayer (Health Canada, 1989). Furthermore, cataracts were induced in people as a result of the former use of dinitrophenol compounds as a weight reducing aid in the 1930s (Hayes, 1982; Gosselin *et al*., 1981).

Dinoseb has high acute toxicity in animals. In long-term oral exposure studies, dinoseb caused significant systemic effects in rodents. Reproductive/ developmental effects were also seen in rodents exposed to dinoseb through the oral route. The U.S. EPA (1993) stated that dinoseb was not classifiable as to human carcinogenicity (U.S. EPA, 1993) based on inadequate studies in rodents.

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