Adopted as Rule: August 2018

Toxicological Summary for: 2,4-Dichlorophenoxyacetic acid

CAS: **94-75-7**

Synonyms: 2,4-D, ACETIC ACID-(2,4-DICHLOROPHENOXY)-, Dichlorophenoxyacetic acid, *IUPAC* name (2,4-Dichlorophenoxy)acetic acid

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

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short\text{-}term}$) = 30 µg/L

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

$$= \frac{\text{(0.048 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.285 L/kg-d)}^{**}}$$

= 33.7 rounded to **30 µg/L**

*Relative Source Contribution: MDH 2008, Section IV.E.1. MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the significant potential non-water sources of exposure an RSC of 0.2 rather than the default of 0.5 has been selected.
**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 = 4.8/100 = 0.048 mg/kg-d (Sprague Dawley rats)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	21 mg/kg-d (NOAEL, MRID 47972101/Marty et al., 2013)
Dose Adjustment Factor (DAF):	Body weight scaling, default (US EPA, 2011)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 21 mg/kg-d x 0.23 = 4.8 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	10 for interspecies differences (toxicokinetic portion retained after DAF application due to remaining uncertainty) and 10 for intraspecies variability
Critical effect(s):	Increased thyroid stimulating hormone in pregnant rats, and decreased adrenal weight and thyroxine in offspring
Co-critical effect(s):	Increased skeletal abnormalities in offspring and decreased offspring body weight
Additivity endpoint(s):	Adrenal, Developmental, Thyroid (E)

Subchronic Non-Cancer Health Risk Limit ($nHRL_{Subchronic}$) = $nHRL_{Short\text{-}term}$ = 30 µg/L

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

$$= \frac{\text{(0.017 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.070 L/kg-d)}^{**}}$$

= 48.6 rounded to 50 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:	(POD x DAF)/Total UF = 0.017 mg/kg-d (Sprague Dawley rats)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	6.8 mg/kg-d (NOAEL, MRID 47972101/Marty et al., 2013)
Dose Adjustment Factor (DAF):	Body weight scaling, default (US EPA, 2011)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 6.8 mg/kg-d x 0.25 = 1.7 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	10 for interspecies differences (toxicokinetic portion retained after DAF application due to remaining uncertainty) and 10 for intraspecies variability
Critical effect(s):	Proximal tubule degeneration in kidney
Co-critical effect(s):	Decreased pup body weight and body weight gain
Additivity endpoint(s):	Developmental, Renal (kidney) system

The Subchronic nHRL must be protective of the short-term exposures that occur within the subchronic period and therefore, the Subchronic nHRL is set equal to the Short-term nHRL of 30 µg/L. Additivity endpoints: Adrenal, Developmental, Thyroid (E)

Chronic Non-Cancer Health Risk Limit ($nHRL_{Chronic}$) = $nHRL_{Short\text{-}term}$ = 30 µg/L

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

$$= \frac{\text{(0.017 mg/kg-d) x (0.2)}^{*} \text{ x (1000 µg/mg)}}{\text{(0.044 L/kg-d)}^{**}}$$

= 77.3 rounded to 80 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:	(POD x DAF)/Total UF = 0.017 mg/kg-d (Sprague Dawley rats)
Source of toxicity value:	Determined by MDH in 2016
Point of Departure (POD):	6.8 mg/kg-d (NOAEL, MRID 47972101/Marty et al., 2013)
Dose Adjustment Factor (DAF):	Body weight scaling, default (US EPA, 2011)
Human Equivalent Dose (MDH, 2011):	POD x DAF = 6.8 mg/kg-d x 0.25 = 1.7 mg/kg-d
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	10 for interspecies differences (toxicokinetic portion retained after DAF application due to remaining uncertainty) and 10 for intraspecies variability
Critical effect(s):	Proximal tubule degeneration in kidney
Co-critical effect(s):	Increased thyroid weight and histopathological changes of the proximal tubule in kidney, decreased pup body weight and body weight gain
Additivity endpoint(s):	Developmental, Renal (kidney) system, Thyroid

The Chronic nHRL must be protective of the short-term exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Short-term nHRL of 30 µg/L. Additivity endpoints: Adrenal, Developmental, Thyroid (E)

Cancer Health Risk Limit (cHRL) = Not Applicable

Cancer classification:	EPA Group D, Not Classifiable as to Human Carcinogenicity (EPA, 1997, EPA, 2013) IARC Group 2B, Possibly Carcinogenic to Humans (IARC, 2016)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable
Tumor site(s):	Not Applicable

Statement regarding carcinogenicity of 2,4-D:
The International Agency for Research on Cancer (IARC, 2016) concluded that 2,4-D is a possible human carcinogen based on strong mechanistic evidence for oxidative stress, moderate evidence for immunosuppression, limited evidence in animals, and inadequate evidence of cancer in humans. In addition, IARC determined that evidence was weak for genotoxicity, receptor activity, and altered cell proliferation following 2,4-D exposure. IARC evaluates cancer hazards without considering exposure levels or route of exposure and does not conduct quantitative cancer risk assessments. Agencies that develop quantitative cancer risk assessments, including the US EPA and the European Food Safety Authority (EFSA), currently conclude that 2,4-D is either not classifiable as a carcinogen or that it is unlikely to pose a cancer risk to humans ingesting foods treated with 2,4-D. Additionally, the

mechanisms for carcinogenicity, suggested by IARC, were threshold or nonlinear in nature, and no tumors were consistently reported in rats or mice at the highest doses tested, which were over 1,000 times higher than the Chronic RfD. MDH will continue to monitor 2,4-D and its associated cancer risks, but at this time the noncancer health-based guidance values are considered protective for possible cancer risks associated with 2,4-D in drinking water.

Volatile: No

Summary of Guidance Value History:
A chronic noncancer HRL for 2,4-D was set at 70 µg/L in 1993. A pesticide rapid assessment value was calculated for 2,4-D in 2014 at 2 µg/L. Short-term, Subchronic, and Chronic nHBVs of 30 µg/L were derived for 2,4-D in 2016. The 2016 nHBVs of 30 µg/L were lower than the 1993 HRL as a result of: 1) the use of more recent toxicological data, 2) the use of MDH's most recent risk assessment methodology, and 3) rounding to one significant digit. The 2016 nHBVs of 30 µg/L were higher than the pesticide rapid assessment due to the methodological differences between rapid assessment values and nHBVs. The 2016 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?	Yes	Yes	Yes	Yes	Yes
Effects observed?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:
[1] Endocrine effects have been thoroughly studied. Estrogenicity and androgenicity have been carefully examined in the critical study, with no treatment-related effects shown at doses nearly 200-fold higher than the short-term reference dose. Multiple studies show effects on thyroid and thyroid hormones, including the critical study, where these effects are important for deriving the short-term reference dose. Overall, thyroid effects occur at relatively high doses, with studies reporting thyroid hormone alterations and thyroid weight decreases at doses 200 -1,000 times higher than the short-term reference dose. Adrenal effects are also identified as a critical effect for short-term guidance. Additionally, hormones involved in milk production for offspring have been reported to be altered at doses nearly 70 times higher than the short-term reference dose.

[2] In humans, contradictory immunotoxicity results based on lymphocyte proliferation have been reported in studies of agricultural pesticide applicators. Several animal studies have examined immunotoxicity following 2,4-D exposure. Effects such as immune system organ weight changes were noted in the absence of other significant toxicity at doses greater than 100 times higher than the short-term reference dose following dietary exposure, while other studies in animals reported both stimulatory and suppressive effects at doses 10 to more than 100 times higher than the short-term

reference dose. IARC (2016) recently determined there was moderate evidence for immune suppression, but the results are mixed and potentially contradictory across species and study types.

[3] The short-term reference dose is partially based on developmental effects. Offspring body weight decreases have been observed in studies at doses 300-750 times higher than the short-term reference dose. One study reported offspring body weight decreases beginning at doses roughly 11 times higher than the short-term reference dose. Other developmental effects include decreased offspring viability, skeletal malformations in developing rats, and litter loss, at doses 300 – 600 times higher than the short-term reference dose.

[4] Reproductive effects have been extensively studied for 2,4-D. In adult animals, male reproductive glands have been altered at doses over 250 times higher than the subchronic reference dose. Milk production and lipid content were reported to be decreased in animals exposed to doses over 10 – 100 times higher than the short-term reference dose. Maternal behavior changes and decreased maternal body weight was altered at doses over 200 times higher than the short-term reference dose. Even in dogs, an organism overtly sensitive to 2,4-D toxicity, reproductive harm in males did not occur until doses exceeded nearly 100 times the subchronic reference dose.

[5] Neurotoxicity has been evaluated in multiple studies, and effects only occur at extremely high doses, especially if given as a single dose all at once (gavage). Animals were noted to have altered coordination and balance issues following doses over 1,000 times higher than the short-term reference dose. In a study with only a single exposure group, it was noted that myelin in the brain is affected at a dose approximately 450 times higher than the short-term reference dose. In pregnant animals, decreased control of movements and lowered overall activity were noted at a dose over 800 times higher than the short-term reference dose. Neurotransmitter levels in the brain have also been shown to be altered following 2,4-D exposure at doses 70 – 100 times higher than the short-term reference dose. Finally, lactating animals exposed to 2,4-D demonstrated altered activity, decreased myelin in their brains, and decreased brain weight at doses 300-450 times higher than the short-term reference dose.

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