Dinoseb; CASRN 88-85-7

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Dinoseb

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	01/31/1987
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	08/01/1989

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 — 01/31/1987

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. 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 the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that 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.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased fetal weight **3-Generation Rat Reproduction Study** **Dow Chemical Co., 1981a**	NOEL: none LEL: 1 mg/kg/day	1000	1	1E-3 mg/kg/day

*Conversion Factors -- None

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.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — 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 — None

I.A.4. Additional Studies/Comments (Oral RfD)

A number of toxicologic issues concerning dinoseb have been raised as a result of the review of the database 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 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 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/Oncogenic Study; Chronic Dog Feeding Study; Rat Teratology Study; Rabbit Teratology Study

I.A.5. Confidence in the Oral RfD

Study — Low
Database — 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 database 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 Work Group Review — 07/08/1985, 07/22/1985, 12/09/1986

Verification Date — 12/09/1986

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Dinoseb conducted in August 2003 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Dinoseb
CASRN — 88-85-7
Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Dinoseb
CASRN — 88-85-7
Last Revised — 08/01/1989

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. 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. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for 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 than the mid dose, there were no decreases in time to tumor, nor any 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.

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 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.

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).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not available.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not available.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA, 1975, 1986

The Toxicology Branch Peer Review Committee reviewed data on dinoseb.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 01/13/1988, 02/03/1988, 11/09/1988, 05/03/1989

Verification Date — 05/03/1989

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Dinoseb conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Dinoseb
CASRN — 88-85-7

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.

VI.B. Inhalation RfC References

None

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.

VII. Revision History

Substance Name — Dinoseb
CASRN — 88-85-7

Date	Section	Description
08/01/1989	II.	Carcinogen summary on-line
10/28/2003	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Dinoseb
CASRN — 88-85-7
Last Revised — 01/31/1987

- 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-
- Premerg
- Sinox General
- Subitex