

# 2,4-D

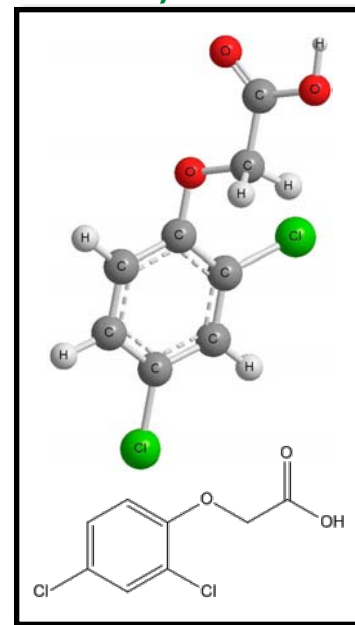
## TECHNICAL FACT SHEET

NPIC Technical Fact Sheets provide information that is complex and intended for individuals with a scientific background and/or familiarity with toxicology and risk assessment. This document is intended to promote informed decision-making. Please refer to the General Fact Sheet for less technical information.

### Chemical Class and Type:

- 2,4-D is an herbicide and secondarily a plant growth regulator.<sup>1</sup> Formulations include esters, acids, and several salts, which vary in their chemical properties, environmental behavior, and to a lesser extent, toxicity.<sup>2,3</sup> The salt and ester forms are derivatives of the parent acid.<sup>2</sup> Unless otherwise stated, the discussion in this fact sheet will refer to the acid form.
- The International Union of Pure and Applied Chemistry (IUPAC) chemical name for the acid form is 2,4-dichlorophenoxyacetic acid, its Chemical Abstracts Service (CAS) registry number is 94-75-7, and the chemical family is the phenoxyacetic acid compounds.<sup>3</sup>
- The dimethyl-amine salt (DMA) and 2-ethylhexyl ester (EHE) forms account for approximately 90-95% of the total global use.<sup>4</sup> The acid form is low in solubility and herbicide formulations consist of more soluble forms of the chemical.<sup>2</sup> Products containing 2,4-D frequently contain other herbicides as well.<sup>5</sup>
- Agent Orange, the herbicide widely used during the Vietnam war, contained 2,4-D. However, the controversy regarding health effects centered around the 2,4,5-T component of the herbicide and its contaminant, dioxin.<sup>6,7</sup>
- 2,4-D has been used in the United States since the 1940s, and it was evaluated for re-registration in 2005 by the United States Environmental Protection Agency (U.S. EPA).<sup>3</sup> The U.S. EPA determined that 2,4-D was eligible for re-registration, but required certain changes to labeled uses to mitigate risk.<sup>3</sup> See the text box on **Laboratory Testing**.

### Molecular Structure - 2,4-D



**Laboratory Testing:** Before pesticides are registered by the U.S. EPA, they must undergo laboratory testing for short-term (acute) and long-term (chronic) health effects. Laboratory animals are purposely given high enough doses to cause toxic effects. These tests help scientists judge how these chemicals might affect humans, domestic animals, and wildlife in cases of overexposure.

### Physical / Chemical Properties:

- 2,4-D and associated forms <sup>8,9</sup>(in table below)

Active Ingredient	CASRN	Form	Vapor pressure <sup>a</sup>	Henry's constant	Molecular Weight	Solubility In water (mg/L) <sup>b</sup>	Log K <sub>ow</sub>	K <sub>oc</sub>
2,4-D acid	94-75-7	White to brown crystalline solid	1.9 x 10 <sup>-5</sup> Pa 1.4 x 10 <sup>-7</sup> mmHg	8.6 x 10 <sup>-6</sup> atm·m <sup>3</sup> /mol	221	pH 5: 29,934 ± 2957 <sup>b</sup> pH 7: 44,558 ± 674 pH 9: 43,134 ± 336	0.001 M sol'n pH 5: 2.14 pH 7: 0.177 pH 9: 0.102	20-136
2,4-D sodium salt	2702-72-9	White powder	Salt dissociates to acid in water		243.03	45,000 mg/L	Salt dissociates to acid in water	
2,4-D-diethanolamine Salt (DEA)	5742-19-8	Cream colored powder	9.98 x 10 <sup>-8</sup> mmHg		326.18	806,000 mg/L	2.24 x 10 <sup>-2</sup> -1.65	
2,4-D dimethyl amine salt (DMA)	2008-39-1	Amber aqueous liquid	1.33 x 10 <sup>-5</sup> Pa 1 x 10 <sup>-7</sup> mmHg	1.4 x 10 <sup>-16</sup> atm·m <sup>3</sup> /mol	266.13	pH 5: 320,632 ± 3645 pH 7: 729,397 ± 86,400 pH 9: 663,755 ± 94,647	See values for 2,4-D acid above	72-136

<sup>a</sup>Vapor pressure measured at 25 °C.

<sup>b</sup>Solubility in water given for unbuffered solution.

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Active Ingredient	CASRN	Form	Vapor pressure <sup>a</sup>	Henry's constant	Molecular Weight	Solubility In water (mg/L) <sup>b</sup>	Log K <sub>ow</sub>	K <sub>oc</sub>
2,4-D -isopropylamine (IPA) salt	5742-17-6	Amber aqueous liquid	Salt dissociates to acid in water		280.04	pH 5: 174,000 mg/L pH 7: 436,000 mg/L pH 9: 331,000 mg/L	Salt dissociates to acid in water	
2,4-D tri-isopropanolamine (TIPA) salt	32341-80-3	Amber aqueous liquid	Salt dissociates to acid in water		412.31	pH 5: 461,000 mg/L pH 7: 461,000 mg/L pH 9: 104,000 mg/L	Salt dissociates to acid in water	
2,4-D BEE	1929-73-3	Dark amber liquid	3.2 x 10 <sup>-4</sup> Pa 2.4 x 10 <sup>-6</sup> mmHg		321.2	Practically insoluble in water	4.1	
2,4-D 2-ethylhexyl ester (EHE)	1928-43-4	Dark amber liquid	4.8 x 10 <sup>-4</sup> Pa 3.6 x 10 <sup>-6</sup> mmHg		333.27	0.0867 mg/L	5.78	
2,4-D -isopropyl ester (IPE)	94-11-1	Pale amber liquid	1.87 Pa 5.3 x 10 <sup>-6</sup> mbar	2.2 x 10 <sup>-6</sup> atm·m <sup>3</sup> /mol	263.12	Practically insoluble in water	253.8 ± 44.4	600

<sup>a</sup>Vapor pressure measured at 25 °C. <sup>b</sup>Solubility in water given for unbuffered solution.

### Uses:

- 2,4-D is used for broadleaf weed control in agricultural and nonagricultural settings, and it is registered for use in both terrestrial and aquatic environments. Major sites include pasture and rangeland, residential lawns, roadways, and cropland. Crops treated with 2,4-D include field corn, soybeans, spring wheat, hazelnuts, sugarcane, and barley.<sup>3</sup> Uses for products containing 2,4-D vary widely. Always read and follow the label when applying pesticide products.
- Approximately 46 million pounds are used each year in the United States, based on data from 1992-2000.<sup>3</sup>
- Signal words for products containing 2,4-D may range from Caution to Danger.<sup>10</sup> The signal word reflects the combined toxicity of the active ingredient and other ingredients in the product. See the pesticide label on the product and refer to the NPIC fact sheets on [Signal Words](#) and [Inert or "Other" Ingredients](#).
- To find a list of products containing 2,4-D which are registered in your state, visit the website [http://npic.orst.edu/reg/state\\_agencies.html](http://npic.orst.edu/reg/state_agencies.html) and search by "active ingredient."

### Mode of Action:

#### Target Organisms

- 2,4-D is used on a wide variety of terrestrial and aquatic broadleaf weeds. It has little effect on grasses.<sup>12</sup> It appears to work by causing uncontrolled cell division in vascular tissue.<sup>12</sup> Abnormal increases in cell wall plasticity, biosynthesis of proteins, and production of ethylene occur in plant tissues following exposure, and these processes are responsible for uncontrolled cell division.<sup>3,12</sup>
- The ester forms of 2,4-D penetrate foliage, whereas plant roots absorb the salt forms.<sup>12</sup> 2,4-D appears to be similar in action to other auxin-type herbicides.<sup>12</sup>

#### Non-target Organisms

- The modes of toxicity to animals from the acid, ester and salt forms of 2,4-D are similar. The primary exception is that the salt and acid forms can be extreme eye irritants.<sup>3</sup> 2,4-D is actively secreted by the proximal tubules of the kidney, and toxicity appears to result when renal clearance capacity is exceeded.<sup>3</sup> Dose-dependent toxic effects include damage to the eye, thyroid, kidney, adrenals, and ovaries or testes.<sup>3</sup> In addition, researchers have observed neurotoxicity, reproductive toxicity, and developmental toxicity.<sup>3</sup> Chlorophenoxy herbicides exhibit a variety of mechanisms of toxicity, including dose-dependent cell membrane damage leading to central nervous system toxicity,<sup>13</sup> interference with cellular metabolism involving acetyl-coenzyme A (CoA),<sup>13</sup> and uncoupling of oxidative phosphorylation due to either the disrupted CoA activity or cellular membrane damage.<sup>13</sup>

### Acute Toxicity:

#### Oral

- LD<sub>50</sub> values range from 639 mg/kg to 1646 mg/kg in rats depending on the chemical form of 2,4-D utilized in the study.<sup>3</sup> Researchers found that 2,4-D was more toxic for mice, reporting an LD<sub>50</sub> of 138 mg/kg.<sup>1</sup> All chemical forms for 2,4-D are considered low in toxicity<sup>11</sup> for acute oral exposure based on tests with rats.<sup>3</sup> See the text boxes on **Toxicity Classification** (page 4) and **LD<sub>50</sub>/LC<sub>50</sub>**.

#### Dermal

- Acute dermal LD<sub>50</sub>s ranged from 1829 mg/kg to greater than 2000 mg/kg in rabbits depending on the chemical form of 2,4-D. All chemical forms of 2,4-D are considered low in toxicity<sup>11</sup> for acute dermal exposure based on studies using rabbits.<sup>3</sup>
- The acid and salt forms of 2,4-D are highly toxic to eye tissue, causing severe eye irritation. This is reflected in the signal word of the formulated product. The ester forms are not considered eye irritants, and have low to very low ocular toxicity.<sup>3</sup>
- The ester and salt forms of 2,4-D are considered slight skin irritants.<sup>3</sup>

**LD<sub>50</sub>/LC<sub>50</sub>:** A common measure of acute toxicity is the lethal dose (LD<sub>50</sub>) or lethal concentration (LC<sub>50</sub>) that causes death (resulting from a single or limited exposure) in 50 percent of the treated animals. LD<sub>50</sub> is generally expressed as the dose in milligrams (mg) of chemical per kilogram (kg) of body weight. LC<sub>50</sub> is often expressed as mg of chemical per volume (e.g., liter (L)) of medium (i.e., air or water) the organism is exposed to. Chemicals are considered highly toxic when the LD<sub>50</sub>/LC<sub>50</sub> is small and practically non-toxic when the value is large. However, the LD<sub>50</sub>/LC<sub>50</sub> does not reflect any effects from long-term exposure (i.e., cancer, birth defects or reproductive toxicity) that may occur at levels below those that cause death.

#### Inhalation

- All chemical forms of 2,4-D are of low to very low toxicity via inhalation based on studies using rats. Acute inhalation LC<sub>50</sub>s for rats ranged from 0.78 mg/L to greater than 5.4 mg/L depending on the chemical form.<sup>3</sup> Most forms of 2,4-D are very low in toxicity, and the parent acid and TIPA salt forms are low in toxicity.<sup>3</sup>

#### Signs of Toxicity - Animals

- Dogs fed 2,4-D exhibited myotonia, vomiting, and weakness; dogs are more sensitive to chlorophenoxy acid herbicides than other animals.<sup>14</sup> In addition, dogs and cats have displayed inappetence, anorexia, ataxia, salivation, diarrhea, lethargy, and convulsions following exposure to 2,4-D, which may include eating treated grass<sup>15</sup> although the potential for this is unclear.<sup>16</sup> Rats demonstrated incoordination, central nervous system depression and muscular weakness following acute oral dosing.<sup>3,17</sup> Biochemical analysis of rat tissues suggested hepatic and muscle damage following acute, subchronic, and chronic oral exposures.<sup>17</sup>

#### Signs of Toxicity – Humans

- No occupational studies were found reporting signs or symptoms following exposure to 2,4-D under normal usage.
- Symptoms of acute oral exposure to 2,4-D include vomiting, diarrhea, headache, confusion, aggressive or bizarre behavior. A peculiar odor is sometimes noted on the breath. Skeletal muscle injury and renal failure may also occur.<sup>18</sup> Systemic toxicity is mainly associated with suicide attempts.<sup>18</sup>
- Symptoms following dermal exposure may include irritation, and inhalation exposure may lead to coughing and burning sensations in the upper respiratory tract and chest.<sup>18</sup> Prolonged exposure may result in dizziness.<sup>18</sup> Chlorophenoxy compounds such as 2,4-D are quickly absorbed when swallowed, but absorption from dermal or inhalation exposure is low.<sup>13,18</sup>
- Case reports and observational studies provide the majority of information regarding the toxicological effects of 2,4-D in incidents involving human poisonings. Researchers compiled the medical cases of 69 people who ingested 2,4-D and other chlorophenoxy herbicides; 23 of these patients died.<sup>13</sup> Ingestion led to vomiting, abdominal pain, diarrhea, and development of hypotension.<sup>13</sup> Peripheral neuromuscular effects including muscle twitching, weakness, and loss of tendon reflexes have been reported.<sup>13</sup> Neuromuscular effects have lasted several weeks to months and have been permanent in some cases.<sup>13</sup>

### TOXICITY CLASSIFICATION - 2,4-D

	High Toxicity	Moderate Toxicity	Low Toxicity	Very Low Toxicity
Acute Oral LD <sub>50</sub>	Up to and including 50 mg/kg (≤ 50 mg/kg)	Greater than 50 through 500 mg/kg (> 50 – 500 mg/kg)	Greater than 500 through 5000 mg/kg (> 500 – 5000 mg/kg)	Greater than 5000 mg/kg (> 5000 mg/kg)
Inhalation LC <sub>50</sub>	Up to and including 0.05 mg/l (≤ 0.05 mg/l)	Greater than 0.05 through 0.5 mg/l (>0.05 – 0.5 mg/l)	Greater than 0.5 through 2.0 mg/l (> 0.5 – 2.0 mg/l)	Greater than 2.0 mg/l (> 2.0 mg/l)
Dermal LD <sub>50</sub>	Up to and including 200 mg/kg (≤ 200 mg/kg)	Greater than 200 through 2000 mg/kg (> 200 - 2000 mg/kg)	Greater than 2000 through 5000 mg/kg (>2000 – 5000 mg/kg)	Greater than 5000 mg/kg (> 5000 mg/kg)
Primary Eye Irritation	Corrosive (irreversible destruction of ocular tissue) or corneal involvement or irritation persisting for more than 21 days (Acid, Salt)	Corneal involvement or other eye irritation clearing in 8 – 21 days	Corneal involvement or other eye irritation clearing in 7 days or less (Ester)	Minimal effects clearing in less than 24 hours (Ester)
Primary Skin Irritation	Corrosive (tissue destruction into the dermis and/or scarring)	Severe irritation at 72 hours (severe erythema or edema)	Moderate irritation at 72 hours (moderate erythema)	Mild or slight irritation at 72 hours (no irritation or erythema) (Ester, Salt)

The highlighted boxes reflect the values in the “Acute Toxicity” section of this fact sheet. Modeled after the U.S. Environmental Protection Agency, Office of Pesticide Programs, Label Review Manual, Chapter 7: Precautionary Labeling. <http://www.epa.gov/oppfead1/labeling/lrm/chap-07.pdf>

- Always follow label instructions and take steps to minimize exposure. If any exposure occurs, be sure to follow the First Aid instructions on the product label carefully. For additional treatment advice, contact the Poison Control Center at 1-800-222-1222. If you wish to report an incident to the National Pesticide Information Center, please call 1-800-858-7378.

## Chronic Toxicity:

### Animals

- Subchronic oral exposure to 2,4-D caused damage to the eye, thyroid, kidney, adrenals, and the ovaries and testes of laboratory animals.<sup>3,19</sup> A subchronic NOEL was established at 15 mg/kg/day based on studies in rats.<sup>19</sup> See the text box on **NOEL**, **NOEL**, **LOEL**, and **LOEL**.
- The chronic toxicity NOEL in rats and mice was determined to be 5 mg/kg/day in two-year studies.<sup>12,20</sup> The maximum tolerated dose in the two-year rat study was 150 mg/kg/day in male rats and 75 mg/kg/day in females.<sup>20</sup> Additional NOEL and NOEL doses were 15 mg/kg for rats in a 90-day study, and 1 mg/kg for dogs in a 12-month study, respectively.<sup>12,21</sup> Rabbits exhibited toxicity following dosing with either acid, salt, or ester forms of 2,4-D at doses of 30 mg/kg/day or greater.<sup>4</sup> Chronic NOELs and LOELs in dogs, however, varied for different parameters studied and by chemical form.<sup>21</sup>
- Rats showed no outward signs of toxicity following exposure to 200 mg/L of 2,4-D in drinking water for 30 and 100 days, but biochemical analysis suggested hepatic and muscle damage.<sup>17</sup>
- Researchers fed rats 2,4-D at doses of 1, 15, 100, and 300 mg/kg/day acid equivalents (ae). Changes in blood and thyroid parameters, organ weight ratios, and body weight gain were noted at 100 and 300 mg/kg/day doses.<sup>19</sup> Chronic toxicity in the eye, kidney, thyroid and liver of the rat were similar to effects found in subchronic studies.<sup>20</sup> Eye lesions were associated only with high doses of 150 mg/kg/day.<sup>20</sup>

**NOAEL: No Observable Adverse Effect Level**  
**NOEL: No Observed Effect Level**  
**LOAEL: Lowest Observable Adverse Effect Level**  
**LOEL: Lowest Observed Effect Level**

### Humans

- No human data were found on chronic effects of 2,4-D other than epidemiological studies of cancer occurrence. Although pesticide use has been linked to Parkinson’s disease and to respiratory disease in farmers, 2,4-D was not implicated in any relationships between pesticide exposure and subsequent disease.<sup>22,23</sup> See the Carcinogenicity section below for more information on 2,4-D and cancer in humans. See the text box on **Exposure** (page 5).

# 2,4-D

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**Exposure: Effects of 2,4-D on human health and the environment depend on how much 2,4-D is present and the length and frequency of exposure. Effects also depend on the health of a person and/or certain environmental factors.**

### Endocrine Disruption:

- Because 2,4-D has demonstrated toxic effects on the thyroid and gonads following exposure, there is concern over potential endocrine-disrupting effects.<sup>3</sup> 2,4-D is included in the U.S. EPA June 2007 Draft List of Chemicals for Tier 1 Screening.<sup>24</sup>

### Carcinogenicity:

#### Animals

- No oncogenic effects were observed in rats or mice following 2 years of dietary exposure of 2,4-D with concentrations ranging from 5-150 mg/kg/day or 5-300 mg/kg/day, respectively.<sup>20</sup> Similarly, researchers did not observe immunotoxic or oncogenic responses in dogs dosed with 1.0-7.5 mg/kg/day for either 13 weeks or 1 year.<sup>21</sup>
- A case-control study in companion dogs concluded that there was a “modest association” between malignant lymphoma in the dogs and the use of 2,4-D in their owners’ yards after accounting for other home and yard pesticide use.<sup>25</sup> Other investigators have questioned the epidemiological association reported in that study.<sup>5,26</sup>
- Overall, there has been no consistent association between exposure to 2,4-D and tumor induction in animals.<sup>27</sup> More recently, non-cytotoxic concentrations of 2,4-D were correlated to DNA damage and altered expression of some genes in hamster embryo cells.<sup>28</sup>

#### Humans

- The U.S. EPA evaluated 2,4-D for carcinogenic effects in 1988, 1992, and again in 2004. Each evaluation has concluded that “the data are not sufficient to conclude that there is a cause and effect relationship between exposure to 2,4-D and non-Hodgkin’s Lymphoma.”<sup>3</sup> 2,4-D was categorized as “Group D - not classifiable as to human carcinogenicity” in 2004.<sup>3</sup> See the text box on **Cancer**.

**Cancer: Government agencies in the United States and abroad have developed programs to evaluate the potential for a chemical to cause cancer. Testing guidelines and classification systems vary. To learn more about the meaning of various cancer classification descriptors listed in this fact sheet, please visit the appropriate reference, or call NPIC.**

- The International Agency for Research on Cancer (IARC), had not assigned 2,4-D a cancer rating as of June 2008. However, in 1987, IARC placed the family of chlorophenoxy herbicides in Group 2B, “possibly carcinogenic to humans.”<sup>29</sup>
- A discussion of the history of classification decisions regarding the carcinogenicity of 2,4-D has been published. A confounding factor in determining the carcinogenicity of 2,4-D is the frequent simultaneous exposure of workers to 2,4-D in addition to 2,4,5-T and its contaminant TCDD (dioxin), or to other herbicides. However, other work examining incidents of exposure to 2,4-D without simultaneous exposure to 2,4,5-T has found some association between 2,4-D and non-Hodgkin’s lymphoma.<sup>26</sup>
- Although the free acid form of 2,4-D did not damage chromosomes, there is limited evidence that commercial formulations may have the potential to do so.<sup>27</sup> Overall, evidence for mutagenicity has been inconsistent.<sup>26,27,30</sup>

### Reproductive or Teratogenic Effects:

#### Animals

- Teratogenic effects were not observed in mice, rats, or rabbits unless the excretion capacity of the mother was overwhelmed following oral exposure to 2,4-D or its salt and ester forms.<sup>26,4</sup> Reduced fetal viability was observed in hamsters following maternal dosing at 40 mg/kg/day during pregnancy, although effects did not follow a dose-response relationship.<sup>31</sup>

- Fetal abnormalities were observed in rats following oral doses of 90 mg/kg/day or greater beginning at fertilization; these doses were toxic to the mothers as well.<sup>4</sup> A NOEL of 25 mg/kg/day was derived for fetal rats in one study, and a NOAEL of 12.5 mg/kg/day for the mothers and a developmental NOAEL of 50 mg/kg/day for the young were derived in another study.<sup>7</sup> The overall maternal NOEL in rats was determined to be 8-17 mg/kg/day and overall developmental NOEL was 30 mg/kg/day 2,4-D acid equivalents.<sup>4</sup>
- Rabbit fetuses were unaffected at doses below 40 mg/kg/day administered to the dams although extra ribs were formed at doses above this threshold.<sup>4</sup> In rabbits, the developmental NOEL was 30 mg/kg/day 2,4-D acid equivalents.<sup>4</sup>

### Humans

- No experimental data are available regarding the effects of 2,4-D exposure on reproduction or development in humans. There are some reports of reproductive effects following occupational exposure to chlorophenoxy herbicides,<sup>7</sup> including reduced sperm motility and viability following occupational exposure. Although motility and viability recovered over a period of several months, malformations were still present.<sup>32</sup> Exposure to multiple pesticides in epidemiological studies make inference difficult.<sup>26</sup>

### Fate in the Body:

#### Absorption

- The greatest absorption rates in humans are from oral exposure, with much less absorption occurring following dermal or inhalation exposures.<sup>18</sup> Absorption rates following ingestion are dose-dependent in laboratory animals, with larger doses persisting in the gastrointestinal tract for longer periods of time.<sup>7</sup> In humans, plasma levels following 5 mg/kg oral ingestion peaked between 4-24 hours post-exposure.<sup>7</sup>
- Dermal exposure is considered the most likely route of exposure during product use.<sup>7</sup> Absorption of 2,4-D across the skin occurs more slowly and is less complete, and varies by chemical form, product formulation, species, and site of application.<sup>7</sup> Dermal absorption may be increased significantly with application of some sunscreens, insect repellents, or by alcohol consumption, as demonstrated in laboratory studies using rats and mice.<sup>33,34,35</sup> Hairless mouse skin absorbed 39% of a 100 µL dose in 24 hours.<sup>34</sup>

#### Distribution

- In laboratory animals, the primary target organs for 2,4-D toxicity were the eye, thyroid, kidney, adrenal glands, and ovaries or testes following subchronic oral exposure at doses above the threshold of saturation for renal clearance.<sup>3</sup> Biochemical changes suggested that liver and muscle damage occurred in rats at acute, subchronic, and chronic doses.<sup>17</sup>
- In humans, 2,4-D has a wide volume of distribution due to its water solubility, but it does not accumulate in any tissue.<sup>7</sup>

#### Metabolism

- Metabolism of 2,4-D is minimal in humans, with nearly all of it excreted unchanged as the parent compound.<sup>36,7</sup> The remainder is excreted as an unspecified 2,4-D conjugate.<sup>37</sup>
- In animals, little 2,4-D is metabolized prior to excretion. Up to 3.2% of the applied dose in rats was excreted as an unspecified polar metabolite.<sup>26</sup> In sheep and cattle, muscle, liver, kidney, and fat tissue contained the metabolite 4-chlorocatechol.<sup>38</sup> Dogs must metabolize the parent compound prior to excretion, due to their reduced ability to excrete organic acids.<sup>39</sup>
- No reactive intermediate metabolic products for 2,4-D have been identified in any species.<sup>26</sup>

### Excretion

- In humans, 2,4-D is rapidly excreted from the body, primarily in the urine.<sup>7</sup> Much of the compound appears to be eliminated unchanged, although some 2,4-D is eliminated from the body as a conjugate.<sup>37</sup> The percent of original dose excreted as a polar, acid-hydrolyzable metabolite was 4.8-27.0%.<sup>26</sup> The elimination half-life from blood plasma in humans orally dosed with 5 mg/kg of 2,4-D was 11.6 hours.<sup>37</sup> These human volunteers excreted more than 75% of 2,4-D in their urine within 96 hours of oral dosing.<sup>36</sup> Concentrations in blood plasma paralleled concentrations excreted in urine.<sup>36</sup> Some 2,4-D may be excreted in perspiration but this process appears to occur more slowly compared with urinary excretion.<sup>7</sup>
- Excretion of 2,4-D in animals depends on the species, formulation, and dose.<sup>40</sup> In rats, elimination of orally administered doses of 5 and 50 mg/kg 2,4-D took 24 hours, and the urine was composed almost entirely of unmetabolized 2,4-D.<sup>39</sup>
- Dogs excreted a 5 mg/kg oral dose primarily in their urine with minor amounts detected in feces.<sup>39</sup> Dogs dosed with 50 mg/kg excreted equal amounts in urine and feces and excretion was incomplete at 120 hours post-dose.<sup>39</sup> Because dogs appear to be deficient in their ability to excrete organic acids, 2,4-D must be metabolized prior to excretion.<sup>39</sup> Dogs orally dosed with 2,4-D excreted the parent compound, several conjugates and one unidentified compound in their urine.<sup>39</sup>
- Excretion of 2,4-D in urine is dose-dependent but nonlinear, with percent excreted in urine declining at higher doses.<sup>7</sup> In all of the species of animals studied, 2,4-D is excreted quickly and almost entirely in the urine.<sup>7</sup>

### Medical Tests and Monitoring:

- Biomarkers of exposure to 2,4-D have been reported in the scientific literature.<sup>41</sup> Scientists used high-performance liquid chromatography with tandem mass spectrometry to detect 2,4-D in urine.<sup>41,42</sup>
- Laboratory testing for 2,4-D is not widely available to physicians.
- 2,4-D was detected at low concentrations in urine samples collected from all age groups in a large study of the American public.<sup>41</sup> However, how these residues may affect human health is presently not clear,<sup>41</sup> and the relationship between exposure level and biomarker is unknown.<sup>43</sup>

### Environmental Fate:

#### Soil

- 2,4-D amine salts and esters are not persistent under most environmental conditions.<sup>3</sup> Typically, the ester and amine forms of 2,4-D are expected to degrade rapidly to the acid form.<sup>3</sup> Soil half-life values have been estimated at 10 days for the acid, diethylamine salt, and ester forms.<sup>44</sup> Another study estimated a soil half-life for the ester form EHE ranging from 1-14 days with a median half-life of 2.9 days.<sup>3</sup> In aerobic mineral soils, a half-life of 6.2 days was estimated.<sup>3</sup> A granular formulation of the BEE form was detected in aquatic sediments for 186 days post-application, perhaps due to either the formulation or slow de-esterification of the sediment-bound chemical.<sup>3</sup> See the text box on **Half-life**.

The "half-life" is the time required for half of the compound to break down in the environment.

1 half-life = 50% remaining

2 half-lives = 25% remaining

3 half-lives = 12% remaining

4 half-lives = 6% remaining

5 half-lives = 3% remaining

Half-lives can vary widely based on environmental factors. The amount of chemical remaining after a half-life will always depend on the amount of the chemical originally applied. It should be noted that some chemicals may degrade into compounds of toxicological significance.

- Microbial degradation of 2,4-D in soil involves hydroxylation, cleavage of the acid side-chain, decarboxylation, and ring opening.<sup>1</sup> The ethyl hexyl form of the compound is rapidly hydrolyzed in soil and water to form the 2,4-D acid.<sup>1</sup> Other comparative studies demonstrated that ester and amine salt forms of 2,4-D have similar soil dissipation rates because they are converted rapidly to the same anionic form.<sup>45</sup>

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- 2,4-D has a low binding affinity in mineral soils and sediment, and in those conditions is considered intermediately to highly mobile.<sup>3</sup> In sandy loam, sand, silty clay loam, and loam soil,  $K_{oc}$  values of 70, 76, 59, and 117 mL/g, respectively, were obtained,<sup>3</sup> indicating low binding affinity in these soil types. Although 2,4-D is highly mobile, rapid mineralization rates may reduce the potential of 2,4-D to affect groundwater.<sup>46</sup> Microbes may play a major role in degradation.<sup>2</sup>
- Break-down products of 2,4-D detected in laboratory experiments included 1,2,4-benzenetriol, 2,4-dichlorophenol (2,4-DCP), 2,4-dichloroanisole (2,4-DCA), 4-chlorophenol, chlorohydroquinone (CHQ), volatile organics, bound residues, and carbon dioxide. These degradates are expected to be of low occurrence in the environment, of low toxicity, or both.<sup>3</sup>

### Water

- The half-life of 2,4-D in aerobic aquatic environments was estimated to be 15 days and in anaerobic aquatic laboratory studies, 41-333 days.<sup>3</sup> A granular formulation of the BEE form degraded rapidly in the water column in alkaline conditions but was present in sediments for 186 days.<sup>3</sup>
- The ethyl hexyl form is rapidly hydrolyzed in water to 2,4-D acid, with a degradation half-life ( $DT_{50}$ ) of less than one day.<sup>1</sup> Ester forms of 2,4-D hydrolyze at rates that are pH dependent; the hydrolysis half-life of the butoxy ester increased from 9 hours at pH 8 to more than one year in more acidic conditions with a pH of 5.<sup>38</sup> The acid form of 2,4-D is very resistant to abiotic hydrolysis.<sup>3</sup>
- 2,4-D has been detected in streams and shallow groundwater at low concentrations, in both rural and urban areas.<sup>3,47,48</sup>

### Air

- Volatility for most forms of 2,4-D is low (see table on page 1 and 2). However, the vapor pressure of some ester forms range from  $1.1 \times 10^{-3}$  to  $2.3 \times 10^{-3}$  mmHg,<sup>2</sup> indicating that these forms readily volatilize. The Henry's Law Constant for 2,4-D acid is  $3.5 \times 10^{-4}$  at pH 7,<sup>49</sup> indicating low potential for movement from water to air.
- No data were found regarding the degradation of 2,4-D in the atmosphere.

### Plants

- The ester forms of 2,4-D penetrate foliage, whereas plant roots absorb the salt forms.<sup>12</sup> Ester forms are converted to the acid within the plant, then accumulate in cells due to passive diffusion down the concentration gradient.<sup>12</sup> Active transport within the plant may also occur.<sup>12</sup> Accumulation occurs primarily at the meristem tissue of roots and shoots.<sup>1</sup>
- Forest dissipation studies indicated that the ethyl hexyl ester form of 2,4-D degraded slowly on foliage and in leaf litter.<sup>3</sup> Residues of an ester form of 2,4-D were detected in samples of dead birch leaves for up to three years post-application.<sup>50</sup>

### Indoor

- No data were available on indoor persistence.

### Food Residue

- 2,4-D was not included in the list of pesticides detectable in regulatory monitoring.<sup>51</sup>
- Traces of 2,4-D were detected in 49.3% of finished drinking water samples and 53.7% of untreated water samples (365 and 367 samples taken, respectively), with detections between 1.1 and 2416.0 parts per trillion (ppt). These concentrations are well below the maximum contaminant level (MCL) of 70,000 ppt set by the U.S. EPA for finished drinking water.<sup>52</sup> In bottled water, only 2 of 367 samples contained 2,4-D, with residues of 3.2 and 4.2 ppt.<sup>52</sup> See the text box on **Maximum Contaminant Level (MCL)**.

**Maximum Contaminant Level (MCL):** The MCL is the highest level of contaminant that is legally allowed in drinking water. The MCL is enforceable. The MCL is typically measured in milligrams (mg) of contaminant per liter (L) of water.

U.S. Environmental Protection Agency. Office of Water. 2002 Edition of the Drinking Water Standards and Health Advisories. EPA 822-R-02-038. <http://www.epa.gov/ost/drinking/standards/dwstandards.pdf>

### Ecotoxicity Studies:

#### Birds

- LD<sub>50</sub> values range from 472 mg/kg for acute oral exposure in pheasants, to 668 mg/kg in pigeons and Japanese quail, to greater than 1000 mg/kg in wild ducks.<sup>1</sup> The acute oral LD<sub>50</sub> for the dimethyl amine salt form of the compound was 500 mg/kg for bobwhite quail, and the acute oral LD<sub>50</sub> for the ethyl hexyl form was 663 mg/kg in mallard ducks. The acute oral LD<sub>50</sub> for wild ducks was in excess of 2025 mg/kg for the sodium salt form of 2,4-D.<sup>1</sup> Overall, 2,4-D is moderately toxic to practically non-toxic to birds. There are no pronounced differences in toxicity based on the form of 2,4-D.<sup>3</sup>
- Five-day studies estimated LC<sub>50</sub> values for bobwhite quail and mallard ducks at greater than 5620 ppm.<sup>1</sup> Chronic studies have also demonstrated low toxicity, with no effects observed below very high exposure levels such as concentrations in drinking water greater than the solubility of the chemical.<sup>2</sup> Under field conditions, eggs of ground-nesting birds could be exposed, but eggshell permeability to 2,4-D is low and treating eggshells with high concentrations of 2,4-D did not reduce hatchability or cause chick abnormalities.<sup>2</sup>

#### Fish and Aquatic Life

- Toxicity to fish and aquatic invertebrates varies widely depending on chemical form, with esters being the most toxic.<sup>1,2</sup> Acid and amine salt LC<sub>50</sub>s range from greater than 80 to 2244 mg acid equivalents per liter (mg ae/L) whereas the esters range from less than 1.0 to 14.5 mg acid equivalents per liter.<sup>3</sup> The greater toxicity generally of the esters in fish is likely due to the greater absorption rates of the esters through the gills, where they are hydrolyzed to the acid form.<sup>2</sup> The acute LC<sub>50</sub> of the dimethyl amine salt form to rainbow trout was 100 mg/L,<sup>1</sup> which is considered slightly toxic.
- The acute LC<sub>50</sub> of the ethyl hexyl form to rainbow trout was greater than its solubility in water.<sup>1</sup> The LD<sub>50</sub> value for the isocetyl form (CASRN 25168-26-7) in cutthroat trout was 0.5-1.2 mg/L,<sup>1</sup> or moderately to highly toxic. Adult fathead minnows exhibited toxic effects at chronic exposures of the butoxyl ethanol ester form that were 1/10 to 1/45 of the 96-hour LC<sub>50</sub> concentrations.<sup>2</sup> Early life stages of fish are more susceptible compared with adult fish or eggs.<sup>2</sup>
- *Daphnia* exposed to the acid form for 21 days exhibited an LC<sub>50</sub> of 235 mg/L when exposed to 2,4-D acid for 21 days, and an LC<sub>50</sub> of 5.2 mg/L when exposed to the ethyl hexyl form for 48 hours.<sup>1</sup> Therefore, the acid form is practically non-toxic to *Daphnia* but the ethyl hexyl form is moderately toxic. As with fish, esters are more toxic than acid or amine salt forms to freshwater aquatic invertebrates, with LC<sub>50</sub> values ranging from 25 to 643 mg ae/L for the acid and amine salt forms but 2.2 to 11.8 mg ae/L for esters.<sup>3</sup> The relative toxicities for acids and salts are slightly toxic to practically non-toxic, whereas the esters are moderately to slightly toxic.
- Marine invertebrate sensitivities are similar to aquatic invertebrates, with LC<sub>50</sub> values of 50-830 mg ae/L for acid and salt forms and >0.092 to >66 mg ae/L for ester forms.<sup>3</sup> The corresponding relative toxicity values are slightly toxic to practically non-toxic for the salts and acid but highly toxic to practically non-toxic for the ester forms.
- Researchers have estimated a No Observed Effect Concentration (NOEC) of 16.1 mg ae/L for the DEA ester and 79.0 mg ae/L for the acid form based on survival and reproduction for DEA and number of young produced for the acid form. The freshwater aquatic invertebrate NOEC for the BEE ester was estimated at 0.2 mg ae/L based on survival and reproduction.<sup>3</sup>
- 2,4-D is marketed for controlling aquatic plants. Therefore, the lethal concentrations are reported as effective concentrations for killing half the target population (EC<sub>50</sub>). Researchers estimated an EC<sub>50</sub> of 0.58 mg/L for duckweed (*Lemna gibba*). A variety of algal species exhibited LC<sub>50</sub> values ranging between 0.23 and greater than 30 mg/L for the ethyl hexyl form.<sup>1</sup> The EC<sub>50</sub> for the dimethyl amine salt form against *Selenastrum capricornutum* was estimated at 51.2 mg/L.<sup>1</sup> No effects were recorded for 19 genera of algae exposed to 2,4-D at concentrations of up to 222 mg/L.<sup>2</sup> However, the ester forms were toxic to some algae at much lower concentrations.<sup>2</sup> See the text box on **EC<sub>50</sub>**.

**EC<sub>50</sub>:** The median effective concentration (EC<sub>50</sub>) may be reported for sublethal or ambiguously lethal effects. This measure is used in tests involving species such as aquatic invertebrates where death may be difficult to determine. This term is also used if sublethal events are being monitored.

Newman, M.C.; Unger, M.A. *Fundamentals of Ecotoxicology*; CRC Press, LLC.: Boca Raton, FL, 2003; p 178.

- A mesocosm study indicated that an unspecified form of 2,4-D applied at 0.117 mL/m<sup>2</sup> had no negative effects on species richness, biomass, or survival on algae and 25 species of aquatic animals, including frog larvae, salamanders, snails, and a range of other invertebrates.<sup>53</sup> Ninety-six-hour LC<sub>50</sub> concentrations for several species of amphibian larvae exceeded 100 mg/L for the amine salt forms.<sup>2</sup> 2,4-D acid, 2,4-D EHE, and 2,4-D DMA are considered practically non-toxic to amphibian larvae based on tests with *Rana pipiens*.<sup>3</sup>
- Bioavailability and uptake of 2,4-D by organisms are strongly influenced by pH, temperature, and other environmental factors.<sup>2</sup> The sensitivity of aquatic invertebrates to 2,4-D increases with temperature; concentrations below those associated with short-term toxic effects impaired reproduction when ambient temperature was elevated.<sup>2</sup> Although some aquatic invertebrates appear to sense and avoid 2,4-D in the water, others do not, even when exposed to lethal concentrations.<sup>2</sup> Fish appear to avoid 2,4-D in a dose-dependent manner until the onset of toxic effects.<sup>2</sup> Toxicity of 2,4-D was increased when fish were simultaneously exposed to 2,4-D and carbaryl or picloram.<sup>2</sup>

### Terrestrial Invertebrates

- LC<sub>50</sub> values for 24-hour exposures in honey bees were estimated to be 104 and 115 µg per bee. Researchers estimated the LD<sub>50</sub> at greater than 10 µg/bee, so 2,4-D is considered practically non-toxic.<sup>3</sup> Effects on bee longevity varied according to dose and 2,4-D form.<sup>2</sup>
- 2,4-D is not considered hazardous to beneficial insects due to its low insecticidal activity and an adequate safety margin when products containing 2,4-D are used at recommended levels.<sup>2,3</sup>
- Carabid beetles exposed to sand dosed with 1 g/m<sup>2</sup> exhibited greater than 50% mortality after 4 days.<sup>2</sup>
- The calculated 48-hour LC<sub>50</sub> concentration for earthworms exposed to filter paper treated with 2,4-D was 61.6 µg/cm.<sup>22</sup>
- Effects of 2,4-D on soil microorganisms were species-dependent.<sup>2</sup>

### Regulatory Guidelines:

- The reference dose (RfD) for 2,4-D is 0.01 mg/kg/day.<sup>54</sup> See the text box on **Reference Dose (RfD)**.
- The U.S. EPA has classified 2,4-D as “Group D - not classifiable with regard to human carcinogenicity” in 2004.<sup>3</sup> IARC had not assigned 2,4-D a cancer rating as of December 2007. However, the chlorophenoxy herbicides as a group were classified in Group 2B, meaning that they are considered to be possibly carcinogenic to humans, by IARC in 1987.<sup>29</sup> See the text box on **Cancer** (page 5).
- The threshold limit value, or TLV, for 2,4-D is 10 mg/m<sup>3</sup> for an 8-hour time weighted average exposure.<sup>55</sup> This limit is based on results of animal feeding experiments.<sup>43</sup> This same dose was selected by the Occupational Safety and Health Administration (OSHA) for the permissible exposure limit (PEL) for an 8 hour time weighted average exposure and by the National Institute for Occupational Safety and Health (NIOSH) for the recommended exposure limit (REL) for a 10-hour workday and a 40-hour workweek.<sup>43</sup>
- The MCL for 2,4-D in drinking water is 0.07 mg/L.<sup>56</sup> See the text box on **Maximum Contaminant Level (MCL)** (page 8).

**Reference Dose (RfD):** The RfD is an estimate of the quantity of chemical that a person could be exposed to every day for the rest of their life with no appreciable risk of adverse health effects. The reference dose is typically measured in milligrams (mg) of chemical per kilogram (kg) of body weight per day.

U.S. Environmental Protection Agency. Office of Water. 2002 Edition of the Drinking Water Standards and Health Advisories. EPA 822-R-02-038.  
<http://www.epa.gov/ost/drinking/standards/dwstandards.pdf>

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