

CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

2,4-Dichlorophenoxyacetic acid (2,4-D) is a free acid pesticide widely used in the United States. While the free acid is itself used as an herbicide, there are nine forms of 2,4-D registered as active ingredients in end use products. These include salts, amines, and esters of 2,4-D. Derivatives include the sodium salt, diethanolamine salt, dimethyl amine salt, isopropylamine salt, triisopropanolamine salt, butoxyethyl ester, ethylhexyl ester, and isopropyl ester. Almost 90–95% of total global use is accounted for by dimethyl amine salt and ethylhexyl ester. 2,4-D and its different chemical forms are listed as an ingredient, either as the singular active ingredient or in conjunction with other ingredients, in about 600 agricultural and residential products. 2,4-D is one of the most widely used agricultural herbicides in the United States with approximately 39 million pounds applied to crops in 2013; pasture and hay fields and wheat, soybean, and corn crops receive the greatest applications. It is also applied to residential or commercial turf for the elimination of a wide variety of broadleaf weeds without causing harm to the grass.

The dominant process affecting the overall environmental fate, transport, and bioaccumulation of 2,4-D is degradation by microbiological activity. 2,4-D has been shown to undergo degradation in pure cultures by particular species of microorganisms. The two main pathways of degradation are via a hydroxyphenoxy acetic acid intermediate or by the corresponding phenol. The half-life of 2,4-D was about 6 days when it was applied to a mineral soil maintained under aerobic conditions. 2,4-D is likely to migrate through the soil and into groundwater since it has high mobility in soils under varying conditions. 2,4-D is not expected to volatilize from water or soil surfaces since most forms of 2,4-D are supplied as amine salts, which do not volatilize, and the ester forms are rapidly transformed to the corresponding acid, which will exist as an anion under environmental conditions. Data suggest that bioconcentration of 2,4-D does not occur to a significant extent in aquatic organisms.

The general population may be exposed to 2,4-D during and after its use in residential and recreational areas. 2,4-D applications often occur to residential lawns, golf courses, parks, cemeteries, and other grassy areas. Since 2,4-D is also used on aquatic weeds, swimmers may also be exposed. 2,4-D can unintentionally be transported into residences if clothing or shoes containing this substance are worn indoors or if pets track in 2,4-D from recently treated lawns. The general population can be exposed to 2,4-D by ingesting food or water contaminated with it or through dermal contact with it when used in residential settings (lawn applications). Populations living within or very near areas of heavy agricultural

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2,4-D use have an increased risk of exposure to relatively larger amounts of 2,4-D through dermal contact with contaminated plants, soils, or surface waters or by inhalation of the mist formed from the applied herbicide. Those likely to receive the highest exposures are those who are involved in the production, formulation, handling, and/or application of 2,4-D. Dermal contact appears to be the major route of exposure for workers, although inhalation exposure and accidental ingestion via hand-to-mouth activity is possible.

Children are expected to be exposed to 2,4-D by the same routes that affect adults. Small children are more likely to come into contact with 2,4-D residues that may be present in soil and dust, due to increased hand-to-mouth activity and playing habits. However, dermal contact with house dust contaminated with small residues of 2,4-D is most likely the major route of exposure for children. Treated play areas (lawns) and pets that may have come in contact with 2,4-D on treated lawns is another possible source of exposure. No human data were located regarding 2,4-D in breast milk; therefore, an adequate determination of the importance of this route of child exposure has not been made.

1.2 SUMMARY OF HEALTH EFFECTS

Information regarding health effects in humans following exposure to 2,4-D comes from case reports of accidental or intentional ingestion of herbicide formulations containing 2,4-D, accidental inhalation and/or skin contact with 2,4-D in products used by farmers and professional residential applicators and homeowners, and occupational exposure during manufacture. Effects that have been reported following oral or dermal exposure to high amounts of 2,4-D include tachypnea, tachycardia, vomiting, leukocytosis, liver and kidney congestion in fatal cases, metabolic acidosis, and neurological effects characterized by sensory and motor abnormalities. In two reports of dermal exposure, signs and symptoms of peripheral neuropathy persisted for a long time. Some of these studies estimated exposure levels and/or measured levels of 2,4-D in the body. A report estimated an ingested dose of approximately 80 mg/kg in a fatal case. In another fatal case, the investigators estimated that the subject had ingested at least 25–35 g of 2,4-D (357–500 mg/kg for a 70 kg body weight). However, there is a report of two individuals who survived after ingesting approximately 40 and 140 g of 2,4-D (571 and 2,000 mg/kg) in herbicide products. These numbers are the result of the combined action of 2,4-D and other substances in commercial formulations. In addition, whether or not deaths occurred may be related to the time elapsed between poisoning and beginning of emergency medical treatment.

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Numerous epidemiological studies, mostly case-control and cohort studies, have examined potential associations between exposure to 2,4-D and multiple health outcomes including respiratory effects, endocrine effects, ocular effects, body weight effects, immunological effects, neurological effects, reproductive effects, developmental effects, various cancers, and death.

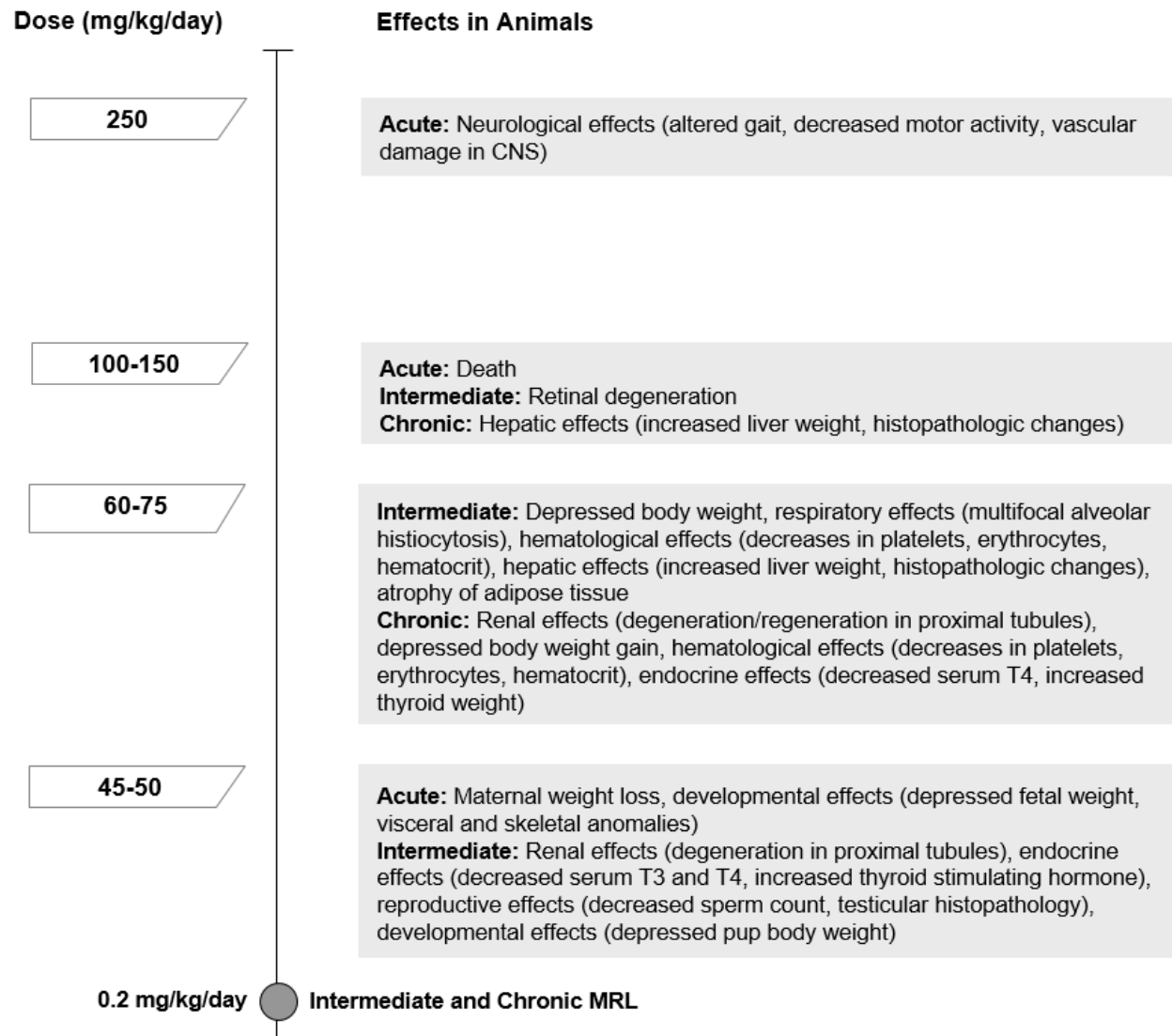
While some of the human studies reported associations between use/exposure to 2,4-D and adverse health outcomes, other studies did not. Pesticide applicators and farm workers are likely to be exposed to multiple chemicals, and even if analyses can be conducted for exposures to individual chemicals, a significant association between use/exposure and increased prevalence of an adverse health outcome does not necessarily imply causality. In general, limitations to the interpretation of reported associations include lack of relationship with frequency or amount of 2,4-D usage, duration of exposure, and/or limited numbers of cases.

The database in animals is extensive and consists almost exclusively of studies that employed the oral route of exposure. Systemic effects reported in repeated exposure oral studies in animals include hematological alterations in rats (decreased hematocrit, platelets, and erythrocyte counts); hepatic effects in rats (histological alterations); renal effects in rats and mice; alterations in thyroid hormone levels in rats; and ocular effects in rats. Review of available animal studies resulted in the conclusion that the kidney is the most sensitive target of 2,4-D toxicity in laboratory animals; 2,4-D kidney toxicity is a presumed health effect for humans.

As illustrated in Figure 1-1, the most sensitive noncancer effects of repeated-dose oral exposure to 2,4-D are kidney effects and developmental effects. Depressed body weight, hematological effects, hepatic effects, endocrine effects, and ocular effects occur at higher exposure levels.

Body Weight Effects. Fofana et al. (2000) reported 3–6% maternal body weight loss among rats administered 2,4-D by gavage at 50–110 mg/kg/day during gestation days (GDs) 6–15; however, the study report only noted that there was no maternal body weight loss among controls (i.e., data regarding maternal body weight gain during the same period were not presented). Bortolozzi et al. (1999) reported 11–12% depressed body weight in rat pups receiving 2,4-D from the food at 70 mg/kg/day during postpartum days 23–75 or 90 after 28 days of maternal exposure. As much as 54% depressed maternal body weight gain was noted for rat dams gavaged with 2,4-D at 100 mg/kg/day during GDs 1–19 (Mazhar et al. 2014). Up to 20% depressed body weight gain was observed in female rats receiving 2,4-D from the diet for 2 years at 75 mg/kg/day (Charles et al. 1996a; EPA 1996a).

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Figure 1-1. Health Effects Found in Animals Following Oral Exposure to 2,4-D

Hematological Effects. Repeated oral exposure of rats at doses in the range of 75–100 mg/kg/day resulted in hematological effects including decreases in platelets, hematocrit, and erythrocyte counts in some studies (Charles et al. 1996a, 1996b; EPA 1996a); however, other studies found no 2,4-D treatment-related hematological effects at doses as high as 90–300 mg/kg/day (EPA 1984; Gorzinski et al. 1987).

Renal Effects. Results from a variety of animal studies identify the kidney as a common target of 2,4-D toxicity. However, there is a degree of uncertainty regarding lowest-observed-adverse-effect levels (LOAELs) for adverse kidney effects. One 13-week study reported a LOAEL of approximately 7.1 mg/kg/day for histological lesions in the kidneys of rats. However, other rat studies of ≤13 weeks

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reported LOAELs for histological alterations in the kidneys only at doses ≥ 20 mg/kg/day. The toxicological significance of the results from some studies is not clear (e.g., alterations in the kidneys from rats and mice characterized as increased homogeneity of the cytoplasm and decreased vacuolization of cells in the renal cortex).

Ocular Effects. Intermediate- and chronic-duration oral studies reported ocular effect such as cataracts and retinal degeneration at doses in the range of 150–300 mg/kg/day (Charles et al. 1996a, 1996b; EPA 1996a).

Endocrine Effects. Decreases in serum thyroid hormones were reported in some intermediate- and chronic-duration studies of laboratory animals receiving 2,4-D from the food at doses in the range of 50–150 mg/kg/day (Charles et al. 1996a, 1996b; EPA 1996a, 1996b; Marty et al. 2013).

Developmental Effects. Developmental effects following gestational exposure of rats and/or mice to 2,4-D at maternal doses in the range of 50–150 mg/kg/day include depressed fetal and/or postpartum pup weight, increased incidence of soft tissue and skeletal anomalies, increased resorptions, and increased pup mortality (Chernoff et al. 1990; Fofana et al. 2000, 2002; Kavlock et al. 1987; Mazhar et al. 2014; Schwetz et al. 1971). Gestational and postpartum exposures of rats at maternal doses in the range of 50–126 mg/kg/day and continued dosing of pups directly resulted in effects including depressed pup weight, neurobehavioral alterations, decreased pup viability, developmental effects on the prostate and liver, and alterations in bone histopathology (Bortolozzi et al. 1999; EPA 1986, 1987b; Hansen et al. 1971; Marty et al. 2013; Pochettino et al. 2016; Saghir et al. 2013a, 2013b; Troudi et al. 2012a, 2012b).

Cancer Effects. 2,4-D has been evaluated for possible associations with a variety of cancer types (lymphatic system cancers, gastrointestinal cancer, breast cancer, cancers of the nervous system, prostate cancer, and others) (e.g., Goodman et al. 2015; Flower et al. 2004; Hoar et al. 1986; Pahwa et al. 2006; Smith et al. 2017; see Section 2.19 for full list of citations). Cancer of the lymphatic system, particularly non-Hodgkin's lymphoma (NHL), has received the most attention. Some case-control studies reported that exposure to 2,4-D increased the risk of NHL, but others did not. The case-control studies included agriculture exposure, residential use of 2,4-D, exposure during manufacture, or children from parents participating in the Agricultural Health Study (AHS). Studies that examined cause-specific mortality among employees engaged in the manufacture, formulation, or packaging of 2,4-D and related salts did not find patterns suggestive of a causal association between exposure to 2,4-D and any particular cause of death, including NHL.

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The carcinogenicity of 2,4-D has been evaluated in a number of animal cancer bioassays; species evaluated include rats, mice, and dogs (Charles et al. 1996a; EPA 1996a, 1996b, 1987a; Hansen et al. 1971). These animal cancer bioassays did not provide convincing evidence of 2,4-D carcinogenicity.

The U.S. Environmental Protection Agency (EPA 2005a) has assigned 2,4-D to carcinogenicity Group D, “not classifiable as to human carcinogenicity.” The International Agency for Research on Cancer (IARC) recently classified 2,4-D as possibly carcinogenic to humans (Group 2B) based on inadequate evidence in humans and limited evidence in experimental animals (IARC 2018). In discussing potential mechanisms by which 2,4-D could induce cancer, IARC noted that the evidence that 2,4-D induces oxidative stress that can operate in humans is strong, the evidence that 2,4-D is genotoxic is weak, the evidence that 2,4-D causes immunosuppression is moderate, the evidence that 2,4-D modulates receptor activity is weak, and the evidence that 2,4-D alters cell proliferation or death is weak. Recently, Canada’s Pest Management Regulatory Agency (PMRA 2016) concluded that 2,4-D cannot be classified as a human carcinogen based on the inconsistent epidemiological associations, the recognition that there are many other factors that may contribute to the etiology of the reported cancer cases, information from the PMRA’s incident report database, and the fact that the weight of evidence from animal studies designed to show causality did not support a carcinogenic effect.

1.3 MINIMAL RISK LEVELS (MRLs)

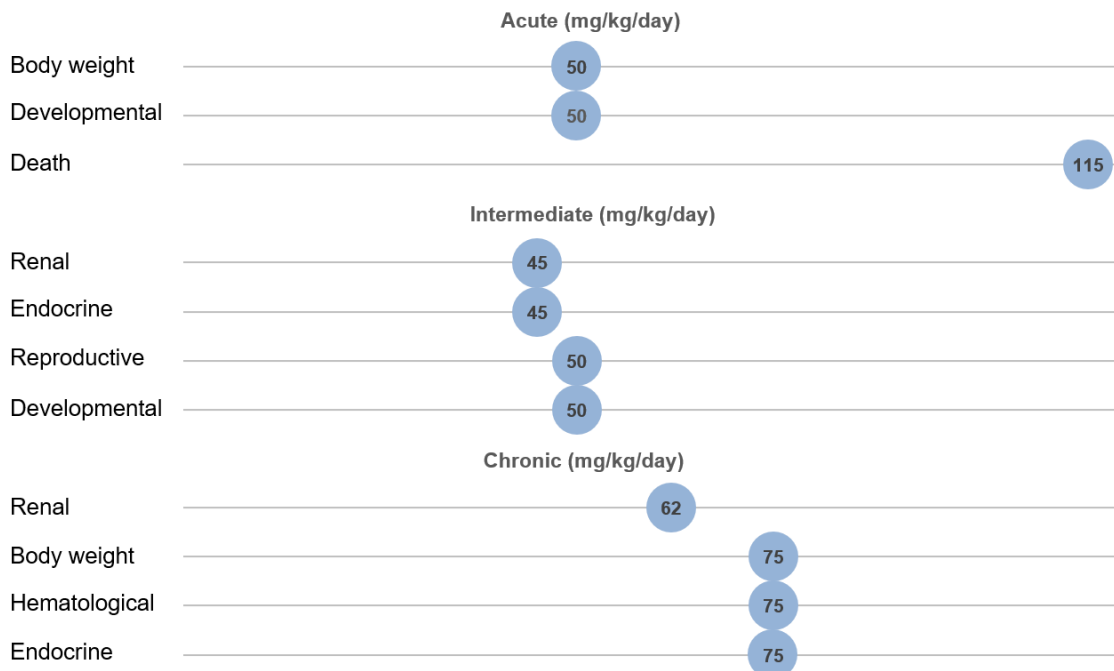
As discussed in Appendix A, the inhalation database was not considered adequate for derivation of acute-, intermediate-, or chronic-duration inhalation MRLs.

As shown in Figure 1-2, the kidney is the most sensitive target of 2,4-D toxicity following oral exposure. The oral database was not considered adequate for derivation of an acute-duration oral MRL for 2,4-D. The oral database was considered adequate for derivation of intermediate- and chronic-duration oral MRLs for 2,4-D.

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Figure 1-2. Summary of Sensitive Targets of 2,4-D – Oral

The kidney is the most sensitive target of 2,4-D oral exposure.
 Numbers in circles are the lowest LOAELs for all health effects in animals.
 No reliable dose response data were available for humans.



The MRL values for 2,4-D are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Table 1-1. Minimal Risk Levels (MRLs) for 2,4-D^a

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	0.2	Kidney lesions	16.6 (NOAEL)	100	Marty et al. 2013
Chronic	0.2	Kidney lesions	16.6 (BMDL ₁₀)	100	Charles et al. 1996a; EPA 1996b

^aSee Appendix A for additional information.

2,4-D = 2,4-dichlorophenoxyacetic acid; BMDL = 95% lower confidence limit on the benchmark dose (subscripts denote benchmark response: i.e., ₁₀ = exposure concentration associated with 10% extra risk); NOAEL = no-observed-adverse-effect level