Adopted as Rule: August 2018

Toxicological Summary for: Dinoseb

CAS**: 88-85-7**

Synonyms: 2-sec-Butyl-4,6-dinitrophenol, dinitrobutylphenol, Dinitro-ortho-sec-butyl phenol, 4,6-Dinitro-o-sec-butylphenol, 2,4-dinitro-6-sec-butylphenol, 4,6-dinitro-2-sec-butylphenol, 2,4-dinitro-6-(1-methylpropyl)phenol, 4,6-dinitro-2-(1-methyl-propyl)phenol, 2,4-dinitro-6-(1-methyl-propyl)phenol

Acute Non-Cancer Health Risk Limit ($nHRL_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 8 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0048 mg/kg-d) x (0.5)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 8.4 rounded to **8 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 1.43/300 = 0.0048 mg/kg-d (SPF Crl;cd rats)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	6.52 mg/kg-d (LOAEL, Matsumoto et al., 2010)
Dose Adjustment Factor (DAF):	0.22 (Body weight scaling, MDH 2001, USEPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 6.52 mg/kg-d x 0.22 = 1.43 mg/kg-d
Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for use of a LOAEL instead of a NOAEL, and 3 for database uncertainty for lack of an adequate multigenerational study and because the current studies were unable to identify a NOAEL.
Critical effect(s):	Increased number of fetuses with skeletal variations and short supernumerary ribs
Co-critical effect(s):	Decreased pup survival at birth, decreased maternal body weight, decreased fetal body weight, decreased body

	weight gain during pregnancy, decreased body weight of live fetuses, increased number of fetuses with external malformations, increased incidence of micropthalmia, increased number of skeletal malformations, decreased placenta weight
Additivity endpoint(s):	Developmental

Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = $nHRL_{Short-term}$ = 8 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0048*** mg/kg-d) x (0.2)* x (1000 µg/mg)}}{\text{(0.070 L/kg-d)**}}$$

= 13.7 rounded to 10 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-8
***The calculated subchronic RfD (0.0091 mg/kg-d) is higher than the short term RfD (0.0048 mg/kg-d), which is based on developmental effects. The subchronic RfD must be protective of all types of adverse effects that could occur as a result of subchronic exposure, including short-term effects (MDH 2008). Therefore, the subchronic RfD is set to the short-term RfD. See the short-term information above for details about the reference dose.

The Subchronic nHRL must be protective of the acute, and short-term exposures that occur within the subchronic period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 8 µg/L. Additivity endpoints: Developmental

Chronic Non-Cancer Health Risk Limit ($nHRL_{Chronic}$) = $nHRL_{Short-term}$ = 8 µg/L

$$\frac{\text{(Reference Dose, mg/kg-d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic Intake Rate, L/kg-d)}}$$

$$= \frac{\text{(0.0030 mg/kg-d) x (0.2)* x (1000 µg/mg)}}{\text{(0.044 L/kg-d)**}}$$

= 13.6 rounded to 10 µg/L

*Relative Source Contribution: MDH 2008, Section IV.E.1.
**Intake Rate: MDH 2008, Section IV.E.1. and US EPA 2011, Exposure Factors Handbook, Tables 3-1 and 3-81

Reference Dose/Concentration:	HED/Total UF = 0.912/300 = 0.0030 mg/kg-d (Sherman rats)
Source of toxicity value:	Determined by MDH in 2016 NOAEL= 0.912 mg/kg-d (Linder et al., 1982, subchronic duration)
Dose Adjustment Factor (DAF):	0.24 (Body weight scaling, MDH 2011, USEPA 2011)
Human Equivalent Dose (HED):	POD x DAF = 3.8 mg/kg-d x 0.24 = 0.912 mg/kg-day

Total uncertainty factor (UF):	300
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, 3 for subchronic-to-chronic extrapolation, and 3 for database uncertainty for lack of an adequate multigenerational study
Critical effect(s):	Decreased sperm counts, and decreased sperm content of the caudae and vasa deferentia
Co-critical effect(s):	Decreased fetal body weight, decreased pup survival, increased incidence of supernumerary ribs, decreased sperm motility and velocity, increased sperm abnormalities
Additivity endpoint(s):	Developmental, Male reproductive system

The Chronic nHRL must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Short-term nHRL of 8 µg/L. Additivity endpoints: Developmental

Cancer Health Risk Limit (cHRL) = Not Applicable

Cancer classification:	D (Not classifiable as to human carcinogenicity, USEPA, 1987b)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Volatile: Yes (moderate)

Summary of Guidance Value History:
Health-Based Values (HBVs) were first derived for Dinoseb in 2017. This guidance was adopted as HRLs in 2018.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):
Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested for specific effect?	No	Yes	Yes	Yes	Yes
Effects observed?	-[1]	Yes[2]	Yes[3]	Yes[4]	-[5]

Comments on extent of testing or effects:

[1] Endocrine effects have not been specifically evaluated. However, a single study reported decreased thyroid gland weights in male rats at a 73 fold higher dose than the chronic reference dose (RfD).

[2] Immunotoxicity has not been adequately evaluated. In a single-dose immunology study where antigen was injected in the footpad, a dinoseb dose more than 700 fold higher than the short-term RfD markedly depressed the cellular immune response and the humoral immune response in hamsters.

[3] An increased number of fetuses with skeletal variations and short supernumerary ribs, developmental effects, are the basis for the short term RfD. Many studies reported decreased weight gain during pregnancy, and decreased weight in dams before and during gestation, and in pups and live embryos, indicating that treatment with dinoseb, is generally toxic to pregnant rats and mice and their offspring. Increases in internal/external malformations and anomalies, such as supernumerary ribs and loss of ossification, were seen at doses ranging from 50 - >1,000 fold higher than the short-term RfD. One study, at nearly 1,000 fold higher dose than the short-term RfD reported neural tube defects as the major common toxicological endpoint. Decreased gravid uterine weight was observed at a dose 400 fold higher than the short-term RfD.

[4] The chronic RfD is based on male reproductive effects. A number of studies reported many abnormal sperm parameters at doses ranging from more than 550-800 fold higher than the chronic RfD. Examples of sperm parameters affected include decreased number of sperm, decreased epididymal motility, decrease weight of seminal vesicle and prostate, abnormal sperm, decreased sperm counts, and decreased motile sperm rate. Two studies reported complete reproductive failure in males treated with more than 450 fold higher doses than the subchronic RfD. All mice dosed with more than 50 fold higher dose than the subchronic RfD were observed with endometrial hyperplasia and atrophy, and testicular atrophy and degeneration with hyperspermatogenesis.

[5] At doses over 450-fold higher than the subchronic RfD, there were no effects reported on discrimination/learning tests in adult rats, yet some increase in locomotor activity was noted. In a separate study, no effects were reported in rats given a series of Functional Observational Battery (FOB) neurotoxicity tests at doses over 300 fold higher than the subchronic RfD. Another multigeneration study using neurobehavioral assessments that tested offspring periodically over 14 weeks did not report any effects from doses up 500 fold higher than the subchronic RfD.

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