An F1-Extended One-Generation Reproductive Toxicity Study in Crl:CD(SD) Rats With 2,4-Dichlorophenoxyacetic Acid (*Toxicological Sci.*, 2013)

Mary Sue Marty,* ‡ Barbara H. Neal,† Carol L. Zablotny,* Barry L. Yano,* Amanda K. Andrus,* Michael R. Woolhiser,* Darrell R. Boverhof,* Shakil A. Saghir,‡§ Adam W. Perala,* Julie K. Passage,* Marie A. Lawson,* James S. Bus,† James C. Lamb, IV, † and Larry Hammond

2,4-Dichlorophenoxyacetic acid (2,4-D) was assessed for systemic toxicity, reproductive toxicity, developmental neurotoxicity (DNT), developmental immunotoxicity (DIT), and endocrine toxicity. CD rats (27/sex/dose) were exposed to 0, 100, 300, 600 (female), or 800 (male) ppm 2,4-D in diet. Nonlinear toxicokinetic behavior was shown at high doses; the renal clearance saturation threshold for 2,4-D was exceeded markedly in females and slightly exceeded in males. Exposure was 4 weeks premating, 7 weeks postmating for P1 males and through lactation for P1 females. F1 offspring were examined for survival and development, and at weaning, pups were divided in cohorts, by sex and dose, and by systemic toxicity (10), DNT (10), DIT (20), and reproductive toxicity (≥ 23). Remaining weanlings were evaluated for systemic toxicity and neuropathology (10–12). Body weight decreased during lactation in high-dose P1 females and in F1 pups. Kidney was the primary target organ, with slight degeneration of proximal convoluted tubules observed in high-dose P1 males and in high-dose F1 males and females. A slight intergenerational difference in kidney toxicity was attributed to increased intake of 2,4-D in F1 offspring. Decreased weanling testes weights and delayed preputial separation in F1 males were attributed to decreased body weights. Endocrine-related effects were limited to slight thyroid hormone changes and adaptive histopathology in high-dose GD 17 dams seen only at a nonlinear toxicokinetic dose. 2,4-D did not cause reproductive toxicity, DNT, or DIT. The “No Observed Adverse Effect Level” for systemic toxicity was 300 ppm in both males (16.6mg/kg/day) and females (20.6mg/kg/day), which is approximately 6700- to 93 000-fold higher than that reported for 2,4-D exposures in human biomonitoring studies.
Impacts of 2,4-dichlorophenoxyacetic acid aquatic herbicide formulations on reproduction and development of the fathead minnow (Pimephales promelas)

Zachary A DeQuattro 1, William H Karasov 2

Affiliations expand

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Abstract

The authors studied the effects of 2 formulations of 2,4-dichlorophenoxyacetic acid, dimethylamine salt (2,4-D) herbicide on fathead minnow reproduction, embryonic development, and larval survival. Groups of reproductively mature fathead minnows were exposed for 28 d to 0.00 ppm, 0.05 ppm, 0.50 ppm, and 2.00 ppm 2,4-D (target) in a flow-through system. Weedestroy® AM40 significantly (p ≤ 0.05) depressed male tubercle presence and significantly increased female gonadosomatic index, and there were statistical trends (0.05 ≤ p ≤ 0.10) for effects on fecundity and hepatic vitellogenin mRNA expression in females and males. The herbicide DMA® 4 IVM also significantly depressed male tubercle presence. Gonads of females exposed to DMA 4 IVM exhibited significantly depressed stage of oocyte maturation, significantly increased severity of oocyte atresia, and a significant presence of an unidentified tissue type. Also, DMA 4 IVM significantly decreased larval survival. It had no impact on hepatic vitellogenin mRNA expression or gonadosomatic index. No significant effects on fertilization, hatchability, or embryonic development were observed in either trial. The formulations tested exhibited different toxicological profiles from pure 2,4-D. These data suggest that the formulations have the potential for endocrine disruption and can exert some degree of chronic toxicity. The present use of 2,4-D formulations in lake management practices and their permitting based on the toxicological profile of 2,4-D pure compound should be reconsidered. Environ Toxicol Chem 2016;35:1478-1488. © 2015 SETAC.

Keywords: 2,4-D; Endocrine-disrupting compounds; Herbicide; Larval survival; Reproductive toxicity.
2,4-D

Technical Fact Sheet

As of 2011, NPIC stopped creating technical pesticide fact sheets. The old collection of technical fact sheets will remain available in this archive, but they may contain out-of-date material. NPIC no longer has the capacity to consistently update them. To visit our general fact sheets, click here. For up-to-date technical fact sheets, please visit the Environmental Protection Agency’s webpage.

Chemical Class and Type

Physical / Chemical Properties

Uses

Mode of Action

Toxicity Classification

Acute Toxicity

Chronic Toxicity

Endocrine Disruption

Carcinogenicity

Reproductive and Teratogenic Effects
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.

Chemical Class and Type:

2,4-D is an herbicide and secondarily a plant growth regulator. Formulations include esters, acids, and several salts, which vary in their chemical properties, environmental behavior, and to a lesser extent, toxicity. The salt and ester forms are derivatives of the parent acid. 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.

The dimethyl-amine salt (DMA) and 2-ethylhexyl ester (EHE) forms account for approximately 90-95% of the total global use. The acid form is low in solubility and herbicide formulations consist of more soluble forms of the chemical. Products containing 2,4-D frequently contain other herbicides as well.

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.

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). The U.S. EPA determined that 2,4-D was eligible for re-registration, but required certain changes to labeled uses to mitigate risk. See the text box on Laboratory Testing.
Physical / Chemical Properties:
2,4-D and associated forms

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>CASRN</th>
<th>Form</th>
<th>Vapor pressurea</th>
<th>Henry's constant</th>
<th>Molecular weight</th>
<th>Solubility in water (mg/L)b</th>
<th>Log Kow</th>
<th>Koc</th>
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<tr>
<td>2,4-D acid</td>
<td>94-75-7</td>
<td>White to brown crystalline solid</td>
<td>1.9 x 10^-5 Pa</td>
<td>1.4 x 10^-7 mmHg</td>
<td>8.6 x 10^-6 atm·m3/mol</td>
<td>221</td>
<td>pH 5: 29,934 ± 2957b</td>
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<td>8.6 x 10^-6 atm·m3/mol</td>
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<td>1.4 x 10^-7 mmHg</td>
<td>8.6 x 10^-6 atm·m3/mol</td>
<td>221</td>
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<td>pH 7: 44,558 ± 674</td>
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<td>pH 9: 43,134 ± 336</td>
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<td>pH 7: 20-136</td>
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<tr>
<td>2,4-D salt</td>
<td>2702-72-9</td>
<td>White powder</td>
<td>Salt dissociates to acid in water</td>
<td>243.03</td>
<td>45,000 mg/L</td>
<td>Salt dissociates to acid in water</td>
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<td>2,4-D-diehtanolamine salt (DEA)</td>
<td>5742-19-8</td>
<td>Cream colored powder</td>
<td>9.98 x 10^-8 mmHg</td>
<td>326.18</td>
<td>806,000 mg/L</td>
<td>2.24 x 10^-2</td>
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<td>pH 5: 320,632 ± 3645</td>
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<td>pH 7: 729,397 ± 86,400</td>
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<td>pH 9: 663,755 ± 94,647</td>
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<td>2,4-D dimethyl amine salt (DMA)</td>
<td>2008-39-1</td>
<td>Amber aqueous liquid</td>
<td>1.33 x 10^-5 Pa</td>
<td>1 x 10^-7 mmHg</td>
<td>1.4 x 10^-6 atm·m3/mol</td>
<td>266.13</td>
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<td>pH 5: 72-136</td>
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<tr>
<td>2,4-D -isopropanolamine (TIPA) salt</td>
<td>3234-18-9</td>
<td>Amber aqueous liquid</td>
<td>Salt dissociates to acid in water</td>
<td>280.04</td>
<td>pH 5: 174,000 mg/L</td>
<td>4.76</td>
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<td>Salt dissociates to acid in water</td>
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<tr>
<td>2,4-D tri-isopropanolamine (TIPA) salt</td>
<td>3234-18-9</td>
<td>Amber aqueous liquid</td>
<td>Salt dissociates to acid in water</td>
<td>412.31</td>
<td>pH 5: 461,000 mg/L</td>
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<td>pH 7: 461,000 mg/L</td>
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</tbody>
</table>
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^-4 Pa

2.4 x 10^-6 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^-4 Pa

3.6 x 10^-6 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^-6 mbar 2.2 x 10^-6 atm·m3/mol 263.12  Practically insoluble in water  253.8 ± 44.4  600

aVapor pressure measured at 25 °C  bSolubility 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.3 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 1992-2000.3

Signal words for products containing 2,4-D may range from Caution to Danger.10 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 select your state then click on the link for "State Products."

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.12 It appears to work by causing uncontrolled cell division in vascular tissue.12 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.3,12

The ester forms of 2,4-D penetrate foliage, whereas plant roots absorb the salt forms.12 2,4-D appears to be similar in action to other auxin-type herbicides.12
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. 2,4-D is actively secreted by the proximal tubules of the kidney, and toxicity appears to result when renal clearance capacity is exceeded. Dose-dependent toxic effects include damage to the eye, thyroid, kidney, adrenals, and ovaries or testes. In addition, researchers have observed neurotoxicity, reproductive toxicity, and developmental toxicity. Chlorophenoxy herbicides exhibit a variety of mechanisms of toxicity, including dose-dependent cell membrane damage leading to central nervous system toxicity, interference with cellular metabolism involving acetyl-coenzyme A (CoA), and uncoupling of oxidative phosphorylation due to either the disrupted CoA activity or cellular membrane damage.

Acute Toxicity:

Oral

LD50 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. Researchers found that 2,4-D was more toxic for mice, reporting an LD50 of 138 mg/kg. All chemical forms for 2,4-D are considered low in toxicity for acute oral exposure based on tests with rats. See the text boxes on Toxicity Classification and LD50/LC50.

LD50/LC50: A common measure of acute toxicity is the lethal dose (LD50) or lethal concentration (LC50) that causes death (resulting from a single or limited exposure) in 50 percent of the treated animals. LD50 is generally expressed as the dose in milligrams (mg) of chemical per kilogram (kg) of body weight. LC50 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 LD50/LC50 is small and practically non-toxic when the value is large. However, the LD50/LC50 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.

Dermal

Acute dermal LD50s 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 for acute dermal exposure based on studies using rabbits.

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.

The ester and salt forms of 2,4-D are considered slight skin irritants.

Inhalation
All chemical forms of 2,4-D are of low to very low toxicity via inhalation based on studies using rats. Acute inhalation LC50s for rats ranged from 0.78 mg/L to greater than 5.4 mg/L depending on the chemical form. Most forms of 2,4-D are very low in toxicity, and the parent acid and TIPA salt forms are low in toxicity.

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. 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 although the potential for this is unclear. Rats demonstrated incoordination, central nervous system depression and muscular weakness following acute oral dosing. Biochemical analysis of rat tissues suggested hepatic and muscle damage following acute, subchronic, and chronic oral exposures.

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. Systemic toxicity is mainly associated with suicide attempts.

Symptoms following dermal exposure may include irritation, and inhalation exposure may lead to coughing and burning sensations in the upper respiratory tract and chest. Prolonged exposure may result in dizziness. Chlorophenoxy compounds such as 2,4-D are quickly absorbed when swallowed, but absorption from dermal or inhalation exposure is low.

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. Ingestion led to vomiting, abdominal pain, diarrhea, and development of hypotension. Peripheral neuromuscular effects including muscle twitching, weakness, and loss of tendon reflexes have been reported. Neuromuscular effects have lasted several weeks to months and have been permanent in some cases.

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 discuss an incident with the National Pesticide Information Center, please call 1-800-858-7378.

TOXICITY CLASSIFICATION - 2,4-D

High Toxicity  Moderate Toxicity  Low Toxicity  Very Low Toxicity
Acute Oral LD50

- 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 LC50

- 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 LD50

- 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, Ester)
- Corneal involvement or other eye irritation clearing in 8 - 21 days (Acid, Ester, Salt)
- 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)


NOAEL: No Observable Adverse Effect Level

NOEL: No Observed Effect Level
LOAEL: Lowest Observable Adverse Effect Level

LOEL: Lowest Observed Effect Level

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.3,19 A subchronic NOEL was established at 15 mg/kg/day based on studies in rats.19 See the text box on NOAEL, NOEL, LOAEL, and LOEL.

The chronic toxicity NOEL in rats and mice was determined to be 5 mg/kg/day in two-year studies.12,20 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.20 Additional NOEL and NOAEL doses were 15 mg/kg for rats in a 90-day study, and 1 mg/kg for dogs in a 12-month study, respectively.12,21 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.4 Chronic NOAELs and LOELs in dogs, however, varied for different parameters studied and by chemical form.21

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.17

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.19 Chronic toxicity in the eye, kidney, thyroid and liver of the rat were similar to effects found in subchronic studies.20 Eye lesions were associated only with high doses of 150 mg/kg/day.20

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.22,23 See the Carcinogenicity section below for more information on 2,4-D and cancer in humans. See the text box on Exposure.

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.\(^3\) 2,4-D is included in the U.S. EPA June 2007 Draft List of Chemicals for Tier 1 Screening.\(^24\)

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.\(^20\) 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.\(^21\)

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.\(^25\) Other investigators have questioned the epidemiological association reported in that study.\(^5,26\)

Overall, there has been no consistent association between exposure to 2,4-D and tumor induction in animals.\(^27\) More recently, non-cytotoxic concentrations of 2,4-D were correlated to DNA damage and altered expression of some genes in hamster embryo cells.\(^28\)

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." 2,4-D was categorized as "Group D - not classifiable as to human carcinogenicity" in 2004.\(^3\) 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.\(^29\)

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.26

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.27 Overall, evidence for mutagenicity has been inconsistent.26,27,30

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.4,26 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.31

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.4 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.7 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.4

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.4 In rabbits, the developmental NOEL was 30 mg/kg/day 2,4-D acid equivalents.4

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,7 including reduced sperm motility and viability following occupational exposure. Although motility and viability recovered over a period of several months, malformations were still present.32 Exposure to multiple pesticides in epidemiological studies make inference difficult.26

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.18 Absorption rates following ingestion are dose-dependent in laboratory animals, with larger doses persisting in the gastrointestinal tract for longer periods of time.7 In humans, plasma levels following 5 mg/kg oral ingestion peaked between 4-24 hours post-exposure.7
Dermal exposure is considered the most likely route of exposure during product use. 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. 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. Hairless mouse skin absorbed 39% of a 100 μL dose in 24 hours.

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. Biochemical changes suggested that liver and muscle damage occurred in rats at acute, subchronic, and chronic doses.

In humans, 2,4-D has a wide volume of distribution due to its water solubility, but it does not accumulate in any tissue.

Metabolism

Metabolism of 2,4-D is minimal in humans, with nearly all of it excreted unchanged as the parent compound. The remainder is excreted as an unspecified 2,4-D conjugate.

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. In sheep and cattle, muscle, liver, kidney, and fat tissue contained the metabolite 4-chlorocatechol. Dogs must metabolize the parent compound prior to excretion, due to their reduced ability to excrete organic acids.

No reactive intermediate metabolic products for 2,4-D have been identified in any species.

Excretion

In humans, 2,4-D is rapidly excreted from the body, primarily in the urine. Much of the compound appears to be eliminated unchanged, although some 2,4-D is eliminated from the body as a conjugate. The percent of original dose excreted as a polar, acid-hydrolyzable metabolite was 4.8-27.0%. The elimination half-life from blood plasma in humans orally dosed with 5 mg/kg of 2,4-D was 11.6 hours. These human volunteers excreted more than 75% of 2,4-D in their urine within 96 hours of oral dosing. Concentrations in blood plasma paralleled concentrations excreted in urine. Some 2,4-D may be excreted in perspiration but this process appears to occur more slowly compared with urinary excretion.

Excretion of 2,4-D in animals depends on the species, formulation, and dose. 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.
Dogs excreted a 5 mg/kg oral dose primarily in their urine with minor amounts detected in feces.39 Dogs dosed with 50 mg/kg excreted equal amounts in urine and feces and excretion was incomplete at 120 hours post-dose.39 Because dogs appear to be deficient in their ability to excrete organic acids, 2,4-D must be metabolized prior to excretion.39 Dogs orally dosed with 2,4-D excreted the parent compound, several conjugates and one unidentified compound in their urine.39

Excretion of 2,4-D in urine is dose-dependent but nonlinear, with percent excreted in urine declining at higher doses.7 In all of the species of animals studied, 2,4-D is excreted quickly and almost entirely in the urine.7

Medical Tests and Monitoring:

Biomarkers of exposure to 2,4-D have been reported in the scientific literature.41 Scientists used high-performance liquid chromatography with tandem mass spectrometry to detect 2,4-D in urine.41,42

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.41 However, how these residues may affect human health is presently not clear,41 and the relationship between exposure level and biomarker is unknown.43

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.

Environmental Fate:

Soil
2,4-D amine salts and esters are not persistent under most environmental conditions. Typically, the ester and amine forms of 2,4-D are expected to degrade rapidly to the acid form. Soil half-life values have been estimated at 10 days for the acid, diethylamine salt, and ester forms. 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. In aerobic mineral soils, a half-life of 6.2 days was estimated. 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. See the text box on Half-life.

Microbial degradation of 2,4-D in soil involves hydroxylation, cleavage of the acid side-chain, decarboxylation, and ring opening. The ethyl hexyl form of the compound is rapidly hydrolyzed in soil and water to form the 2,4-D acid. 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.

2,4-D has a low binding affinity in mineral soils and sediment, and in those conditions is considered intermediatively to highly mobile. In sandy loam, sand, silty clay loam, and loam soil, Koc values of 70, 76, 59, and 117 mL/g, respectively, were obtained, 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.

Microbes may play a major role in degradation.

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-chlorphenol, 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.

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. A granular formulation of the BEE form degraded rapidly in the water column in alkaline conditions but was present in sediments for 186 days.

The ethyl hexyl form is rapidly hydrolyzed in water to 2,4-D acid, with a degradation half-life (DT50) of less than one day. 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 5.38 The acid form of 2,4-D is very resistant to abiotic hydrolysis.

2,4-D has been detected in streams and shallow groundwater at low concentrations, in both rural and urban areas.

Air

Volatility for most forms of 2,4-D is low (see the table on 2,4-D and associated forms). However, the vapor pressure of some ester forms range from 1.1 x 10^-3 to 2.3 x 10^-3 mmHg, indicating that these forms readily volatilize. The Henry's Law Constant for 2,4-D acid is 3.5 x 10^-4 at pH 7, 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. Ester forms are converted to the acid within the plant, then accumulate in cells due to passive diffusion down the concentration gradient. Active transport within the plant may also occur. Accumulation occurs primarily at the meristem tissue of roots and shoots.

Forest dissipation studies indicated that the ethyl hexyl ester form of 2,4-D degraded slowly on foliage and in leaf litter. Residues of an ester form of 2,4-D were detected in samples of dead birch leaves for up to three years post-application.

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.

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, Region 5, Water, Underground Injection Control Terms, 2011. http://epa.gov/r5water/uic/glossary.htm#mcl

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. In bottled water, only 2 of 367 samples contained 2,4-D, with residues of 3.2 and 4.2 ppt. See the text box on Maximum Contaminant Level (MCL).

Ecotoxicity Studies:

Birds

LD50 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. The acute oral LD50 for the dimethyl amine salt form of the compound was 500 mg/kg for bobwhite quail, and the acute oral LD50 for the ethyl hexyl form was 663 mg/kg in mallard ducks. The acute oral LD50 for wild ducks was in excess of 2025 mg/kg for the sodium salt form of 2,4-D. 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.

Five-day studies estimated LC50 values for bobwhite quail and mallard ducks at greater than 5620 ppm. 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.
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.2

Fish and Aquatic Life

Toxicity to fish and aquatic invertebrates varies widely depending on chemical form, with esters being the most toxic.1,2 Acid and amine salt LC50s 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.3 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.2 The acute LC50 of the dimethyl amine salt form to rainbow trout was 100 mg/L,1 which is considered slightly toxic.

The acute LC50 of the ethyl hexyl form to rainbow trout was greater than its solubility in water.1 The LD50 value for the isooctyl form (CASRN 25168-26-7) in cutthroat trout was 0.5-1.2 mg/L,1 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 LC50 concentrations.2 Early life stages of fish are more susceptible compared with adult fish or eggs.2

Daphnia exposed to the acid form for 21 days exhibited an LC50 of 235 mg/L when exposed to 2,4-D acid for 21 days, and an LC50 of 5.2 mg/L when exposed to the ethyl hexyl form for 48 hours.1 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 LC50 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.3 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 LC50 values of 50-830 mg ae/L for acid and salt forms and >0.092 to >66 mg ae/L for ester forms.3 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.3

2,4-D is marketed for controlling aquatic plants. Therefore, the lethal concentrations are reported as effective concentrations for killing half the target population (EC50). Researchers estimated an EC50 of 0.58 mg/L for duckweed (Lemna gibba). A variety of algal species exhibited LC50 values ranging between 0.23 and greater than 30 mg/L for the ethyl hexyl form.1 The EC50 for the dimethyl amine salt form against Selenastrum capricornutum was estimated at 51.2 mg/L.1 No effects were recorded for 19 genera of algae exposed to 2,4-D at concentrations of up to 222 mg/L.2 However, the ester forms were toxic to some algae at much lower concentrations.2 See the text box on EC50.
EC50: The median effective concentration (EC50) 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/m² 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. Ninety-six-hour LC₅₀ concentrations for several species of amphibian larvae exceeded 100 mg/L for the amine salt forms. 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.

Bioavailability and uptake of 2,4-D by organisms are strongly influenced by pH, temperature, and other environmental factors. 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. Although some aquatic invertebrates appear to sense and avoid 2,4-D in the water, others do not, even when exposed to lethal concentrations. Fish appear to avoid 2,4-D in a dose-dependent manner until the onset of toxic effects. Toxicity of 2,4-D was increased when fish were simultaneously exposed to 2,4-D and carbaryl or picloram.

Terrestrial Invertebrates

LC₅₀ values for 24-hour exposures in honey bees (Apis mellifera) were estimated to be 104 and 115 μg per bee. Researchers estimated the LD₅₀ at greater than 10 μg/bee, so 2,4-D is considered practically non-toxic. Effects on bee longevity varied according to dose and 2,4-D form.

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.

Carabid beetles (Carabidae) exposed to sand dosed with 1 g/m² exhibited greater than 50% mortality after 4 days.

The calculated 48-hour LC₅₀ concentration for earthworms (Lumbricus rubellus) exposed to filter paper treated with 2,4-D was 61.6 μg/cm².

Effects of 2,4-D on soil microorganisms were species-dependent.

Regulatory Guidelines:

The reference dose (RfD) for 2,4-D is 0.01 mg/kg/day. See the text box on Reference Dose (RfD).

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.
The U.S. EPA has classified 2,4-D as "Group D - not classifiable with regard to human carcinogenicity" in 2004.3 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 1987.29 See the text box on Cancer.

The threshold limit value, or TLV, for 2,4-D is 10 mg/m3 for an 8-hour time weighted average exposure.55 This limit is based on results of animal feeding experiments.43 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.43

The MCL for 2,4-D in drinking water is 0.07 mg/L.56 See the text box on Maximum Contaminant Level (MCL).

Date Reviewed: November 2008

http://npic.orst.edu/factsheets/archive/2,4-DTech.html.

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Intergrated Risk Information System, 2,4-Dichlorp
Chemical Name: 2,4-dichlorophenoxyacetic acid, ethyl ester

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If the result came up blank, you might want to click 'Cancelled' or 'Registered' button and see if it'll return any row(s).

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Details for WEEDONE (CONCENTRATE 48) THE 2,4-D ETHYL ESTER WEED CONTROL

EPA Registration Number: 264-6
Company Name: BAYER CROPSCIENCE LP
Address: 800 N. LINDBERGH BLVD.
City, State Zip: ST LOUIS, MO 63167
First Registered Date: MARCH 02, 1948
Current Status (Date): Inactive (OCTOBER 10, 1989)
Restricted Use N/O

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Provided below is the information for the product you selected. To view the label, click on the date in the Accepted Date Field. The latest label is at the top of the list.
What is 2,4-D?
2,4-Dichlorophenoxyacetic acid, commonly known as 2,4-D, is a widely used herbicide in the phenoxy class of chemicals. It is the most commonly used pesticide in the non-agricultural sector and the sixth most common in the agricultural sector, with over 40 million pounds being used in the U.S. annually. 2,4-D production supports a world market of over $300 million. While the herbicide is manufactured and marketed by many different companies, Dow AgroSciences is currently the biggest producer.

2,4-D is a general use pesticide, and does not require a license to use or purchase. It is used in a wide variety of locations, including agricultural, residential, and public areas. 2,4-D can be found in many lawn care products, it is used as a treatment for road sides and rights of way, and to control aquatic weeds. In agriculture it is used as a herbicide for grass-like crops, including wheat and barley. Products containing 2,4-D are often marketed as “weed and feed” and include Aqua-Kleen, Ortho Weed B Gon, Salvo, Spectracide, Scotts Green Sweep, UltraStop, and Weedone.

2,4-D is a selective herbicide, used to kill broadleaf weeds with little harm to grass crops. It is a plant growth regulator, and mimics the natural plant growth hormone, auxin. Unlike auxins, 2,4-D stays at high levels within plant tissues rather than fluctuating. As a result, it causes rapid cell growth and plants die when their transport systems become blocked and destroyed by abnormally fast growth. While 2,4-D is normally applied to a plant’s leaves, it can also be absorbed through the roots and stems. The half-life of 2,4-D in soil is about 1-2 weeks and 1-3 weeks in water.

Health effects of 2,4-D are of particular concern due to its widespread distribution. In a 2003 study of indoor air toxins, 2,4-D was found in the dust of 63% of sampled homes. In a 2001 study, levels of 2,4-D in indoor air and on surfaces (floors, tables, windowsills) increased following lawn application of the herbicide. This resulted in exposure levels for children that were ten times higher than pre-application and shows that 2,4-D is easily tracked into homes.

Chronic Toxicity
Although a mounting body of evidence links 2,4-D to various cancers, particularly non-Hodgkin’s lymphoma, EPA has been reluctant to classify it as a carcinogen in the face of industry pressure. EPA lists the herbicide in class D for carcinogenicity. Chemicals in this class are considered to have inadequate evidence for carcinogenicity, or not enough data is available. However, the link between 2,4-D and non-Hodgkin’s lymphoma has been demonstrated in the United States, Italy, Canada, Denmark, and Sweden. A 1986 National Cancer Institute (NCI) study found that farmers in Kansas exposed to 2,4-D for 20 or more days per year had a six-fold higher risk of developing non-Hodgkin’s lymphoma than non-farmers. The risk of cancer was higher for farmers who mixed or applied the pesticide themselves. Another study done in 1990 found a 50% increase in non-Hodgkin’s lymphoma in farmers who handle 2,4-D. A manufacturer’s study submitted to EPA in 1986 indicated that the herbicide can cause rare brain tumors in rats. In 1991, an NCI study found that dogs were more likely to contract canine malignant lymphoma if their owners use 2,4-D on their lawns than if owners did not use the herbicide. When 2,4-D was applied four or more times per year, dogs were twice as likely to contract lymphoma. In addition to these epidemiological studies, a laboratory study conducted by the Food and Drug Administration (FDA) found a 4% incidence of lymphoma in rats exposed to 2,4-D and no lymphoma in unexposed rats. Despite these studies, the carcinogenic potential of 2,4-D remains

2,4-D has been linked to

- Cancer
- Endocrine Disruption
- Reproductive Toxicity
- Neurotoxicity
- Kidney/Liver Damage
- Toxicity to Dogs, Fish, Birds, Earthworms, and Beneficial Insects

Acute Toxicity
2,4-D is produced in several forms, including acids, salts, amines and esters, and its toxicity varies between the different forms. The EPA toxicity class ranges from I-IV (on a I-IV scale with I being the most toxic) depending on the form and method of exposure. The diethylamine salt is the most toxic (class I) by eye exposure. Inhalation generally leads to coughing, burning, dizziness, and loss of muscle coordination. Oral consumption irritates the digestive tract, results in nausea, diarrhea, vomiting, and can lead to kidney and liver damage. 2,4-D is one of few herbicides to cause nervous system damage; both digestion and inhalation affect the central nervous system. Effects to the nervous system include inflamed nerve endings, lack of coordination, stiffness in the arms and legs, inability to walk, fatigue, stupor, coma, and death. 2,4-D is a serious skin and eye irritant. For the acid form, the LD 50 in rats is 375-666 mg/kg orally and approximately 1500 mg/kg dermally.

BEYOND PESTICIDES
701 E Street, S.E., Suite 200, Washington DC 20003
202-543-5450 (v) • 202-543-4791 (f)
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controversial. The pesticide industry has criticized some of the studies mentioned here and cites other studies, which support its claim that 2,4-D does not cause cancer.  

Long-term exposure to 2,4-D also results in a wide range of other health problems. Chronic (long-term) oral intake results in lesions of the kidney and liver in both rats and dogs. In humans, two studies showed a connection between hepatitis cases and chronic oral consumption of 2,4-D, by golfers who habitually licked their golf balls.  

2,4-D is also an endocrine disruptor, a chemical that can interfere with the body’s hormone messaging system and can alter many essential processes. The National Institute of Health Sciences lists 2,4-D as a suspected endocrine disruptor. In studies with rats, 2,4-D has been shown to alter levels of metabolism and sex hormones. Several studies have demonstrated that 2,4-D can be a mutagen, or a substance that induces genetic mutations. Workers who apply 2,4-D had a higher number of white blood cells with multiple nuclei than people who were not exposed. In rabbits, 2,4-D exposure resulted in unusual numbers of chromosomes in brain cells. Genetic problems like these can have further consequences in terms of cancer and reproductive problems.  

Reproductive toxicity has also been observed in relation to 2,4-D. Residues of 2,4-D are detectable in urine and semen samples of men who apply the herbicide. In rats, exposure resulted in fetuses with abnormal cavity bleeding, increased mortality and genetic damage. A 1996 study of private pesticide applicators in Minnesota found a higher rate of birth defects among the children of applicators than the general public. It also found the birth defect rate to be highest in areas where 2,4-D use was the highest. Another study conducted in 2003 examined the wheat producing states of Montana, Minnesota, South Dakota and North Dakota, where more than 85% of the acreage is treated with chlorophenoxy herbicides, including 2,4-D. Children conceived during the time or herbicide production (April–June) were more likely to have birth defects.  

Environmental Effects  
Due to its relatively short half-life, 2,4-D is said to have low persistence in both soil and water. However, 2,4-D has a high potential to leach from soils, and therefore a potential for contaminating ground water. The herbicide has been detected in ground water in at least five states and Canada. Low concentrations have also been detected in surface water and drinking water in the US.  

2,4-D has been shown to have negative impacts on a number of animals. In birds, 2,4-D exposure reduced hatching success and caused birth defects. It also indirectly affects birds by destroying their habitat and food source. The toxicity of 2,4-D to fish is variable. The butoxyethanol ester is very toxic to fish, but other forms are less toxic. 2,4-D also bio-accumulates in fish, meaning that fish tissues will contain a higher concentration of 2,4-D than the water surrounding them, which puts them at even greater risk. 2,4-dichlorophenol, a breakdown product of 2,4-D, is extremely toxic to earthworms, 15 times more toxic than 2,4-D itself. The herbicide also has negative effects on a range of beneficial insects. It reduces offspring numbers in honeybees, kills predatory beetles and ladybug larvae. This reduction in ladybug numbers caused an increase in aphids, a major pest, in oat fields. Consumption of plants treated with 2,4-D has killed cattle and horses and 2,4-D can also indirectly affect many wild mammal species, including moose, gophers, and voles, by damaging or killing plants they rely on for food.  

Regulatory Status and History  
2,4-D was one of the first herbicides to be commercially marketed. It was first introduced in the United States in the late 1940’s. 2,4-D made up a major portion (about 50%) of the herbicide known as Agent Orange, which was used during the Vietnam War. However, it is thought that most of the health problems related to Agent Orange were actually due to dioxin contamination of the other major component, 2,4,5-T. While 2,4,5-T was the main culprit and has now been banned, several forms of dioxin have also been found in 2,4-D, including 2,4,7,8-TCDD.  

The history of dioxin contamination further increases the dangers related to 2,4-D, particularly for the amine and ester forms. Dioxins are highly carcinogenic and can cause health problems as severe as weakening of the immune system, decreased fertility, altered sex hormones, miscarriage, birth defects, and cancer. EPA studies in 1994 detected dioxins in a number of 2,4-D products. The Washington Department of Agriculture also detected dioxins in a 2,4-D product in 1998.  

2,4-D is currently undergoing EPA’s reregistration process. According to EPA the Reregistration Eligibility Decision (RED) is scheduled for May 2005. On June 23, 2004, the EPA released to the public a series of risk assessment documents summarizing current data on the human health and environmental effects of 2,4-D. This began a comment period during which the EPA will accept statements from any interested parties, which will then be considered in the final reregistration decision. As part of the reregistration process, EPA also required over 200 new studies on 2,4-D. A group of major manufacturers of 2,4-D set up the “Industry Task Force II on 2,4-D Research Data” which has now funded 270 of these studies. According to EPA, there are still several data gaps in the current 2,4-D research. The risk assessment indicates that a 28-day inhalation study is needed because there are no data available on the effects of repeated inhalation of 2,4-D. A developmental neurotoxicity study is also needed, as well as a 2-generation reproductive study that addresses endocrine disruptor concerns.
2,4-D chemical WATCH Factsheet Bibliography


5 See Ref 2


9 See Ref 4


11 See Ref 6 and Ref 10

12 See Ref 6


31 See Ref 2 and Ref 6


33 World Health Organization. 1989. 2,4-Dichlorophenoxyacetic acid (2,4-D)-Environmental aspects. Geneva, Switzerland.


38 See Ref 37

39 See Ref 21

40 See Ref 6

41 See Ref 6 and Ref 14


46 Hammond, L. 1996. New Perspectives on an Essential Product: 2,4-D. Down to Earth 50(2).

47 See Ref 20


Updated July 2004
Reregistration Eligibility Decision for 2,4-D
Reregistration Eligibility Decision

for

2,4-D

List A
Case 0073

Approved By:

____________________________________________________________________
Debra Edwards, Ph.D.
Director, Special Review and Reregistration Division

____________________________________________________________________
Date
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## Glossary of Terms and Abbreviations

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<th>Definition</th>
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<tr>
<td>A</td>
<td>Acre</td>
</tr>
<tr>
<td>AGDCI</td>
<td>Agricultural Data Call-In</td>
</tr>
<tr>
<td>ae</td>
<td>Acid Equivalent</td>
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<tr>
<td>ai</td>
<td>Active Ingredient</td>
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<tr>
<td>aPAD</td>
<td>Acute Population Adjusted Dose</td>
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<tr>
<td>AR</td>
<td>Anticipated Residue</td>
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<tr>
<td>BCF</td>
<td>Bioconcentration Factor</td>
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<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>cPAD</td>
<td>Chronic Population Adjusted Dose</td>
</tr>
<tr>
<td>CSF</td>
<td>Confidential Statement of Formula</td>
</tr>
<tr>
<td>CSFII USDA</td>
<td>Continuing Surveys for Food Intake by Individuals</td>
</tr>
<tr>
<td>DCI</td>
<td>Data Call-In</td>
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<tr>
<td>DEEM</td>
<td>Dietary Exposure Evaluation Model</td>
</tr>
<tr>
<td>DFR</td>
<td>Dislodgeable Foliar Residue</td>
</tr>
<tr>
<td>DWLOC</td>
<td>Drinking Water Level of Comparison</td>
</tr>
<tr>
<td>EC</td>
<td>Emulsifiable Concentrate Formulation</td>
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<tr>
<td>EDSP</td>
<td>Endocrine Disruption Screening Program</td>
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<tr>
<td>EDWC</td>
<td>Estimated Drinking Water Concentration</td>
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<tr>
<td>EEC</td>
<td>Estimated Environmental Concentration</td>
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<tr>
<td>EPA</td>
<td>Environmental Protection Agency</td>
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<tr>
<td>EUP</td>
<td>End-Use Product</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FIFRA</td>
<td>Federal Insecticide, Fungicide, and Rodenticide Act</td>
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<tr>
<td>FFDDCA</td>
<td>Federal Food, Drug, and Cosmetic Act</td>
</tr>
<tr>
<td>FQPA</td>
<td>Food Quality Protection Act</td>
</tr>
<tr>
<td>FOB</td>
<td>Functional Observation Battery</td>
</tr>
<tr>
<td>G</td>
<td>Granular Formulation</td>
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<tr>
<td>GENEEC</td>
<td>Tier I Surface Water Computer Model</td>
</tr>
<tr>
<td>GLN</td>
<td>Guideline Number</td>
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<tr>
<td>HAFT</td>
<td>Highest Average Field Trial</td>
</tr>
<tr>
<td>HAT</td>
<td>Hour After Treatment</td>
</tr>
<tr>
<td>IR</td>
<td>Index Reservoir</td>
</tr>
<tr>
<td>LC50</td>
<td>Median Lethal Concentration. A statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/l, mg/kg or ppm.</td>
</tr>
<tr>
<td>LD50</td>
<td>Median Lethal Dose. A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal, e.g., mg/kg.</td>
</tr>
<tr>
<td>LOC</td>
<td>Level of Concern</td>
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<tr>
<td>LOD</td>
<td>Limit of Detection</td>
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<tr>
<td>LOAEL</td>
<td>Lowest Observed Adverse Effect Level</td>
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</table>
MATC  Maximum Acceptable Toxicant Concentration
μg/g  Micrograms Per Gram
μg/L  Micrograms Per Liter
mg/kg/day  Milligram Per Kilogram Per Day
mg/L  Milligrams Per Liter
MOE  Margin of Exposure
MRID  Master Record Identification (number). EPA's system of recording and tracking studies submitted
MSWC  Maximum Swimming Water Concentration
MUP  Manufacturing-Use Product
NA  Not Applicable
NAWQA  USGS National Water Quality Assessment
NCOD  National Drinking Water Contaminant Occurrence Database
NPDES  National Pollutant Discharge Elimination System
NR  Not Required
NOAEL  No Observed Adverse Effect Level
OP  Organophosphate
OPP  EPA Office of Pesticide Programs
OPPTS  EPA Office of Prevention, Pesticides and Toxic Substances
ORETF  Outdoor Residential Exposure Task Force
PAD  Population Adjusted Dose
PCA  Percent Crop Area
PDIC  Product-Specific Data Call-In
PDP  USDA Pesticide Data Program
PHED  Pesticide Handler's Exposure Data
PHI  Preharvest Interval
ppb  Parts Per Billion
PPE  Personal Protective Equipment
ppm  Parts Per Million
PRZM/EXAMS  Tier II Surface Water Computer Model
Q1*  The Carcinogenic Potential of a Compound, Quantified by the EPA's Cancer Risk Model
RAC  Raw Agriculture Commodity
RED  Reregistration Eligibility Decision
REI  Restricted Entry Interval
RfD  Reference Dose
RQ  Risk Quotient
SCI-GROW  Tier I Ground Water Computer Model
SAP  Science Advisory Panel
SF  Safety Factor
SLC  Single Layer Clothing
SLN  Special Local Need (Registrations Under Section 24(c)) of FIFRA
STORET  Storage and Retrieval Environmental Data System
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>TGAI</td>
<td>Technical Grade Active Ingredient</td>
</tr>
<tr>
<td>TRR</td>
<td>Total Radioactive Residue</td>
</tr>
<tr>
<td>TWAM</td>
<td>Time Weighted Annual Mean</td>
</tr>
<tr>
<td>USDA</td>
<td>United States Department of Agriculture</td>
</tr>
<tr>
<td>USGS</td>
<td>United States Geological Survey</td>
</tr>
<tr>
<td>UF</td>
<td>Uncertainty Factor</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
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<tr>
<td>WPS</td>
<td>Worker Protection Standard</td>
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2,4-D Reregistration Eligibility Decision Team

Office of Pesticide Programs:

Biological and Economic Analysis Assessment
Elisa Rim
Rafael Prieto
Steve Jarboe
Tim Kiely

Environmental Fate and Effects Risk Assessment
Mark Corbin
Bill Evans
James Hetrick
Sid Abel

Health Effects Risk Assessment
Bill Hazel
Timothy Dole
Linda Taylor
Felecia Fort
Toiya Jimerson
Michael Metzger
Whang Phang

Risk Management
Katie Hall
Mark Seaton
Moana Appleyard
Tom Myers
Margaret Rice
Executive Summary

EPA has completed its review of public comments on the preliminary risk assessments and is issuing its risk management decision for 2,4-D. The revised risk assessments are based on review of the required target data base supporting the use patterns of the currently registered products and additional information received from the 2,4-D Task Force II. After considering the risks identified in the revised risk assessment and comments and mitigation suggestions from interested parties, EPA developed its risk management decision for uses of 2,4-D that pose risks of concern. The decision is discussed fully in this document.

2,4-D is an herbicide in the phenoxy or phenoxyacetic acid family that is used post-emergence for selective control of broadleaf weeds. 2,4-D is registered for use on a variety of food/feed sites including field, fruit, and vegetable crops. 2,4-D is also registered for use on turf, lawns, rights-of-way, aquatic and forestry applications. Residential homeowners may use 2,4-D on lawns.

Based primarily on pesticide usage information from 1992 through 2000 for agriculture and 1993 through 1999 for non-agriculture, total annual domestic usage of 2,4-D is approximately 46 million pounds, with 30 million pounds (66%) used for agriculture and 16 million pounds (34%) used for non-agriculture. In terms of pounds, total 2,4-D usage is allocated mainly to pasture/rangeland (24%), lawn by homeowners with fertilizer (12%), spring wheat (8%), winter wheat (7%), lawn/garden by lawn care operators/landscape maintenance contractors (7%), lawn by homeowners alone (without fertilizer) (6%), field corn (6%), soybeans (4%), summer fallow (3%), hay other than alfalfa (3%) and roadways (3%). Agricultural sites with at least 10% of U.S. acreage treated include spring wheat (51%), filberts (49%), sugarcane (36%), barley (36%), seed crops (29%), apples (20%), rye (16%), winter wheat (15%), cherries (15%), oats (15%), millet (15%), rice (13%), soybeans (12%), and pears (10%). For 2,4-D, rates per application and rates per year are generally less than 1.50 pounds acid equivalent (a.e.) per acre and 2.00 pounds a.e. per acre (lbs ae/A), respectively. 2,4-D is used predominantly in the Midwest, Great Plains, and Northwestern United States.

The Food Quality Protection Act (FQPA) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider “available information” concerning the cumulative effects of a particular pesticide’s residues and “other substances that have a common mechanism of toxicity.” Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to 2,4-D and any other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that 2,4-D has a common mechanism of toxicity with other substances. For information regarding EPA’s efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA’s Office of Pesticide Programs (OPP) concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA’s website at http://www.epa.gov/pesticides/cumulative/.

Dietary Risk
Acute and chronic dietary exposures for food and drinking water do not exceed the Agency’s level of concern; therefore, no mitigation is warranted at this time for any dietary exposure to 2,4-D.

The maximum contaminant level (MCL) established by EPA’s Office of Water (OW) for 2,4-D is 70 micrograms/liter (ug/l; ppb). Further, it is important to note that an MCL is an enforceable limit under the Safe Drinking Water Act (SDWA). To minimize the possibility that aquatic applications will result in drinking water concentrations in excess of the MCL, registrants and the Agency have developed label language for the direct aquatic use of 2,4-D to control aquatic weeds.

Residential Risk

Potential exposures are anticipated as a result of homeowner and commercial applications in residential areas. Applications can be made to lawns. In addition to residential areas, there are also potential postapplication exposure scenarios that may occur in public areas such as parks, recreational areas, and golf courses. The Agency evaluated 2,4-D exposures to residential handlers during mixing, loading and application to turf/ornamentals and 2,4-D postapplication exposure to residues by adults and children on treated turf.

In preliminary versions of the risk assessment, when considered alone, acute and short-term residential risks posed by the use of 2,4-D were not of concern to the Agency; however, when considered as part of an aggregate exposure with food and drinking water, exposures did exceed the Agency’s level of concern. As a result, 2,4-D registrants agreed to reduce the maximum application rate to turf and residential lawns from 2.0 lbs ae/A to 1.5 lbs ae/A. Chronic residential exposures to 2,4-D are not expected due to its use pattern.

Aggregate Risk

An aggregate risk assessment looks at the combined risk from dietary exposure (food and drinking water pathways), as well as exposures from non-occupational sources (e.g., residential uses). In the preliminary and revised risk assessments, the estimated acute and short-term exposures exceeded the Agency’s level of concern. As a result, 2,4-D registrants agreed to reduce the maximum application rate to turf and residential lawns from 2.0 pounds acid equivalent per acre (lbs ae/A) to 1.5 lbs ae/A. The current risk assessment considers exposures from the reduced application rate for residential turf.

Two methods of aggregate risk calculations were employed in assessing the aggregate risk of 2,4-D. The first method is the drinking water level of concern (DWLOC) method. OPP (Office of Pesticide Programs) has traditionally compared estimates of concentrations of a pesticide in drinking water to DWLOCs. A DWLOC is the portion of the acute population adjusted dose (aPAD) or chronic population adjusted dose (cPAD) remaining after estimated dietary (food only) exposures have been subtracted and the remaining exposure has been converted to a concentration (ug/liter or ppb). This concentration value (DWLOC) represents the available or allowable exposure through drinking water. The second method is the forward calculation method. In this approach, food, drinking water, and residential exposures are aggregated and compared to an appropriate endpoint.
population adjusted dose, or PAD, is the reference dose (RfD) adjusted for the FQPA safety factor. A risk estimate that is less than 100% of the acute PAD (aPAD), the dose at which an individual could be exposed over the course of a single day and no adverse health effects would be expected, does not exceed EPA’s level of concern. Likewise, risk estimate that is less than 100% of the chronic PAD (cPAD), the dose at which an individual could be exposed over the course of a lifetime and no adverse health effects would be expected, does not exceed EPA’s level of concern.

In the case of 2,4-D, the DWLOCs were calculated for comparison to the MCL established by the EPA Office of Water and aggregate risks were calculated using the forward calculation approach for comparison to the appropriate endpoint. The respective DWLOCs and aggregate risks are shown for acute, chronic and short term exposures in the following sections.

**Acute aggregate risk.** The acute aggregate risk assessments address exposure to 2,4-D residues in food and water using both the DWLOC and forward calculation approach. Acute residential exposures from swimming in treated water bodies or playing on treated turf were not included because exposures are unlikely to co-occur with acute dietary exposures. The acute DWLOCs are 432 ppb or greater with the most sensitive population being females 13-49 years old. The estimated drinking water concentrations (EDWCs) of 118 ug/liter for surface water and 15 ug/liter for groundwater are substantially less than the DWLOCs which means that the risks are not of concern.

Acute aggregate risks were also assessed by aggregating acute food exposures and acute water exposures using Lifeline. The acute aggregate risks are not of concern because they are less than 100 percent of the aPAD. The highest risks (58 percent of the aPAD) are for females 13-49 years old because these risks are based upon the lower no-observed adverse effect level (NOAEL) of 25 mg/kg/day from a developmental study in rats.

**Short-term aggregate risk.** Short term aggregate risk assessments were conducted by calculating DWLOCs based upon short term turf exposures, chronic food exposures and short term endpoints. Short term exposures from swimming in treated water bodies were not included because these exposures represent high-end unlikely scenarios. The short term DWLOCs were calculated only for females 13-49 and children 1-6 because these population subgroups have the highest exposure and are protective of the other subgroups. The DWLOCs range from 24 to 54 ug/liter. These DWLOCs are all greater than the EDWCs, which range from 15 to 23 ug/liter, and indicate that short term risks are not of concern.

Short term aggregate risks were also assessed by aggregating short term turf exposures, chronic food exposures and chronic water exposures using the forward calculation approach. Short term aggregate risks were calculated only for females 13-49 and children 1-6 because these population subgroups have the highest exposure and are protective of the other subgroups. The short term aggregate margins of exposure (MOEs) indicate that the short term risks are not of concern because the MOEs equal or exceed the target MOE of 1000.
**Chronic (non-cancer) aggregate risk.** Chronic DWLOCs were calculated based upon chronic dietary exposures. As there are no chronic residential exposures, residential exposures were not included in the chronic DWLOC calculations. The chronic DWLOCs are 47 ug/liter or greater with the most sensitive populations being infants and children. The EDWCs, which range from 1.5 to 23 ug/liter, are less than the DWLOCs which means that the risks are not of concern. It should be noted that the master label indicates that potable water consumption from a treated water body cannot begin until the 2,4-D concentration is 70 ug/liter or below, therefore an annual average exposure at the MCL of 70 ug/liter would not occur because dissipation would reduce the initial concentration of 70 ug/liter to an annual average concentration of 11 ug/liter.

Chronic aggregate risks were also assessed by aggregating chronic food exposures and chronic water exposures using the forward calculation approach. The chronic aggregate risks are presented as percent cPAD are not of concern because they are less than 100 percent of the cPAD. The highest risks (38 percent of the cPAD) are for children 1-2 years old.

**Occupational Risk**

Based on current use patterns, occupational handlers (mixers, loaders, and applicators) may be exposed to 2,4-D during and after normal use. The Agency identified 18 handler scenarios resulting from mixing/loading and applying 2,4-D for crop and non-crop uses. For the occupational use of 2,4-D, EPA is concerned about any Margin of Exposure (MOE) less than 100, which incorporates uncertainty factors of 10x for interspecies variation and 10x for intraspecies variation.

With the exception of mixing/loading wettable powder, all of the short-term and intermediate-term MOEs exceed the target of 100 with baseline personal protective equipment (PPE) (i.e., long-sleeved shirt, long pants, shoes plus socks, no respirator) or single layer PPE (i.e., long-sleeved shirt, long pants, shoes plus socks, gloves, no respirator) and are not of concern. The MOEs for handling wettable powder are above 100 with engineering controls (i.e., water soluble bags).

**Ecological Risk**

*Fish and Aquatic Invertebrates:* Estimated risk quotients (RQs) from use of 2,4-D acid and amine salts in aquatic weed control through direct subsurface application to water bodies exceed the restricted use LOCs for freshwater invertebrates. There are no chronic LOC exceedances for this use. Estimated RQs from use of 2,4-D BEE in weed control through direct subsurface application to water bodies exceed the acute risk level of concern (LOC) for freshwater fish and invertebrates and chronic risk LOC for freshwater and estuarine fish and freshwater invertebrates when compared on an acid equivalent basis. Estimated RQs from use of 2,4-D acid and amine salts in rice paddies exceed the acute endangered species LOCs for freshwater invertebrates.

*Non-Target Aquatic Plants:* For non-target aquatic plants, estimated RQs from the runoff/drift of 2,4-D acid and amine salts from use on terrestrial crops exceed the aquatic vascular plant endangered species LOCs for use of 2,4-D acid and amine salts on pasture and apples. Consideration of average application rates and assuming a proportional reduction in EECs results in RQs below the
endangered species LOC. Likewise, there are no LOC exceedances from the drift of the ester forms to aquatic water bodies or from the runoff of the ester forms to water bodies from use on terrestrial sites.

Estimated RQs for the scenario of direct application to water for aquatic weed control for 2,4-D acid and amine salts exceed the acute and endangered species LOCs for aquatic vascular and acute the LOC for non-vascular plants, while estimated RQs from use of 2,4-D BEE (the only ester registered for aquatic weed control) for direct application to water for weed control exceed all LOCs for vascular and the acute LOC for non-vascular plants.

Estimated RQs for use of 2,4-D acid and amine salts in rice paddies exceed the acute and endangered species LOCs for aquatic vascular plants. Consideration of average application rates results in RQs below the endangered species LOCs.

**Birds:** For non-granular spray applications of 2,4-D acid, amine salts, and esters, estimated RQs exceed acute LOCs for most crop scenarios for short grass, tall grass, and broadleaf forage exposures. For birds that eat fruit and large insects, acute endangered LOCs are exceeded for non-cropland, forest, and cranberry scenarios. Chronic LOCs are exceeded for birds that forage on short grass when the application rate of 2,4-D ranges from 2.0 to 4.0 lbs ae/A such as with non-cropland areas, cranberries, or asparagus. For granular broadcast applications, acute LOCs are exceeded for several different crop scenarios and bird weights. The chronic LOC is not exceeded for granular broadcast applications.

**Mammals:** For non-granular formulations of 2,4-D, estimated RQs exceed acute LOCs for mammals feeding on plants and insects for all uses assessed for small and medium size mammals, except potatoes and citrus. There were no exceedances for granivores exposed to non-granular formulations of 2,4-D. LOCs for acute exposure to granular 2,4-D products are exceeded for all sites with the following exceptions: 1000 g mammals in turf, aquatic areas, and cranberries. Mammalian chronic RQs range from 0.05 to 200 and chronic LOCs were exceeded in all cases with the exception of potatoes and citrus (large insects, seeds). Consideration of average application rates results in acute RQs below the LOCs for non-granular and granular applications. However, consideration of average application rates for non-granular and granular applications did not result in RQs below the chronic LOC.

**Insects:** Since study results show that 2,4-D DMAS and 2,4-D EHE are practically non-toxic to honey bees, the potential for 2,4-D and its salts and esters is predicted to pose minimal risk to pollinators and other beneficial insects.

**Non-Target Terrestrial Plants:** Estimated RQs exceed acute LOCs for both non-endangered and endangered plants for non-granular and granular uses at many use sites. Consideration of average application rates did not result in RQs below LOCs.

In summary, some ecological risks are of concern on some sites for some species. The Agency’s characterization of its assessment of ecological risk is provided in section III.B.3 of this document. The mitigation measures of (1) reducing maximum application rates, and (2) specifying a
required spray droplet size of “Medium to Coarse” or coarser (i.e., prohibiting “fine” sprays) are expected to lessen, but not eliminate, the risk of 2,4-D to wildlife and plants.

Summary of Mitigation Measures

EPA has determined that 2,4-D is eligible for reregistration provided the mitigation outlined in this document is implemented.

Dietary Risk

• Acute and chronic dietary exposures for food and drinking water do not exceed the Agency’s level of concern; therefore, no mitigation is warranted at this time for any dietary exposure to 2,4-D.

Residential Risk

• Maximum turf rate is reduced from 2.0 lbs ae/A to 1.5 lbs ae/A.
• At the agreed-upon maximum application rate of 1.5 lbs ae/A for residential turf, acute and short-term residential risks posed by the use of 2,4-D are not of concern to the Agency. Due to its use pattern, chronic residential exposures to 2,4-D are not expected.

Occupational Risk

• Risks from handling wettable-powder products will be mitigated by requiring wettable powder products to be packaged in water-soluble packaging.
• Personal protective equipment (PPE) prescribed in the exposure reduction plan set forth in 1992 will be replaced with the PPE requirements outlined in this document.

Ecological Risk

• The measures to control spray drift are expected to reduce the risk of 2,4-D to non-target plants.
• Maximum turf rate is reduced from 2.0 lbs ae/A to 1.5 lbs ae/A.
• Implementation of the application rates set forth in the Master Label will reduce rates (as compared to current rates on existing labels) for field corn, popcorn, sweet corn, small grains, fallowland/stubble, non-cropland, turf, aquatic applications (surface), pasture, and soybean.
I. Introduction

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) was amended in 1988 to accelerate the reregistration of products with active ingredients registered prior to November 1, 1984. The amended Act calls for the development and submission of data to support the reregistration of an active ingredient, as well as a review of all submitted data by the U.S. Environmental Protection Agency (referred to as EPA or "the Agency"). Reregistration involves a thorough review of the scientific database underlying a pesticide's registration. The purpose of the Agency's review is to reassess the potential hazards arising from the currently registered uses of the pesticide; to determine the need for additional data on health and environmental effects; and to determine whether or not the pesticide meets the "no unreasonable adverse effects" criteria of FIFRA.

On August 3, 1996, the Food Quality Protection Act of 1996 (FQPA) was signed into law. This Act amends FIFRA and the Federal Food Drug and Cosmetic Act (FFDCA) to require reassessment of all existing tolerances for pesticides in food. FQPA also requires EPA to review all tolerances in effect on August 3, 1996 by August 3, 2006. In reassessing these tolerances, the Agency must consider, among other things, aggregate risks from non-occupational sources of pesticide exposure, whether there is increased susceptibility to infants and children, and the cumulative effects of pesticides with a common mechanism of toxicity. When a safety finding has been made that aggregate risks are not of concern and the Agency concludes that there is a reasonable certainty of no harm from aggregate exposure, the tolerances are considered reassessed. EPA decided that, for those chemicals that have tolerances and are undergoing reregistration, tolerance reassessment will be accomplished through the reregistration process.

As mentioned above, FQPA requires EPA to consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity" when considering whether to establish, modify, or revoke a tolerance. Potential cumulative effects of chemicals with a common mechanism of toxicity are considered because low-level exposures to multiple chemicals causing a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any one of these individual chemicals. For information regarding EPA’s efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by the EPA’s Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA’s website at http://www.epa.gov/pesticides/cumulative/.

Unlike other pesticides for which EPA has considered cumulative risk based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for 2,4-dichlorophenoxyacetic acid (2,4-D). Therefore, for the purposes of tolerance reassessment and a decision on reregistration eligibility, EPA is assuming that 2,4-D does not share a common mechanism of toxicity with other compounds. In the future, if information suggests 2,4-D shares a common mechanism of toxicity with other compounds, additional testing may be required and a cumulative assessment may be necessary.
This document presents summaries of EPA’s revised human health and ecological risk assessments, tolerance reregistration decision, and the reregistration eligibility decision for 2,4-D. The document consists of six sections. Section I contains the regulatory framework for reregistration/tolerance reassessment. Section II provides a profile of the use and usage of the chemical. Section III gives an overview of the revised human health and environmental effects risk assessments based on data, public comments, and other information received in response to the preliminary risk assessments. Section IV presents the Agency’s reregistration eligibility and risk management decisions. Section V summarizes label changes necessary to implement the risk mitigation measures outlined in Section IV. Finally, the Appendices list related information, supporting documents. The preliminary and revised risk assessments for 2,4-D are available in the Public Docket, under docket number OPP-2004-0167 and on the Agency’s web page, http://www.epa.gov/edockets.
II. Chemical Overview

A. Regulatory History

2,4-D has been used as an herbicide since the mid-1940s. Currently over 600 end-use products are registered for use on over 300 distinct agricultural and residential sites, and there are over 100 tolerances for 2,4-D listed in the Code of Federal Regulations. 2,4-D was the subject of a Registration Standard and a Registration Standard Guidance Document dated February 16, 1988 and September 9, 1988, respectively. These documents summarized the regulatory conclusions based on available data, and specified the additional data required for reregistration purposes. Numerous data submissions have been received and evaluated since the Registration Standard Guidance Document was published.

Special Review

2,4-D has been in pre-Special Review status since September 22, 1986, because of carcinogenicity concerns. More specifically, there were concerns for epidemiological links of 2,4-D to non-Hodgkin’s lymphoma from both occupational and residential exposure. A proposed decision not to initiate Special Review was published (53 FR 9590) on March 23, 1988 based on findings that such a link could not be established. The final decision was deferred until reregistration. In part to address these concerns, the 2,4-D Task Force agreed to risk reduction measures in September 1992 that included an exposure reduction plan effected through modifications of technical and manufacturing-use product labels and implementation of a user education program.

A Science Advisory Board/Scientific Advisory Panel Special Joint Committee reviewed available epidemiological and other data on 2,4-D in 1992 and 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.” 2,4-D was classified as a Group D, not classifiable as to human carcinogenicity. The Agency requested further histopathological examinations of rat brain tissues and mouse spleen tissues in question. These exams were submitted and reviewed, and on March 16, 1999, the Agency notified the 2,4-D Task Force that the Agency would continue to classify 2,4-D as a Group D carcinogen.

The Agency has twice recently reviewed epidemiological studies linking cancer to 2,4-D. In the first review, completed January 14, 2004, EPA concluded there is no additional evidence that would implicate 2,4-D as a cause of cancer (EPA, 2004). The second review of available epidemiological studies occurred in response to comments received during the Phase 3 Public Comment Period for the 2,4-D RED. EPA’s report, dated December 8, 2004 and authored by EPA Scientist Jerry Blondell, Ph.D., found that none of the more recent epidemiological studies definitively linked human cancer cases to 2,4-D.

Final notice of the Agency’s decision not to initiate Special Review will be issued at the completion of the reregistration process.
Residue Tolerances

Tolerances for residues of 2,4-D in/on plant and processed food/feed commodities, fish, and potable water are expressed in terms of 2,4-D per se [40 CFR §180.142(a)(1-6 and 9-12) and (b)]. There are currently approximately 110 tolerances for 2,4-D.

The Industry Task Force II on 2,4-D Research Data (Task Force II) is supporting the reregistration of 2,4-D. The members of the Task Force currently include Agro-Gor Corp (jointly owned by Atanor, S.A. and PBI-Gordon Corp.), Dow AgroSciences, and Nufarm USA. In addition, USDA’s Interregional Project No. 4 (IR-4) is supporting the reregistration of a number of minor crop uses for 2,4-D, and the California Citrus Quality Council (CCQC) is supporting selected uses of 2,4-D isopropyl ester (IPE) on citrus fruits.

B. Chemical Identification

2,4-D [2,4-dichlorophenoxyacetic acid] is a List A pesticide active ingredient classified as an herbicide, a plant growth regulator, and a fungicide. It is, however, mainly used as a selective postemergence herbicide for the control of broadleaf weed species in a variety of food/feed sites including field, fruit, and vegetable crops. In addition to the acid form, there are numerous salts and esters of 2,4-D in Reregistration Case 0073, each with an assigned PC Code number, that are presently registered as active ingredients in end-use products (EPs). Nine forms of 2,4-D are currently supported; these forms are listed in Table 1 below. With regards to analytical methodology, the quantitative recovery of residues of concern are enhanced by the formation of the more polar acid form of 2,4-D. Given that results of 2,4-D analyses are typically expressed in terms of the quantified levels of the acid form, 2,4-D concentrations in product formulations are typically referred to in terms of acid equivalents (ae).

Chemical structures and information are presented in Tables 1 and 2 for 2,4-D acid and those salts and esters with registered manufacturing-use and/or end-use products (MPs/EPs) being supported by 2,4-D Task Force II and its member companies.

Table 1. Chemical Structures for Supported Forms of 2,4-D Acid, Amine Salts, and Esters

<table>
<thead>
<tr>
<th>2,4-D active ingredients with registered MPs/EPs</th>
<th>2,4-D sodium salt (Na)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2,4-D acid</strong></td>
<td><strong>Empirical Formula:</strong> C_8H_6Cl_2O_3</td>
</tr>
<tr>
<td><strong>Molecular Weight:</strong> 221.0</td>
<td><strong>Molecular Weight:</strong> 243.03</td>
</tr>
<tr>
<td><strong>CAS Registry No.:</strong> 94-75-7</td>
<td><strong>CAS Registry No.:</strong> 2702-72-9</td>
</tr>
<tr>
<td><strong>PC Code:</strong> 030001</td>
<td><strong>PC Code:</strong> 030004</td>
</tr>
<tr>
<td>2,4-D active ingredients with registered MPs/EPs</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>![Chemical Structure] ![Chemical Structure]</td>
<td></td>
</tr>
<tr>
<td><strong>2,4-D diethanolamine salt (DEA)</strong></td>
<td></td>
</tr>
<tr>
<td>Empirical Formula: C\textsubscript{12}H\textsubscript{17}Cl\textsubscript{2}NO\textsubscript{5}</td>
<td></td>
</tr>
<tr>
<td>Molecular Weight: 326.18</td>
<td></td>
</tr>
<tr>
<td>CAS Registry No.: 5742-19-8</td>
<td></td>
</tr>
<tr>
<td>PC Code: 030016</td>
<td></td>
</tr>
<tr>
<td><strong>2,4-D dimethylamine salt (DMA)</strong></td>
<td></td>
</tr>
<tr>
<td>Empirical Formula: C\textsubscript{10}H\textsubscript{13}Cl\textsubscript{2}NO\textsubscript{3}</td>
<td></td>
</tr>
<tr>
<td>Molecular Weight: 266.13</td>
<td></td>
</tr>
<tr>
<td>CAS Registry No.: 2008-39-1</td>
<td></td>
</tr>
<tr>
<td>PC Code: 030019</td>
<td></td>
</tr>
<tr>
<td>![Chemical Structure] ![Chemical Structure]</td>
<td></td>
</tr>
<tr>
<td><strong>2,4-D isopropylamine salt (IPA)</strong></td>
<td></td>
</tr>
<tr>
<td>Empirical Formula: C\textsubscript{11}H\textsubscript{15}Cl\textsubscript{2}NO\textsubscript{3}</td>
<td></td>
</tr>
<tr>
<td>Molecular Weight: 280.04</td>
<td></td>
</tr>
<tr>
<td>CAS Registry No.: 5742-17-6</td>
<td></td>
</tr>
<tr>
<td>PC Code: 030025</td>
<td></td>
</tr>
<tr>
<td><strong>2,4-D triisopropanolamine salt (TIPA)</strong></td>
<td></td>
</tr>
<tr>
<td>Empirical Formula: C\textsubscript{17}H\textsubscript{27}Cl\textsubscript{2}NO\textsubscript{6}</td>
<td></td>
</tr>
<tr>
<td>Molecular Weight: 412.31</td>
<td></td>
</tr>
<tr>
<td>CAS Registry No.: 32341-80-3</td>
<td></td>
</tr>
<tr>
<td>PC Code: 030035</td>
<td></td>
</tr>
<tr>
<td>![Chemical Structure] ![Chemical Structure]</td>
<td></td>
</tr>
<tr>
<td><strong>2,4-D 2-butoxyethyl ester (BEE)</strong></td>
<td></td>
</tr>
<tr>
<td>Empirical Formula: C\textsubscript{14}H\textsubscript{18}Cl\textsubscript{2}O\textsubscript{4}</td>
<td></td>
</tr>
<tr>
<td>Molecular Weight: 321.20</td>
<td></td>
</tr>
<tr>
<td>CAS Registry No.: 1929-73-3</td>
<td></td>
</tr>
<tr>
<td>PC Code: 030053</td>
<td></td>
</tr>
<tr>
<td><strong>2,4-D 2-ethylhexyl ester (2-EHE)</strong></td>
<td></td>
</tr>
<tr>
<td>Empirical Formula: C\textsubscript{16}H\textsubscript{22}Cl\textsubscript{2}O\textsubscript{3}</td>
<td></td>
</tr>
<tr>
<td>Molecular Weight: 333.27</td>
<td></td>
</tr>
<tr>
<td>CAS Registry No.: 1928-43-4</td>
<td></td>
</tr>
<tr>
<td>PC Code: 030063</td>
<td></td>
</tr>
</tbody>
</table>
2,4-D active ingredients with registered MPs/EPs

<table>
<thead>
<tr>
<th>2,4-D isopropyl ester (IPE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical Formula: $\text{C}<em>{11}\text{H}</em>{12}\text{Cl}_2\text{O}_3$</td>
</tr>
<tr>
<td>Molecular Weight: 263.12</td>
</tr>
<tr>
<td>CAS Registry No.: 94-11-1</td>
</tr>
<tr>
<td>PC Code: 030066</td>
</tr>
</tbody>
</table>

Formerly identified as the isooctyl ester.

Available data concerning identification of the active ingredients are summarized in Table 2 for 2,4-D acid, salts, and esters with registered MPs/EPs.
<table>
<thead>
<tr>
<th>Active ingredient (PC Code)</th>
<th>Color</th>
<th>Physical State</th>
<th>Melting Point/Boiling Point</th>
<th>Density/Specific Gravity</th>
<th>Octanol/Water Partition Coeff.</th>
<th>Vapor Pressure</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4-D acid (030001)</td>
<td>white</td>
<td>crystalline solid</td>
<td>m.p. 138-141°C</td>
<td>s.g. = 1.416 at 25°C</td>
<td>Log K&lt;sub&gt;OW&lt;/sub&gt; 0.001 M sol’n pH 5 2.14, pH 7 0.177, pH 9 0.102</td>
<td>1.4 x 10&lt;sup&gt;-7&lt;/sup&gt; mm Hg at 25°C</td>
<td>water = 569 mg/L at 20°C</td>
</tr>
<tr>
<td>2,4-D Na salt (030004)</td>
<td>white</td>
<td>powder</td>
<td>m.p. 200°C</td>
<td>bulk = 42.2 lb/ft&lt;sup&gt;3&lt;/sup&gt; at 25°C</td>
<td>N/A&lt;sup&gt;2&lt;/sup&gt;; salt dissociates to acid in water</td>
<td></td>
<td>water = 4.5 g/100 mL at 25°C</td>
</tr>
<tr>
<td>2,4-D DEA salt (030016)</td>
<td>cream</td>
<td>powder</td>
<td>m.p. 83°C</td>
<td>bulk = 0.762 g/cm&lt;sup&gt;3&lt;/sup&gt; at 25°C</td>
<td>2.24 x 10&lt;sup&gt;-2&lt;/sup&gt; at 25°C</td>
<td>&lt;1 x 10&lt;sup&gt;-5&lt;/sup&gt; Pa at 25°C</td>
<td>mg/g at 25°C; water = 806</td>
</tr>
<tr>
<td>2,4-D DMA salt (030019)</td>
<td>amber</td>
<td>aqueous liquid</td>
<td>m.p. 118-120°C (PAI)</td>
<td>s.g. = 1.23 at 20°C</td>
<td>N/A; salt dissociates to acid in water</td>
<td></td>
<td>g/100 mL at 20°C; water = 72.9 (pH 7)</td>
</tr>
<tr>
<td>2,4-D IPA salt (030025)</td>
<td>amber</td>
<td>aqueous liquid</td>
<td>m.p. 121°C (PAI)</td>
<td>s.g. = 1.15 at 20°C</td>
<td>N/A; salt dissociates to acid in water</td>
<td></td>
<td>g/100 mL at 20°C; water = 17.4 (pH 5.3)</td>
</tr>
<tr>
<td>2,4-D TIPA salt (030035)</td>
<td>amber</td>
<td>aqueous liquid</td>
<td>m.p. 87-110°C (PAI)</td>
<td>s.g. = 1.21 at 20°C</td>
<td>N/A; salt dissociates to acid in water</td>
<td></td>
<td>g/100 mL at 20°C; water = 46.1 (pH 7)</td>
</tr>
<tr>
<td>2,4-D BEE (030053)</td>
<td>dark amber</td>
<td>liquid</td>
<td>b.p. 89°C</td>
<td>s.g. = 1.225 at 20°C</td>
<td>log = 4.13-4.17 at 25°C</td>
<td>2.4 x 10&lt;sup&gt;8&lt;/sup&gt; mm Hg at 25°C</td>
<td>g/100 mL at 20°C; water = insoluble</td>
</tr>
<tr>
<td>2,4-D 2-EHE (030063)</td>
<td>dark amber</td>
<td>liquid</td>
<td>b.p. 300°C</td>
<td>s.g. = 1.152 at 20°C</td>
<td>log = 5.78 (temp N/A)</td>
<td>3.6 x 10&lt;sup&gt;8&lt;/sup&gt; mm Hg (temp N/A)</td>
<td>water = 86.7 ppb</td>
</tr>
<tr>
<td>2,4-D IPE (030066)</td>
<td>pale amber</td>
<td>liquid</td>
<td>b.p. 240°C</td>
<td>s.g. = 1.252 at 25°C</td>
<td>253.8 ± 44.4 (temp N/A)</td>
<td>5.3 x 10&lt;sup&gt;6&lt;/sup&gt; mbar</td>
<td>water = 0.023 g/100 mL</td>
</tr>
</tbody>
</table>

<sup>1</sup> Data assembled from Agency memoranda and comprehensive review documents, including the 2,4-D Reregistration Standard.

<sup>2</sup> N/A = Not available.
C. Use Profile

2,4-D comes in multiple chemical forms and is found in numerous end-use products intended for use in a wide range of use patterns. 2,4-D is an ingredient in approximately 660 agricultural and home use products, as a sole active ingredient and in conjunction with other active ingredients. 2,4-D is formulated primarily as an amine salt in an aqueous solution or as an ester in an emulsifiable concentrate. Chemical forms covered by this risk assessment are as 2,4-D acid, 2,4-D DMAS, 2,4-D IPA, 2,4-D TIPA, 2,4-D EHE, 2,4-D BEE, 2,4-D DEA, 2,4-D IPE, and 2,4-D sodium salt. Copies of all labels may be found at http://www.cdpr.ca.gov/docs/epa/m2.htm. The following is information on the currently registered uses including an overview of use sites and application methods. A detailed table of the uses of 2,4-D eligible for reregistration is contained in Appendix A.

Type of Pesticide: Herbicide

Target organism(s): A wide variety of broadleaf weeds and aquatic weeds

Mode of action: 2,4-D is thought to increase cell-wall plasticity, biosynthesis of proteins and the production of ethylene. The abnormal increase in these processes is thought to result in uncontrolled cell division and growth which damages vascular tissue.

Use Sites: Table 3 presents a summary of the registered 2,4-D uses.

Use Classification: General use

Formulation Types: Formulation types registered include emulsifiable concentrate, granular, soluble concentrate/solid, water dispersible granules, and wettable powder.

Application Methods: 2,4-D may be applied with a wide range of application equipment including fixed-wing aircraft, backpack sprayer, band sprayer, boom sprayer, granule applicator, ground-directed sprayers, hand held sprayer, helicopter, injection equipment, tractor-mounted granule applicator, and tractor-mounted sprayers.

Application Rates: For 2,4-D, rates per application and rates per year are generally less than 1.5 pounds acid equivalent (ae) per acre per year and 2.0 pounds a.e. per acre per year (lbs ae/A), respectively. Maximum rates are 4.0 lbs ae/A per year for asparagus, forestry uses, and non-cropland uses, among others. The maximum rate for aquatic uses is 10.8 lbs ae/acre foot for submerged aquatic plants.

Application Timing: Timing of 2,4-D application can include at emergence, before bud break, during dormancy, to established plantings, foliar, post-emergence, pre-emergence, pre-harvest, and pre-plant.
### Table 3. Registered 2,4-D Uses

<table>
<thead>
<tr>
<th>Crop Grouping</th>
<th>Representative Crops</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terrestrial food crop</td>
<td>Pear, Pistachio, Stone fruits</td>
</tr>
<tr>
<td>Terrestrial food and feed crop</td>
<td>Agricultural fallow/idleland; Agricultural rights-of-way/fencerows/hedgerows;</td>
</tr>
<tr>
<td></td>
<td>Agricultural uncultivated areas; Apple; Barley; Citrus fruits; Corn (unspecified);</td>
</tr>
<tr>
<td></td>
<td>Corn, field; Corn, pop; Corn, sweet; Fruits (unspecified), Grapefruit, Lemon, Oats,</td>
</tr>
<tr>
<td></td>
<td>Orange, Pome fruits, Rice, Rye, Small fruits, Soil, preplant/outdoor, Sorghum,</td>
</tr>
<tr>
<td></td>
<td>Sorghum (unspecified), Soybeans (unspecified), Sugarcane, Tangelo, Tree nuts, Wheat</td>
</tr>
<tr>
<td>Terrestrial feed crop</td>
<td>Grass forage/fodder/hay, Pastures, Rangeland, Rye, Sorghum</td>
</tr>
<tr>
<td>Terrestrial non-food crop</td>
<td>Agricultural fallow/idleland, Agricultural rights-of-way/fencerows/hedgerows,</td>
</tr>
<tr>
<td></td>
<td>Agricultural uncultivated areas, Airports/landing fields, Christmas tree plantations,</td>
</tr>
<tr>
<td></td>
<td>Commercial/industrial lawns, Commercial/institutional/industrial, premises/equipment</td>
</tr>
<tr>
<td></td>
<td>(outdoor), Forest nursery plantings (for transplant purposes), Golf course turf,</td>
</tr>
<tr>
<td></td>
<td>Grasses grown for seed, Industrial areas (outdoor), Nonagricultural outdoor</td>
</tr>
<tr>
<td></td>
<td>buildings/structures, Nonagricultural rights-of-way/hedgerows, Nonagricultural</td>
</tr>
<tr>
<td></td>
<td>uncultivated areas/soils, Ornamental and/or shade trees, Ornamental lawns and turf,</td>
</tr>
<tr>
<td></td>
<td>Ornamental sod farm (turf), Ornamental woody shrubs and vines, Paved areas (private</td>
</tr>
<tr>
<td></td>
<td>roads/sidewalks), Potting soil/topsoil, Recreation area lawns, Recreational areas,</td>
</tr>
<tr>
<td></td>
<td>Soil, preplant/outdoor, Urban areas</td>
</tr>
<tr>
<td>Terrestrial non-food and outdoor</td>
<td>Fencerows/hedgerows, Nonagricultural rights-of-way/hedgerows, Ornamental and/or</td>
</tr>
<tr>
<td>residential</td>
<td>shade trees, Ornamental lawns and turf, Ornamental woody shrubs and vines, Paths/</td>
</tr>
<tr>
<td></td>
<td>patios, Paved areas (private roads/sidewalks), Urban areas</td>
</tr>
<tr>
<td>Aquatic food crop</td>
<td>Agricultural drainage systems, Aquatic areas/water, Commercial fishery water systems,</td>
</tr>
<tr>
<td></td>
<td>Irrigation systems, Lakes/ponds/reservoirs (with human or wildlife use), Rice,</td>
</tr>
<tr>
<td></td>
<td>Streams/rivers/channeled water, Swamps/marshes/wetlands/stagnant water</td>
</tr>
<tr>
<td>Aquatic non-food outdoor</td>
<td>Aquatic areas/water, Streams/rivers/channeled water, Swamps/marshes/wetlands/stagnat</td>
</tr>
<tr>
<td>industrial</td>
<td>water</td>
</tr>
<tr>
<td>Forestry</td>
<td>Drainage systems, Industrial waste disposal systems, Lakes/ponds/reservoirs (without</td>
</tr>
<tr>
<td></td>
<td>human or wildlife use)</td>
</tr>
<tr>
<td>Outdoor residential</td>
<td>Residential lawns</td>
</tr>
<tr>
<td>Indoor non-food</td>
<td>Commercial transportation facilities-nonfeed/nonfood</td>
</tr>
</tbody>
</table>

### D. Estimated Usage of Pesticide

Based primarily on pesticide usage information from 1992 through 2000 for agriculture and 1993 through 1999 for non-agriculture, total annual domestic usage of 2,4-D is approximately 46 million pounds, with 30 million pounds (66%) used by agriculture and 16 million pounds (34%) used by non-agriculture (see the OPP Biological and Economic Assessment Division [BEAD] quantitative use analysis [QUA] which is available on EPA’s Pesticide Docket OPP-2004-0167 located at:
http://www.epa.gov/edockets). In terms of pounds, total 2,4-D usage is allocated mainly to pasture/rangeland (24%), lawn by homeowners with fertilizer (12%), spring wheat (8%), winter wheat (7%), lawn/garden by lawn care operators/landscape maintenance contractors (7%), lawn by homeowners alone (without fertilizer) (6%), field corn (6%), soybeans (4%), summer fallow (3%), hay other than alfalfa (3%), and roadways (3%).

Agricultural sites with at least 10% of U.S. acreage treated include spring wheat (51%), filberts (49%), sugarcane (36%), barley (36%), seed crops (29%), apples (20%), rye (16%), winter wheat (15%), cherries (15%), oats (15%), millet (15%), rice (13%), soybeans (12%) and pears (10%). For 2,4-D, rates per application and rates per year are generally less than 1.5 lbs ae/A per year and 2.0 lbs ae/A per year, respectively. 2,4-D is used predominantly in the Midwest, Great Plains, and Northwestern United States (Figure 1).
Figure 1. Estimated 2,4-D usage (lbs ae/square mile). The estimates are based on pesticide use rates compiled by the National Center for Food and Agricultural Policy (NCFAP) and modified by Thelin, G.P. and Gianessi, L.P., 2000 (USGS Open-File Report 00-250).
Application Rates, Timing and Frequency of Applications

The 2,4-D master label (available in EPA docket #OPP-2004-0167) has been developed by the 2,4-D Task Force and represents the maximum supported application rates for agricultural and non-agricultural uses. All end-use product manufacturers obtain 2,4-D starting material from companies represented by the 2,4-D Task Force. EPA used the master label rates in the 2,4-D human health and ecological risk assessments. Some master label rates are lower than the rates present on existing labels. The Agency and the task force have agreed that all of the 2,4-D labels will be updated with the new master label rates as part of the registration process. All of the registrants, including those that are not in the 2,4-D task force, will have to conform to the master label rates. The master label agreement is discussed in an internal Agency memo (EPA, March 18, 2003), which is available on EPA’s Pesticide Docket OPP-2004-0167 located at: http://www.epa.gov/edockets.

Typically, one to three applications are made per growing season. Applications are made to the target weeds prior to crop emergence, after crop emergence, prior to harvest, and in the dormant season, depending upon the crop. The label required spray volumes for ground applications range from 0.0375 lbs ae/A for applications to low bush blueberries to 4.0 lbs ae/A for brush control. 2,4-D can be applied over the top to tolerant crops such as small grains and rice, but must be directed or shielded for the more sensitive crops such as fruits and berries.

The application rates on the master label are included in Table 4 for non-crop areas and Table 5 for agricultural crops. The average application rates from the 2,4-D QUA report (EPA BEAD 2001) are shown for comparison. With the exception of filberts, the QUA data indicate that only one application is made to most crops. The National Agricultural Pesticide Impact Assessment Program (NAPIAP) report on Phenoxy Herbicides indicates that on average one 2,4-D application is made annually to turfgrass.

### Table 4. 2,4-D Application Rates for Non-Crop Areas

<table>
<thead>
<tr>
<th>Aquatic Areas, Forestry, Non-Crop Areas and Turf</th>
<th>Acid Equivalent lbs (ae) Application Rates Per Application/Per crop or Year</th>
<th>Master Label</th>
<th>Amount Used per QUA Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aquatic Areas - Floating Weeds</td>
<td>2.0/4.0 per acre</td>
<td></td>
<td>512,000 lbs</td>
</tr>
<tr>
<td>Aquatic Areas - Submerged Weeds</td>
<td>10.8 per acre foot</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tree and Brush Control - Tree Injection</td>
<td>1 to 2 ml per inch of trunk diameter</td>
<td>136,000 lbs</td>
<td></td>
</tr>
<tr>
<td>Forestry - Weed and Brush Control</td>
<td>4.0/4.0 per acre</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forestry - Conifer Release</td>
<td>4.0/4.0 per acre</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irrigation Ditch Banks</td>
<td>2.0/4.0 per acre</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rights of Way Areas</td>
<td>2.0/4.0 per acre</td>
<td>2.1 million lbs</td>
<td></td>
</tr>
<tr>
<td>Rangeland, Pastures</td>
<td>2.0/4.0 per acre</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turf - Grass Grown for Seed or Sod</td>
<td>2.0/4.0 per acre</td>
<td></td>
<td>351,000 lbs</td>
</tr>
</tbody>
</table>
Aquatic Areas, Forestry, Non-Crop Areas and Turf

Acid Equivalent lbs (ae) Application Rates Per Application/Per crop or Year

<table>
<thead>
<tr>
<th>Master Label Amount Used per QUA Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turf - Ornamental 2.0/4.0 per acre *</td>
</tr>
<tr>
<td>11.6 million lbs</td>
</tr>
</tbody>
</table>

A. According to the NAPIAP report about 98,000 acres were treated for floating weeds and about 5,000 acres were treated for submerged weeds by state agencies in 1993.

B. The registrants have agreed to reduce the ornamental turf rate from 2.0 to 1.5 lbs ae per acre. The new maximum yearly rate will be 3.0 lbs ae per acre.

Table 5. 2,4-D Application Rates for Agricultural Crops

<table>
<thead>
<tr>
<th>Agricultural Crops</th>
<th>Acid Equivalent lbs (ae) Application Rates per Acre Per Application/Per crop or Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Master Label</td>
</tr>
<tr>
<td>Asparagus</td>
<td>2.0/4.0</td>
</tr>
<tr>
<td>Blueberries - Low Bush Wiper Bar</td>
<td>0.0375 lb/GA</td>
</tr>
<tr>
<td>Blueberries - High Bush</td>
<td>1.4/2.8</td>
</tr>
<tr>
<td>Citrus (Growth Regulator)</td>
<td>0.1</td>
</tr>
<tr>
<td>Conifer Plantations</td>
<td>4.0/4.0</td>
</tr>
<tr>
<td>Corn (sweet)</td>
<td>0.5 to 1.0/1.5</td>
</tr>
<tr>
<td>Corn (field and pop)</td>
<td>0.5 to 1.5/3.0</td>
</tr>
<tr>
<td>Cranberries - granular applications</td>
<td>4.0/4.0</td>
</tr>
<tr>
<td>Cranberries - liquid applications</td>
<td>1.2/2.4</td>
</tr>
<tr>
<td>Fallowland and Crop Stubble</td>
<td>2.0/4.0</td>
</tr>
<tr>
<td>Filberts</td>
<td>1.0 lb per 100 Ga/4 Apps per year</td>
</tr>
<tr>
<td>Grapes</td>
<td>0.5 to 1.0/1.0</td>
</tr>
<tr>
<td>Grains</td>
<td>1.36/1.36</td>
</tr>
<tr>
<td>Orchard Floors (Pome and Stone Fruits, Tree Nuts)</td>
<td>2.0/4.0</td>
</tr>
<tr>
<td>Potatoes</td>
<td>0.07/0.14</td>
</tr>
<tr>
<td>Rice</td>
<td>1.0 or 1.5/1.5</td>
</tr>
<tr>
<td>Soybeans (Preplant burndown)</td>
<td>0.5 or 1.0/1.0</td>
</tr>
<tr>
<td>Strawberries (Except CA or FL)</td>
<td>1.5/1.5</td>
</tr>
<tr>
<td>Sugarcane</td>
<td>2.0/4.0</td>
</tr>
<tr>
<td>Cereal Grains (Wheat, Barley, Millet, Oats and Rye)</td>
<td>0.5 or 1.25/1.75</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Agricultural Crops</th>
<th>Acid Equivalent lbs (ae) Application Rates per Acre Per Application/Per crop or Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Master Label</td>
</tr>
<tr>
<td>Wild Rice (MN only)</td>
<td>0.25/0.25</td>
</tr>
</tbody>
</table>
III. Summary of 2,4-D Risk Assessment

The following is a summary of EPA’s human health and ecological risk findings and conclusions for 2,4-D, as presented fully in the documents “2,4-D. HED’s Revised Human Health Risk Assessment for the Reregistration Eligibility Decision (RED) Revised to Reflect Public Comments” dated May 12, 2005, and the “Environmental Fate and Effects Division’s Risk Assessment for the Reregistration Eligibility Decision for 2,4-D,” dated October 28, 2004.

The purpose of this section is to summarize the key features and findings of the risk assessment in order to help the reader better understand the risk management decisions reached by the Agency. While the risk assessments and related addenda are not included in this document, they are available in the public docket OPP-2004-0167, and on the Agency's website at http://www.epa.gov/pesticides/reregistration/status.htm

A. Human Health Risk Assessment

EPA released its preliminary risk assessments for 2,4-D for public comment on June 23, 2004, thereby starting Phase 3 of a six phase public participation process. In response to comments received during Phase 3, the human health risk assessment was updated. EPA issued the revised risk assessments for 2,4-D for a second public comment period on January 12, 2005 (Phase 5 of the public participation process). The risk assessments were revised again in response to Phase 5 public comments, and are available for review.

The 2,4-D degradates detected in the various laboratory environmental fate studies were 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. The OPP Metabolism Assessment Review Committee (MARC) determined that all residues other than 2,4-D are not of risk concern due to low occurrence under environmental conditions, comparatively low toxicity, or a combination thereof. Therefore, the Agency assessed risks from 2,4-D per se.

1. Toxicity of 2,4-D

With very few exceptions, the effects and relative toxicities of the salt and ester forms of 2,4-D are quite similar to those of the acid form. Thus, the acid form was selected as being representative of all members of the 2,4-D reregistration case (Case No. 0073). The member chemicals in the 2,4-D case exhibit low to slight acute toxicity with the exception of the acid and salt forms being severe eye irritants. The Agency has reviewed all toxicity studies submitted for 2,4-D and has determined that the toxicological database is sufficient for reregistration. Further details on the toxicity of 2,4-D can be found in the technical support documents cited in Appendix C.

a. Toxicity Profile

Major features of the toxicology profile are presented below. In acute studies, 2,4-D generally has low acute toxicity (Toxicity Category III or IV) via the oral, dermal and inhalation routes of
exposure. 2,4-D is not a skin irritant (Toxicity Category III or IV), nor a skin sensitizer. Although
the 2,4-D ester forms are not eye irritants (Toxicity Category III or IV), the acid and salt forms are
considered to be severe eye irritants (Toxicity Category I). The acute toxicity of all 2,4-D forms is
listed in Table 6.

Table 6. Acute Toxicity Data for 2,4-D acid, 2,4-D ester forms, and 2,4-D amine salts.

<table>
<thead>
<tr>
<th>Guideline No</th>
<th>Study Type</th>
<th>MRID Numbers</th>
<th>Results</th>
<th>Toxicity Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>870.1100</td>
<td>Acute Oral</td>
<td>2,4-D acid</td>
<td>00101605</td>
<td>rat LD₅₀ = 639 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DEA salt</td>
<td>41920901</td>
<td>rat LD₅₀ = 735 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DMA salt</td>
<td>00157512</td>
<td>rat LD₅₀ = 949 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPA salt</td>
<td>00252291</td>
<td>rat LD₅₀ = 1646 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPE ester</td>
<td>41709901</td>
<td>rat LD₅₀ = 1250 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TIPA salt</td>
<td>41413501</td>
<td>rat LD₅₀ = 1074 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BEE ester</td>
<td>40629801</td>
<td>rat LD₅₀ = 866 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EHE ester</td>
<td>41209001</td>
<td>rat LD₅₀ = 896 mg/kg</td>
</tr>
<tr>
<td>870.1200</td>
<td>Acute Dermal</td>
<td>2,4-D acid</td>
<td>00101596</td>
<td>rabbits LD₅₀ &gt; 2000 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DEA salt</td>
<td>41920911</td>
<td>rabbits LD₅₀ &gt; 2000 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DMA salt</td>
<td>00157513</td>
<td>rabbit LD₅₀ = 1829 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPA salt</td>
<td>00252291</td>
<td>rabbits LD₅₀ &gt; 2000 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPE ester</td>
<td>41709902</td>
<td>rabbits LD₅₀ &gt; 2000 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TIPA salt</td>
<td>41413502</td>
<td>rabbits LD₅₀ &gt; 2000 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BEE ester</td>
<td>40629802</td>
<td>rabbits LD₅₀ &gt; 2000 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EHE ester</td>
<td>41209002</td>
<td>rabbits LD₅₀ &gt; 2000 mg/kg</td>
</tr>
<tr>
<td>870.1300</td>
<td>Acute Inhalation</td>
<td>2,4-D acid</td>
<td>00161660</td>
<td>rat LC₅₀ &gt; 1.79 mg/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DEA salt</td>
<td>41986601</td>
<td>rat LC₅₀ &gt; 3.5 mg/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DMA salt</td>
<td>00157514</td>
<td>rat LC₅₀ &gt; 3.5 mg/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPA salt</td>
<td>40085501</td>
<td>rat LC₅₀ = 3.1 mg/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPE ester</td>
<td>40352701</td>
<td>rat LC₅₀ &gt; 4.97 mg/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TIPA salt</td>
<td>41957601</td>
<td>rat LC₅₀ = 0.78 mg/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BEE ester</td>
<td>40629803</td>
<td>rat LC₅₀ = 4.6 mg/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EHE ester</td>
<td>42605202</td>
<td>rat LC₅₀ &gt; 5.4 mg/L</td>
</tr>
<tr>
<td>870.2400</td>
<td>Primary Eye Irritation</td>
<td>2,4-D acid</td>
<td>41125302</td>
<td>severe eye irritant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DEA salt</td>
<td>41920902</td>
<td>severe eye irritant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DMA salt</td>
<td>00157515</td>
<td>severe eye irritant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPA salt</td>
<td>00252291</td>
<td>severe eye irritant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IP ester</td>
<td>40352702</td>
<td>not an eye irritant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TIPA salt</td>
<td>41413504</td>
<td>severe eye irritant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BEE ester</td>
<td>40629804</td>
<td>not an eye irritant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EHE ester</td>
<td>44725303</td>
<td>not an eye irritant</td>
</tr>
<tr>
<td>870.2500</td>
<td>Primary Skin Irritation</td>
<td>2,4-D acid</td>
<td>42232701</td>
<td>unacceptable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DEA salt</td>
<td>41920903</td>
<td>slight skin irritant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DMA salt</td>
<td>00157516</td>
<td>slight skin irritant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPA salt</td>
<td>00252291</td>
<td>slight skin irritant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPE ester</td>
<td>40352703</td>
<td>slight skin irritant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TIPA salt</td>
<td>41413505</td>
<td>slight skin irritant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BEE ester</td>
<td>40629805</td>
<td>very mild irritant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EHE ester</td>
<td>41413505</td>
<td>not a skin irritant</td>
</tr>
</tbody>
</table>
The mechanisms responsible for renal clearance of 2,4-D have been investigated in several species. 2,4-D is actively secreted by the proximal tubules. This mechanism of renal clearance is consistent with results seen with other phenoxy acids. It has been suggested that observed dose-dependent, non-linear, pharmacokinetics of 2,4-D are primarily due to the saturation of this renal secretory transport system. Due to a limited capacity to excrete organic acids, the dog is more sensitive to the effects of 2,4-D than the rat with respect to repeated dosing.

In laboratory animals, following subchronic, oral exposure at dose levels of 2,4-D above the threshold of saturation for renal clearance, the primary target organs are the eye, thyroid, kidney, adrenals, and ovaries/testes. Changes in these organs are also observed following exposure to the amine salts and esters of 2,4-D. Systemic toxicity was not observed following repeated dermal exposure to 2,4-D, EHE, and TIPA at or above the limit dose or following repeated dermal exposure to BEE and IPA at the highest dose tested. Liver toxicity was observed following repeated high-dose dermal exposure to DEA, and one death occurred following repeated high-dose dermal exposure to DMA.

There are no repeat-dose inhalation exposure data available on 2,4-D. The most reliable way to characterize inhalation toxicity and to quantify inhalation risk is through the use of inhalation toxicity studies. In general, chemicals tend to be more toxic by the inhalation route than by the oral route due to rapid absorption and distribution, bypassing of the liver’s metabolic protection (portal circulation), and potentially serious portal-of-entry effects, such as irritation, edema, cellular transformation, degeneration, and necrosis. An inhalation risk assessment that is based on oral data generally underestimates the inhalation risk because it cannot account for these factors. However, in the case of 2,4-D, based on the limited metabolism of 2,4-D via the oral route, the moiety to which the body would be exposed would be the same for both routes of exposure. With regard to portal-of-entry effects, these can only be assessed in an inhalation study. Therefore, a subchronic (28-day) inhalation study is required for 2,4-D.

Developmental toxicity, characterized mainly as an increased incidence of skeletal abnormalities in the rat, was observed following exposure to 2,4-D and its amine salts and esters at dose levels that were at or above the threshold of saturation of renal clearance. Similarly, developmental toxicity was observed in the rabbit only following exposure to 2,4-D (abortions) and DEA (increased number of litters with fetuses having 7th cervical ribs) at or above the threshold of
renal clearance.

Reproductive toxicity, characterized as an increase in gestation length, was observed following exposure to 2,4-D at a dose level above the threshold of saturation of renal clearance. A repeat 2-generation reproduction study (using the revised EPA protocol) is required to address concerns for endocrine disruption.

Neurotoxicity was demonstrated following exposure to 2,4-D at relatively high dose levels. Clinical signs of neurotoxicity (ataxia, decreased motor activity, myotonia, prostration, lateral recumbency, impaired/loss of the righting reflex, and skin cold to the touch) were observed in pregnant rabbits following exposure to 2,4-D and its amine salts and esters. Neuropathology (retinal degeneration) was observed following 2,4-D exposure in several studies in female rats. Incoordination and slight gait abnormalities (forepaw flexing or knuckling) were observed following acute dosing and increased forelimb grip strength was observed following chronic exposure to 2,4-D at dose levels that exceeded the threshold of saturation of renal clearance. A developmental neurotoxicity study in the rat is required for 2,4-D.

2,4-D is classified as a Group D chemical (not classifiable as to human carcinogenicity). Based on the overall pattern of responses observed in both *in vitro* and *in vivo* genotoxicity tests, 2,4-D was not mutagenic, although some cytogenic effects were observed. 2,4-D acid is currently considered to be representative of all nine member chemicals of the 2,4-D case.

The toxicological endpoints that were used to complete the risk assessments are summarized in Table 7. These endpoints were selected by the Agency from animal studies. With respect to dermal exposures, the Agency previously selected a dermal absorption factor of 5.8 percent based on the average absorbed dose value from a human dermal absorption study. That factor (5.8 percent) was used in previous versions of the human health risk assessment. Based on comments received during the Phase 5 comment period, the dermal absorption study and resulting absorption factor were reconsidered. In order to account for the variability observed in the dermal absorption study, the dermal absorption factor was changed from 5.8 percent to 10 percent. In their “Re-evaluation of the Lawn and Turf Uses of 2,4-D,” which was made available to the public for review, Health Canada also selected a factor of 10 percent based upon the weight of evidence from several published studies, taking into account the variability in the data and the limitations of the various studies. These studies include the Feldman and Maibach study discussed above and studies from Harris and Solomon 1992, Moody et. al. 1990, Wester et. al. 1996, and Pelletier et al. 1988.

### b. Safety and Database Uncertainty Factors

The Food Quality Protection Act (FQPA) directs the Agency to use an additional tenfold (10X) safety factor to protect for special sensitivity of infants and children to specific pesticide residues in food, drinking water, or residential exposures, or to compensate for an incomplete database. FQPA authorizes the Agency to modify the tenfold safety factor only if reliable data demonstrate that another factor would be appropriate.

*FQPA Special Safety Factor.* After evaluating hazard and exposure data for 2,4-D, EPA...
removed the default 10X FQPA special safety factor. The toxicity database for 2,4-D includes acceptable developmental and reproductive toxicity studies. Developmental toxicity studies were conducted in both rats and rabbits for most 2,4-D forms. There is qualitative evidence of susceptibility in the rat developmental toxicity study with 2,4-D acid and DEA salt where fetal effects (skeletal abnormalities) were observed at a dose level that produced less severe maternal toxicity (decreased body-weight gain and food consumption). There is no evidence of increased (quantitative or qualitative) susceptibility in the prenatal developmental toxicity study in rabbits or in the 2-generation reproduction study in rats on 2,4-D. Regarding the 2,4-D amine salt and ester forms, no evidence of increased susceptibility (quantitative or qualitative) was observed in the prenatal developmental toxicity study in rats and rabbits (except for 2,4-D DEA) dosed with any of the amine salts or esters of 2,4-D. There is evidence of increased susceptibility (qualitative) in the prenatal developmental study in rabbits for 2,4-D DEA salt.

After establishing developmental toxicity endpoints to be used in the risk assessment with traditional uncertainty factors (10x for interspecies variability and 10x for intraspecies variability), the Agency has no residual concerns for the effects seen in the developmental toxicity studies. Therefore, the 10X FQPA special safety factor was reduced to 1X.

**Database Uncertainty Factor.** On April 8, 2003, based on the weight of evidence presented, the Agency reaffirmed the previous conclusion that a developmental neurotoxicity (DNT) study in rats is required for 2,4-D because there is a concern for developmental neurotoxicity resulting from exposure to 2,4-D. There is evidence of neurotoxicity, including clinical signs such as ataxia and decreased motor activity in pregnant rabbits following dosing during gestation days 6-15 in studies on 2,4-D itself and 2,4-D amine salts and esters, and tremors in dogs that died on test following repeat exposure to 2,4-D. Incoordination and slight gait abnormalities (forepaw flexing or knuckling) were also observed following dosing in the acute neurotoxicity study with 2,4-D. There is also evidence of developmental toxicity, as discussed above in the FQPA Special Safety Factor section. In addition, the Agency determined that a repeat 2-generation reproduction study using the new protocol is required to address specific concerns for endocrine disruption (thyroid and immunotoxicity measures). Therefore, the Agency determined that a 10X database uncertainty factor (UF_DB) is needed to account for the lack of these studies.

c. Carcinogenicity

A Science Advisory Board/Scientific Advisory Panel Special Joint Committee reviewed available epidemiological and other data on 2,4-D in 1992 and 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.” 2,4-D has been classified as a Category D chemical (i.e., not classifiable as to human carcinogenicity), by the EPA/OPP Cancer Peer Review Committee in 1996. The Agency requested further histopathological examinations of rat brain tissues and mouse spleen tissues in question. These exams were submitted and reviewed and on March 16, 1999, the Agency notified the 2,4-D Task Force that the Agency would continue to classify 2,4-D as a Group D carcinogen.

The Agency has twice recently reviewed epidemiological studies linking cancer to 2,4-D. In the first review, completed January 14, 2004, EPA concluded there is no additional evidence that
would implicate 2,4-D as a cause of cancer (EPA, 2004). The second review of available epidemiological studies occurred in response to comments received during the Phase 3 Public Comment Period for the 2,4-D RED. This report, dated December 8, 2004 and authored by EPA Scientist Jerry Blondell, Ph.D., found that none of the more recent epidemiological studies definitively linked human cancer cases to 2,4-D.

2,4-D Diethanolamine (DEA). The Agency recently reviewed the available toxicology data on diethanolamine (DEA) and related compounds. The Agency concluded that it was not likely that exposure to the DEA salt of 2,4-D resulting from occupational use would pose a carcinogenic risk to humans. While liver tumors were observed in mice following dermal exposure to DEA, there was no evidence of carcinogenicity in rats following dermal exposure, and there was no evidence of a genotoxic or mutagenic concern. Although no formal assessment has been performed on the proposed mode of action (choline deficiency), this mode of action was considered plausible for the mouse hepatocellular tumors observed following dermal exposure to DEA, as were other confounding factors, including the use of ethanol as a vehicle for dose administration and the fact that humans are generally refractive to choline deficiency. Additionally, the low use pattern for 2,4-D DEA indicates that there is no potential long-term dermal exposure to the diethanolamine salt of 2,4-D in agricultural uses. The Agency also determined that, at this time, no carcinogenicity studies are required for the DEA salt of 2,4-D.

d. Cumulative Assessment

FQPA requires EPA to consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity" when considering whether to establish, modify, or revoke a tolerance. Potential cumulative effects of chemicals with a common mechanism of toxicity are considered because low-level exposures to multiple chemicals causing a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any one of these individual chemicals. 2,4-D is a member of the alkylphenoxy herbicide class of pesticides. A cumulative risk assessment has not been performed as part of this human health risk assessment because the Agency has not yet made a determination whether or not phenoxy herbicides have a common mechanism of toxicity. For information regarding EPA’s efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by the EPA’s Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA’s website at http://www.epa.gov/pesticides/cumulative/

e. Endocrine Effects

EPA is required under the Federal Food, Drug, and Cosmetic Act (FDCA), as amended by the Food Quality Protection Act (FQPA), to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate."
When the appropriate screening and/or testing protocols being considered under the Agency’s Endocrine Disruption Screening Program (EDSP) have been developed, 2,4-D may be subject to additional screening and/or testing to better characterize effects related to endocrine disruption.

Based on currently available toxicity data, which demonstrate effects on the thyroid and gonads following exposure to 2,4-D, there is concern regarding its endocrine disruption potential. There have been no studies on 2,4-D that specifically assess its endocrine disruption potential. The Agency has determined that a repeat 2-generation reproduction study using the most recent protocol is required to address both the concern for thyroid effects (comparative assessment between the young and adult animals) and immunotoxicity, as well as a more thorough assessment of the gonads and reproductive/developmental endpoints.

f. Toxicological Endpoints for Risk Assessment

The toxicological endpoints used in the human health risk assessment for 2,4-D are listed in Table 7. The safety factors used to account for interspecies extrapolation, intraspecies variability, special susceptibility of infants and children, and database uncertainties are also described in Table 7 below. This table also describes any absorption factors used to extrapolate from one route of exposure to another (e.g., oral to dermal).

<table>
<thead>
<tr>
<th>Exposure Scenario</th>
<th>Dose Used in Risk Assessment, UF</th>
<th>Special FQPA SF and Level of Concern for Risk Assessment</th>
<th>Study and Toxicological Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dietary Exposures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Dietary (Females 13-49 years of age)</td>
<td>NOAEL = 25 mg/kg/day UF = 1000</td>
<td>FQPA SF = 1X aPAD = acute RfD(0.025) FQPA SF (1) = 0.025 mg/kg/day</td>
<td>Rat Developmental Toxicity Study, LOAEL = 75 mg/kg/day based on skeletal abnormalities</td>
</tr>
<tr>
<td></td>
<td>Acute RfD = 0.025 mg/kg/day</td>
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<tr>
<td></td>
<td>MRID 00130407, 00130408</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Dietary (General population including infants and children)</td>
<td>NOAEL = 67 mg/kg/day UF = 1000</td>
<td>FQPA SF = 1X aPAD = acute RfD (0.067) FQPA SF (1) = 0.067 mg/kg/day</td>
<td>Acute Neurotoxicity Study in Rats LOAEL = 227 mg/kg/day based on gait abnormalities</td>
</tr>
<tr>
<td></td>
<td>Acute RfD = 0.067 mg/kg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MRID 43115201</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Dietary (All populations)</td>
<td>NOAEL = 5 mg/kg/day UF = 1000</td>
<td>FQPA SF = 1X cPAD = chronic RfD (0.005) FQPA SF (1) = 0.005 mg/kg/day</td>
<td>Rat Chronic Toxicity Study LOAEL = 75 mg/kg/day based on decreased body-weight gain (females) and food consumption (females), alterations in hematology, and clinical chemistry parameters, decreased T4 (both sexes), glucose (females), cholesterol (both sexes), and triglycerides (females).</td>
</tr>
<tr>
<td></td>
<td>Chronic RfD = 0.005 mg/kg/day</td>
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<tr>
<td></td>
<td>MRID 43612001</td>
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<td></td>
</tr>
</tbody>
</table>

**Table 7. Toxicity Endpoints for Human Health Risk Assessment for 2,4-D**

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<table>
<thead>
<tr>
<th>Exposure Scenario</th>
<th>Dose Used in Risk Assessment, UF</th>
<th>Special FQPA SF and Level of Concern for Risk Assessment</th>
<th>Study and Toxicological Effects</th>
</tr>
</thead>
</table>
| Short-Term Incidental Oral (1-30 days) | NOAEL = 25 mg/kg/day | **Residential** LOC for MOE = 1000  
**Occupational** = NA | Rat developmental toxicity study  
LOAEL = 75 mg/kg/day based on decreased maternal body-weight gain |
| Intermediate-Term Incidental Oral (1-6 months) | NOAEL = 15 mg/kg/day | **Residential** LOC for MOE = 1000  
**Occupational** = NA | Rat Subchronic Oral Toxicity  
LOAEL = 100 mg/kg/day based on decreased body weight/body-weight gain, alterations in some hematology, and clinical chemistry parameters, and cataract formation. |
| Short-Term Dermal* | Oral study NOAEL = 25 mg/kg/day | **Residential** LOC for MOE = 1000  
**Occupational** LOC for MOE = 100 | Rat Developmental Toxicity Study  
LOAEL = 75 mg/kg/day based on decreased maternal body-weight gain and skeletal abnormalities |
| Intermediate-Term Dermal* | Oral study NOAEL = 15 mg/kg/day | | Rat Subchronic Oral Toxicity (same as for intermediate-term incidental oral) |
| Long-Term Dermal* | Oral study NOAEL = 5 mg/kg/day | | Rat Chronic Toxicity Study (same as for chronic dietary) |
| Short-Term Inhalation* | Oral study NOAEL = 25 mg/kg/day | | Rat Developmental Toxicity Study (same as for short-term dermal) |
| Intermediate-Term Inhalation* | Oral study NOAEL = 15 mg/kg/day | | Rat Subchronic Oral Toxicity (same as intermediate-term incidental oral) |
| Long-Term Inhalation* | Oral study NOAEL = 5 mg/kg/day | | Rat Chronic Toxicity Study (same as for chronic dietary) |

**Cancer Classification:** Group D [not classifiable as to human carcinogenicity]

The dermal absorption factor is 10 percent and the inhalation absorption factor is 100 percent.

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic), RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

**Dermal Absorption.** A dermal absorption study utilizing human volunteers is available.  
Excretion following dermal application was 5.8 ± 2.4 percent (mean ± S.D.) of the administered dose and after intravenous administration was 100 ± 2.5 percent. The Agency previously selected a dermal
Absorption factor of 5.8 percent based on the human dermal absorption study. This factor was used in previous versions of this risk assessment. Based on comments received during the Phase 5 comment period, this dermal absorption study and factor were reconsidered. In order to account for the variability observed in the dermal absorption study, the dermal absorption factor was changed from 5.8 percent to 10 percent. In their “Re-evaluation of the Lawn and Turf Uses of 2,4-D,” which was made available to the public, Health Canada also selected a factor of 10 percent based upon the weight of evidence from several published studies, taking into account the variability in the data and the limitations of the various studies. These studies include the Feldman and Maibach study discussed above and studies from Harris and Solomon 1992, Moody et. al. 1990, Wester et. al. 1996, and Pelletier et al. 1988.

2. Dietary Exposure and Risk from Food

a. Exposure Assumptions

Acute and chronic dietary exposure and risk analyses for 2,4-D were conducted using the Lifeline™ Model Version 2.0 and Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 1.33). DEEM incorporates consumption data from USDA’s Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. Lifeline™ uses food consumption data from the United States Department of Agriculture’s (USDA’s) Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. Lifeline™ models the individual’s dietary exposures over a season by selecting a new CSFII diary each day from a set of similar individuals based on age and season attributes. Lifeline™ uses recipe files contained within the program to relate raw agricultural commodities (RACs) to foods “as-eaten.” Lifeline™ converts the RAC residues into food residues by randomly selecting a RAC residue value from the “user defined” residue distribution (created from the residue, percent crop treated, and processing factors data), and calculating a net residue for that food based on the ingredients’ mass contribution to that food item.

Lifeline™ models the individual’s dietary exposures over a season by selecting a new CSFII diary each day from a set of similar individuals based on age and season attributes. Lifeline™ groups CSFII diaries based on the respondent’s age and the season during which the food diary was recorded. Based on analysis of the 1994-96, and 1998 CSFII consumption data, which took into account dietary patterns and survey respondents, the Agency concluded that it is most appropriate to report risk for the following population subgroups: the general U.S. population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youths 13-19, adults 20-49, females 13-49, and adults 50+ years old. The most highly exposed population subgroup for 2,4-D using both DEEM and Lifeline was children 1-2 years of age.

The acute dietary assessment was only slightly refined as the following assumptions were made: tolerance-level exposure values for most commodities, the highest field trial residue value for citrus commodities, and 100% crop treated (%CT). Note that half of the average level of detection (LOD) from the United States Department of Agriculture (USDA) Pesticide Data Program (PDP) monitoring data was used as the milk residue value because no milk sample contained detectable 2,4-D residues over several years of PDP sampling.
The chronic dietary assessment was moderately refined, making use of the following assumptions: tolerance-level exposure values for most commodities; averages of field trial data and processing study factors for small grains, citrus, and sugarcane sugar and molasses; %CT information for all commodities; and the MCL (70 ppb) as well as the highest observed groundwater monitoring concentration (15 ppb) for drinking water in a forward calculation. As in the case of the acute assessment, half of the average LOD from PDP monitoring data was used for milk.

b. Population Adjusted Dose

A population adjusted dose, or PAD, is the reference dose (RfD) adjusted for the FQPA safety factor. A risk estimate that is less than 100% of the acute PAD (aPAD), the dose at which an individual could be exposed over the course of a single day and no adverse health effects would be expected, does not exceed EPA’s level of concern. Likewise, a risk estimate that is less than 100% of the chronic PAD (cPAD), the dose at which an individual could be exposed over the course of a lifetime and no adverse health effects would be expected, does not exceed EPA’s level of concern.

In the case of 2,4-D, the FQPA SF has been removed (equivalent to a factor of 1x), so the acute or chronic RfD is identical to the respective aPAD or cPAD. In addition, an uncertainty factor is determined for each chemical. In the acute and chronic dietary risk assessments for 2,4-D, the total uncertainty factor (UF) is 1000x; 10x for interspecies variability, 10x for intraspecies variability, and 10x for database uncertainty.

c. Food Risk Estimates

**Acute:** Risk to the general U.S. population was 18% and 17% of the aPAD using both DEEM and Lifeline, respectively. The most highly exposed population subgroup using both DEEM and Lifeline was children 1-2 years of age; risks were 33% and 32% of the aPAD, respectively. Risk to females 13-49 years of age was 31% of the aPAD using DEEM and 42% of the aPAD using Lifeline; these higher calculated risks for women of child-bearing age are due to the 2.7x lower toxicological point of departure for developmental effects applicable to Females 13-49 years of age. These acute dietary (food) risks are all less than the Agency’s level of concern (100% of the aPAD).

**Chronic:** Risk to the general U.S. population was 4.1% and 3.8% of the cPAD, using DEEM and Lifeline, respectively. Risk to children 1-2 years of age, the most highly exposed population subgroup, was 8.5% of the cPAD using DEEM and Lifeline.

3. Dietary Exposure and Risk from Drinking Water

Drinking water exposure to pesticides can occur through surface and ground water contamination. EPA considers acute (one day) and chronic (lifetime) drinking water risks and uses either modeling or monitoring data, if available and of sufficient quality, to estimate those exposures. In assessing drinking water risks, EPA compares model results to concentrations that would be acceptable in drinking water from a human health perspective (e.g., DWLOCs). If the estimated drinking water concentrations (EDWCs) in water are less than the DWLOCs, EPA does not have
concern from consuming drinking water. If the EDWCs are greater than DWLOCs, EPA will conduct further analysis to characterize the potential dietary risk from drinking water. Risks from exposure to 2,4-D in drinking water are further discussed in the section III.A.5.

2,4-D is an herbicide used in a wide variety of environments. As the major route of degradation is aerobic microbial metabolism, 2,4-D is non-persistent ($t_{1/2}=6.2$ days) in terrestrial (aerobic) environments, moderately persistent ($t_{1/2}=45$ days) in aerobic aquatic environments, and highly persistent ($t_{1/2}=231$ days) in anaerobic terrestrial and aquatic environments. Because 2,4-D will be anionic ($X$-$COO^-$ $H^+$) under most environmental conditions, it is expected to be mobile ($K_{oc}=61.7$) in soil and aquatic environments.

The 2,4-D degradates detected in the various laboratory environmental fate studies were 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. The Agency has determined that residues other than 2,4-D are of no risk concern due to low occurrence under environmental conditions, comparatively low toxicity, or a combination thereof.

Estimated Environmental Concentrations (EEC) were derived through an evaluation of monitoring data and modeling. A number of different scenarios were assessed and EECs provided for each. Scenarios evaluated included the direct application of 2,4-D to water bodies for aquatic weed control, a rice use scenario, and terrestrial uses including food and nonfood uses.

a. Surface Water

Modeling: The Tier II screening models, Pesticide Root Zone Model and Exposure Analysis Modeling System (PRZM-EXAMS), with the Index Reservoir and Percent Crop Area adjustment (IR-PCA PRZM/EXAMS) were used to estimate 2,4-D residues in surface water used for drinking water.

The Index Reservoir represents a watershed that is more vulnerable than most watersheds used as drinking water sources. It was developed from a watershed in western Illinois that has been used for drinking water purposes. The Index Reservoir is used as a standard watershed that, in combination with local soils types, weather conditions, and cropping practices, represents a vulnerable watershed that could support a drinking water supply.

For terrestrial uses of 2,4-D, EECs were calculated from aquatic exposure modeling using PRZM/EXAMS with the Index Reservoir and a percent crop area treated (PCA) adjustment (Tier II). Fifteen scenarios were chosen for aquatic exposure modeling, including sugarcane in Florida; turf in Florida and Pennsylvania; spring wheat in North Dakota; winter wheat in Oregon; corn in Illinois and California; sorghum in Kansas and Texas; soybean in Mississippi; pasture in North Carolina; apples in North Carolina, Oregon, and Pennsylvania; and filberts in Oregon. Although this only represents a portion of the crops for which 2,4-D has a labeled use, it does represent crops with higher application rates and crops which have a large percentage of their total acreage treated with 2,4-D.

Surface water concentrations were modeled using PRZM version 3.12 and EXAMS version...
2.98.04. Ground water concentrations were modeled using SCIGROW version 2.2. The 15 crop scenarios listed above were modeled using PRZM/EXAMS. Based on the maximum modeled values, (more specifically, the North Carolina apple model scenario), the model-estimated, surface-water-derived drinking water concentrations for the use of 2,4-D are:

- **118 ug/L** for the 1 in 10 year annual peak concentration (acute)
- **64 ug/L** for the 1 in 10 year 90-day average
- **23 ug/L** for the 1 in 10 year annual mean concentration (chronic)

**Monitoring**: Monitoring data considered in the assessment were the United States Geological Survey’s (USGS) National Water Quality Assessment Program (NAWQA) groundwater and surface water database, USGS/EPA reservoir monitoring database, National Drinking Water Contaminant Occurrence Database (NCOD), and US EPA’s Storage and Retrieval environmental data system (STORET). Review of these databases was conducted to provide peak and median concentrations. Additionally, the quality of data was evaluated for targeting pesticide use areas, detection limits, and analytical recoveries. The monitoring data indicate that 2,4-D is detected in groundwater and surface water. Also, 2,4-D is detected in finished drinking water. Maximum concentrations of 2,4-D in surface source water and ambient groundwater are 58 ug/L and 14.8 ug/L, respectively. The highest median 2,4-D concentration of 1.18 ug/L was derived from finished water samples in the NCOD database. The highest time weighted annual mean (TWAM) concentration was 1.45 ug/L from the NAWQA database containing nontargeted data reflecting pesticide concentrations in flowing water as opposed to more stationary bodies of water such as ponds, lakes, and reservoirs.

The PRZM/EXAMS surface water-derived drinking water model estimate that would be appropriate for acute exposure (118 ug/L) is approximately two times the peak concentration of 58 ug/L detected in the surface water monitoring data evaluated as part of this assessment. However, since 70 ug/l is the current maximum contaminant level (MCL) established under the Safe Drinking Water Act, and is the label-prescribed 2,4-D concentration in treated water to be used for drinking water, this MCL limit is a reasonable and practical value to be used for the surface water concentration of 2,4-D for acute risk assessment purposes.

Note that the peak surface water concentration of 58 ug/L is consistent with the 70-ppb label instruction (also the MCL). Although the surface water monitoring was not specifically targeted to known 2,4-D- treated sites or even areas of high 2,4-D usage, this agreement suggests that, from a practical standpoint, the MCL is a reasonable regulatory limit.

Although of high quality, the available monitoring data is not targeted to 2,4-D use. However, the data provide context to model results and indicate that there is little evidence that concentrations are likely to be found exceeding these levels.

**b. Ground Water**

**Monitoring**: The maximum 2,4-D concentration detected in ground water is 14.89 ug/L based on the USGS NAWQA program and 8 ug/L based on the NCOD monitoring data. The next highest
The concentration detected in the NAWQA groundwater data is 4.54 ug/L which is consistent with the NCOD-reported concentration. Therefore, the Agency is using 15 ug/L based on monitoring for the groundwater EDWC.

c. EDWCs Selected for Risk Assessment

The EDWCs for 2,4-D in surface and ground water are listed in Table 8 below. The EDWCs were selected from both modeling calculations and monitoring data.

**Table 8. Surface and Ground Water Estimated Drinking Water Concentrations (EDWCs)**

<table>
<thead>
<tr>
<th>Drinking Water Source</th>
<th>Duration</th>
<th>EDWC (ppb) (ppb = ug/liter)</th>
<th>Data Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surface Water</strong></td>
<td>Acute (Peak)</td>
<td>70 ug/liter (aquatic applications)</td>
<td>Maximum Contaminant Level (MCL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>118 ug/liter (terrestrial applications)</td>
<td>Modeling - PRZM-EXAMS (NC apple scenario)</td>
</tr>
<tr>
<td></td>
<td>Short and Intermediate</td>
<td>70 ug/liter (aquatic applications)</td>
<td>Maximum Contaminant Level (MCL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>64 ug/liter (terrestrial applications)</td>
<td>Modeling - PRZM-EXAMS (NC apple 1 in 10 year annual average)</td>
</tr>
<tr>
<td></td>
<td>Chronic</td>
<td>11 ug/liter (aquatic application)</td>
<td>Modeling - Dissipation modeling of aquatic application</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23 ug/liter (terrestrial application)</td>
<td>Modeling - PRZM-EXAMS worst case terrestrial use (NC apple scenario)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.5 ug/liter (terrestrial application)</td>
<td>Monitoring - Maximum time weighted annual mean from NAWQA database</td>
</tr>
<tr>
<td><strong>Ground Water</strong></td>
<td>All Duration</td>
<td>15 ug/liter</td>
<td>Monitoring - Highest monitored value from NAWQA database</td>
</tr>
</tbody>
</table>

4. Residential and Other Non-occupational Exposure

Residential exposure assessment considers all potential pesticide exposure, other than exposure due to residues in foods or in drinking water. Exposure may occur during and after application on lawns and turf, golf courses, parks, cemeteries, and other grass areas. Exposure may also occur to recreational swimmers while swimming in waters treated with 2,4-D for aquatic weeds. Each route
of exposure (oral, dermal, inhalation) is assessed, where appropriate, and risk is expressed as a Margin of Exposure (MOE), which is the ratio of estimated exposure to an appropriate NOAEL. 2,4-D products are marketed for homeowner use on residential lawns and turf. 2,4-D containing products are also marketed for use by professional applicators on residential turf, golf courses, and on other turf such as recreational or commercial areas. Based on these uses, 2,4-D has been assessed for the residential mixing/loading/applicator (or “handler”) exposure for applications by homeowners to home lawns. For post-application exposure, 2,4-D has been assessed for toddlers playing on treated turf, adults performing yardwork on treated turf, adults playing golf on treated turf, and children and adults swimming in bodies of water treated with 2,4-D for aquatic weed control.

a. Toxicity

The toxicological endpoints, and associated uncertainty factors used for assessing the non-dietary risks for 2,4-D are listed in Table 9.

In a dermal absorption study utilizing human volunteers, excretion following dermal application was 5.8 ± 2.4% and after i.v. administration was 100 ± 2.5%. In previous risk assessments, the Agency selected a dermal absorption factor of 5.8 percent based on the human dermal absorption study. Based on comments received during the Phase 5 comment period, this dermal absorption study and factor were reconsidered. In order to account for the variability observed in the dermal absorption study, the dermal absorption factor was changed from 5.8 percent to 10 percent. In their “Re-evaluation of the Lawn and Turf Uses of 2,4-D,” which was made available to the public, Health Canada also selected a factor of 10 percent based upon the weight of evidence from several published studies, taking into account the variability in the data and the limitations of the various studies. These studies include the Feldman and Maibach study discussed above and studies from Harris and Solomon 1992, Moody et. al. 1990, Wester et. al. 1996, and Pelletier et al. 1988.

Chronic endpoints were not used in the residential assessment because chronic occupational and residential exposures to 2,4-D are not expected to occur. Per the 2,4-D Master Label, the maximum label frequency for application of 2,4-D to turf is two times per year. 2,4-D also rapidly dissipates from foliage and is readily excreted from the human body.

A MOE greater than or equal to 1000 is considered adequately protective for the residential exposure assessment. The MOE of 1000 includes 10x for interspecies extrapolation, 10x for intraspecies variation, and 10x for a database uncertainty factor. Table 9 lists the toxicity endpoints selected for assessing residential risk for 2,4-D.

### Table 9. Toxicity Endpoints Selected for Assessing Residential Risk for 2,4-D

<table>
<thead>
<tr>
<th>Exposure Scenario</th>
<th>Dose Used in Risk Assessment, UF</th>
<th>Level of Concern for Risk Assessment</th>
<th>Study and Toxicological Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupational and Residential Non-Dietary Exposures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure Scenario</td>
<td>Dose Used in Risk Assessment, UF</td>
<td>Level of Concern for Risk Assessment</td>
<td>Study and Toxicological Effects</td>
</tr>
<tr>
<td>-------------------</td>
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<td>---------------------------------</td>
</tr>
<tr>
<td>Short-Term Incidental Oral (1-30 days) MRID 00130407, 00130408</td>
<td>NOAEL = 25 mg/kg/day UF_{da} = 10</td>
<td>Residential LOC for MOE = 1000 Occupational = NA</td>
<td>rat developmental toxicity study LOAEL = 75 mg/kg/day based on decreased maternal body-weight gain</td>
</tr>
<tr>
<td>Intermediate-Term Incidental Oral (1-6 months) MRID 41991501</td>
<td>NOAEL = 15 mg/kg/day</td>
<td>Residential LOC for MOE = 1000 Occupational = NA</td>
<td>subchronic oral toxicity - rat LOAEL = 100 mg/kg/day based on decreased body weight/body-weight gain, alterations in some hematology, and clinical chemistry parameters, and cataract formation.</td>
</tr>
<tr>
<td>Short-Term Dermal* MRID 00130407, 00130408</td>
<td>Oral study NOAEL = 25 mg/kg/day</td>
<td>Residential LOC for MOE = 1000 Occupational LOC for MOE = 100</td>
<td>rat developmental toxicity study LOAEL = 75 mg/kg/day based on decreased maternal body-weight gain and skeletal abnormalities</td>
</tr>
<tr>
<td>Intermediate-Term Dermal* MRID 00130407, 00130408</td>
<td>Oral study NOAEL = 15 mg/kg/day</td>
<td>subchronic oral toxicity - rat (same as for incidental oral)</td>
<td></td>
</tr>
<tr>
<td>Long-Term Dermal* MRID 43612001</td>
<td>Oral study NOAEL = 5 mg/kg/day</td>
<td>rat chronic toxicity study (same as for chronic dietary)</td>
<td></td>
</tr>
<tr>
<td>Short-Term Inhalation* MRID 00130407, 00130408</td>
<td>Oral study NOAEL = 25 mg/kg/day</td>
<td>rat developmental toxicity study (same as for short-term dermal)</td>
<td></td>
</tr>
<tr>
<td>Intermediate-Term Inhalation* MRID 00130407, 00130408</td>
<td>Oral study NOAEL = 15 mg/kg/day</td>
<td>subchronic oral toxicity - rat (same as incidental oral)</td>
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<tr>
<td>Long-Term Inhalation* MRID 43612001</td>
<td>Oral study NOAEL = 5 mg/kg/day</td>
<td>rat chronic toxicity study (same as for chronic dietary)</td>
<td></td>
</tr>
</tbody>
</table>

Cancer Classification: Group D [not classifiable as to human carcinogenicity]

*The dermal absorption factor is 10 percent and the inhalation absorption factor is 100 percent.

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic), RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

b. Residential Handler

1) Exposure Scenarios, Data, and Assumptions

Homeowners (or others) may be exposed to 2,4-D while treating their lawns. All homeowner-use products are available in liquid or granular form. 2,4-D is applied using hose-end sprayers, pump sprayers, ready-to-use sprayers, broadcast spreaders, bellygrinders, and hand application, either before or after seasonal weed emergence, at a rate up to 1.5 lbs ae/A. A number of assumptions, or
estimates, such as adult body weight and area treated per application, are made by the Agency for residential risk assessment. Also, note that residential handlers are addressed somewhat differently than occupational handlers in that homeowners are assumed to complete all elements of an application (mix/load/apply) without use of personal protective equipment (assessments are based on an assumption that individuals will be wearing short pants and short-sleeved shirts).

The quantitative exposure/risk assessment developed for residential handlers is based on these scenarios:

1) Hand application of granules
2) Belly grinder application
3) Load/apply granules with a broadcast spreader
4) Mix/load/apply with a hose-end sprayer (mix your own)
5) Mix/load/apply with a hose-end sprayer (ready-to-use)
6) Mix/load/apply with hand held pump sprayer
7) Mix/load/apply with ready-to-use sprayer

Exposure estimates for these scenarios are taken from the Pesticide Handlers Exposure Database (PHED, Version 1.1 August 1998) which is used to assess handler exposures when chemical-specific monitoring data are not available. In addition to PHED data, the residential risk assessment relies on data from the Outdoor Residential Exposure Task Force (ORETF) and proprietary studies. Three turf transferable residue studies submitted by the Broadleaf Turf Herbicide Turf Transferable Residue (TTR) Task Force. These studies measured the dissipation of several phenoxy herbicides, including 2,4-D, using the ORETF roller technique. Scenarios #1 through #5 use ORETF or PHED data; scenarios #6 and #7 use exposure data from the Carbaryl Mixer/Loader/Applicator Exposure Study (EPA MRID 444598-01).

The results of a biomonitoring study (Harris and Solomon 1992) were also used to calculate dermal MOEs for post application exposure on turf. The study was conducted with adult volunteers who were exposed to 2,4-D while performing controlled activities for one hour on turf treated with 2,4-D. The controlled activities were conducted at 1 hour after treatment (HAT) and at 24 HAT. Ten volunteers participated in the study. Five volunteers wore long pants, a tee shirt, socks and closed footwear. The other five wore shorts and a tee shirt and were barefoot. The volunteers walked on the turf for a period of 5 minutes and then sat or lay on the area for 5 minutes and then continued in this fashion for 50 more minutes. Each volunteer collected all urine for the next 96 hours immediately following the exposure. The MOEs for the DAT 1 volunteers who wore shorts and no shoes ranged from 1000 to 26000 with the lowest MOE corresponding to a volunteer who removed his shirt during the exposure period. The MOEs for the remaining volunteers ranged from 17000 to 27000.

For more information, see “2,4-D. HED’s Revised Human Health Risk Assessment for the Reregistration Eligibility Decision (RED) Revised to Reflect Public Comments. PC Code 030001; DP Barcode D316597” dated May 12, 2005, and the “2,4-D: 3rd Revised Occupational and Residential Exposure and Risk Assessment and Response to Public Comments for the Registration Eligibility Decision (RED) Document” dated May 4, 2005.
Assumptions Regarding Residential Handlers

- Clothing would consist of a short-sleeved shirt, short pants and no gloves.
- Broadcast spreaders and hose end sprayers would be used for broadcast treatments and the other application methods would be used for spot treatments only.
- An area of 0.023 acre (1000 square feet) would be treated per application during spot treatments and an area of 0.5 acre would be treated during broadcast applications.
- The application rate is 1.5 lb ae/acre representing the most recent revision to the master label.
- Average body weight of an adult handler is 70 kg.
- The duration of exposure is expected to be short-term (1-30 days) for residential handlers of 2,4-D. Intermediate- and long-term exposures of residential applicators are not anticipated based on 2,4-D’s residential use pattern.

2) Residential Handler Risk Estimates

Based on toxicological criteria and potential for exposure, the Agency has conducted both a dermal and an inhalation exposure assessment. Risk assessment for short-term inhalation exposure is based on a rat developmental study. An assumption is made that 100% of the estimated inhalation dose will be absorbed. A dermal absorption factor of 10 percent was selected for converting dermal exposures to oral equivalent doses. An MOE greater than or equal to 1000 (10x for interspecies extrapolation, 10x for intraspecies variation, and 10x for database uncertainty) is considered adequately protective for this assessment. Since all residential handler MOEs are greater than 1000, risk to residential handlers is not of concern. The 2,4-D risk estimates are presented in Table 10 below.

In preliminary versions of the risk assessment, when considered alone, acute and short-term residential risks posed by the use of 2,4-D were not of concern to the Agency; however, when considered as part of an aggregate exposure with food and drinking water, exposures did exceed the Agency’s level of concern. As a result, 2,4-D registrants agreed to reduce the maximum application rate to turf and residential lawns from 2.0 lbs ae/A to 1.5 lbs ae/A. The revised application rate (1.5 lbs ae/A) was used in the current risk assessment.

Table 10. 2,4-D Short Term Risk Estimates for Residential Handlers

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Application Rate (lbs ae/acre)</th>
<th>Treated Area (acres/day)</th>
<th>MOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hand Application of Granules</td>
<td>1.5</td>
<td>0.023</td>
<td>3,700</td>
</tr>
<tr>
<td>2. Belly Grinder Application</td>
<td>1.5</td>
<td>0.023</td>
<td>3,900</td>
</tr>
<tr>
<td>3. Load/Apply Granules with a Broadcast Spreader</td>
<td>1.5</td>
<td>0.5</td>
<td>29,000</td>
</tr>
<tr>
<td>4. Mix/Load/Apply with a Hose-end Sprayer (Mix your own)</td>
<td>1.5</td>
<td>0.5</td>
<td>1,800</td>
</tr>
<tr>
<td>5. Mix/Load/Apply with a Hose-end Sprayer (Ready to Use)</td>
<td>1.5</td>
<td>0.5</td>
<td>7,400</td>
</tr>
<tr>
<td>6. Mix/Load/Apply with Hand Held Pump Sprayer</td>
<td>1.5</td>
<td>0.023</td>
<td>11,000</td>
</tr>
</tbody>
</table>
For more information, see Appendix F of “2,4-D: 3rd Revised Occupational and Residential Exposure and Risk Assessment and Response to Public Comments for the Reregistration Eligibility Decision (RED) Document (PC Code 030001, DP Barcode D316596)” dated May 4, 2005.

c. Residential Postapplication Risk

1) Exposure Scenarios, Data, and Assumptions

2,4-D uses in the residential setting include applications to home lawns. The following scenarios were assessed for residential post application risks:

1) Toddlers playing on treated turf
2) Adults performing yardwork on treated turf
3) Adults playing golf on treated turf

These scenarios chosen for risk assessment represent what the Agency considers the likely upper-end estimates of possible exposure. An MOE of 1000 (or more) is considered protective for this assessment.

Assumptions Regarding Residential Postapplication Risk

- An assumed initial turf transferable residue (TTR) value of 5.0% of the application rate is used for assessing hand to mouth exposures.
- An assumed initial TTR value of 20% of the application is used for assessing object to mouth exposures.
- Soil residues are contained in the top centimeter and soil density (i.e., the ratio of the mass of dry solids to the bulk volume of the soil occupied by those dry solids) is 0.67 gram/mL.
- Three year old toddlers are expected to weigh 15 kg.
- Hand-to-mouth exposures are based on a frequency of 20 events/hour and a surface area per event of 20 cm² representing the palmar surfaces of three fingers.
- Saliva extraction efficiency is 50 percent. Every time the hand goes in the mouth approximately half of the residues on the hand are removed.
- Adults are assessed using a transfer coefficient of 14,500 cm²/hour.
- Toddlers are assessed using a transfer coefficient of 5,200 cm²/hour.
- Golfers are assessed using a transfer coefficient of 500 cm²/hour.
- An exposure duration of 2 hours per day is assumed for toddlers playing on turf or adults performing heavy yardwork.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Application Rate (lbs ae/acre)</th>
<th>Treated Area (acres/day)</th>
<th>MOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Mix/Load/Apply with Ready to Use Sprayer</td>
<td>1.5</td>
<td>0.023</td>
<td>7,900</td>
</tr>
</tbody>
</table>

Note: 1000 square feet equals 0.023 acres
The following assumptions that are specific to 2,4-D are used for assessing residential post application exposures.

- The master label application rate of 1.5 lbs ae/acre was used.
- The exposure following the application of granular formulations was not assessed because there were no TTR data submitted for granular formulations. It was assumed this exposure would be less than or equal to the exposure from liquid formulations.

Other residential exposure standard operating procedures (SOPs) may be viewed at the following website: [http://www.epa.gov/oscpmont/sap/1997/september/sopindex.htm](http://www.epa.gov/oscpmont/sap/1997/september/sopindex.htm).

**Calculation Method for Postapplication Exposure for Toddlers on Treated Turf**

MOEs were calculated for acute toddler exposures using the maximum TTR value along with the acute dietary NOAEL of 67 mg/kg/day. This NOAEL was adapted to acute dermal exposures by using the dermal absorption factor of 10 percent to account for route to route extrapolation. The MOEs for toddler short term exposures were calculated using the seven day average TTR value because the short term NOAEL was based upon decreased body weight gain which occurred after several days of exposure. MOEs for acute and adult short term exposures were calculated using the maximum TTR value because the acute and short term NOAELs are the same and are based upon the developmental effects which could have occurred following one day of exposure.

The quantitative exposure/risk assessment for postapplication risk to children is based on these scenarios:

1) **Dermal activity from treated turf**: Postapplication exposure to children from the dermal exposure of pesticide residues from activity on treated turf.

2) **Hand-to-mouth activity from treated turf**: Postapplication exposure to children from the “incidental” ingestion of pesticide residues on treated turf from hand-to-mouth transfer (i.e., those residues that end up in the mouth from children touching turf and then putting their hands in their mouths).

3) **Object-to-mouth activity from treated turf**: Postapplication exposure to children from incidental ingestion of pesticide residues on treated turf from object-to-mouth transfer (i.e., those residues that end up in the mouth from a child mouthing a handful of treated turf).

4) **Soil ingestion activity**: Postapplication exposure to children from incidental ingestion of soil in a treated area.

For more information on formulas used for calculating occupational and residential exposures to 2,4-D, see Appendix A of “2,4-D: 3rd Revised Occupational and Residential Exposure and Risk Assessment and Response to Public Comments for the Reregistration Eligibility Decision (RED) Document” dated May 4, 2005.

**2) Postapplication Risk Estimates**
Risk assessment for children’s postapplication exposure is based on a NOAEL of 67 mg/kg/day from an oral study of acute neurotoxicity study in rats. A Margin of Exposure (MOE) of 1000 (10x for interspecies extrapolation, 10x for intraspecies variation, and 10x for database uncertainty) is considered adequately protective for this assessment. Table 11 below presents the MOEs for Post-Application Exposure in Children. Since all MOEs meet or exceed 1000, postapplication exposure to children is not of concern.

Table 11. Children Post-Application Exposure to Turf Treated with 2,4-D

<table>
<thead>
<tr>
<th>Application Scenario</th>
<th>Application Rate (lbs ae/acre)</th>
<th>Dermal MOE</th>
<th>Hand-to-Mouth MOE</th>
<th>Object to Mouth MOE</th>
<th>Soil Ingestion MOE</th>
<th>Total MOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Toddler Risks Using the Maximum TTR</strong> (North Carolina Trial 1 using 2,4-D DMA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAT 0</td>
<td>1.5</td>
<td>1,900</td>
<td>3000</td>
<td>12,000</td>
<td>&gt;100,000</td>
<td>1,100</td>
</tr>
<tr>
<td><strong>Short Term Toddlers Risks Using California TTR Data</strong> (DMA Mix, No Rain)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAT 0 to DAT 6</td>
<td>1.5</td>
<td>3,900</td>
<td>2,100</td>
<td>8,500</td>
<td>&gt;100,000</td>
<td>1,200</td>
</tr>
<tr>
<td><strong>Short Term Toddler Risks Using North Carolina TTR Data from Trial 1</strong> (DMA and DMA Mix, No Rain)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAT 0 to DAT 6</td>
<td>1.5</td>
<td>5,100</td>
<td>4,400</td>
<td>18,000</td>
<td>&gt;100,000</td>
<td>2,100</td>
</tr>
<tr>
<td><strong>Short Term Toddler Risks Using North Carolina TTR Data from Trial 2</strong> (DMA Mix, Some Rain)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAT 0 to DAT 6</td>
<td>1.5</td>
<td>12,000</td>
<td>7,000</td>
<td>28,000</td>
<td>&gt;100,000</td>
<td>3,900</td>
</tr>
</tbody>
</table>

The acute NOAEL is 67 mg/kg/day for neurotoxic effects observed in the acute neurotoxicity study. The short term NOAEL is 25 mg/kg/day for maternal effects observed in the developmental study.

Table 12 below lists the adult acute/short term MOEs for exposure to turf treated with 2,4-D. The acute/short term NOAEL is 25 mg/kg/day from the rat developmental toxicity study. The LOAEL was 75 mg/kg/day based on skeletal abnormalities from a developmental toxicity study in rats. All MOEs meet or exceed 1000, so postapplication exposure to adults is not of concern.

Table 12. Adult Acute/Short Term MOEs for Exposure to Turf Treated with 2,4-D

<table>
<thead>
<tr>
<th>Exposure Scenario</th>
<th>Application Rate (lbs ae/acre)</th>
<th>TTR (ug/cm²)</th>
<th>Acute/Short Term Dermal MOE¹ on Day 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy Yardwork</td>
<td>1.5</td>
<td>0.50</td>
<td>1000</td>
</tr>
<tr>
<td>Playing Golf</td>
<td></td>
<td></td>
<td>15000</td>
</tr>
</tbody>
</table>

¹. The acute/short term NOAEL is 25 mg/kg/day for developmental effects observed in the developmental study.

d. Recreational Swimmer Risk
1) Exposure Scenarios, Data, and Assumptions

The master label indicates that 2,4-D can be used for aquatic weed control of surface weeds such as water hyacinth and submersed weeds such as Eurasian milfoil. Surface weeds are controlled by foliar applications at a maximum rate of 4.0 lb ae/acre. Submersed weeds are controlled by subsurface injection of liquids to achieve a target concentration of 2 to 4 ppm in the water column surrounding the weeds. This requires 5.4 to 10.8 lb ae per acre foot of water depth (e.g., 5.4 lbs ae would be required to achieve 2 ppm in a one acre pond that has an average depth of 1 foot). Granular formulations of BEE (Aquakleen and Navigate) are also used to control submersed weeds. The granular formulations resist rapid decomposition in water and release the herbicide into the root zone.

Although many herbicide treatments are applied to aquatic areas where recreational swimming is not likely to occur, some of the subsurface treatments are made at recreational lakes. These treatments are made because the Eurasian milfoil interferes with recreation and other activities. This problem is particularly prevalent in the northern states such as Minnesota and Washington and in the New England region.

The following exposure scenarios are assessed for recreational swimmers:

1) Adult Recreational Swimmer
2) Child Recreational Swimmer

Assumptions Regarding Recreational Swimmer Risk

The following assumptions were used for the assessment of swimmer risks. Many of these assumptions were taken from the Residential SOPs and are also used in the SWIMODEL.

- The skin surface area of adults is assumed to be 21,000 cm² (Residential SOPs). This is the 95th percentile value for females (EPA Exposure Factors Handbook, 1997).
- The body weight for children is assumed to be 22 kg as cited in the Residential SOPs. This is a mean value for 6 year old children.
- The skin surface area for children is assumed to be 9,000 cm² as cited in the Residential SOPs. This is the 90th percentile value for male and female children.
- The assumed mean ingestion rate is 0.05 liters per hour for both adults and children as cited in the Residential SOP. This value may be greater for young children playing in water and accidentally ingesting a remarkable quantity of water (U.S. EPA SAP, 1999).
- The exposure time is assumed to be 3 hours per day. This is the 90th percentile value for time spent swimming in a freshwater pool (EPA Child Specific Exposure Factors Handbook, 2002).
- The body weight for female adult acute exposures is assumed to be 60 kg.
- The body weight for male adult acute exposures is assumed to be 70 kg.
- The body weight for adult short term exposure is assumed to be 60 kg because the endpoint is gender specific.
- Risks were not calculated for foliar treatments because the application rate of 2.0 lb ae/acre would result in water concentration of only 0.25 ppm in a three foot water column.
even if all of the spray were to run off the leaves into the water.

**Calculation Method for Recreational Swimmer Exposure**

The Agency used the Swimmer Exposure Assessment Model (SWIMODEL) to calculate exposures to swimmers in water treated with 2,4-D for aquatic weed control. The SWIMODEL estimates exposure for up to six exposure routes (i.e., oral ingestion, dermal absorption, inhalation, buccal/sublingual, nasal/orbital, and aural routes), or calculates exposure as a function of any one of the three major exposure routes (i.e., oral ingestion, dermal absorption, or inhalation). Other factors used in the SWIMODEL formulae for dermal and ingestion exposure which are described in Appendix A of “2,4-D: 3rd Revised Occupational and Residential Exposure and Risk Assessment and Response to Public Comments for the Reregistration Eligibility Decision (RED) Document” dated May 4, 2005.

The SWIMODEL formulas for the other dermal pathways (aural, buccal/sublingual and orbital/nasal) were not used in the 2,4-D human health risk assessment because these formulas are based upon recreational swimmers in swimming pools who swim with their heads partially immersed. It is anticipated that recreational swimmers in weed infested areas would be less likely to swim with their heads immersed than recreational swimmers in weed-free swimming pools. In addition, the formulas for the buccal/sublingual and orbital/nasal pathways contain a default absorption factor of 0.01 which is based upon the absorption of nitroglycerin. This factor would greatly overestimate the risk of 2,4-D exposure because 2,4-D is absorbed at a much lower rate.

Because the 2,4-D water concentrations can vary depending upon the application rate and site conditions the Maximum Swimming Water Concentration (MSWC) was calculated. The MSWC is the water concentration at which the combined dermal and ingestion MOE meets or exceeds the target MOE of 1000. The MSWCs were calculated for children’s acute exposures using the acute NOAEL of 67 mg/kg/day and the MSWCs for children’s short term exposures were calculated using the short term NOAEL of 25 mg/kg/day for maternal effects. The MSWCs for adult acute/short term exposures were calculated using a NOAEL of 25 mg/kg/day that is based upon developmental effects which could have occurred following one day of exposure.

**2) Recreational Swimmer Risk Estimates**

The MSWCs are summarized in Table 13 and the detailed calculations are included in Appendix H of the 3rd Revised Occupational and Residential Exposure Assessment for 2,4-D. The acute MSWCs range from 1.2 ppm for 2,4-D BEE to 9.8 ppm for 2,4-D acid while the short term MSWCs range from 0.9 ppm for 2,4-D BEE to 3.6 ppm for 2,4-D acid or amine. The MSWCs for 2,4-D BEE are lower because based on its chemical properties, 2,4-D BEE is expected to have a much higher dermal absorption value.
Table 13. Maximum Swimming Water Concentrations for 2,4-D Aquatic Applications

<table>
<thead>
<tr>
<th>Exposure Duration</th>
<th>NOAEL (mg/kg/day)</th>
<th>2,4-D Form</th>
<th>2,4-D MSWC* (ppm)</th>
<th>Dermal MOE</th>
<th>Ingestion MOE</th>
<th>Combined MOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute/Short Term</td>
<td>25</td>
<td>Acid or Amine</td>
<td>9.8</td>
<td>97000</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>BEE</td>
<td>1.2</td>
<td>1200</td>
<td>8300</td>
<td>1000</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>67</td>
<td>Acid or Amine</td>
<td>9.8</td>
<td>425000</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td>67</td>
<td>BEE</td>
<td>2.4</td>
<td>1300</td>
<td>4100</td>
<td>1000</td>
</tr>
<tr>
<td>Short Term</td>
<td>25</td>
<td>Acid or Amine</td>
<td>3.6</td>
<td>230000</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>BEE</td>
<td>0.90</td>
<td>1300</td>
<td>4100</td>
<td>1000</td>
</tr>
</tbody>
</table>

* The MSWC is the concentration below which the combined MOE would be above 1000 and the risks would not be of concern.

The Acute MSWC of 9.8 ppm for exposures to 2,4-D acid or amine is greater than the master label application rate of 4.0 ppm, therefore, acute exposures to 2,4-D acid or amine are not of concern. The MSWC of 3.6 ppm for short-term exposures to 2,4-D acid or amine is also not of concern because some dissipation or dispersion is likely to occur which would cause the 7-day average of 2,4-D concentrations to be less than 3.6 ppm. Dissipation studies submitted to EFED indicated that the half lives following pond and lake liquid treatments ranged from 3.2 days to 27.8 days which yield 7 day average concentrations of 1.9 ppm when the half life equals 3.2 days to 3.6 ppm when the half life equals 27.8 days.

The MSWCs for 2,4-D BEE are less than the master label application rate of 4 ppm, but they are unlikely to be of concern for the following reasons:

- 2,4-D BEE degrades rapidly by abiotic hydrolysis in sterile water to form 2,4-D acid particularly when the pH is 7.5 or above.

- 2,4-D BEE degrades to 2,4-D acid by microbial hydrolysis with an average half life of 2.6 ± 1.8 hours at a bacterial concentration of 5 x 10⁸ organisms per liter. Therefore, degradation of 2,4-D BEE to 2,4-D under typical environmental conditions will be rapid leading to significantly lower risk estimates because the 2,4-D acid has a lower rate of dermal absorption.

- Modeling predicts direct water application of 2,4-D BEE will yield surface water concentrations of 2,4-D BEE concentrations in the Agency standard pond of 624 ug/L for peak (24 hour average), 30 ug/L for the 21-day average, and 10 ug/L for the 60-day average.

- The existing label rates for 2,4-D BEE products are also lower than the master label rate.
5. Aggregate Exposure and Risk

OPP has traditionally compared estimates of concentrations of a pesticide in drinking water to DWLOCs. A DWLOC is the portion of the acute PAD or chronic PAD remaining after estimated dietary (food only) exposures have been subtracted and the remaining exposure has been converted to a concentration (ug/L or ppb). This concentration value (DWLOC) represents the available or allowable exposure through drinking water. In an acute risk assessment, the remaining portion of the aPAD is based on dietary exposures at the percentile of exposure appropriate for a given risk assessment and depends on each relevant population subgroup considered. Estimated Drinking Water Concentrations (EDWCs) of 2,4-D in ground and surface water that are less than the DWLOCs do not exceed the Agency’s level of concern. DWLOC values vary for population subgroups depending on dietary exposure through foods for each subgroup, assumptions made about the volume of drinking water consumed, and default body weights for each subgroup.

More recently, OPP has adopted the forward calculation approach for the assessment of aggregate risks. In this approach, food, drinking water and residential exposures are aggregated and compared to an appropriate endpoint.

In the case of 2,4-D, the DWLOCs were calculated for comparison to the MCL established by the EPA Office of Water and aggregate risks were calculated using the forward calculation approach for comparison to the appropriate endpoint. The respective DWLOCs and aggregate risks are shown for acute, chronic and short term exposures in the following sections.

a. Acute Aggregate Risk Assessment

DWLOC Approach

Acute DWLOCs were calculated based upon acute dietary exposures. Acute residential exposures from swimming in treated water bodies or playing on treated turf were not included because exposures are unlikely to co-occur with acute dietary exposures. The acute DWLOCs are summarized in Table 14 and are 432 ppb or greater with the most sensitive population being females 13-49 years old. The EDWCs of 118 ug/liter for surface water and 15 ug/liter for groundwater are substantially less than the DWLOCs which means that the risks are not of concern.
### Table 14. Acute DWLOC Calculations

<table>
<thead>
<tr>
<th>Population Subgroup</th>
<th>Body Weight (kg)</th>
<th>Water Consumption (liters/day)</th>
<th>aPAD (mg/kg/day)</th>
<th>Food Exp₁ (mg/kg/day)</th>
<th>Max Water Exposure (mg/kg/day)</th>
<th>DWLOC (µg/L)³</th>
</tr>
</thead>
<tbody>
<tr>
<td>General U.S. Population</td>
<td>70</td>
<td>2.0</td>
<td></td>
<td>0.0118</td>
<td>0.0552</td>
<td>1932</td>
</tr>
<tr>
<td>All Infants (&lt; 1 year old)</td>
<td>10</td>
<td>1.0</td>
<td>0.067</td>
<td>0.0132</td>
<td>0.0538</td>
<td>538</td>
</tr>
<tr>
<td>Children 1-2 years old</td>
<td>10</td>
<td>1.0</td>
<td></td>
<td>0.0221</td>
<td>0.0449</td>
<td>449</td>
</tr>
<tr>
<td>Children 3-5 years old</td>
<td>10</td>
<td>1.0</td>
<td></td>
<td>0.0206</td>
<td>0.0464</td>
<td>464</td>
</tr>
<tr>
<td>Children 6-12 years old</td>
<td>10</td>
<td>1.0</td>
<td></td>
<td>0.0147</td>
<td>0.0523</td>
<td>523</td>
</tr>
<tr>
<td>Females 13-49 years old</td>
<td>60</td>
<td>2.0</td>
<td>0.025</td>
<td>0.0106</td>
<td>0.0144</td>
<td>432</td>
</tr>
</tbody>
</table>

1. Food exposure values are the maximum of the acute DEEM or Lifeline values.
2. Maximum water exposure (mg/kg/day) = [(acute PAD - food exposure)]
3. DWLOC (µg/L) = [maximum water exposure x body weight] ÷ [water consumption x 10⁻³ mg/µg].

Surface Water EDWC = 70 ug/liter (aquatic applications) or 118 ug/liter (terrestrial applications)
Ground Water EDWC = 15 ug/liter

---

### Forward Calculation Approach

Acute aggregate risks were assessed by aggregating acute food exposures and acute water exposures. The acute aggregate risks are presented in Table 15 and are not of concern because they are less than 100 percent of the aPAD. The highest risks (58 percent of the aPAD) are for females 13-49 years old because these risks are based upon the lower NOAEL of 25 mg/kg/day.

### Table 15. 2,4-D Aggregate Acute MOEs

<table>
<thead>
<tr>
<th>Population Subgroup</th>
<th>Body Weight (kg)</th>
<th>Water Consumption (liters/day)</th>
<th>Food Exposure¹ (mg/kg/day)</th>
<th>Drinking Water Exposure² (mg/kg/day)</th>
<th>Aggregate Exposure³ (mg/kg/day)</th>
<th>aPAD⁴ (mg/kg/day)</th>
<th>Percent aPAD⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>General U.S. Population</td>
<td>70</td>
<td>2.0</td>
<td>0.0118</td>
<td>0.00337</td>
<td>0.0152</td>
<td>0.067</td>
<td>23</td>
</tr>
<tr>
<td>Females 13-49 yrs old</td>
<td>60</td>
<td>2.0</td>
<td>0.0106</td>
<td>0.0039</td>
<td>0.015</td>
<td>0.025</td>
<td>58</td>
</tr>
</tbody>
</table>

Notes for Table X
1. Food exposure values are the maximum of the DEEM or Lifeline acute values.
2. Drinking Water Exposure = (EDWC * daily water consumption) / (1000 ug/mg * Body Weight); where the EDWC = 118 ug/liter
3. Aggregate Exposure = Food Exposure + Drinking Water Exposure
4. aPAD = NOAEL/1000; where the NOAEL is 25 mg/kg/day for females 13-49 and 67 mg/kg/day for all other population subgroups
5. Percent aPAD = (Aggregate Exposure/aPAD) * 100
b. Chronic Aggregate Risk Assessment

DWLOC Approach

Chronic DWLOCs were calculated based upon chronic dietary exposures. As there are no chronic residential exposures, residential exposures were not included in the chronic DWLOC calculations. The chronic DWLOCs are summarized in Table 16 and are 46 ug/liter or greater with the most sensitive population being children. The EDWCs, which range from 1.5 to 23 ug/liter, are less than the DWLOCs which means that the risks are not of concern. It should be noted that the master label indicates that potable water consumption from a treated water body cannot begin until the 2,4-D concentration is 70 ug/liter or below, therefore an annual average exposure at the MCL of 70 ug/liter would not occur because dissipation would reduce the initial concentration of 70 ug/liter to an annual average concentration of 11 ug/liter.

Table 16. Chronic DWLOC Calculations

<table>
<thead>
<tr>
<th>Population Subgroup</th>
<th>Body Weight (kg)</th>
<th>Water Consumption (liters/day)</th>
<th>cPAD (mg/kg/day)</th>
<th>Food Exp¹ (mg/kg/day)</th>
<th>Max Water Exposure² (mg/kg/day)</th>
<th>DWLOC (µg/L)³</th>
</tr>
</thead>
<tbody>
<tr>
<td>General U.S. Population</td>
<td>70</td>
<td>2.0</td>
<td></td>
<td>0.00020</td>
<td>0.0048</td>
<td>168</td>
</tr>
<tr>
<td>All Infants (&lt; 1 year old)</td>
<td>10</td>
<td>1.0</td>
<td></td>
<td>0.00016</td>
<td>0.00484</td>
<td>48</td>
</tr>
<tr>
<td>Children 1-2 years old</td>
<td>10</td>
<td>1.0</td>
<td></td>
<td>0.00042</td>
<td>0.00458</td>
<td>46</td>
</tr>
<tr>
<td>Children 3-5 years old</td>
<td>10</td>
<td>1.0</td>
<td></td>
<td>0.00037</td>
<td>0.00463</td>
<td>46</td>
</tr>
<tr>
<td>Children 6-12 years old</td>
<td>10</td>
<td>1.0</td>
<td></td>
<td>0.00026</td>
<td>0.00474</td>
<td>47</td>
</tr>
<tr>
<td>Youth 13-19 years old</td>
<td>60</td>
<td>2.0</td>
<td></td>
<td>0.00019</td>
<td>0.00481</td>
<td>144</td>
</tr>
<tr>
<td>Adults 20-49 years old</td>
<td>70</td>
<td>2.0</td>
<td></td>
<td>0.00019</td>
<td>0.00481</td>
<td>168</td>
</tr>
<tr>
<td>Adults 50+ years old</td>
<td>70</td>
<td>2.0</td>
<td></td>
<td>0.00018</td>
<td>0.00482</td>
<td>169</td>
</tr>
<tr>
<td>Females 13-49 years old</td>
<td>60</td>
<td>2.0</td>
<td></td>
<td>0.00020</td>
<td>0.0048</td>
<td>144</td>
</tr>
</tbody>
</table>

¹. Food exposure values are the maximum of the DEEM or Lifeline chronic dietary values.
². Maximum water exposure (mg/kg/day) = (chronic PAD - food exposure)
³. DWLOC (µg/L) = [maximum water exposure x body weight] ÷ [water consumption x 10⁻³ mg/µg].

Surface Water EDWC (maximum time weighted annual mean from the NAWQA database) = 1.5 ug/liter
Surface Water EDWC (dissipation modeling of aquatic application when 70 ppb occurs at time zero) = 11 ug/liter
Ground Water EDWC (the highest monitored value from the NAWQA database) = 15 ug/liter

Forward Calculation Approach

Chronic aggregate risks were also assessed by aggregating chronic food exposures and chronic water exposures in a forward calculation approach. The chronic aggregate risks are presented as percent cPAD in Table 17 and are not of concern because they are less than 100 percent of the cPAD. The highest risks (38 percent of the cPAD) are for children 1-2 years old.

Table 17. 2,4-D Aggregate Chronic Risks

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### c. Short-term Aggregate Risk Assessments

**DWLOC Approach**

Short-term aggregate risks assessments were conducted by calculating DWLOCs based upon short term turf exposures, chronic food exposures and short term endpoints. Short-term exposures from swimming in treated water bodies were not included because these exposures represent episodic scenarios that are unlikely to occur the same day as an acute dietary exposure. The short-term DWLOCs were calculated only for females 13-49 and children 1-6 because these population subgroups have the highest exposure and are protective of the other subgroups. The DWLOCs are listed in Table 18 and range from 24 to 54 µg/liter. These DWLOCs are all greater than the EDWCs, which range from 15 to 23 µg/liter, and indicate that short term risks are not of concern.

<table>
<thead>
<tr>
<th>Population Subgroup</th>
<th>Body Weight (kg)</th>
<th>Water Consumption (liters/day)</th>
<th>NOAEL/UF (mg/kg/day)</th>
<th>Turf Exposure (mg/kg/day)</th>
<th>Food Exp1 (mg/kg/day)</th>
<th>Max Water Exposure (mg/kg/day)2</th>
<th>cPAD4 (mg/kg/day)</th>
<th>Percent cPAD5</th>
</tr>
</thead>
<tbody>
<tr>
<td>General U.S. Population</td>
<td>70</td>
<td>2.0</td>
<td>0.00020</td>
<td>0.00043</td>
<td>0.0006</td>
<td>0.005</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Children 1-2 yrs old</td>
<td>10</td>
<td>1.0</td>
<td>0.00042</td>
<td>0.0015</td>
<td>0.002</td>
<td>0.005</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

1. Food exposure values are from Table X and are the maximum of the DEEM or Lifeline chronic dietary values.
2. Drinking Water Exposure = (EDWC * daily water consumption) / (1000 ug/mg * Body Weight); where the EDWC = 15 ug/liter
3. Aggregate Exposure = Food Exposure + Drinking Water Exposure
4. cPAD = NOAEL of 5 mg/kg/day / 1000
5. Percent cPAD = (Aggregate Exposure/aPAD) * 100

**Table 18. Short-Term DWLOC Calculations for 2,4-D**

<table>
<thead>
<tr>
<th>Pop. Subgroup</th>
<th>Body Weight (kg)</th>
<th>Water Consumption (liters/day)</th>
<th>NOAEL/UF (mg/kg/day)</th>
<th>Turf Exposure (mg/kg/day)</th>
<th>Food Exp (mg/kg/day)</th>
<th>Max Water Exposure (mg/kg/day)2</th>
<th>DWLOC (µg/L)3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children 1-6</td>
<td>15</td>
<td>1.0</td>
<td>0.025</td>
<td>0.021</td>
<td>0.00042</td>
<td>0.00358</td>
<td>54</td>
</tr>
<tr>
<td>Females 13-49</td>
<td>60</td>
<td>2.0</td>
<td>0.025</td>
<td>0.024</td>
<td>0.00020</td>
<td>0.00080</td>
<td>24</td>
</tr>
</tbody>
</table>

1. Food exposure values are the maximum of the DEEM or Lifeline chronic dietary values.
2. Maximum water exposure (mg/kg/day) = [(NOAEL/UF) - (Turf exposure + food exposure)]
3. DWLOC (µg/L) = [maximum water exposure x body weight] + [water consumption x 10^-3 mg/µg].

**Forward Calculation Approach**

Short-term aggregate risks were also assessed by directly aggregating short-term turf exposures, chronic food exposures and chronic water exposures. Short-term aggregate risks were calculated only for females 13-49 and children 1-6 because these population subgroups have the highest exposure and are protective of the other subgroups. The short term aggregate MOEs are presented in Table 19 and indicate that the short term risks are not of concern because the MOEs equal or exceed the target MOE of 1000.
Table 19. 2,4-D Aggregate Short-Term MOEs Including Turf Exposures

<table>
<thead>
<tr>
<th>Population Subgroup</th>
<th>Turf Application Rate (lbs ae/acre)</th>
<th>Chronic Food Exposure (mg/kg/day)</th>
<th>Short-Term Turf Exposure (mg/kg/day)</th>
<th>Chronic EDWC (ug/liter)</th>
<th>Drinking Water Exposure (mg/kg/day)</th>
<th>Aggregate Exposure (mg/kg/day)</th>
<th>Aggregate MOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females 13 - 49</td>
<td>1.5</td>
<td>0.000195</td>
<td>0.024</td>
<td>15</td>
<td>0.00050</td>
<td>0.0247</td>
<td>1000</td>
</tr>
<tr>
<td>Children 1 - 6</td>
<td>1.5</td>
<td>0.000424</td>
<td>0.021</td>
<td>15</td>
<td>0.0010</td>
<td>0.0224</td>
<td>1100</td>
</tr>
<tr>
<td>Females 13 - 49</td>
<td>1.5</td>
<td>0.000195</td>
<td>0.024</td>
<td>23</td>
<td>0.00077</td>
<td>0.0250</td>
<td>1000</td>
</tr>
<tr>
<td>Children 1 - 6</td>
<td>1.5</td>
<td>0.000424</td>
<td>0.021</td>
<td>23</td>
<td>0.0015</td>
<td>0.0230</td>
<td>1100</td>
</tr>
</tbody>
</table>

1. Body weights are 60 kg (females) and 15 kg (children). Water consumption values are 2 liter/day (females) and 1.0 liter/day (children).
2. The food exposure for females is from Lifeline. The food exposure for children is from DEEM and is for 1-2 year old children.
3. Female’s turf exposures are from the dermal route only. Children’s turf exposures are from the dermal and incidental oral routes.
4. EDWC is 15 ug/liter for ground water and 23 ug/liter for surface water.
5. Drinking Water Exposure = (EDWC * daily water consumption) / (1000 ug/mg * Body Weight)
6. Aggregate Exposure = Turf Exposure + Food Exposure + Drinking Water Exposure
7. Aggregate MOE = NOAEL/Aggregate Exposure where the NOAEL is 25 mg/kg/day.

d. Cancer Aggregate Risk

2,4-D was classified as a Category D chemical, i.e., not classifiable as to human carcinogenicity, by the EPA/OPP Cancer Peer Review Committee in 1996. Thus, no aggregate cancer assessment is warranted.

e. Aggregate Risk Characterization

The highest aggregate risks are the short term risks that include the turf exposure scenarios. For the most sensitive subpopulation (females 13-49), these risks just meet the target MOE of 1000 and the turf exposure is the risk driver as it contributes 96 percent of the risk. It is important to note, however, that the turf exposure estimate is based upon modeling and is greater than exposure measurements obtained from biomonitoring. The results of a biomonitoring study (Harris and Solomon 1992) were also used to calculate dermal MOEs for post application exposure on turf. The study was conducted with adult volunteers who were exposed to 2,4-D while performing controlled activities for one hour on turf treated with 2,4-D. The controlled activities were conducted at 1 hour after treatment (HAT) and at 24 HAT. Ten volunteers participated in the study. Five volunteers wore long pants, a tee shirt, socks and closed footwear. The other five wore shorts and a tee shirt and were barefoot. The volunteers walked on the turf for a period of 5 minutes and then sat or lay on the area for 5 minutes and then continued in this fashion for 50 more minutes. Each volunteer collected all urine for the next 96 hours immediately following the exposure. The MOEs for the DAT 1 volunteers who wore shorts and no shoes ranged from 1000 to 26000 with the lowest MOE corresponding to a volunteer who removed his shirt during the exposure period. The MOEs for the remaining volunteers ranged from 17000 to 27000. If the calculated MOE of 1000 is considered in conjunction with the biomonitoring results, it is clear that the short term risks are upper bound estimates and not likely to be of concern.
6. Occupational Risk

Workers can be exposed to a pesticide through mixing, loading, and/or applying a pesticide, or re-entering treated sites. Occupational handlers of 2,4-D include workers in agricultural areas, workers in forest areas, workers in rights-of-way and non-cropland areas, workers in lawn and turf areas (including turf grown for seed or sod), and workers applying 2,4-D for aquatic weed control. Occupational risk for all of these potentially exposed populations is measured by an MOE which determines how close the occupational exposure comes to a NOAEL. In the case of 2,4-D, MOEs greater than 100 do not exceed the Agency’s level of concern. For workers entering a treated site, MOEs are calculated for each day after application to determine the minimum length of time required before workers can safely reenter.

Occupational risk estimates are expressed as MOEs, which are the ratio of estimated exposure to an established dose level (NOAEL). 2,4-D MOEs are determined by a comparison of specific exposure scenario estimates to the NOAELs for short-term assessment and intermediate-term assessment, respectively. The NOAEL for short-term dermal and inhalation exposure is 25 mg/kg/day from a rat developmental toxicity study, and the NOAEL for intermediate-term dermal and inhalation exposure is 15 mg/kg/day from a rat subchronic oral toxicity study. The dermal absorption factor is 10 percent and the inhalation absorption factor is 100 percent. For 2,4-D users an MOE of 100 has been determined to be adequately protective (for both short- and intermediate-term exposure) based on the standard uncertainty factors of 10x for interspecies extrapolation and 10x for intraspecies variability. Long-term worker exposure is not expected for 2,4-D.

Occupational risk is assessed for exposure at the time of application (termed “handler” exposure) and assessed for exposure following application, or postapplication exposure. Application parameters are generally defined by the physical nature of the formulation (e.g., formula and packaging), by the equipment required to deliver the chemical to the use site, and by the application rate required to achieve an efficacious dose. Post-application risk is assessed for activities such as scouting, irrigating, pruning, and harvesting and is based primarily on dermal exposure estimates.

Occupational risk estimates are calculated based on assumptions concerning acres treated per day and the seasonal duration of exposure. For more information on the assumptions and calculations of potential risk of 2,4-D to workers, see the Occupational Exposure Assessment (Section 7.0) in “2,4-D: 3rd Revised Occupational and Residential Exposure and Risk Assessment and Response to Public Comments for the Reregistration Eligibility Decision (RED) Document,” dated May 4, 2005.

a. Occupational Toxicity

Table 20 provides a listing of the toxicological endpoints used in the 2,4-D occupational risk assessment.
### Table 20. Toxicological Endpoints for the Occupational Risk Assessment

<table>
<thead>
<tr>
<th>Exposure Scenario</th>
<th>Dose Used in Risk Assessment, UF</th>
<th>Level of Concern for Risk Assessment</th>
<th>Study and Toxicological Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-Term Dermal*</td>
<td>Oral study NOAEL = 25 mg/kg/day</td>
<td>Occupational LOC for MOE = 100</td>
<td>Rat developmental toxicity study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LOAEL = 75 mg/kg/day based on decreased maternal body-weight gain and skeletal abnormalities</td>
</tr>
<tr>
<td>Intermediate-Term Dermal*</td>
<td>Oral study NOAEL = 15 mg/kg/day</td>
<td></td>
<td>Subchronic oral toxicity - rat</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LOAEL = 100 mg/kg/day based on decreased body weight/body-weight gain, alterations in some hematology, and clinical chemistry parameters, and cataract formation.</td>
</tr>
<tr>
<td>Long-Term Dermal*</td>
<td>Oral study NOAEL = 5 mg/kg/day</td>
<td></td>
<td>Rat Chronic Toxicity Study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LOAEL = 75 mg/kg/day based on decreased body-weight gain (females) and food consumption (females), alterations in hematology, and clinical chemistry parameters, decreased T4 (both sexes), glucose (females), cholesterol (both sexes), and triglycerides (females).</td>
</tr>
<tr>
<td>Short-Term Inhalation*</td>
<td>Oral study NOAEL = 25 mg/kg/day</td>
<td></td>
<td>Rat developmental toxicity study (same as for dermal)</td>
</tr>
<tr>
<td>Intermediate-Term Inhalation*</td>
<td>Oral study NOAEL = 15 mg/kg/day</td>
<td></td>
<td>Subchronic oral toxicity - rat (same as incidental oral)</td>
</tr>
<tr>
<td>Long-Term Inhalation*</td>
<td>Oral study NOAEL = 5 mg/kg/day</td>
<td></td>
<td>Rat chronic toxicity study (same as for chronic dietary)</td>
</tr>
</tbody>
</table>

Cancer: **Classification**: Group D [not classifiable as to human carcinogenicity]

*The dermal absorption factor is 10 percent and the inhalation absorption factor is 100 percent.

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic), RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

For more occupational toxicity information, see “2,4-D: HED’s Revised Human Health Risk Assessment for the Reregistration Eligibility Decision (RED) Revised to Reflect Public Comments,” dated January 4, 2005.

### b. Occupational Handler Exposure

Occupational handler risk estimates have been assessed for both short- and intermediate-term exposure durations. Because 2,4-D is typically applied only a few times per season and because the agricultural scenarios occur for only a few months per year, it is anticipated that 2,4-D exposures would primarily be short-term. Intermediate-term risk estimates are provided as an upper-bound assessment.

Occupational handler assessments are conducted using increasing levels of protection. The
Agency typically evaluates all exposures with minimal protection and then considers additional protective measures using a tiered approach (going from minimal to maximum levels of protection). The lowest tier is represented by the baseline clothing scenario (i.e., single layer clothing, socks, and shoes), followed by, if MOEs are of concern, increasing levels of risk mitigation such as personal protective equipment (PPE) and engineering controls (EC). With the exception of mixing and loading wettable powders, MOEs for most occupational exposure scenarios are above 100 at baseline PPE (long-sleeved shirt, long pants, socks, and shoes) or single layer PPE (long-sleeved shirt, long pants, socks, shoes, and gloves). The MOEs for handling wettable powder are acceptable with engineering controls (i.e. water soluble bags). While the generic assessment for 2,4-D as an active ingredient does not indicate a need for additional PPE, evaluation of end-use product toxicity data may. End-use product PPE will be assessed on a product-by-product basis.

c. Occupational Handler Risk Summary

The Agency has determined that there are potential exposures to individuals who mix, load, apply, and otherwise handle 2,4-D during the usual use patterns associated with the pesticide’s use. Based on the use patterns, 18 major occupational handler exposure scenarios were identified as follows:

**Mixer/Loader**
(1a) Mix/Load Wettable Powder for Aerial Application
(1b) Mix/Load Wettable Powder for Groundboom Application
(1c) Mix/Load Wettable Powder for Aquatic Subsurface Application
(1e) Mix/Load Wettable Powder for 10 Man Crew Backpack Application
(1f) Mix/Load Wettable Powder for Row Sprayer
(1g) Mix/Load Wettable Powder for Aquatic Foliar Application
(1h) Mix/Load Wettable Powder for Turfgun Application
(2a) Mix/Load Liquids for Aerial Application
(2b) Mix/Load Liquids for Groundboom
(2c) Mix/Load Liquids for Aquatic Subsurface Application
(2d) Mix/Load Liquids for Airblast Application
(2e) Mix/Load Liquids for 10 Man Crew Backpack Application
(2f) Mix/Load Liquids for Row Sprayer
(2g) Mix/Load Liquids for Aquatic Foliar Application
(2h) Mix/Load Liquids for Turfgun Application
(3) Load Granules for Broadcast Spreader

**Applicator**
(4) Aerial Application
(5) Groundboom Application
(6) Subsurface Application of Liquids to Submersed Aquatic Weeds
(7) Airblast Application
(8) Backpack Application
(9) Rights of Way (ROW) Application
(10) Foliar Application of Liquids to Floating Aquatic Weeds
(11) Turfgun Application
(12) Broadcast Spreader Application

Mixer/Loader/Applicator
(13) Mix/Load/Apply Wettable Powder with a Turfgun
(14) Mix/Load/Apply Liquids with a Turfgun
(15) Mix/Load/Apply Water Dispersable Granules with a Turfgun
(16) Mix/Load/Apply Liquids with a Backpack Sprayer
(17) Load/Apply Granules with a Push Spreader

Flagger
(18) Flag Aerial Application

Occupational Handler Exposure Assumptions

When possible, the assumptions for daily areas treated are taken from the Health Effects Division Science Advisory Committee on Exposure Policy 9: Standard Values for Daily Acres Treated in Agriculture (July 5, 2000). In other instances, the daily areas treated were defined for each handler scenario by best scientific judgement, or the best information available, as footnoted below in Table 21.

Analyses were completed using acceptable surrogate exposure data for the scenario assessed. Several handler assessments were completed using data from the Pesticide Handler Exposure Database (PHED) (version 1.1). PHED data were used primarily for the large scale agricultural and forestry scenarios. Some handler assessments (i.e., handheld handgun equipment, push-type spreader, and other lawn care scenarios) were completed using data from the Outdoor Residential Exposure Task Force (ORETF). California Department of Pesticide Regulation (CA DPR) data were used for the backpack applicator forestry scenario where multiple applicators are supplied by a nurse tank.

The following assumptions and factors were used in order to complete the exposure and risk assessments for occupational handlers and applicators:

- The average work day was 8 hours.
- A listing of application methods and amounts of acreage treated per 8 hour day is included in Table 22 and Table 23.
- The application rate for submerged aquatic weeds is based upon the master label rate of 10.8 lbs a.e. per acre foot times an average lake depth of 5 feet.
- Maximum application rates and daily acreage were used to evaluate short term exposures.
- Average application rates were used to evaluate intermediate term exposures.
- A body weight of 60 kg was assumed for short-term exposures because the short-term endpoint relates to females 13-50 years of age.
- A body weight of 70 kg was assumed for intermediate-term exposures because the
intermediate-term endpoint is not gender-specific.

- The dermal absorption rate is 10%.
- The inhalation absorption rate is 100%.
- Baseline PPE includes long sleeve shirts, long pants and no gloves or respirator.
- Single Layer PPE includes baseline PPE with gloves.
- Double Layer PPE includes coveralls over single layer PPE.
- Double Layer PPE PF5 includes above with a PF5 respirator (i.e. a dustmask).
- Double Layer PPE PF10 includes above with a PF10 cartridge respirator.
- Only closed cockpit airplanes are used for aerial application.
- There are very little exposure data to evaluate the exposure in helicopters; therefore, the exposure data for fixed-wing aircraft are used as a surrogate.
- Airplane and helicopter pilots do not wear chemical resistant gloves.

### Table 21. 2,4-D Application Methods and Assumptions

<table>
<thead>
<tr>
<th>Application Method</th>
<th>Typical Crops Treated</th>
<th>Treated Area¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerial</td>
<td>Small Grain, Field Corn, Sugarcane</td>
<td>1200</td>
</tr>
<tr>
<td></td>
<td>Citrus Growth Regulation</td>
<td>350</td>
</tr>
<tr>
<td>Groundboom</td>
<td>Small Grains, Field Corn, Sugarcane</td>
<td>200</td>
</tr>
<tr>
<td></td>
<td>Orchard/Vineyard Floors</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Strawberries</td>
<td>80</td>
</tr>
<tr>
<td>Subsurface Application of Liquids</td>
<td>Submersed Aquatic Weeds</td>
<td>30²</td>
</tr>
<tr>
<td>Airblast</td>
<td>Citrus Growth Regulation</td>
<td>40</td>
</tr>
<tr>
<td>Backpack Sprayer - Mix/Load/Apply</td>
<td>Christmas Tree Plantations</td>
<td>2³</td>
</tr>
<tr>
<td>Backpack Sprayer - Apply Only</td>
<td>Conifer Release</td>
<td>4⁴</td>
</tr>
<tr>
<td>Right of Way (ROW) Sprayer</td>
<td>Weed Control - 20 gallons per acre</td>
<td>50⁵</td>
</tr>
<tr>
<td></td>
<td>Brush Control - 400 gallons per acre</td>
<td>2.5³</td>
</tr>
<tr>
<td>Foliar Application of Liquids</td>
<td>Floating Aquatic Weeds</td>
<td>10⁶</td>
</tr>
<tr>
<td>Broadcast Spreader - Tractor Drawn or Boat Mounted</td>
<td>Turf</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Submersed Aquatic Weeds</td>
<td>50⁷</td>
</tr>
<tr>
<td>Turfgun</td>
<td>Turf</td>
<td>5</td>
</tr>
<tr>
<td>Broadcast Spreader - Push Type</td>
<td>Turf</td>
<td>5</td>
</tr>
</tbody>
</table>

1. Except as noted, the acres treated per day values are from ExpoSAC Policy #9 “Standard Values for Daily Acres Treated in Agriculture”, Revised 7/5/2000.
2. The area treated for aquatic application of liquids to submersed aquatic weeds is based on information provided in an email of 12/11/03 from Dr. Kurt Getsinger of the US Army Corps of Engineers to Timothy C. Dole of the US EPA Office of Pesticide Programs.
3. The area treated for Backpack Sprayer (Mix/Load/Apply) is 40 gallons per day from ExpoSAC Policy #9 divided by the label recommended spray volume of 20 gallons per acre.
4. The area treated for Backpack Sprayer (Apply Only) is 4 acres per day based upon the acreage treated in CA DPR HS-1769 normalized to an 8 hour day.
5. The area treated for ROW sprayers was determined by the dividing the daily spray volume handled (1000 gallons per
day) from ExpoSAC Policy #9 by the label recommended spray volume of 20 gallons per acre for weed control and 400 gallons per acre for woody brush control.
6. The area treated for foliar application of liquids to floating aquatic weeds is based upon use information reported in the HED Memorandum “Occupational and Residential Exposure Characterization/Risk Assessment for Triclopyr Triethylamine for Aquatic Weed Control, DP Barcode D269448 of 7/22/2002.
7. The area treated for application of granules to submersed aquatic weeds is based upon information provided in an email of 11/22/2000 from Jim Kannenburg of Marine Biochemists/Applied Biochemists to Troy Swackhammer of the US EPA Office of Pesticide Programs.

Summary of Risk Concerns and Data Gaps for Handlers

The MOEs for handlers are summarized in Tables 22 and 23 below. With the exception of mixing/loading wettable powder, all of the short-term and intermediate-term MOEs exceed the target of 100 with baseline PPE (i.e., long-sleeved shirt, long pants, shoes plus socks, no respirator) or single layer PPE (i.e., long-sleeved shirt, long pants, shoes plus socks, gloves, no respirator) and are not of concern. The MOEs for handling wettable powder are adequate with engineering controls (i.e. water soluble bags).

### Table 22. MOEs for Short-Term Risk to Occupational Handlers

<table>
<thead>
<tr>
<th>Exposure Scenario</th>
<th>Crop Type</th>
<th>Application Rate (lb ae/acre)</th>
<th>Acres/Day</th>
<th>Base-line PPE</th>
<th>Single Layer PPE</th>
<th>Eng. Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixer/Loader (M/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M/L WP</td>
<td>All Crops</td>
<td>0.25 to 4</td>
<td>5 to 1200</td>
<td>≥1</td>
<td>≥5</td>
<td>≥260</td>
</tr>
<tr>
<td>M/L Liquids</td>
<td>All Crops</td>
<td>0.25 to 4</td>
<td>5 to 1200</td>
<td>≥1</td>
<td>≥89</td>
<td>≥330</td>
</tr>
<tr>
<td>M/L Liquids</td>
<td>Submersed Weeds</td>
<td>54</td>
<td>30</td>
<td>3.2</td>
<td>260</td>
<td>980</td>
</tr>
<tr>
<td>Load Granulars for Broadcast Spreader</td>
<td>Golf Courses and Aquatic Areas</td>
<td>2 to 54</td>
<td>40 or 50</td>
<td>≥220</td>
<td>≥230</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Applicator (APP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aerial Application</td>
<td>All Crops</td>
<td>1.25 to 4.0</td>
<td>1200</td>
<td>ND</td>
<td>ND</td>
<td>&gt;550</td>
</tr>
<tr>
<td>Groundboom Application</td>
<td>All Crops</td>
<td>1.25 to 4</td>
<td>40 to 200</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Subsurface Aquatic Application of Liquids</td>
<td>Submersed Weeds</td>
<td>54</td>
<td>30</td>
<td>430</td>
<td>430</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Airblast Application</td>
<td>Citrus</td>
<td>0.1</td>
<td>40</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Backpack Application</td>
<td>Conifer Release</td>
<td>4</td>
<td>4</td>
<td>ND</td>
<td>140</td>
<td>ND</td>
</tr>
<tr>
<td>ROW Application</td>
<td>Weed Control</td>
<td>2</td>
<td>50</td>
<td>110</td>
<td>350</td>
<td>ND</td>
</tr>
<tr>
<td>Foliar Aquatic Application of Liquids</td>
<td>Floating Weeds</td>
<td>2</td>
<td>10</td>
<td>280</td>
<td>870</td>
<td>ND</td>
</tr>
<tr>
<td>Turfgun Application</td>
<td>turf</td>
<td>1.5</td>
<td>5</td>
<td>ND</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Broadcast Spreader Application</td>
<td>Golf Courses and Aquatic Areas</td>
<td>1.5 or 54</td>
<td>40 or 50</td>
<td>≥250</td>
<td>≥290</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

Mixer/Loader/Applicator (M/L/A)
<table>
<thead>
<tr>
<th>Exposure Scenario</th>
<th>Crop Type</th>
<th>Application Rate (lb ae/acre)</th>
<th>Acres/Day</th>
<th>Base-line</th>
<th>Single Layer</th>
<th>Eng. Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/L/A Liquids with Backpack Sprayer</td>
<td>Christmas Trees</td>
<td>4</td>
<td>2</td>
<td>ND</td>
<td>730</td>
<td>ND</td>
</tr>
<tr>
<td>M/L/A WD Granules with a Turf Gun</td>
<td>turf</td>
<td>1.5</td>
<td>5</td>
<td>ND</td>
<td>&gt;1000</td>
<td>ND</td>
</tr>
<tr>
<td>M/L/A Wetttable Powder with a Turf Gun</td>
<td>turf</td>
<td>1.5</td>
<td>5</td>
<td>ND</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>M/L/A Liquid Flowables with a Turfgun</td>
<td>turf</td>
<td>1.5</td>
<td>5</td>
<td>ND</td>
<td>&gt;1000</td>
<td>ND</td>
</tr>
<tr>
<td>Load/Apply Granules with a Push Spreader</td>
<td>turf</td>
<td>1.5</td>
<td>5</td>
<td>ND</td>
<td>710</td>
<td>ND</td>
</tr>
</tbody>
</table>

**Flagger**

| Flaggner                               | All Crops                  | 1.25 to 4.0                  | 1200      | ≥210      | ≥200         | ≥1000        |

MOEs in **bold font** do not exceed the target MOE of 100 and are of concern

ND not determined

**Table 23. MOEs for Intermediate-Term Risk to Occupational Handlers**

<table>
<thead>
<tr>
<th>Exposure Scenario</th>
<th>Crop Type</th>
<th>Application Rate (lb ae/acre)</th>
<th>Acres/Day</th>
<th>Base-line</th>
<th>Single Layer</th>
<th>Eng. Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mixer/Loader (M/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M/L WP</td>
<td>All Crops</td>
<td>0.25 to 4</td>
<td>5 to 1200</td>
<td>&gt;1.1</td>
<td>≥7.3</td>
<td>≥360</td>
</tr>
<tr>
<td>M/L Liquids</td>
<td>All Crops</td>
<td>0.25 to 4</td>
<td>5 to 1200</td>
<td>≥1.5</td>
<td>≥130</td>
<td>≥460</td>
</tr>
<tr>
<td>M/L Liquids Submersed Weeds</td>
<td>54</td>
<td>30</td>
<td>2.2</td>
<td>190</td>
<td>690</td>
<td></td>
</tr>
<tr>
<td>Load Granulars for Broadcast Spreader</td>
<td>Golf Courses or Aquatic Areas</td>
<td>1.5 or 54</td>
<td>40 or 50</td>
<td>≥150</td>
<td>≥160</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

**Applicator (APP)**

<table>
<thead>
<tr>
<th>Application</th>
<th>All Crops</th>
<th>0.5 to 2.0</th>
<th>1200</th>
<th>ND</th>
<th>ND</th>
<th>&gt;770</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groundboom Application</td>
<td>All Crops</td>
<td>0.5 to 4</td>
<td>40 to 200</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Subsurface Aquatic Application</td>
<td>Submersed Weeds</td>
<td>54</td>
<td>30</td>
<td>300</td>
<td>300</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Airblast Application</td>
<td>Citrus</td>
<td>0.1</td>
<td>40</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Backpack Application</td>
<td>Conifer Release</td>
<td>2</td>
<td>4</td>
<td>ND</td>
<td>200</td>
<td>ND</td>
</tr>
<tr>
<td>ROW Application</td>
<td>Weed Control</td>
<td>2</td>
<td>50</td>
<td><strong>78</strong></td>
<td>240</td>
<td>ND</td>
</tr>
<tr>
<td>Foliar Aquatic Application of Liquids</td>
<td>Floating Weeds and Wild Rice</td>
<td>4 or 0.25</td>
<td>10</td>
<td>≥200</td>
<td>≥610</td>
<td>ND</td>
</tr>
<tr>
<td>Turf Gun Application</td>
<td>turf</td>
<td>1.5</td>
<td>5</td>
<td>ND</td>
<td>&gt;1000</td>
<td>ND</td>
</tr>
<tr>
<td>Broadcast Sprayer Application</td>
<td>Golf Courses and Aquatic Areas</td>
<td>1.5 or 54</td>
<td>40 or 50</td>
<td>≥180</td>
<td>≥200</td>
<td>ND</td>
</tr>
</tbody>
</table>

**Mixer/Loader/Applicator (M/L/A)**
### Exposure Scenario

<table>
<thead>
<tr>
<th>Exposure Scenario</th>
<th>Crop Type</th>
<th>Application Rate (lb ae/acre)</th>
<th>Acres/Day</th>
<th>Base-line</th>
<th>Single Layer</th>
<th>Eng. Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/L/A Liquids with Backpack Sprayer</td>
<td>Conifer Plantations</td>
<td>4</td>
<td>2</td>
<td>ND</td>
<td>510</td>
<td>ND</td>
</tr>
<tr>
<td>M/L/A WD Granules with a Turfgun</td>
<td>turf</td>
<td>1.5</td>
<td>5</td>
<td>ND</td>
<td>&gt;1000</td>
<td>ND</td>
</tr>
<tr>
<td>M/L/A Wettable Powder with a Turf Gun</td>
<td>turf</td>
<td>1.5</td>
<td>5</td>
<td>ND</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>M/L/A Liquid Flowables with a Turfgun</td>
<td>turf</td>
<td>1.5</td>
<td>5</td>
<td>ND</td>
<td>&gt;1000</td>
<td>ND</td>
</tr>
<tr>
<td>Load/Apply Granules with a Push Spreader</td>
<td>turf</td>
<td>1.5</td>
<td>5</td>
<td>ND</td>
<td>500</td>
<td>ND</td>
</tr>
</tbody>
</table>

**Flagger**

| Flag Aerial Liquid Application | All Crops | 0.50 to 2.0 | 1200 | ≥660 | ≥610 | ≥1000 |

MOEs in **bold font** do not exceed the target MOE of 100 and are of concern

---

### d. Occupational Postapplication Risk

Post application 2,4-D exposures can occur in the agricultural environment when workers enter fields recently treated with 2,4-D to conduct tasks such as scouting and irrigation. In the Worker Protection Standard (WPS), a restricted entry interval (REI) is defined as the duration of time which must elapse before residues decline to a level so entry into a previously treated area and engaging in a specific task or activity would not result in exposures that are of concern. The WPS REI for 2,4-D is 12 hours for the ester and sodium salt forms and is 48 hours for the acid and amine salt forms.

1) **Exposure Scenarios, Data, and Assumptions**

Postapplication dislodgeable foliar residue (DFR) data were submitted for 2,4-D as well as turf transferable residue (TTR) data from treated turf. Three turf transferable residue (TTR) studies were submitted by the Broadleaf Turf Herbicide TTR Task Force. These studies are described in “2,4-D: 3rd Revised Occupational and Residential Exposure (ORE) and Risk Assessment and Response to Public Comments for the Reregistration Eligibility Decision (RED) Document” dated May 4, 2005, and in Appendix F of that document. These data were used in the human health risk assessment along with standard transfer coefficients based on EPA Science Advisory Council guidance to assess potential exposures to workers reentering treated sites.

For all other postapplication activities, EPA used the EPA Science Advisory Council for Exposure (Exposure SAC) policy on agricultural transfer coefficients.

The following assumptions were made regarding postapplication occupational exposure:

- Short term risks were assessed using master label rates.
- Intermediate term risks were assessed using average application rates when available.
• The transfer coefficients are from an interim transfer coefficient policy developed by HED’s Science Advisory Council for Exposure using proprietary data from the Agricultural Re-entry Task Force (ARTF) database (US EPA, August 7, 2001). This policy will be periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information will originate from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature.

• The transfer coefficients for turf harvesting and maintenance are based upon recently conducted ARTF studies that are being reviewed by EPA.

• In cases where applications would be made in such a way as to minimize contact with crop foliage postapplication exposures are expected to be negligible and are not assessed. These cases are included in “2,4-D: 3rd Revised Occupational and Residential Exposure and Risk Assessment and Response to Public Comments for the Reregistration Eligibility Decision (RED) Document (PC Code 030001, DP Barcode D316596)”, dated May 4, 2005.

• The initial percent of application rate as Dislodgeable Foliar Residue (DFR) was assumed to be 20% for all crops except turf. This is the standard value used in the absence of chemical specific data.

2) Occupational Postapplication Risk Estimates

All short- and intermediate-term MOEs are above 100 on day zero. All occupational postapplication risk scenarios are not of concern. Short-term and intermediate-term risk estimates are shown in Tables 24 and 25 below.

<table>
<thead>
<tr>
<th>Crop Group</th>
<th>Application Rate (lb a.e./acre)</th>
<th>Low Exposure Scenarios</th>
<th>Medium Exposure Scenarios</th>
<th>High Exposure Scenarios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field/row crop, low/med (cereal grains)</td>
<td>1.25</td>
<td>6,700</td>
<td>450</td>
<td>NA</td>
</tr>
<tr>
<td>Field/row crop, low/med (rice)</td>
<td>1.5</td>
<td>5,600</td>
<td>370</td>
<td>NA</td>
</tr>
<tr>
<td>Field/row crop, tall (corn)</td>
<td>1.5</td>
<td>5,600</td>
<td>1,400</td>
<td>560</td>
</tr>
<tr>
<td>Pre-harvest rate for field corn</td>
<td>0.5</td>
<td>17,000</td>
<td>4,200</td>
<td>NA</td>
</tr>
<tr>
<td>Post-emergence rate for sweet corn</td>
<td>1.0</td>
<td>8,400</td>
<td>2,100</td>
<td>NA</td>
</tr>
<tr>
<td>Field/row crop, tall (sorghum)</td>
<td>2.0</td>
<td>NA</td>
<td>420</td>
<td>210</td>
</tr>
<tr>
<td>Sugarcane</td>
<td>2.0</td>
<td>1,900</td>
<td>NA</td>
<td>950</td>
</tr>
<tr>
<td>Turf - California</td>
<td>2.0</td>
<td>860</td>
<td>NA</td>
<td>430</td>
</tr>
<tr>
<td>Turf - North Carolina</td>
<td>2.0</td>
<td>860</td>
<td>NA</td>
<td>430</td>
</tr>
</tbody>
</table>
Table 25. 2,4-D Postapplication Intermediate Term Worker Risks

<table>
<thead>
<tr>
<th>Crop Group</th>
<th>Application Rate+ (lb a.e./acre)</th>
<th>Low Exposure Scenarios</th>
<th>Medium Exposure Scenarios</th>
<th>High Exposure Scenarios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field/row crop, low/med (cereal grains)</td>
<td>0.5</td>
<td>12,000</td>
<td>780</td>
<td>NA</td>
</tr>
<tr>
<td>Field/row crop, low/med (rice)</td>
<td>0.92</td>
<td>6,400</td>
<td>420</td>
<td>NA</td>
</tr>
<tr>
<td>Field/row crop, tall (field corn)</td>
<td>0.44</td>
<td>13,000</td>
<td>3,300</td>
<td>1,300</td>
</tr>
<tr>
<td>Field/row crop, tall (sweet corn)</td>
<td>0.48</td>
<td>13,000</td>
<td>3,100</td>
<td>NA</td>
</tr>
<tr>
<td>Field/row crop, tall (sorghum)</td>
<td>0.46</td>
<td>13,000</td>
<td>3,100</td>
<td>NA</td>
</tr>
<tr>
<td>Sugarcane</td>
<td>0.75</td>
<td>NA</td>
<td>780</td>
<td>390</td>
</tr>
<tr>
<td>Turf - California</td>
<td>2.0</td>
<td>1,600</td>
<td>NA</td>
<td>810</td>
</tr>
<tr>
<td>Turf - North Carolina</td>
<td>2.0</td>
<td>610</td>
<td>NA</td>
<td>300</td>
</tr>
</tbody>
</table>

+ Average application rates as reported in the QUA report or NASS report were used when available.

7. Human Incident Data

In evaluating incidents to humans, the Agency reviewed reports from the National Poison Control Centers, the EPA OPP’s Incident Data System (IDS), the California Pesticide Illness Surveillance Program, and the National Pesticide Telecommunications Network (NPTN).

The Agency reviewed 2,4-D incident reports in January 2004. A total of 45 incidents were reported in the OPP Incident Data System and many of these incidents involved irritant effects to the eyes, skin and occasionally respiratory passages. Poison Control Center Incident Data (1993 to 1998) indicated that 2,4-D is generally less likely than other pesticides to cause minor, moderate or life threatening symptoms. The most common symptoms were dermal irritation and ocular problems. Incident data from the California Pesticide Illness Surveillance Program indicated that the number of cases generally ranges from 0 to 3 per year and most of these cases were due to eye or skin effects. Incident data from the National Pesticide Information Center for the years 1996 to 2002 indicated that an average of 3 cases definitely or probably related to 2,4-D exposure were reported per year.

8. Cancer Epidemiology Studies

A Science Advisory Board/Scientific Advisory Panel Special Joint Committee reviewed available epidemiological and other data on 2,4-D in 1992 and 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” and 2,4-D was classified as a Group D, not classifiable as to human carcinogenicity. The Agency has twice recently reviewed epidemiological studies linking cancer to 2,4-D. In the first review, completed January 14, 2004, EPA concluded there is no additional evidence that would implicate 2,4-D as a cause of cancer (EPA, 2004). The second recent review of available epidemiological studies occurred in response to comments received during the Phase 3 Public Comment Period during the reregistration process for 2,4-D. EPA’s report, dated December 8,
2004 and authored by Jerry Blondell, Ph.D., found that none of the more recent epidemiological studies definitively linked human cancer cases to 2,4-D.

B. Environmental Risk Assessment

A summary of the Agency’s environmental risk assessment for 2,4-D is presented below. The Agency has conducted an assessment of potential risks to aquatic and terrestrial organisms resulting from the use of 2,4-D and its associated chemical forms including 2,4-D dimethylamine salt (2,4-D DMAS), 2,4-D isopropylamine salt (2,4-D IPA), 2,4-D triisopropanolamine salt (2,4-D TIPA), 2,4-D ethylhexyl ester (2,4-D EHE), 2,4-D butoxyethyl ester (2,4-D BEE), 2,4-D-diethanolamine salt (2,4-D DEA), 2,4-D isopropyl ester (2,4-D IPE) and 2,4-D sodium salt. In this document, the term “chemical form” is used to refer to the supported technical formulations listed above, while the term “formulation” refers to the physical nature (e.g. granular or emulsifiable concentrate) of the applied product, and the term “end use product” is used to refer to any formulated product including mixtures of pesticide sold in the United States.

2,4-D has the following registered uses, which result in environmental exposures: pasture/rangeland, turf, wheat, corn, soybeans, fallowland, hay other than alfalfa, noncropland (roadways, rights-of-way, ditches, industrial sites, etc.), forestry, rice, sugarcane, pome fruits, stone fruits, nut orchards, filberts, grass grown for seed and sod, aquatic weed control, potatoes, asparagus, strawberries, blueberries, grapes, cranberries, and citrus.

This summary will present exposure estimates and hazard determinations associated with 2,4-D and its various chemical forms. In addition, risks of concern, as determined in the environmental assessment, will be identified and characterized. More detailed information associated with the potential environmental risk from the use of 2,4-D can be found in the Environmental Fate and Effects Division’s Risk Assessment for the Reregistration Eligibility Document for 2,4-Dichlorphenoxyacetic Acid, (2,4-D), dated October 28, 2004. The complete environmental risk assessment is not included in this RED, but may be accessed in the OPP Public Docket (OPP-2004-0167) and on the Agency’s website at [http://www.epa.gov/pesticides/reregistration/status.htm](http://www.epa.gov/pesticides/reregistration/status.htm).

1. Environmental Exposure

   a. Environmental Fate and Transport

   The environmental fate database is sufficient to characterize the environmental exposure associated with 2,4-D use. However, there are some studies that will be required as a result of the reregistration process. An aerobic aquatic metabolism study for 2,4-D BEE in acidic aquatic environments is required, along with several other dissipation studies. See section V.A.1 of this reregistration eligibility decision (RED) document for a complete list of all required studies. EPA intends to issue a DCI as part of this RED to require submission of additional data to address areas of uncertainty. These data are expected to confirm the conclusions of this environmental risk assessment.
Database

A complete database has been assembled for 2,4-D acid. The dissipation of 2,4-D appears to be dependent on oxidative microbial-mediated mineralization, photodegradation in water, and leaching. 2,4-D is stable to abiotic hydrolysis. Photodegradation of 2,4-D was observed [half life (t_{1/2}) =12.9 calendar days or 7.57 days of constant light] in pH 5 buffer solution. However, the 2,4-D photodegradation half-life on soil was 68 days.

Degradation Summary

The degradation of 2,4-D was rapid (t_{1/2} = 6.2 days) in aerobic mineral soils. The half-life of 2,4-D in aerobic aquatic environments was 15 days. 2,4-D was moderately persistent to persistent (t_{1/2} = 41 to 333 days) in anaerobic aquatic laboratory studies.

Several degradates were detected in the laboratory fate studies reviewed. The degradates detected were 1,2,4-benzenetriol, 2,4-DCP, 2,4-DCA, chlorohydroquinone (CHQ), 4-chlorophenol, volatile organics, bound residues, and carbon dioxide. For a complete listing of 2,4-D degradates for each route of degradation, please see the environmental risk assessment. No degradates were considered for further analysis in water or the terrestrial ecological assessment.

Mobility

2,4-D has a low binding affinity (K_{ad} < 3 and K_{de} < 1) in mineral soils and sediment. The mobility of 2,4-D in supplemental soil thin layer chromatography (TLC) studies was classified as intermediately mobile (R_f=0.41) to very mobile (R_f=1.00) in "sieved" mineral soils. Aged radiolabeled residues of 2,4-D appeared to be immobile in supplemental soil column studies. 2,4-D was studied in sandy loam, sand, silty clay loam and loam soil. Freundlich K_{ads} values were 0.17 for the sandy loam soil, 0.36 for the sand soil, 0.52 for the silty clay loam soil, and 0.28 for the loam soil. Corresponding K_{oe} values were 70, 76, 59 and 117 mL/g.

Bridging Strategy

The 1988 2,4-D Registration Standard proposed an environmental fate strategy for bridging the degradation of 2,4-D esters and 2,4-D amine salts to 2,4-D acid. The bridging provides information on the dissociation of 2,4-D amine salts and hydrolysis of 2,4-D esters is included in the ecological risk assessment. The bridging data indicate esters of 2,4-D are rapidly hydrolyzed in alkaline aquatic environments, soil/water slurries, and moist soils. The 2,4-D amine salts have been shown to dissociate rapidly in water. However, 2,4-D esters may persist under sterile acidic aquatic conditions and on dry soil. These bridging data indicate under most environmental conditions 2,4-D esters and 2,4-D amines will degrade rapidly to form 2,4-D acid.

2,4-D Amine Salts

Additional data submitted subsequent to establishment of the environmental fate bridging strategy generally support the strategy for the amine salts. Direct evidence of the stability of 2,4-D amine salts in soil and aquatic environments is difficult due to the lack of analytical methods. Based on maximum application rates for 2,4-D amine salts (at 4 lbs ae/A), 2,4-D amine salts are expected to fully dissociate in soil environments because their theoretical concentrations in soil solution does not exceed water solubilities. Additionally, dissociation studies indicate the time for complete
dissociation is rapid (less than 3 minutes). Although the analytical methods in the field studies for 2,4-D DMAS were not capable of separating and identifying 2,4-D DMAS from 2,4-D acid, the most conservative half-lives of 2,4-D DMAS would be equivalent to the 2,4-D acid half-lives in field studies. Half-lives of 2,4-D in 2,4-DMAS field studies ranged from 1.1 days to 30.5 days with a median half-life of 5.6 days.

2,4-D Esters

The conversion of 2,4-D esters to the acid and an associated alcohol moiety is more difficult to generalize. Unlike the physical dissociation mechanism of 2,4-D amine salts, the de-esterification of 2,4-D esters is dependent on abiotic and microbial-mediated processes. Any environmental variable influencing microbial populations or microbial activity could theoretically influence the persistence of the 2,4-D ester. Soil properties including clay mineralogy, organic carbon content, temperature, and moisture content are known to influence hydrolysis rates (Wolfe, et al, 1989 and Wolfe, 1990).

Registrant-sponsored research indicates the 2,4-D esters (ethylhexyl, isopropyl, butoxyethyl) degrade rapidly (half life less than 24 hours) in soil slurries, aerobic aquatic environments, and anaerobic, acidic aquatic environments. In terrestrial field dissipation studies for 2,4-D EHE, the half-lives for 2,4-D EHE ranged from 1 to 14 days with median half-life of 2.9 days. 2,4-D BEE, applied as a granule formulation, degraded rapidly in the water column in aquatic field dissipation studies under alkaline conditions. However, the 2,4-D BEE residues were detected in sediment samples from Day 0 (immediately posttreatment) to 186 days posttreatment. It is unclear whether 2,4-D BEE persistence in sediment is due to the slow release of the granule formulation or to slow deesterification of sediment bound 2,4-D BEE. Available open-literature and registrant sponsored laboratory data would suggest slow granule dissolution prolonged the persistence of 2,4-D BEE. In forest dissipation studies, the 2,4-D EHE ester degraded slowly on foliage and in leaf litter.

Persistant of 2,4-D Amine Salts and 2,4-D Esters

The weight of evidence from open-literature and registrant sponsored data indicates that 2,4-D amine salts and 2,4-D esters are not persistent under most environmental conditions including those associated with most sustainable agricultural conditions. 2,4-D amine salt dissociation is expected to be instantaneous (< 3 minutes) under most environmental conditions. Although the available data on de-esterification of 2,4-D ester may not support instantaneous conversion from the 2,4-D ester to 2,4-D acid under all conditions, it does show 2,4-D esters in normal agriculture soil and natural water conditions are short lived compounds (< 2.9 days). Under these conditions, the environmental exposure from 2,4-D esters and 2,4-D amines is expected to be minimal in both terrestrial and aquatic environments.

b. Aquatic Organism Exposure

For exposure to aquatic fish and invertebrates, EPA considers surface water exposure only, since most aquatic organisms are not found in ground water. Surface water models are used to estimate exposure to freshwater aquatic animals. Unlike the drinking water assessment described in the human health risk assessment section of this document, the ecological water resource assessment does not include the Index Reservoir (IR) and Percent-Crop Area (PCA) factor refinements. The IR
and PCA factors represent a drinking water reservoir, not the variety of aquatic habitats, such as ponds adjacent to treated fields, relevant to a risk assessment for aquatic animals. Therefore, the EEC values used to assess exposure to aquatic animals are not the same as the values used to assess human dietary exposure from drinking water sources.

1) Exposure to 2,4-D Acid in Surface Water

The aquatic exposure assessment for 2,4-D has relied on a combination of monitoring data and modeling. Both Tier I (SCiGROW and screening level models for aquatic uses) and Tier II (PRZM/EXAMS) models have been used to estimate exposure to 2,4-D and its various chemical forms in a variety of exposure scenarios. Concentrations used for ecological assessment are 62.8 µg ae/L for peak, 55.1 µg ae/L for the 21-day average concentration, and 45.4 µg ae/L for the 60-day average. The predicted 2,4-D concentrations in surface water are slightly higher than reported monitoring data. The modeling predictions are expected to indicate upper bound concentration ranges for 2,4-D. Model input and output files for the ecological assessment may be found in the ecological risk assessment for 2,4-D.

2) Surface Water Modeling of 2,4-D Esters

The Agency’s strategy for bridging the fate data requirements for the ester and amine salt forms of 2,4-D to the acid form was supported by laboratory data which indicated rapid conversion of the amine and ester forms of 2,4-D to the acid form. However, 2,4-D esters may persist under acidic aquatic conditions. In order to account for the potential impact of the spray application of 2,4-D esters to aquatic environments, and to account for runoff during the time in which 2,4-D EHE may remain in the field, the Agency conducted additional modeling with PRZM/EXAMS to assess the potential for aquatic organisms to be exposed to 2,4-D EHE through spray drift or runoff. The peak (acute) estimated environmental concentrations (EECs) for the 2,4-D esters were estimated for each scenario and range from 0.6 µg ae/L (CA citrus) to 7.4 µg ae/L (NC pasture). A chronic EEC was not provided in this scenario because the hydrolysis soil slurry data indicate that dissipation in a non-sterile water body will occur at all pHs and therefore long-term exposures are unlikely.

3) Modeling of Direct Application of 2,4-D for Control of Aquatic Weeds

Because there are no aquatic herbicide model scenarios, a first approximation of an aquatic ecological EEC was predicted assuming direct application to the standard pond. For this assessment, the Agency developed a simple spreadsheet model that incorporates degradation based on an acceptable aerobic aquatic metabolism study for the EFED standard pond with no flow. In this model, the 21-day average and 60-day average concentrations were calculated assuming first-order dissipation from aerobic aquatic degradation, but does not assume dissipation.

The interpretation of the label for aquatic weed control is that the target rate for 2,4-D amine (2,4-D DMAS) and ester (2,4-D BEE) use is based on concentration and not application rate. In order to account for this scenario it was assumed that 2,4-D would be applied at a rate to meet the target concentration of 4000 µg/l. This assumption would be applicable across all water bodies since
the target rate is based on a rate per acre foot of water (10.8 lbs ae/acre-foot) and would be independent of water body geometry/volume. This scenario included the assumption of uniform application across the entire water body; however, this application scenario will over-predict actual concentrations because 2,4-D is not applied to more than 50% of a water body in a single treatment. Treating more than 50% of a water body will result in oxygen depletion due to decaying plant material. Typically, 2,4-D is applied to control aquatic weeds in littoral zones that make up less than 50% of the water body. Modeling the 2,4-D concentration that results when 100% of the water body is treated predicts direct water application of 2,4-D will yield surface water concentrations of 2,4-D concentrations in the EFED standard pond of 4000 ug ae/L for peak, 3417 ug ae/L for the 21-day average, and 2610 ug ae/L for the 60-day average. Actual concentrations are expected to be less given the conservative treatment area assumption as described above, and the likely effects of dispersion on 2,4-D concentrations.

EFED evaluated the potential for exposure to 2,4-D BEE using a similar approach. Modeling predicts direct water application of 2,4-D BEE will yield surface water concentrations of 2,4-D BEE concentrations in the EFED standard pond of 624 ug/L for peak (24 hour average), 30 ug/L for the 21-day average, and 10 ug/L for the 60-day average.

4) Modeling of 2,4-D Use on Rice

Finally, the use of 2,4-D on rice was evaluated using a screening level model. 2,4-D is registered for use in rice paddies for the acid and amine salt forms of 2,4-D (esters are not registered for rice use) with a maximum seasonal application rate of 1.5 pounds ae per acre. Modeling of this use rate results in an estimated acute 2,4-D concentration in the rice paddy of 1431 ug ae/L. This value is expected to represent upper percentile concentrations for edge of paddy concentrations because of the lack of consideration for degradation, dilution and dispersion. EFED conducted a preliminary evaluation of the effect of degradation and holding times on EECs for the use of 2,4-D on rice. As with the previous rice model, this refined model provides a single EEC which represents both an acute and chronic exposure and is an approximation of the EEC at the point of release into a receiving water body. Modeling with all three scenarios predict initial concentrations in the paddy water between 678 ug ae/L (California) and 762 ug ae/L (Louisiana) and decreasing concentrations with holding times based on degradation due to aerobic aquatic metabolism.

c. Terrestrial Organism Exposure

The Agency assessed exposure to terrestrial organisms by first predicting the amount of 2,4-D residues found on animal food items and then by determining the amount of pesticide consumed by using information on typical food consumption by various species of birds and mammals. The amount of residues on animal feed items are based on the Fletcher nomogram (a model developed by Fletcher, Hoerger, Kenaga, et al.) and the current maximum application rate as stated in the Master Label for 2,4-D. For terrestrial uses of 2,4-D, the Master Label allows a maximum single application of 4 lbs ae/A and up to two 2 lbs ae/A applications per season for a total seasonal maximum rate of 4
lbs ae/A. Therefore, for terrestrial uses, EPA modeled the maximum and mean residues of 2,4-D in various food items immediately after the 4 lb lbs ae/A application. The Agency assumed no dilution due to the growth of the plants or degradation of 2,4-D. EPA’s estimates of 2,4-D residues on various wild animal food items are summarized in Table 26. EPA used these EECs and standard food consumption values to estimate dietary exposure levels for 2,4-D to birds and mammals.

Table 26. Estimated Environmental Concentrations on Avian and Mammalian Food Items (ppm) Following a Single Application at 1 lb ae/A

<table>
<thead>
<tr>
<th>Food Items</th>
<th>EEC (ppm) Predicted Maximum Residue(^1)</th>
<th>EEC (ppm) Predicted Mean Residue(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short grass</td>
<td>240</td>
<td>85</td>
</tr>
<tr>
<td>Tall grass</td>
<td>110</td>
<td>36</td>
</tr>
<tr>
<td>Broadleaf/forage plants and small insects</td>
<td>135</td>
<td>45</td>
</tr>
<tr>
<td>Fruits, pods, seeds, and large insects</td>
<td>15</td>
<td>7</td>
</tr>
</tbody>
</table>

\(^1\) Predicted maximum and mean residues are for a 1 lb ae/a application rate and are based on Hoerger and Kenaga (1972) as modified by Fletcher et al. (1994).

1) Birds and Mammals

The Agency expects exposure to birds and mammals from residues of 2,4-D on food items. Exposure is probable because 2,4-D is applied in many different environments that provide habitats rich in food sources attractive to various avian and mammalian species.

   a) Exposure to Nongranular (Liquid) Formulations

   Toxicant concentrations on food items following multiple applications are predicted based on a first-order residue decline using the Agency's FATE5 model. The FATE5 model allows determination of residue dissipation over time by incorporating degradation half-life. Predicted maximum and mean EECs resulting from multiple applications are calculated by taking into account the maximum or mean initial EEC from the first application, the total number of applications, the time interval between applications, and a first-order foliar degradation rate of 8.8 days.

   b) Exposure to Granular Formulations

   Birds and small mammals may be exposed to granular formulations through ingestion of granules. The number of lethal doses (LD\(_{50}\)) that are available within one square foot immediately after application (LD\(_{50}/\text{ft}^2\)) is used as the risk quotient (RQ) for granular products. RQs are calculated for three separate weight classes of birds (1000 g, 180 g, and 20 g) and mammals (15 g, 35 g, and 1000 g, 35 g, and 15 g).

2) Non-target Terrestrial Plants
Due to the differences in the solubilities of the acid and amine salts when compared to the solubilities of the esters, risks for these two groups were calculated separately for the non-target terrestrial plant risk assessment. The terrestrial plant toxicity data for the 2,4-D acid and amine salts were bridged as one group, while that of the esters were bridged as another group.

Terrestrial plants inhabiting dry and semi-aquatic areas may be exposed to pesticides from runoff, spray drift or volatilization. EPA’s runoff exposure estimate assumes a 1-in-10 year rain event and is based on a pesticide's water solubility and the amount of pesticide present on the soil surface and its top one inch, characterized as "sheet runoff" (one treated acre to an adjacent acre) for dry areas, characterized as "channelized runoff" (10 treated acres to a distant low-lying acre) for semi-aquatic areas, and is based on percent runoff values of 0.01, 0.02, and 0.05 for water solubility of <10 ppm, 10-100 ppm, and >100 ppm, respectively. The modeled runoff exposure estimates likely overestimate actual exposures from runoff, given the conservative 1-in-10 year rain event assumption, and also given that farming practices, intended to minimize soil loss from runoff, are not taken into account.

Spray drift exposure from ground and overhead chemigation applications is assumed to be 1% of the application rate. Spray drift from aerial, airblast, and forced-air applications is assumed to be 5% of the application rate with an application efficiency (i.e., the amount that lands on the target area) of 60%. The effects of multiple applications are addressed by summing the application rates from individual applications.

Applications of granular formulations may pose risks to terrestrial plants inhabiting dry and semi-aquatic areas. Exposure is assumed to be from runoff only, and drift is assumed not to occur with granular applications of pesticides. Therefore, the Agency's runoff scenario is essentially the same as that used in the non-granular scenario described above, with the exception that the drift component is removed.

The EECs for the acid and amine salts as well as the esters to dry and semi-aquatic areas are tabulated in Appendix F of the 2,4-D ecological risk assessment for single applications to the targeted use sites. The percent runoff value based on water solubility is assumed to be 5% for the acid and amines and 1% for the esters.

2. Environmental Effects (Toxicity)

a. Toxicity to Aquatic Organisms

Freshwater and Estuarine/Marine Fish

The available acute toxicity data on 2,4-D indicate that the acid and amine salts are practically non-toxic to freshwater or marine fish. The esters are highly to slightly toxic to marine or freshwater fish. Toxicities for the acid and amine salts range from a LC₅₀ of >80.24 to 2244 milligrams acid equivalent per liter (mg ae/L). The ester toxicities range from a LC₅₀ of >0.1564 to 14.5 mg ae/L.
Chronic toxicity, based on length and larval survival from the early life stage studies, range from a NOEC of 14.2 to 63.4 mg ae/L for 2,4-D acid, 2,4-D DEA and 2,4-D DMAS. The NOEC based on larval fish survival for the fish full life cycle studies ranged from 0.0555 to 0.0792 mg ae/L for 2,4-D BEE and 2,4-D EHE.

**Amphibians**

Although not currently required by the Agency, freshwater amphibian studies were conducted on frog tadpoles (Rana pipiens). Tests were conducted using the ASTM (American Society for Testing and Materials) Standard E729-88a. Tests indicate that 2,4-D acid, 2,4-D DMA, and 2,4-D EHE are practically non-toxic to tadpoles.

**Freshwater and Estuarine/Marine Invertebrates**

Acute toxicity of 2,4-D acid and amine salts to freshwater aquatic invertebrates ranges from a LC50 of 25 to 642.8 mg ae/L (slightly toxic to practically non-toxic). The freshwater toxicities of the esters range from 2.2 mg ae/L for the 2,4-D IPE to 11.88 mg ae/L for the 2,4-D EHE (moderately toxic to slightly toxic). The freshwater invertebrate LC50 s range from >0.092 to >66 mg ae/L for the 2,4-D esters (highly toxic to practically non-toxic). These toxicities indicate that the esters are more toxic than the acid and amine salts. Although acute data are missing for some of the amine salts, these studies will not be required because none of the RQs exceed the aquatic levels of concern for the acid amine salts.

Chronic toxicity tests for freshwater and estuarine/marine invertebrates were performed on 2,4-D acid, 2,4-D DEA, 2,4-D DMAS, and 2,4-D BEE. The toxicity ranged from a NOEC of 16.05 mg ae/l for 2,4-D DEA (survival and reproduction) and 79 mg ae/L for the 2,4-D acid (number of young). The chronic freshwater NOEC is 0.20 mg ae/L for the 2,4-D BEE (survival and reproduction). There are no freshwater or marine chronic toxicity data for any of the other 2,4-D esters.

Although an estuarine/marine invertebrate life-cycle toxicity test using the TGAI is required to establish the toxicity of products containing the 2,4-D acid, salts, and amines, a chronic study will not be required. The data from the freshwater invertebrate studies will be bridged to the estuarine/marine invertebrates for the 2,4-D acid and amine salts. The RQs for the freshwater chronic studies were well below the levels of concern, and the chronic risk for estuarine/marine invertebrates would be expected to be low. However, there is a risk concern for estuarine/marine invertebrates for the 2,4-D esters. A chronic study will be required for 2,4-D BEE to reduce the uncertainty to estuarine/marine invertebrates.

**Aquatic Plants**

The vascular plant EC50 toxicity data for the acid and amine salts range from 0.29 mg ae/L for 2,4-D DEA to 1.28 mg ae/L for 2,4-D TIPA. The EC50 toxicity data for the more toxic esters range from 0.33 mg ae/L for 2,4-D EHE to 0.3974 mg ae/L for 2,4-D BEE. The same trend is shown for the...
non-vascular plant EC₅₀. The nonvascular plant EC₅₀ toxicity data range for the acid and amine salts is 3.88 to 156.5 mg ae/L for 2,4-D DMA. The range for the esters is 0.066 mg ae/L for 2,4-D EHE to 19.8 mg ae/L for 2,4-D EHE. In addition, based on the data available, it appears that the vascular plants are more than two orders of magnitude more sensitive than the non-vascular plants.

**b. Toxicity to Terrestrial Organisms**

The bird and mammal toxicity values of the 2,4-D acid, salts, amine salts, and esters were pooled because the toxicity values were within one to two orders of magnitude for all the chemical forms.

**Birds**

Toxicity ranges for birds do not show distinct differences between the acid, salts, amine salts, and esters, as indicated for aquatic animals. All studies have been conducted with the active ingredient, and have been converted to the acid equivalent since use rates on the master label are given in pounds acid equivalent per acre.

2,4-D is classified as moderately toxic to practically non-toxic to birds on an acute oral basis, since the oral LD₅₀ ranges from 500 mg ai/kg (415 mg ae/kg) for 2,4-D DMAS to >1000 mg ae/kg for the 2,4-D acid.

The chronic NOEC of 962 ppm is based on the endpoints of eggs cracked and a decreased number of eggs laid for the 2,4-D acid. There is no comparable study for the mallard duck and no other avian chronic study was performed on any of the other active ingredients.

**Mammals**

The Agency expects exposure to mammals from residues of 2,4-D on food items, since 2,4-D is used in many different mammalian habitats, including pasture and rangeland, and turf lawns. Toxicity ranges for mammals do not show distinct differences between the acid, salts, amine salts, and esters as indicated for aquatic animals. All studies have been conducted with the active ingredient, and have been converted to the acid equivalent since all use rates on the master label are given in pounds acid equivalent per acre. The rat LD₅₀ ranged from 579 to 1300 mg ae/kg.

Mammalian chronic toxicity values are from rat and rabbit developmental toxicity studies for the 2,4-D acid and all amine salts, and esters. In addition, the 2-generation rat study is also available for the 2,4-D acid. The NOAEL in the rat chronic toxicity study was 5 mg/kg/day, with a LOAEL of 75 mg/kg/day based on decreased body-weight gain and alterations in hematology. The NOAEL in the rabbit developmental toxicity study was 30 mg/kg/day, and the LOAEL was 90 mg/kg/day based on clinical signs, loss of righting reflex, and abortions.
Non-Target Insects

Available data from a honey bee acute toxicity study indicated that technical 2,4-D is practically non-toxic to the honey bee. The LD$_{50}$ in the honey bee acute toxicity study is greater than 10 micrograms per bee; see MRID 445173-04 for 2,4-D DMA and MRID 445173-01 for 2,4-D EHE. Minimal risk is expected to non-target insects from 2,4-D use.

Terrestrial Plants

The terrestrial plant runoff exposure scenario is based on the solubility of the 2,4-D compound. The water solubilities differ greatly between 2,4-D esters and 2,4-D acid and amine salts. The terrestrial plant toxicity values for 2,4-D acid and amine salts is summarized in Table 27, and have been listed as the acid equivalent. The sensitivity ranges for the monocot and dicot species are listed for the seedling emergence and vegetative vigor studies.

Table 27. Terrestrial Plant Toxicity Summary for 2,4-D Acid and amine salts

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Most sensitive Crop / Active Ingredient</th>
<th>EC25 / NOEC (lb ae/A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seedling Emergence</td>
<td>Monocot Sorghum / 2,4-D DMAS</td>
<td>0.026 / 0.015</td>
</tr>
<tr>
<td></td>
<td>Dicot Mustard / 2,4-D DEA</td>
<td>0.045 / &lt;0.045</td>
</tr>
<tr>
<td>Vegetative Vigor</td>
<td>Monocot Onion / 2,4-D Acid</td>
<td>&lt;0.0075 / &lt;0.0075</td>
</tr>
<tr>
<td></td>
<td>Dicot Tomato / 2,4-D DEA</td>
<td>0.003 / 0.002</td>
</tr>
</tbody>
</table>

The terrestrial plant toxicity for the 2,4-D esters is summarized in Table 28. The sensitivity ranges for the monocot and dicot species are listed for the seedling emergence and vegetative vigor studies.

Table 28. Terrestrial Plant Toxicity Summary for 2,4-D Esters

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Most sensitive Crop / Active Ingredient</th>
<th>EC25 / NOEC (lb ae/A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seedling Emergence</td>
<td>Monocot Onion / 2,4-D IPE</td>
<td>0.01 / 0.005628</td>
</tr>
<tr>
<td></td>
<td>Dicot Lettuce / 2,4-D IPE</td>
<td>0.00081 / 0.00047</td>
</tr>
<tr>
<td>Vegetative Vigor</td>
<td>Monocot Corn / 2,4-D IPE</td>
<td>0.2016 / 0.0252</td>
</tr>
<tr>
<td></td>
<td>Dicot Lettuce / 2,4-D IPE</td>
<td>0.00126 / 0.006132</td>
</tr>
</tbody>
</table>

3. Ecological Risk Estimation (RQs)

The Agency’s ecological risk assessment compares toxicity endpoints from ecological toxicity studies to estimated environmental concentrations (EECs) based on environmental fate characteristics and pesticide use data. To evaluate the potential risk to non-target organisms from the use of 2,4-D
products, the Agency calculates a Risk Quotient (RQ), which is the ratio of the EEC to the most sensitive toxicity endpoint values. These RQ values are then compared to the Agency’s levels of concern (LOCs), given in Table 29, which indicate whether a pesticide, when used as directed, has the potential to cause adverse effects on non-target organisms. When the RQ exceeds the LOC for a particular category (e.g., endangered species), the Agency presumes a risk of concern to that category. These risks of concern may be addressed by further refinements of the risk assessment or by mitigation. Use, toxicity, fate, exposure, and incidents are considered when characterizing the risk, as well as the levels of uncertainty in the assessment.

Table 29. EPA’s Levels of Concern and Associated Risk Presumptions.

<table>
<thead>
<tr>
<th>Risk Presumption</th>
<th>LOC terrestrial animals</th>
<th>LOC aquatic animals</th>
<th>LOC Plants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Risk - there is potential for acute risk; regulatory action may be warranted in addition to restricted use classification.</td>
<td>0.5</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Acute Restricted Use - there is potential for acute risk, but may be mitigated through restricted use classification.</td>
<td>0.2</td>
<td>0.1</td>
<td>N/A</td>
</tr>
<tr>
<td>Acute Endangered Species - endangered species may be adversely affected; regulatory action may be warranted.</td>
<td>0.1</td>
<td>0.05</td>
<td>1</td>
</tr>
<tr>
<td>Chronic Risk - there is potential for chronic risk; regulatory action may be warranted.</td>
<td>1</td>
<td>1</td>
<td>N/A</td>
</tr>
</tbody>
</table>

For a more detailed explanation of the ecological risks posed by the use of 2,4-D, refer to Environmental Fate and Effects Division’s Risk Assessment for the Reregistration Eligibility Document for 2,4- Dichlorophenoxyacetic Acid (2,4-D), dated October 28, 2004.

a. Risk to Aquatic Organisms

The RQs for aquatic organisms are presented in detail in Appendix F of the ecological risk assessment for 2,4-D.

1) Fish and Aquatic Invertebrates

There were no acute or chronic Level of Concern (LOC) exceedances for aquatic organisms through use of 2,4-D acid and amine salts due to runoff/drift from use on terrestrial sites, no acute LOC exceedances for aquatic organisms due to drift-only of 2,4-D esters to water bodies from use on terrestrial sites, and, there were no acute LOC exceedances for aquatic organisms due to the runoff/drift of 2,4-D esters to water bodies from use on terrestrial sites. Chronic concerns were not evaluated for terrestrial uses of 2,4-D esters.

Estimated risk quotients (RQs) from use of 2,4-D acid and amine salts in aquatic weed control through direct subsurface application to water bodies exceed the restricted use LOCs for freshwater
invertebrates. There are no chronic LOC exceedances for this use. Estimated RQs for use of 2,4-D BEE in weed control through direct subsurface application to water bodies exceed the acute risk LOC for freshwater fish and invertebrates and chronic risk LOC for freshwater and estuarine fish and freshwater invertebrates when compared on an acid equivalent basis.

Additional characterization of the potential risk associated with the direct application of 2,4-D for aquatic weed control was completed by back-calculating the target concentration needed to reduce EECs below LOCs. This type of consideration provides context to the characterization of potential risk and indicates that for all 2,4-D chemical forms target concentration reduction of up to 10-fold still exceeds all LOCs for aquatic organisms.

While noting the potential risks identified above, it is important to note the benefits gained through the direct application of 2,4-D to aquatic bodies, for the control of invasive species. The U.S Army Corps of Engineers (USACE), among others, has identified 2,4-D as an important tool for protecting the nation's waters from the invasion and establishment of some of the world's worst species of exotic nuisance vegetation. 2,4-D has a reputation as a selective and economical means to remove invasive plants, enhance the growth and recovery of desirable native vegetation, restore water quality, reduce sedimentation rates in reservoirs, and improve fish and wildlife habitat. 2,4-D products are used to control invasive weeds, such as Eurasian watermilfoil (*Myriophyllum spicatum*) in the northern tier states and water hyacinth (*Eichhornia crassipes*) in the Gulf Coast states. Effective control of these plants can benefit public health with respect to reducing levels of mosquito habitat. In addition, according to USACE, no other product (or alternative technique) can control these plants in a more cost-effective manner (K. Getsinger, USACE, Public Comment; Docket ID# OPP-2004-0167-0053).

Estimated RQs for use of 2,4-D acid and amine salts in rice paddies exceed the acute endangered species LOCs for freshwater invertebrates. The rice model used to predict these EECs is a screening level model which predicts concentration in tailwater at the point of release from the paddy. It is anticipated that once released, the concentration will be reduced and subsequently is expected to decrease away from the point of release. Additional characterization was conducted by considering average application rates (average rates are presented in the quantitative usage analysis dated August 9, 2001 prepared by the Biological and Economic Affairs Division of EPA/OPP) versus maximum label rates and assuming a proportional reduction in EECs. Consideration of average application rates results in EECs below the endangered species LOC.

### 2) Aquatic Plants

For non-target, aquatic plants, estimated RQs resulting from the runoff/drift of 2,4-D acid and amine salts from use on terrestrial crops exceed the aquatic vascular plant endangered species LOCs for use of 2,4-D acid and amine salts on pasture and apples. Consideration of average application rates and assuming a proportional reduction in EECs results in RQs below the endangered species LOC. Likewise, there are no LOC exceedances from the drift of the ester forms to aquatic water bodies or from the runoff of the ester forms to water bodies from use on terrestrial sites.
Estimated RQs for the scenario of direct application to water for aquatic weed control for 2,4-D acid and amine salts indicate acute and endangered species LOC exceedances for aquatic vascular plants and acute LOC exceedances for non-vascular plants, while estimated RQs for the use of 2,4-D BEE for direct application to water to control aquatic weeds exceed all LOCs for vascular and one acute LOC exceedance for non-vascular plants. Risk to endangered non-vascular plants is not evaluated because at this time there are no listed endangered nonvascular plant species. Additional characterization of potential risk for the direct application of 2,4-D for aquatic weed control was completed by back-calculating the target concentration needed to reduce the RQs below LOCs. This type of consideration provides context to the characterization of potential risk and indicates that for all 2,4-D chemical forms target concentration reduction of up to 100-fold still exceeds all LOCs for aquatic plants.

While noting the potential risks identified above, it is important to note the benefits gained through the direct application of 2,4-D to aquatic bodies, for the control of invasive species. The U.S Army Corps of Engineers (USACE), among others, has identified 2,4-D as an important tool for protecting the nation's waters from the invasion and establishment of some of the world's worst species of exotic nuisance vegetation. 2,4-D has a reputation as a selective and economical means to remove invasive plants, enhance the growth and recovery of desirable native vegetation, restore water quality, reduce sedimentation rates in reservoirs, and improve fish and wildlife habitat. 2,4-D products are used to control invasive weeds, such as Eurasian watermilfoil (Myriophyllum spicatum) in the northern tier states and water hyacinth (Eichhornia crassipes) in the Gulf Coast states. Effective control of these plants can benefit public health with respect to reducing levels of mosquito habitat. In addition, according to USACE, no other product (or alternative technique) can control these plants in a more cost-effective manner (K. Getsinger, USACE, Public Comment; Docket ID# OPP-2004-0167-0053).

Estimated RQs for use of 2,4-D acid and amine salts in rice paddies exceed the acute and endangered species LOCs for aquatic vascular plants. Consideration of average application rates results in RQs below the endangered species LOCs.

b. Risk to Non-target Terrestrial Organisms

1) Birds

The RQs for birds are presented in detail in Appendix F of the ecological risk assessment for 2,4-D. Potential risks were evaluated for non-granular and granular formulations applied both as banded and broadcast applications.

EPA has relied on risk estimates from oral gavage studies on birds (LD₅₀ of 415 mg ae/kg-bw) to assess risk because no definitive endpoint was determined from dietary studies. Therefore, it is likely that the risk estimates associated with the gavage studies overestimate the actual exposure of birds in the field. For predicted maximum exposures when compared with oral gavage data there are exceedances of acute LOCs for all use sites except potatoes and citrus for most small birds and some medium birds. There are also exceedances of acute restricted use and endangered species LOCs for medium and large birds feeding on short grass, tall grass, and broadleaf forage/small insects at all use sites except potatoes and citrus. However, comparison with the lowest dietary LC₅₀ of >5620 mg
ae/kg-diet would result in no acute LOC exceedances. As noted previously, no definitive endpoint was available from the avian acute dietary studies and, hence, risk was not evaluated using this endpoint.

The RQs are presented below in Table 30 for the avian risk due to 2,4-D residues on various food items.

Table 30. Avian Risk Quotient Summaries for Non-granular Spray Applications of 2,4-D acid, amine salts and esters

<table>
<thead>
<tr>
<th>Use Site (Acute &amp; Chronic Risk)</th>
<th>Scenario</th>
<th>Short Grass</th>
<th>Tall Grass</th>
<th>Broadleaf, forage, small insects</th>
<th>Fruit, large insects,</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fallow areas and Crop Stubble; Turf (Golf courses, Residential Lawns, Grasses Grown for Seed, and Sod); Pastures, Rangeland, Perennial Grassland; Sugarcane (2 lbs ae/A/app, 2 app., ground/aerial, 30 day interval)</td>
<td>Acute RQ Exceedance</td>
<td>0.1* - 1.91***</td>
<td>0.04 - 0.88***</td>
<td>0.04 - 0.78***</td>
<td>-</td>
</tr>
<tr>
<td>Non-Cropland (Fencerows, Hedgerows, Roadsides, Ditches, Rights-of-Way, Utility Power Lines, Railroads, Airports, Industrial Sites, etc.); Forest Uses, Cranberry (4.0 lbs ae/A/app, 1 app., ground/aerial,)</td>
<td>Acute RQ Exceedance</td>
<td>0.18* - 3.5***</td>
<td>0.07 - 1.6***</td>
<td>0.07 - 1.43***</td>
<td>0.01 - 0.15*</td>
</tr>
<tr>
<td>Fruit, Small Grains (Except Corn), Asparagus (1.4 to 2.0 lbs ae/A/app)</td>
<td>Acute RQ Exceedance</td>
<td>0.09 - 1.75***</td>
<td>0.04 - 0.81***</td>
<td>0.03 - 0.72***</td>
<td>-</td>
</tr>
<tr>
<td>Corn (1.5 lbs ae/A/app, 2 app., 7 day interval, ground or aerial)</td>
<td>Acute RQ Exceedance</td>
<td>0.1* - 2.07***</td>
<td>0.04 - 0.81***</td>
<td>0.03 - 0.72***</td>
<td>-</td>
</tr>
</tbody>
</table>

* indicates an exceedance of Endangered Species Level of Concern (LOC). ** indicates an exceedance of Acute Restricted Use LOC. *** indicates an exceedance of Acute Risk LOC.

Chronic risk calculations resulted in RQ’s of 1.0 to 1.1 on birds which forage on short grass when the application rate of 2,4-D ranges from 2.0 to 4.0 lb ae/A such as seen with rights-of-way, cranberries or asparagus. The chronic risk LOC is 1.0.

Non-granular Banded Applications - According to the Master Label for 2,4-D, products that allow for banded applications of sprays to row crops require all formulators to adjust the application rates according to a formula provided. Many current labels do not advise applicators to adjust the application rates, and the resulting treatment can be interpreted to concentrate the per acre application rate into a narrow band. Birds, at least in theory, could be exposed to the higher concentration of toxicant by foraging or wandering into the treated band. EPA/OPP evaluated the banded risk by comparing the RQs from unadjusted band rates to those using the adjusted band rates to illustrate the increased risk. OPP assumed a 6 inch band and 30 inch row space as a typical banded application. The RQs indicate that levels of concern are not exceeded for 1000 g birds for rates adjusted due to band widths. LOCs are also not exceeded for these adjusted rates for potatoes for all weight classes of birds. The unadjusted band width rate, however, exceeds LOCs for all weight classes of birds for all uses with the exception of potatoes.

Granular Broadcast Applications - Acute RQs for granular products are calculated for three separate
weight classes of birds using the LD_{50}/ft^2: 1000 g (e.g., waterfowl), 180 g (e.g., upland gamebird), and 20 g (e.g., songbird). The acute RQs for broadcast applications of granular products are tabulated below for the use sites from the 2,4-D Master Label which support granular formulations.

Table 31: Avian Acute Risk Quotient Calculations for Granular Broadcast Applications

<table>
<thead>
<tr>
<th>Bird Body Weight (g)</th>
<th>Acute RQ (LD_{50} per ft^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>5.02***</td>
</tr>
<tr>
<td>180</td>
<td>0.55***</td>
</tr>
<tr>
<td>1000</td>
<td>0.1*</td>
</tr>
</tbody>
</table>

**Non-Cropland** (4.0 lbs ae/A/app, 1 app., ground/airial,)
Aquatic areas (4.0 lb ae/A/app, 3 wks between apps)
Cranberry (4.0 lbs ae/A/app, 1 app., ground)

<table>
<thead>
<tr>
<th>Bird Body Weight (g)</th>
<th>Acute RQ (LD_{50} per ft^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>2.5***</td>
</tr>
<tr>
<td>180</td>
<td>0.3**</td>
</tr>
<tr>
<td>1000</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Turf** (2.0 lbs ae/A/app, 2 app., ground/airial, 30 day interval)
Aquatic areas - Ditchbank applications (2.0 lb ae/A/app., 2 app., ground)

<table>
<thead>
<tr>
<th>Bird Body Weight (g)</th>
<th>Acute RQ (LD_{50} per ft^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>13.55***</td>
</tr>
<tr>
<td>180</td>
<td>1.5***</td>
</tr>
<tr>
<td>1000</td>
<td>0.27**</td>
</tr>
</tbody>
</table>

**Aquatic areas - Surface application or subsurface injection** (10.8 lb ae/acre-foot to an average pond depth of 5 feet)

<table>
<thead>
<tr>
<th>Bird Body Weight (g)</th>
<th>Acute RQ (LD_{50} per ft^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>13.55***</td>
</tr>
<tr>
<td>180</td>
<td>1.5***</td>
</tr>
<tr>
<td>1000</td>
<td>0.27**</td>
</tr>
</tbody>
</table>

\[ RQ = \frac{\text{App. Rate (lbs ae)} \times 453,590 \text{ mg}}{\text{Acre}} \times \frac{\text{Acre}}{43,560 \text{ ft}^2} \times \frac{1}{\text{Animal weight (g)}} \times \frac{1000 \text{ g}}{1 \text{ kg}} \times \frac{\text{LD50 mg}}{\text{Kg}} \]

* indicates an exceedance of Endangered Species Level of Concern (LOC).
** indicates an exceedance of Acute Restricted Use LOC.
*** indicates an exceedance of Acute Risk LOC.

Granular Banded Applications - In addition to broadcast applications of granular formulations, a number of labels instruct the applicators to apply unincorporated banded treatments of granular products to crops. As explained for banded spray treatments above, many labels adjust application rates according to band width and row spaces, but many others do not. If banded granular applications were used at the same sites as banded spray applications, the risk would be similar.

2) Mammals

Acute LOCs for mammals feeding on plants and insects were exceeded when considering non-granular formulations, for all uses assessed for small and medium size mammals, except potatoes and citrus. There were no exceedances for granivores. Banded applications result in exceedances of acute LOCs at all use sites.

Mammalian chronic RQs range from 0.05 to 200 and chronic LOCs were exceeded in all cases with the exception of potatoes and citrus (large insects, seeds). Consideration of average application rates results in EECs below the LOCs for non-granular, granular, or banded applications. However, consideration of average application rates for non-granular, granular and banded applications did not result in exposure below the chronic LOC.
**Acute Exposure from Nongranular 2,4-D Products**  The acute RQs for broadcast applications of nongranular products are tabulated for herbivores/insectivores and granivores in Appendix F of the ecological risk assessment for 2,4-D. When the LD<sub>50</sub> of 1072 mg ai/kg (579 mg ae/kg) is used for in herbivore/insectivore RQ calculations, endangered species LOCs are exceeded at many sites for mammals foraging on short and tall grass, broadleaf plants, and small insects. The RQs range from 1.72 for asparagus to < 0.01 for potatoes. There are no LOC exceedances for granivorous mammals.

As described above for avian risk, in addition to broadcast spray, a number of labels instruct the applicators to apply unincorporated banded treatments of sprays to row crops. Using the same assumptions as described above for birds, the RQs for mammals are presented in Table 32. Again, for purposes of comparison, the unadjusted rates that appear on many of the current labels have been included. Using the mammalian LD<sub>50</sub> of 579 mg ae/kg, acute levels of concern are exceeded at all use sites and for 15, 35, and 1000 g mammals when banded rates are not adjusted. When the banded rates are adjusted, LOCs are not exceeded for 1000 g mammals. The results of these calculations are tabulated in Appendix F of the ecological risk assessment for 2,4-D.

**Acute Exposure to Granular 2,4-D Products**  - Mammalian species also may be exposed to granular pesticides by ingesting granules. The number of lethal doses (LD<sub>50</sub>) that are available within one square foot immediately after application can be used as a RQ (LD<sub>50</sub>/ft<sup>2</sup>) for the various types of exposure to pesticides. RQs are calculated for three separate weight classes of mammals: 15 g, 35 g, and 1000 g. The LOCs are exceeded for all sites with the following exceptions: no LOCs are exceeded for 1000 g mammals in turf, aquatic areas (ditchbanks and surface applications), or cranberries.

The acute RQs for broadcast applications of granular products are tabulated below for the use sites from the master label which support granular formulations.

**Table 32: Mammalian Acute Risk Quotient Calculations for Granular Broadcast Applications**

<table>
<thead>
<tr>
<th>Animal Body Weight (g)</th>
<th>Acute RQ (LD&lt;sub&gt;50&lt;/sub&gt; per ft&lt;sup&gt;2&lt;/sup&gt;)&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>4.8 ***</td>
</tr>
<tr>
<td>35</td>
<td>2.1 ***</td>
</tr>
<tr>
<td>1000</td>
<td>0.1 *</td>
</tr>
<tr>
<td>15</td>
<td>2.4 ***</td>
</tr>
<tr>
<td>35</td>
<td>1.0 ***</td>
</tr>
<tr>
<td>1000</td>
<td>??</td>
</tr>
<tr>
<td>15</td>
<td>12.9 ***</td>
</tr>
<tr>
<td>35</td>
<td>5.5 ***</td>
</tr>
<tr>
<td>1000</td>
<td>0.2 **</td>
</tr>
</tbody>
</table>

RQ = App. Rate (lbs ae) / Acre x 453,590 mg / Lb x Acre / 43,560 ft<sup>2</sup> x 1 / Animal weight (g) x 1000 g / 1 kg x Kg / LD<sub>50</sub> mg

* indicates an exceedence of Endangered Species Level of Concern (LOC).
** indicates an exceedence of Acute Restricted Use LOC.
*** indicates an exceedence of Acute Risk LOC.
**Chronic Exposure to Mammals** - The chronic RQs for broadcast applications of nongranular products are tabulated in Appendix F of the 2,4-D ecological risk assessment for all classes of mammals. The parental toxicity NOAELs ranged from 5 mg/kg/day based on female body weight gain and male renal tubule alteration for the 2,4-D acid. The FATE program was used to determine the maximum and 56-day average residues that occur in a one year time period. The application rate, minimum number of applications, and the interval between applications were determined from the 2,4-D Master Label and represent the highest single application rates. Levels of concern were exceeded in all cases with the exception of potatoes and citrus (large insects, seeds) and RQs ranged from 0.1 to 200.

3) **Non-Target Insects**

The Agency currently does not quantify risks to terrestrial non-target insects. RQs are therefore not calculated for these organisms. Since the test results from one of the salts (2,4-D DMAS) and 2,4-D EHE was practically non-toxic to honey bees (LD$_{50}$ of $>100$ µg/bee), the potential for 2,4-D and its salts and esters is predicted to pose minimal risk to pollinators and other beneficial insects.

4) **Non-target Terrestrial Plants**

Acute LOCs for both non-endangered and endangered terrestrial plants were exceeded for non-granular and granular uses at many use sites. Consideration of average application rates did not result in exposure below LOCs.

RQs for terrestrial plants in dry and semi-aquatic areas are calculated for multiple and single spray applications for endangered and non-endangered species. As mentioned above in the exposure section, the runoff scenarios are based on solubility, and as a consequence, the environmental concentrations must be calculated separately for the esters and the acid and amine salts. The environmental concentrations for the esters were calculated separately at a percent runoff value of 0.01, while that of the acid and amine salts were calculated at a value of 0.05. A 60% efficiency factor is also included for aerial applications. In addition, banded applications granular and non-granular formulations are also calculated. The detailed calculations for terrestrial plants are tabulated in Appendix F of the ecological risk assessment.

**Risk Quotient (RQ) Calculations** - To calculate the RQs for non-endangered plants the EC$_{25}$ value of the most sensitive species in the seedling emergence study is compared to runoff and drift exposure to determine the RQ (EEC/toxicity value). The EC$_{25}$ value of the most sensitive species in the vegetative vigor study is compared to the drift exposure to determine the acute RQ. RQs are calculated for the most sensitive monocot and dicot species.

**RQs for Endangered Plants** - To calculate the RQs for endangered plants the NOEC or EC$_{05}$ value of the most sensitive species in the seedling emergence study is compared to runoff and drift exposure (EEC/toxicity value). The NOEC or EC$_{05}$ value of the most sensitive species in the vegetative vigor study is compared to the drift exposure to determine the acute RQ. RQs are calculated for the most sensitive monocot and dicot species. The RQ ranges for single and multiple applications are summarized below for non-endangered and endangered plants for the acid and amine salts, and
separately for the esters.

- **Single Spray Applications** - Most use sites on the 2,4-D Master Label allow multiple applications. However, the following use sites are labeled for maximum application rate for a single application.

**Table 33. 2,4-D Use Sites With Maximum Labeling for a Single Application**

<table>
<thead>
<tr>
<th>Use Site</th>
<th>Application Rate/Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-crop ¹, Forest Uses, Cranberry</td>
<td>Ground &amp; Aerial Applications (4.0 lbs ae/A/app.,)</td>
</tr>
<tr>
<td>Strawberry, Rice</td>
<td>Ground &amp; Aerial Applications (1.5 lbs ae/ac/app.)</td>
</tr>
<tr>
<td>Grapes</td>
<td>Ground Applications (1.36 lbs ae/A/app.)</td>
</tr>
<tr>
<td>Sorghum, Soybean</td>
<td>Ground and Aerial Applications (1.0 lbs ae/A/app.)</td>
</tr>
<tr>
<td>Soybean</td>
<td>Ground &amp; Aerial Applications (1.0 lbs ae/A/app.)</td>
</tr>
<tr>
<td>Citrus</td>
<td>Ground or Aerial Applications (0.1 lbs ae/A/app.)</td>
</tr>
</tbody>
</table>

¹ Woody plants in rights-of-way. Other non-crop sites may have up to 2 applications of 2 lbs each.

The detailed RQ calculations for single applications are tabulated in detail in Appendix F of the ecological assessment for 2,4-D, and a summary is presented below.

**Table 34. Terrestrial Plant Risk Quotients for Single Applications**

<table>
<thead>
<tr>
<th>Chemical Group (acid / ester)</th>
<th>Plant Group (non-endangered / endangered)</th>
<th>Risk Quotient Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4-D Acid and Amine Salt</td>
<td>non-endangered</td>
<td>0.18 - 67</td>
</tr>
<tr>
<td></td>
<td>endangered</td>
<td>0.13 - 136</td>
</tr>
<tr>
<td>2,4-D Ester</td>
<td>non-endangered</td>
<td>&lt;0.01 - 543.21</td>
</tr>
<tr>
<td></td>
<td>endangered</td>
<td>0.04 - 936.17</td>
</tr>
</tbody>
</table>

**Multiple spray applications** - Most of the 2,4-D products on the 2,4-D Master Label allow second applications at prescribed intervals ranging from 7 to 30 days with the exception of pome fruit which allows a 75 day interval. The RQs for multiple applications follow a linear pattern for changes in application rates, and since a maximum of two applications is allowed, the RQ doubles for these applications. The detailed calculations are tabulated in detail in Appendix F of the 2,4-D ecological risk assessment, and a summary is presented below.

**Table 35. Terrestrial Plant Risk Quotients for Multiple Applications**

<table>
<thead>
<tr>
<th>Chemical Group (acid / ester)</th>
<th>Plant Group (non-endangered / endangered)</th>
<th>Risk Quotient Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4-D Acid and Amine Salt</td>
<td>non-endangered</td>
<td>0.19 - 157</td>
</tr>
<tr>
<td></td>
<td>endangered</td>
<td>0.19 - 272</td>
</tr>
</tbody>
</table>
**Chemical Group (acid / ester)** | **Plant Group (non-endangered / endangered)** | **Risk Quotient Range**
---|---|---
2,4-D Ester | non-endangered | 0.01 - 12
| endangered | 0.01 - 33

**Banded Spray Applications** - Banded spray applications are allowed on a number of labels and instruct the applicators to apply unincorporated banded treatments of sprays to row crops. Many labels adjust application rates according to band width and row spaces, but others do not. For the labels which do not adjust the application rates, the treatments could be more concentrated in the bands. Since non-target plants do not migrate from treated to untreated bands as is the case with birds and mammals, exposure to plants is characterized as "sheet runoff" (one treated acre to an adjacent acre) for dry areas and "channelized runoff" (10 treated acres to a distant low-lying acre) for semi-aquatic areas. Therefore, the higher per acre rates in the concentrated bands do not affect the exposure to non-target plants when label rates are not adjusted.

The 2,4-D Task Force proposal to require all formulators to adjust the application rates for banded applications will reduce the exposure to non-target plants. If we assume use of the same 6 inch band and 30 inch row space that we used for the analysis of birds and mammals, the per acre banded application rate would be reduced by 1/5 of the broadcast application rate. The RQs are detailed in Appendix F of the ecological risk assessment for 2,4-D, and summarized for multiple and single applications in the following table.

**Table 36. Non-target Plant Risk Quotient Summary of Adjusted Band Applications to Selected Row Crops.**

<table>
<thead>
<tr>
<th>Chemical Group (acid / ester)</th>
<th>Plant Group (non-endangered / endangered)</th>
<th>Risk Quotient Range (Single Applications)</th>
<th>Risk Quotient Range (Multiple Applications)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4-D Acid and Amine Salt</td>
<td>non-endangered</td>
<td>0.02 - 60</td>
<td>0.04 - 120</td>
</tr>
<tr>
<td></td>
<td>endangered</td>
<td>0.02 - 439</td>
<td>0.04 - 878</td>
</tr>
<tr>
<td>2,4-D Ester</td>
<td>non-endangered</td>
<td>&lt;0.01 - 27</td>
<td>&lt;0.01 - 54</td>
</tr>
<tr>
<td></td>
<td>endangered</td>
<td>&lt;0.01 - 47</td>
<td>&lt;0.01 - 94</td>
</tr>
</tbody>
</table>

**Granular Applications** - The only currently approved granular applications which are currently allowed on the master label are on grass grown for seed or sod, turf, cranberries, non-crop land, and aquatic weed control sites. The non-target terrestrial plant RQ summaries for the acid and amine salts for the esters are presented below. Detailed RQs are presented in Appendix F of the ecological risk assessment for 2,4-D.
Table 37. Non-target Plant Risk Quotient Summary of Granular Applications to Selected Uses.

<table>
<thead>
<tr>
<th>Chemical Group (acid / ester)</th>
<th>Plant Group (non-endangered / endangered)</th>
<th>Risk Quotient Range (Single Applications)</th>
<th>Risk Quotient Range (Multiple Applications)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4-D Acid and Amine Salt</td>
<td>non-endangered</td>
<td>2.2 - 77</td>
<td>4.4 - 154</td>
</tr>
<tr>
<td></td>
<td>endangered</td>
<td>2.2 - 133</td>
<td>4.4 - 266</td>
</tr>
<tr>
<td>2,4-D Ester</td>
<td>non-endangered</td>
<td>2.0 - 494</td>
<td>4.0 - 987.62</td>
</tr>
<tr>
<td></td>
<td>endangered</td>
<td>3.57 - 851</td>
<td>7.14 - 1702.12</td>
</tr>
</tbody>
</table>

1 Turf is only site for multiple applications of granular products.

4. Ecological Incidents

Aquatic Incidents

The EFED Ecological Incident Information System (EIIS) database reports pesticide incidents that have been voluntarily submitted to EPA by state agencies. The report assigns a certainty index of 0 (unrelated), 1 (unlikely), 2 (possible) 3 (probable) or 4 (highly probable) to each incident. In addition, a judgement of registered use, accidental misuse, intentional misuse, or undetermined is assigned. There were 227 incidents reported for 2,4-D, and 24 of these incidents were reported as aquatic incidents under the 2,4-D acid only.

The two “highly probable” registered use incidents occurred when 2,4-D was applied to corn and a railroad right-of-way. The corn application resulted in bluegill and largemouth bass mortalities in Missouri, while the right-of-way application resulted in a kill of 23,000 (presumably) fish.

The corn incident affected bluegill, catfish, crappie, fox squirrel, greengill, largemouth bass, silver minnow, smallmouth bass, sunfish and watersnake. This incident was determined to be “highly probable” and was not listed as a misuse, however, no residue analysis was obtained. Another incident was recorded as “possible” and the use was “undetermined.” The species affected included bass, catfish, crappie, grass carp, and perch.

Results from these incidents should be regarded with caution since it is not clear exactly which products or tank mixes might be involved. In addition, residue analysis was not available in almost all instances.

Terrestrial Incidents

There were 227 terrestrial incidents reported for 2,4-D, and 155 of these incidents were reported as plant incidents under the acid form only. Two incidents were reported as both terrestrial and aquatic.

Eighty-four incidents to plants were listed as registered uses and most were considered “probable.” Crop damage was reported to have occurred on numerous crops, but most common non-target plant damages occurred on grass and corn. However, most of these incidents resulted from applications to lawns/turf and corn, respectively.

Results from the incident reports should be regarded with caution since it is not clear exactly which products or tank mixes might be involved. In addition, residue analysis was not available in almost all instances.

5. Endangered Species Concerns
The Agency has developed the Endangered Species Protection Program to identify pesticides whose use may cause adverse impacts on endangered and threatened species, and to implement mitigation measures that address these impacts. The Endangered Species Act requires federal agencies to ensure that their actions are not likely to jeopardize listed species or adversely modify designated critical habitat. To analyze the potential of registered pesticide uses to affect any particular species, EPA puts basic toxicity and exposure data developed for REDs into context for individual listed species and their locations by evaluating important ecological parameters, pesticide use information, the geographic relationship between specific pesticide uses and species locations, and biological requirements and behavioral aspects of the particular species. This analysis will take into consideration any regulatory changes recommended in the RED that are being implemented at this time. A determination that there is a likelihood of potential impact to a listed species may result in limitations on use of the pesticide, other measures to mitigate any potential impact, or consultations with the Fish and Wildlife Service and/or the National Marine Fisheries Service as necessary.

The Endangered Species Protection Program as described in a Federal Register notice (54 FR 27984-28008, July 3, 1989) is currently being implemented on an interim basis. As part of the interim program, the Agency has developed County Specific Pamphlets that articulate many of the specific measures outlined in the Biological Opinions issued to date. The Pamphlets are available for voluntary use by pesticide applicators on EPA’s website at www.epa.gov/espp.

The preliminary risk assessment for endangered species indicates that 2,4-D exceeds the endangered species LOCs for the following combinations of analyzed uses and species:

- Estimated risk quotients (RQs) from use of 2,4-D DMAS in weed control through direct subsurface application to water bodies exceed the endangered species LOC for freshwater and estuarine fish, and estuarine invertebrates. However, there are currently no endangered estuarine/marine invertebrates.
- Estimated RQs from use of 2,4-D BEE in weed control through direct subsurface application to water bodies exceed the endangered species LOC for freshwater fish and invertebrates and estuarine fish.
- Estimated RQs from use of 2,4-D acid and amine salts in rice paddies exceed endangered species LOCs for freshwater invertebrates. The rice model used to predict these EECs is a screening level model which predicts concentration in tailwater at the point of release from the paddy. It is anticipated that once released, the concentration will be reduced and subsequently, RQs will decrease.
- The scenario of the direct application to water for weed control for the acid and amine salts indicates a endangered species concern for aquatic vascular plants. Estimated RQs from use of 2,4-D BEE for direct application to water for weed control exceed all LOCs for both vascular and non-vascular plants. Potential risk to endangered non-vascular plants is not evaluated because at this time there are no listed endangered non-vascular plant species.
- Target acute RQs for birds and mammals were exceeded for endangered species risks for multiple crops and multiple animal weights. Banded and granular applications result in higher RQs at more use sites.
- Target acute LOCs for both non-endangered and endangered plants were exceeded for non-granular and granular for multiple uses, based on predicted EECs.
In December 2004, EPA completed a refined assessment for 2,4-D's potential effects to 26 environmentally significant units (ESUs) of Pacific Salmonids (salmon and steelhead). That refined assessment concluded that 2,4-D has "no effect" on these species when used according to label directions on terrestrial sites. Further, that assessment concluded that use of 2,4-D on rice "may affect but is not likely to adversely affect" 4 ESU's and will have "no effect" on 22 ESU's. That same analysis concluded that use of 2,4-D "may affect" each of the 26 ESU's when used for aquatic weed control purposes. As a result of that assessment, EPA is currently engaged in consultation with the National Marine Fisheries Service regarding those scenarios that resulted in a determination that 2,4-D "may affect but is not likely to adversely affect" the species, or "may affect" the species.

The Agency’s level of concern for endangered and threatened freshwater fish and invertebrates, estuarine invertebrates, birds, mammals, aquatic vascular plants, and terrestrial non-target plants is exceeded for the use of 2,4-D. The Agency recognizes that there are no Federally listed estuarine/marine invertebrates. The registrant must provide information on the proximity of Federally listed freshwater vascular plants, birds, mammals, and non-target terrestrial plants (there are no listed estuarine/marine invertebrates) to the 2,4-D use sites. This requirement may be satisfied in one of three ways: 1) having membership in the FIFRA Endangered Species Task Force (Pesticide Registration [PR] Notice 2000-2); 2) citing FIFRA Endangered Species Task Force data; or 3) independently producing these data, provided the information is of sufficient quality to meet FIFRA requirements. The information will be used by the OPP Endangered Species Protection Program to develop recommendations to avoid adverse effects to listed species.

6. Risk Characterization

The Agency has considered available information on 2,4-D’s toxicity, use areas, usage, fate properties, and application methods and formulations in characterizing ecological risks related to normal use. Upon review and synthesis of this information, the Agency concludes use of 2,4-D for aquatic weed control presents risk to aquatic organisms, while 2,4-D use on terrestrial sites presents the greatest potential risks to small mammals, birds, and non-target terrestrial plants.

a. Characterization of risk to aquatic organisms from direct aquatic application

Whereas the maximum labeled target concentration for control of aquatic weeds is 4 ppm, the typical target concentration is 2 ppm. Moreover, the risks to aquatic organisms were estimated based on a 2,4-D application that resulted in a whole-reservoir concentration of 4 ppm. Treating 100% of the water body would result in a large amount of decaying plant life, thereby creating an oxygen-depleted environment that would most likely result in fish kills. To avoid that scenario, the 2,4-D label advises the applicator to avoid treating more than 50% of a water body in a single application. In actual practice, aquatic weeds that 2,4-D controls tend to grow in littoral zones. As a result, generally a maximum of 20-30% of a water body is treated in a single application. Applying the typical rate of 2 ppm, and taking into account a typical maximum treated area of 30% would decrease calculated RQs by approximately 6-fold.

While noting the potential risks to aquatic organisms from the direct application of 2,4-D for the control of aquatic weeds identified above, it is important to note the benefits gained through the direct application of 2,4-D to aquatic bodies, for the control of invasive species. The U.S Army Corps of
Engineers (USACE), among others, has identified 2,4-D as an important tool for protecting the nation's waters from the invasion and establishment of some of the world's worst species of exotic nuisance vegetation. 2,4-D has a reputation as a selective and economical means to remove invasive plants, enhance the growth and recovery of desirable native vegetation, restore water quality, reduce sedimentation rates in reservoirs, and improve fish and wildlife habitat. 2,4-D products are used to control invasive weeds, such as Eurasian watermilfoil (*Myriophyllum spicatum*) in the northern tier states and water hyacinth (*Eichhornia crassipes*) in the Gulf Coast states. Effective control of these plants can benefit public health with respect to reducing levels of mosquito habitat. In addition, according to USACE, no other product (or alternative technique) can control these plants in a more cost-effective manner (K. Getsinger, USACE, Public Comment; Docket ID# OPP-2004-0167-0053).

### b. Characterization of risk to mammals from terrestrial use

All of the calculated RQs for mammalian acute risk for the non-granular use of 2,4-D were based on maximum labeled application rates. The QUA from BEAD (Quantitative Usage Analysis for 2,4-D, Case Number: 0073, Date: 8-9-01, A. Halvorson) suggests that the average application rates for many crops are considerably less than the modeled maximum application rates. For non-granular spray application mammalian acute concerns, the highest RQ was 1.72 for use on asparagus for small mammals feeding on short grass based on a maximum application rate of 4 lbs ae/acre; however, the average application rate was only 1.10 lbs ae/acre (BEAD QUA). If the modeled application rate was reduced to the reported average application rate of 1.10 lbs ae/acre for asparagus, the RQ would be 1.08 which is still above the acute LOC of 0.5. However, asparagus is representative of a minor 2,4-D use, and risk to mammals from use of 2,4-D on asparagus would be minimal, given that fact.

To add context to the acute mammalian assessment, the effect of assuming an average application rate was determined. Major 2,4-D crops include pasture/rangeland, turf, wheat, corn, and soybeans. For pasture/rangeland, the highest acute RQ was 0.86 for small mammals feeding on short grass based on a maximum application rate of 4 lbs ae/acre. However, the average application rate was only 0.62 lbs ae/acre (BEAD QUA). If the modeled application rate was reduced to 0.62 lbs ae/acre for pasture/rangeland, the resulting RQ is 0.31 which is below the acute LOC, but above the restricted use LOC of 0.2. Similar trends are noted for other major use sites.

Calculated chronic risks to mammals were greatest for small herbivores/insectivores. For 15 g mammalian herbivores/insectivores, chronic RQs based on maximum residues and mean residues ranged from <1 to 200 and <1 to 70, respectively. For major use sites, including rangeland/pasture, RQs were approximately 100. These chronic risk estimates are likely conservative as described below.

**Exposure**

The chronic RQs calculated for mammalian herbivores/insectivores are based on conservative estimates of exposure that are not likely to occur in nature. In the example of pasture/rangeland, the chronic RQ of approximately 100 for maximum residues (35 for mean residues) was calculated based on an application rate of 4 lbs ae/A. This maximum application rate was determined based on the knowledge that the maximum rate of 2 lbs ae/A may be applied twice per year, at a 30 day interval. However, the Biological and Economic Analysis Division within OPP has determined that the average application rate on pasture/rangeland is only 0.62 lbs ae/acre (BEAD QUA). Moreover, information from several state contacts indicate that a once per year application of less than 1 lb ae/A
is typical (personal communications). As the typical rate is approximately 25% of the assessed rate, use of the typical rate would be expected to decrease the RQ for the pasture/rangeland scenario to approximately 25 for maximum residues and 9 for mean residues.

A second example of the conservative assumptions included in the assessment of exposure to mammalian herbivores/insectivores is the assumption that 100% of the long term diet is limited to single food types foraged only from treated fields. The assumption of 100% diet from a single food type may be realistic for acute exposures, but diets are likely to be more variable over longer periods of time. Moreover, currently Agency models do not account for the uptake of 2,4-D by plants and therefore assume that all non-dissipated pesticide applied to the field is present for exposure to organisms. In fact, many pesticides, including 2,4-D, are systemic and are absorbed by plants in the field so that the current approach may overestimate the amount of 2,4-D available for exposure in terrestrial systems. Therefore, the percent of diet assumption is likely to be conservative and will tend to overestimate potential risks for chronic exposure, especially for larger organisms that have larger home ranges.

Hazard

The mammalian chronic risk assessment utilized a toxicity endpoint from a rat two-generation reproduction test. This endpoint was the NOAEL of 5 mg/kg-bw/day for growth rate reductions in F1b offspring. The agency considers that reduced growth (reductions in pup body weight gains relative to controls) in offspring as a potentially important effect with implications for the survivability of offspring and therefore a potential impact on fecundity. Because the endpoint is the no effect level for this measured parameter, evaluations of the significance of any exposures above this endpoint were conducted. From the same two-generation rat reproduction study, the LOAEL associated with F1b pup growth rate reduction was 20 mg/kg-bw/day. This LOAEL corresponds with body-weight gain reductions of 15 to 17% (males and females) relative to controls. The 20 mg/kg-bw/day dose level also represents a NOAEL for increased gestational length and incidents of skeletal anomalies and reduced ossification in F1b pups. The LOAEL for these gestational and skeletal effects is 80 mg/kg-bw/day.

In addition to the available rat two generation reproduction study, a number of developmental toxicity studies are available in rats and rabbits for the acid, amine salts and esters. These data are from studies involving short-term exposures during critical periods of fetal development and are useful to determine if long-term or short-term exposure events are necessary for the types of effects observed in the two-generation reproduction study. MRID 41747601, developmental toxicity in rabbits with the acid, shows a NOAEL of 30 mg/kg-bw/day for increased rate of fetal abortions, with a LOAEL 90 mg/kg-day. Similar NOAEL and LOAEL thresholds were observed in studies in rabbits with the amine salts and esters of 2,4-D. MRID 000251031, developmental toxicity in rats with the acid, showed a NOAEL of 25 mg/kg-bw/day and a LOAEL of 75 mg/kg-bw/day for increased incidence of skeletal malformations. Similar results are reported in other studies with rats involving the amine salt and esters of 2,4-D.

c. Characterization of risk to birds from terrestrial use

The assessment of risk to birds from exposure to 2,4-D is likely conservative as follows. Currently, Agency models do not account for the uptake of 2,4-D by plants and therefore assume that
all non-dissipated pesticide applied to the field is present for exposure to organisms. In fact, many pesticides, including 2,4-D, are systemic and are absorbed by plants in the field and therefore, the current approach may overestimate the amount of 2,4-D available for exposure in terrestrial and aquatic systems.

For non-granular spray application, the highest acute avian RQ (3.50) was from the cranberry scenario, for birds feeding on short grass. That assessment was based on a maximum application rate of 4 lbs ae/acre; however, the average application rate is 1.83 lbs ae/acre (see the BEAD QUA). If the modeled application rate was reduced to 1.83 lbs ae/acre for cranberries, and an assumption made that the resulting EEC will be reduced linearly, the RQ would be 1.60.

To determine the hazard associated with acute exposures to birds, the assessment has considered two types of data, a suite of dietary studies and a suite of gavage studies. For avian acute exposures, the dietary studies result in non-definitive endpoints which are not appropriate for estimating risk. Therefore, the assessment has relied on the gavage studies to estimate avian acute risks. The Agency recognizes that this approach may overestimate risk to birds due to the fact that birds would not typically be expected to consume 2,4-D in this manner.

Given the conservative assumptions in both exposure scenarios and hazard determinations, the Agency finds that the acute risk to birds from 2,4-D exposure does not exceed the Agency’s level of concern.

Potential chronic risks to birds is limited to a few use sites. These include non-cropland, forest, asparagus, and cranberry. The RQs for these sites range from 1 -1.09. Further characterization of these use sites by evaluating average application rates versus maximum application rates lower these RQs to below the LOCs.

d. Characterization of risk to non-target plants from terrestrial use

Acute LOCs for both non-endangered and endangered terrestrial plants were exceeded for non-granular and granular uses at many use sites. Consideration of average application rates did not result in exposure below LOCs. However, the exposure estimates used to develop the RQs were likely conservative, as follows.

In the exposure calculation for non-target plants, the major contributor is run-off from the application site. The run-off and leaching vulnerability schemes used in this assessment were adapted from a vulnerability scheme developed by the USDA (Kellogg et al, 1998), and incorporate several conservative assumptions. For example, a 1-in-10 year rain event is modeled, resulting in 3 cm of runoff water. USDA identified several caveats to be considered when using this vulnerability scheme which could contribute to the uncertainty associated with this assessment. Among these are that estimates of runoff and leaching vulnerability are estimated through the use of algorithms (i.e. they represent estimates of vulnerability and not actual field measurements), fate and transport processes (i.e. dilution and recharge) are not included, farm management practices are not considered, and some watershed estimates are based on major crops only. The effect of these factors on the vulnerability assessment is unknown, however, there is a low probability that a 1-in-10 year rain event will coincide with the first few days following a 2,4-D application at the maximum application rate. Also, it is likely that farm management practices would be in place to limit run-off, as run-off events are detrimental to the farm as a whole for reasons other than pesticide damage.

Currently Agency models do not account for the uptake of 2,4-D by plants and therefore assume that all non-dissipated pesticide applied to the field is present for exposure to organisms. In fact, many pesticides, including 2,4-D, are systemic and are absorbed by plants in the field and
therefore, the current approach may overestimate the amount of 2,4-D available for exposure in terrestrial and aquatic systems.
IV. Risk Management, Reregistration, and Tolerance Reassessment Decision

A. Determination of Reregistration Eligibility

Section 4(g)(2)(A) of FIFRA calls for the Agency to determine, after submission of relevant data concerning an active ingredient, whether or not products containing the active ingredient are eligible for reregistration. The Agency has previously identified and required the submission of the generic (i.e., active ingredient-specific) data to support reregistration of products containing 2,4-D as an active ingredient. The Agency has completed its review of these generic data, and has determined that the data are sufficient to support reregistration of all products containing 2,4-D.

The Agency has completed its assessment of the dietary, occupational, residential, and ecological risk associated with the use of pesticide products containing the active ingredient 2,4-D. Based on a review of these data and on public comments on the Agency’s assessments for the active ingredient 2,4-D, the Agency has sufficient information on the human health and ecological effects of 2,4-D to make decisions as part of the tolerance reassessment process under FFDCA and reregistration process under FIFRA, as amended by FQPA. The Agency has determined that 2,4-D containing products are eligible for reregistration provided that: (i) current data gaps and confirmatory data needs are addressed; (ii) the risk mitigation measures outlined in this document are adopted; and (iii) label amendments are made to implement these measures. Label changes are described in Section V. Appendix A summarizes the uses of 2,4-D that are eligible for reregistration. Appendix B identifies the generic data requirements that the Agency reviewed as part of its determination of reregistration eligibility of 2,4-D, and lists the submitted studies that the Agency found acceptable. Data gaps are identified as generic data requirements that have not been satisfied with acceptable data.

Based on its evaluation of 2,4-D, the Agency has determined that 2,4-D products, unless labeled and used as specified in this document, would present risks inconsistent with FIFRA. Accordingly, should a registrant fail to implement any of the risk mitigation measures identified in this document, the Agency may take regulatory action to address the risk concerns from the use of 2,4-D. If all changes outlined in this document are incorporated into the product labels, then all current risks for 2,4-D will be adequately mitigated for the purposes of this determination.

B. Public Comments and Responses

Through the Agency’s public participation process, EPA worked extensively with stakeholders and the public to reach the regulatory decisions for 2,4-D. During the public comment period on the revised risk assessments, which closed on March 14, 2005, the Agency received comments from numerous parties. These comments in their entirety are available in the public docket (OPP-2004-0167) at http://www.epa.gov/edockets. Individual responses to these comments are also available in the public docket (OPP-2004-0167).

The RED and technical supporting documents for 2,4-D are available to the public through EPA’s electronic public docket and comment system, EPA Dockets, under docket identification number OPP-2004-0167. The public may access EPA Dockets at http://www.epa.gov/edockets. In
addition, the 2,4-D RED may be downloaded or viewed through the Agency’s website at http://www.epa.gov/pesticides/reregistration/status.htm.

C. Regulatory Position

1. Food Quality Protection Act Findings

   a. “Risk Cup” Determination

   As part of the FQPA tolerance reassessment process, EPA assessed the risks associated with this pesticide. EPA has determined that risk from dietary (food sources only) exposure to 2,4-D is within its own “risk cup.” An aggregate assessment was conducted for exposures through food, drinking water, and residential uses. The Agency has determined that the aggregate human health risks from these combined exposures are within the risk cup. In other words, EPA has concluded that the tolerances for 2,4-D meet FQPA safety standards. In reaching this determination, EPA has considered the available information on the special sensitivity of infants and children, as well as aggregate exposure from food, water, and residential uses.

   b. Determination of Safety to U.S. Population

   The Agency has determined that the established tolerances for 2,4-D, with amendments and changes as specified in this document, meet the safety standards under the FQPA amendments to section 408(b)(2)(D) of the FFDCA, and that there is a reasonable certainty no harm will result to the general population or any subgroup from the use of 2,4-D. In reaching this conclusion, the Agency has considered all available information on the toxicity, use practices and exposure scenarios, and the environmental behavior of 2,4-D. Both the acute dietary (food alone) and chronic dietary risk from 2,4-D are not of concern.

   Acute and chronic risks from drinking water exposures are not of concern. Models have been used to estimate surface water concentrations. The surface water EECs are below the DWLOCs for all population subgroups. Drinking water monitoring data from the USGS NAWQA Program confirm that concentrations of 2,4-D are less than modeled estimates for surface water. The maximum concentration detected in ground water monitoring (from USGS NAWQA) has been used as the ground water EEC. The ground water EEC is below the DWLOCs for all populations subgroups.

   EPA has determined that the established tolerances for 2,4-D, with amendments and changes as specified in this document, meet the safety standards under the FQPA amendments to section 408(b)(2)(C) of the FFDCA, that there is a reasonable certainty of no harm for infants and children. The safety determination for infants and children considers the factors noted above for the general population, but also takes into account the possibility of increased dietary exposure due to the specific consumption patterns of infants and children, as well as the possibility of increased susceptibility to the toxic effects of 2,4-D residues in this population subgroup. FQPA directs EPA, in setting pesticide tolerances, to use an additional tenfold margin of safety to protect infants and children, taking into account the potential for pre- and postnatal toxicity and the completeness of the toxicology and exposure databases. The statute authorizes EPA to replace this tenfold FQPA safety factor with a
different FQPA factor only if reliable data demonstrate that the resulting level of exposure would be safe for infants and children.

**FQPA Special Safety Factor**

EPA concludes that the toxicology database for 2,4-D is substantially complete since all required studies have been submitted. After evaluating hazard and exposure data for 2,4-D, EPA removed the default 10X FQPA special safety factor. The toxicity database for 2,4-D includes acceptable developmental and reproductive toxicity studies. Developmental toxicity studies were conducted in both rats and rabbits for most 2,4-D forms. There is qualitative evidence of susceptibility in the rat developmental toxicity study with 2,4-D acid and DEA salt where fetal effects (skeletal abnormalities) were observed at a dose level that produced less severe maternal toxicity (decreased body-weight gain and food consumption). There is no evidence of increased (quantitative or qualitative) susceptibility in the prenatal developmental toxicity study in rabbits or in the 2-generation reproduction study in rats on 2,4-D. Regarding the 2,4-D amine salt and ester forms, no evidence of increased susceptibility (quantitative or qualitative) was observed in the prenatal developmental toxicity study in rat and rabbits (except for 2,4-D DEA) dosed with any of the amine salts or esters of 2,4-D. There is evidence of increased susceptibility (qualitative) in the prenatal developmental study in rabbits for 2,4-D DEA salt.

After establishing developmental toxicity endpoints to be used in the risk assessment with traditional uncertainty factors (10x for interspecies variability and 10x for intraspecies variability), the Agency has no residual concerns for the effects seen in the developmental toxicity studies. Therefore, the 10X FQPA special safety factor was reduced to 1X.

**Database Uncertainty Factor**

The EPA has concluded that there is a concern for developmental neurotoxicity resulting from exposure to 2,4-D, and that a developmental neurotoxicity (DNT) study in rats is required for 2,4-D. The Agency has also concluded that a 2-generation reproduction study is required to address both the concern for thyroid effects and immunotoxicity, as well as a more thorough assessment of the gonads and reproductive/developmental endpoints. EPA has determined that a 10X database uncertainty factor (UF_{DB}) is needed to account for the lack of these studies. This Uncertainty Factor is applied only to exposure scenarios that are expected for children or pregnant women, and thus is not applied to occupational exposure scenarios.

2. **Endocrine Disruptor Effects**

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) “may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other endocrine effects as the Administrator may designate.” When the appropriate screening and/or testing protocols being considered under the EDSP have been developed, 2,4-D may be subject to additional screening and/or testing to better characterize effects related to endocrine disruption.

3. **Cumulative Risks**
The Food Quality Protection Act (FQPA) requires EPA to consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity" when considering whether to establish, modify, or revoke a tolerance. Potential cumulative effects of chemicals with a common mechanism of toxicity are considered because low-level exposures to multiple chemicals causing a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any one of these individual chemicals. 2,4-D is a member of the alkylphenoxy herbicide class of pesticides. A cumulative risk assessment has not been performed as part of this human health risk assessment because the Agency has not yet made a determination of whether 2,4-D and other alkylphenoxy compounds have a common mechanism of toxicity. For information regarding EPA’s efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements by the EPA’s Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA’s website at http://epa.gov/pesticides/cumulative/.[

4. Special Review Disposition

2,4-D has been in pre-Special Review status since September 22, 1986, because of carcinogenicity concerns. In 1994 a Science Advisory Panel/Scientific Advisory Board classified 2,4-D as a Group D carcinogen (not classifiable to human carcinogenicity). The Agency requested further histopathological examinations of rat brain tissues and mouse spleen tissues in question. These exams were submitted and reviewed, and on March 16, 1999, The Agency notified the 2,4-D Task Force that the Agency would continue to classify 2,4-D as a Group D carcinogen. Also, in a 1994 review of all relevant epidemiological studies, EPA found that none of the more recent epidemiological studies definitively linked human cancer cases to 2,4-D. A final notice of the Agency’s intent not to initiate Special Review will be published in concert with the release of this RED document.

5. Dioxin Contaminants

Exposure

In 1987, a DCI titled “Data Call-In Notice for Product Chemistry Relating to Potential Formation of Halogenated Dibenzo-p-dioxin or Dibenzofuran Contaminants in Certain Active Ingredients,” was issued to identify pesticides that may contain halogenated dibenzo-p-dioxin and dibenzofuran contaminants. A second DCI in 1987, “Data Call-In for Analytical Chemistry Data on Polyhalogenated Dibenzo-p-Dioxins/Dibenzofurans (HDDs and HDFs),” was issued, under which registrants whose products did not qualify for an exemption or waiver were required to generate and submit analytical methods and certification limits of dioxins and furans.

The specific results of analysis of multiple 2,4-D technical products, submitted to EPA in response to both DCIs, are considered confidential business information (CBI) and cannot be released by EPA to the public. In summary, two of eight technical products had concentrations of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD; dioxin) greater than the limit of quantitation (LOQ; LOQ = 0.1 ppb) and three of eight had concentrations of 1,2,3,7,8-pentachlorodibenzo-p-dioxin (PCDD) greater than the LOQ (LOQ = 0.5 ppb).

In 1991, the EPA’s Office of Research and Development (EPA/ORD) began an assessment of
the health risks of exposure to dioxins. The most recent revision of that assessment has recently been submitted to the National Academies of Science (NAS) for review. In that document and elsewhere, a source inventory of dioxin was published. As a result of the 1987 DCI data, and the amount of 2,4-D applied to agricultural and residential settings (approximately 50 million pounds per year), the current draft dioxin source inventory (see The Inventory of Sources and Environmental Releases of Dioxin-Like Compounds in the United States: The Year 2000 Update, EPA/600/P-03/002A, External Review Draft, March 2005) identifies 2,4-D as a source of dioxin emissions (28.9 g TEQDF-WHO98; TEQ = Toxic EQuivalent amount, or an amount of total dioxin equivalent to 28.9 g of the most toxic dioxin congener, 2,3,7,8-TCDD). It should be noted that this estimate of dioxin release assumes all products are contaminated and does not take into account manufacturing changes since the DCI. Moreover, that estimate is specific for the year 1995, and therefore should not be considered the current estimate of dioxin release.

The 1995 estimate for dioxin emissions from 2,4-D, taken together with NAS estimates for 2002/2004 releases from other sources of dioxin in the U.S., suggest that 2,4-D applications to land ranks seventh (2.6% of all dioxin sources) behind backyard burning (57%), sewage sludge application (6.9%), residential wood burning (5.7%), coal-fired utilities (5.4%), diesel trucks (3.2%), and secondary aluminum smelting (2.6%) in terms of dioxin emissions (see The Inventory of Sources and Environmental Releases of Dioxin-Like Compounds in the United States: The Year 2000 Update, EPA/600/P-03/002A, External Review Draft, March 2005). According to 2,4-D registrants, since the 1990’s, the manufacturing processes for 2,4-D and its chemical intermediate, dichlorophenol, have been modified, and those modifications decrease the chance that TCDD and PCDD are formed during the manufacturing process. The following description of the current 2,4-D manufacturing process summarizes information submitted by the 2,4-D Task Force II.

A key chemical intermediate in the manufacture of 2,4-D is 2,4-dichlorophenol (2,4-DCP) and the purity of this intermediate has a strong correlation to the purity of 2,4-D acid produced from it. In the manufacture of 2,4-DCP, multiple positions around the phenyl ring structure may be chlorinated. The desired positions for chlorination are carbons two and four of the phenyl ring, but the reaction may yield small quantities of compounds chlorinated at different positions. Certain combinations of these chlorinated structures may form precursors to the dioxin 2,3,7,8-TCDD.

Manufacture of the 2,4-DCP intermediate has been optimized by controlling processing conditions necessary to drive the chlorination reaction to the preferred two and four carbon positions, thereby limiting the formation of impurities that can lead to dioxin formation. Controlled temperature and residence time during the chlorination reaction, programmed addition of the chlorinating agent, and efficient agitation in the reaction vessel are processing factors that contribute to the purity of 2,4-DCP. Additionally, distillation of 2,4-DCP is a technique that may be employed post-chlorination to increase purity. Moreover, quality control sampling and analytical procedures are also utilized to verify product quality at various steps of the 2,4-DCP process. According to Results of testing of 2,4-DCP, performed in response to the Toxic Substances Control Act (TSCA) Dioxin/Furan Test Rule, showed no detectable concentrations of 2,3,7,8-substituted tetra- through hepta-CDD/CFDs.

In the manufacture of 2,4-D acid per se, there are additional process conditions and procedures that must be controlled to maximize yield and purity. Details regarding these measures are dependent on specific manufacturing methodologies and, as such, are protected under FIFRA Section 10 as Confidential Business Information.

**Anticipated Residues**
The Agency’s most recent evaluations of anticipated dioxin and furan residues resulting from 2,4-D applications are based on the concentrations of dioxins and furans present in technical grade 2,4-D as determined by review of analytical data submitted in response to the 1987 DCI. In those evaluations, completed in the early 1990's, the ratios of individual chlorodibenzo-p-dioxin (CDD; dioxin) or chlorodibenzo-p-furan (CDF; furan) contaminant concentrations to 2,4-D acid concentrations were calculated, and those ratios were used with 2,4-D tolerance expressions to calculate an anticipated residue in eggs, fruits, grains, kidney (hogs), meat (hogs), milk, nuts, poultry, and sugarcane, for each detected dioxin or furan. For each technical 2,4-D formulation for which the Agency received data, calculation of an anticipated dietary exposure was based on a worst-case scenario in which the highest anticipated residue was used, and an assumption was made that 100% of the diet consisted of the food item with the highest anticipated residue.

Toxicological Significance

Based on the calculation of dietary exposures, using the worst-case scenario described above, both the cancer and non-cancer risks from dietary exposure to dioxins and furans as contaminants of 2,4-D acid were considered to be of no toxicological concern at the time of the assessment.

Risk Management

Members of the 2,4-D Task Force II have submitted information about the current manufacturing process for the 2,4-D intermediate, 2,4-DCP, as well as for 2,4-D acid itself, and have included in their submissions explanatory text on how current manufacturing processes minimize the chance of dioxin and furan formation. To confirm that the changes to the manufacturing processes since the time of the 1987 DCI have resulted in lower concentrations of dioxin congeners in technical 2,4-D products, the Agency is requiring that five recent batches of all technical products be analyzed for 2,3,7,8-TCDD, 2,3,7,8-TCDF and their respective higher substituted chlorinated congeners using validated analytical methods. The Agency is specifying that the manufacturers use the most current state-of-the art laboratory methods for measuring 2,3,7,8-TCDD and TCDF at levels less than 1 part per trillion (EPA Method 1613, Tetra- through Octa-Chlorinated Dioxins and Furans by Isotope Dilution HRGC/HRMS). Because 1,2,3,7,8-PeCDD is equi-potent to 2,3,7,8-TCDD in the TEF scheme, the Agency is adding this compound to our testing requirements. The pentachloro-congener was reported as present in 2,4-D in the 1987 Data Call-in. Registrants are encouraged to submit their analytical methods and sampling plans to the Agency for review prior to commencing these studies.

D. Tolerance Reassessment Summary

1. Tolerances Currently Listed Under 40 CFR §180.142

Tolerances for residues of 2,4-D in/on plant RACs and processed commodities, fish, and potable water are currently expressed in terms of 2,4-D per se [40 CFR §180.142(a)(1-6 and 9-12) and (b)]. Tolerances for residues in livestock commodities are currently expressed in terms of 2,4-D and/or its metabolite 2,4-dichlorophenol (2,4-DCP) [40 CFR §180.142(a)(8)]. EPA has concluded that 2,4-D is the residue of concern and that tolerances listed in 40 CFR §180.142 are to be defined as residues of 2,4-D, both free and conjugated, determined as the acid.

The listing for 2,4-D tolerances in 40 CFR §180.142 should be recodified into parts (a), (b), (c), and (d). Part (a) should be reserved for commodities with permanent tolerances reflecting at least a
preharvest (field) or postharvest use, part (b) for Section 18 emergency exemptions, part (c) for tolerances with regional use registrations, and part (d) for commodities bearing 2,4-D residues solely inadvertently, including irrigated crops. A summary of 2,4-D tolerance reassessments and recommended recodifications is presented in Table 37 along with any recommended changes in commodity definitions.

Note that some commodities currently are the subject of two or more separate tolerances depending on the use pattern, the 2,4-D form applied, timing of treatment (preharvest or postharvest), or degree of intent to deposit residues (direct treatment or inadvertent). Direct treatment involves intentional field treatment of crop sites or postharvest treatment of harvested commodities on registered labels. Inadvertent deposition involves the incidental exposure of crops when water passing through 2,4-D-treated irrigation ditchbanks or diverted from 2,4-D-treated bodies of water is used to irrigate crops. EPA is proposing to remove most such use-pattern or FIFRA-related language at 180.142. Due to the complicated nature of the routes of residue deposition, we are proposing to subsume the lower tolerances in the highest existing or reassessed tolerance established in the same commodity - even if that results in 180.142(a) containing some tolerances that reflect 2,4-D residues that could potentially result from two or more exposure routes. An example is citrus which has tolerances for 2,4-D in the RAC resulting from preharvest use + postharvest use, irrigation ditchbank treatment (inadvertent), and direct water body treatment (also inadvertent). If there are no registered uses on a given commodity and residues are likely to occur on that commodity solely inadvertently, i.e., via irrigation, then the tolerance in that commodity will be located under 180.142(d). In most cases, residues, and hence the tolerance, resulting from a direct, registered use are higher than the residues (and the tolerance) resulting inadvertently. EPA proposes these revisions because we know that an enforcement agency, having detected 2,4-D residues in a commodity, would: (i) not be able to distinguish which form of 2,4-D had been applied; (ii) rarely be able to determine who applied the pesticide, when, or for what purpose; and (iii) not know whether a sample is violative if the 2,4-D concentration falls between two tolerance levels.

**Tolerances Listed Under 40 CFR §180.142(a)(1):**

Adequate data are available to reassess the established tolerances for the following commodities: apple, apricot, citrus fruit, pear, potato and quince.

The available apple and pear residue data will support a crop group tolerance at 0.05 ppm for pome fruits under the redesignated section 180.142(a). The separate tolerances on apple, pear, and quince should be revoked concomitant with establishing a new pome fruit crop group tolerance.

The 5 ppm tolerance on citrus fruits should be reassessed to 3.0 ppm to reflect any combination of the preharvest use on citrus, the postharvest use of 2,4-D on lemons in the U.S., a similar postharvest use on oranges imported into the U.S., and any inadvertent (irrigation) residues that may be incurred as a result of 2,4-D use in aquatic sites. The tolerances in citrus fruit of 0.1 ppm at 180.142(a)(3) and 1.0 ppm at 180.142(a)(6), both reflecting inadvertent residues, should be revoked as they will be subsumed by the reassessed tolerance of 3.0 ppm at 180.142(a).

The tolerance for residues in/on apricots should be revoked as residues in/on apricots will be covered by the tolerance in stone fruits.

**Tolerances Listed Under 40 CFR §180.142(a)(2):**
Adequate data are available to reassess all the tolerances listed under 180.142(a)(2). All reassessed tolerances should be recodified under the revised section 180.142(a).

Based on the available residue data, the current tolerances on grass hay and tree nuts are adequate. However, tolerances can be lowered on the following commodities: blueberry, sweet corn (kernel plus cob with husks removed), corn forage and grain, cranberry, stone fruits, grape, grass forage, pistachio, rice straw, sorghum forage, grain and stover, and sugarcane. Tolerances should be increased on the following commodities: corn stover, rice grain, and wheat grain and forage.

The available residue data for wheat commodities will be used to reassess tolerances on similar commodities from barley, millet, oats, and rye. Tolerances should be increased accordingly on: barley grain; millet grain, forage and straw; oat forage and grain; and rye forage and grain.

The tolerance for residues in sugarcane forage should be revoked because it is no longer considered a significant livestock feed item (OPPTS GLN 860.1000).

Tolerances Listed Under 40 CFR §180.142(a)(3):

Tolerances listed in 40 CFR §180.142(a)(3) are established for negligible residues of 2,4-D in irrigated crops from application of its dimethylamine salt to irrigation ditch banks in the Western United States in programs of the Bureau of Reclamation, U.S. Department of Interior; cooperating water user organizations; the Bureau of Sport Fisheries, U.S. Department of Interior; Agricultural Research Service, U.S. Department of Agriculture; and the Corps of Engineers, U.S. Department of Defense. Where tolerances are established at higher levels resulting from other uses of 2,4-D, the higher tolerance applies also to residues in crops from the irrigation ditch bank use cited in this paragraph.

The tolerances in crops or crop groups listed under 40 CFR §180.142(a)(3) that do not have a direct treatment tolerance under 180.142(a) should be recodified as 180.142(d), i.e., inadvertent residue tolerances.

The available irrigated crop data support tolerances for inadvertent residues at 0.2 ppm in foliage of legume vegetables (group 7) and non-grass animal feed (group 18) and at 0.05 ppm in/on the following crops groups: bulb vegetables (group 3), legume vegetables (group 6), cucurbit vegetables (group 9), and fruiting vegetables (group 8).

In addition, tolerances resulting from the primary use of 2,4-D on grasses, citrus fruits, and tree nuts are high enough to cover any inadvertent residues in these crops that may result from the use of 2,4-D treated irrigation water. Therefore, separate tolerances for inadvertent residues in/on these crops are not required.

Separate tolerances for inadvertent residues are unnecessary in pome fruits, stone fruits, pistachios, grapes, blueberry, and strawberry as these crops all have tolerances resulting from the direct use of 2,4-D. However, the tolerances in all of these commodities have been reassessed at 0.05 ppm, the limit of quantitation of the enforcement method, to reflect only direct treatment at this time. It is reasonably possible that inadvertent residues resulting from irrigation with treated water could contribute concentrations of 2,4-D in the commodities necessitating tolerances higher than 0.05 ppm. Therefore, confirmatory irrigated crop residue data are required for a representative perennial crop (strawberry). Also, additional residue data on sugar beets and tops irrigated with water containing 2,4-D at 0.1 ppm are required to permit reassessment of the tolerances in the Root and Tuber Vegetables Group and the Leaves of Root and Tuber Vegetables Group resulting inadvertently due to
irrigation with 2,4-D-treated water. These data may also be used to reassess inadvertent tolerances established at 180.142(d) as a result of the 2,4-D RED.

Tolerance Listed Under 40 CFR §180.142(a)(4):

The established tolerance for residues in/on asparagus is reassessed at the current level under the revised tolerance expression and is to be recodified as 40 CFR §180.142(a).

Tolerance Listed Under 40 CFR §180.142(a)(5):

The established tolerance for residues in/on strawberry is reassessed at the current level under the revised tolerance expression and is to be recodified as 40 CFR §180.142(a).

Tolerances Listed Under 40 CFR §180.142(a)(6):

Tolerances listed in 40 CFR §180.142(a)(6) are established for residues of 2,4-D from application of its dimethylamine salt for water hyacinth control in ponds, lakes, reservoirs, marshes, bayous, drainage ditches, canals, rivers, and streams that are quiescent or slow moving in programs conducted by the Army Corps of Engineers or other Federal, State, or local public agencies. Where tolerances are established at higher levels from other uses of the dimethylamine salt of 2,4-D on crops included within these commodity groups, the higher tolerances also apply to residues from the aquatic uses cited in this paragraph.

Based on the available residue data, the current tolerance in shellfish is adequate and the tolerance in fish can be reduced to 0.1 ppm. Both tolerances should be recodified under the revised section 180.142(a).

Tolerances for residues in/on the irrigated crops and crop groups at the current §180.142(a)(6) are set at 1.0 ppm whereas the tolerances in/on the identical crops/crop groups at §180.142(a)(3) are at 0.1 ppm for the irrigation ditchbank use. The recommended/reassessed tolerances from §180.142(a)(3) to be recodified under sections §180.142(a) or §180.142(d) concomitantly address the reassessments/recodifications recommended for tolerances at §180.142(a)(6), depending on whether residues are incurred directly and/or inadvertently, as explained above.

Tolerances Listed Under 40 CFR §180.142(a)(8):

Tolerances listed in 40 CFR §180.142(a)(8) are established for residues of 2,4-D and/or its metabolite 2,4-DCP in livestock commodities. As indicated by the Agency, the regulated residue in animal commodities is 2,4-D (free and conjugated). As a result of this residue definition change, all reassessed livestock tolerances should be recodified to §180.142(a).

Based upon the available livestock feeding study, the 0.1 ppm tolerance in milk is reassessed at 0.05 ppm and the tolerances in cattle, goat, horse, and sheep commodities are reassessed at: 0.3 ppm in fat, meat, and meat byproducts except kidney and 4.0 ppm in kidney.

The established tolerances for 2,4-D residues in hog commodities may be revoked. Based on the MTDB for swine (1.6 ppm) and the results of the ruminant feeding study, there is no reasonable expectation of finite 2,4-D residues occurring in hog commodities [Category 3 of 40 CFR §180.6(a)(3)].

In addition, the established tolerances for 2,4-D residues in eggs and poultry tissues may be revoked. Based on the results of the 2,4-D poultry metabolism study, there is no reasonable expectation of finite residues in poultry tissues and eggs [Category 3 of 40 CFR §180.6(a)(3)].
Tolerance Listed Under 40 CFR §180.142(a)(9):

Tolerances listed in 40 CFR §180.142(a)(9) are established for residues of 2,4-D from applications of its dimethylamine salt or its butoxyethanol ester for Eurasian water milfoil control in programs conducted by the Tennessee Valley Authority in dams and reservoirs of the TVA system.

The tolerance for 2,4-D residues in fish at 40 CFR §180.142(a)(9) should be revoked and this section deleted. There is no need for two 2,4-D tolerances in fish. It has already been recommended that the 1.0 ppm tolerance in fish currently at §180.142(a)(6) be reassessed at 0.1 ppm and that this reassessed tolerance be recodified at the new 40 CFR §180.142(a).

Tolerance Listed Under 40 CFR §180.142(a)(10):

The tolerance listed in 40 CFR §180.142(a)(10) is a regional registration as defined in Sec. 180.1(n) and is established for the residues of 2,4-D in raspberries. The tolerance includes residues from the application of 2,4-D and its N-oleyl-1,3-propylenediamine salt.

As the members of Task Force II are not supporting 2,4-D use on this commodity, the tolerance for residues in/on raspberries should be revoked unless another party wishes to support a use on this crop. 40 CFR §180.142(a)(10) should be deleted and any tolerances with regional use registration should be established under the revised section 40 CFR §180.142(c).

Tolerance Listed Under 40 CFR §180.142(a)(11):

A time-limited tolerance of 0.02 ppm has been established for residues of 2,4-D resulting from the preplant use of 2,4-D ester or amine in/on soybean seed [40 CFR §180.142(a)(11)], expired on December 31, 2004. Adequate residue data are available to support permanent tolerances on soybean commodities. Section 180.142(a)(11) should be deleted, and permanent tolerances for 2,4-D residues in/on soybean seed, forage, and hay are recommended to be established under the revised section 180.142(a).

Tolerances Listed Under 40 CFR §180.142(a)(12):

Tolerances listed at 40 CFR §180.142(a)(12) are established for residues of 2,4-D in processed feeds. Such residues may be present therein only as a result of application to the growing crop of the herbicides identified in this section. Tolerances formerly listed at 40 CFR §180.1450 were moved to 40 CFR §180.142(a)(12) (63 FR 34829, 6/26/98).

The tolerance for residues in sugarcane bagasse should be revoked because it is no longer considered a significant livestock feed item and has been deleted from Table 1 (OPPTS GLN 860.1000).

40 CFR §180.142(a)(12) should be deleted. The tolerance for 2,4-D residues in milled fractions derived from barley, oats, rye, and wheat should be revoked as the commodity definition will change and the tolerances will be increased and recodified at the revised 40 CFR §180.142(a) for residues in barley bran, rye bran, and wheat bran. No tolerances in other processed products of small grains are necessary because concentration of residues does not occur in them.

Tolerances Listed Under 40 CFR §180.142(a)(13):

Tolerances listed at CFR §180.142(a)(13) are established for residues of 2,4-D in processed foods and potable water.
40 CFR §180.142(a)(13) should be deleted. The tolerances for 2,4-D residues in sugarcane molasses and in milled fractions derived from barley, oats, rye, and wheat should be revoked as tolerances will be recodified under the revised 40 CFR §180.142(a) for residues in sugarcane molasses, barley bran, rye bran, and wheat bran.

The established tolerance for residues of 2,4-D in potable water should be revoked as EPA/OPPTS/OPP no longer establishes pesticide tolerances in potable water. Instead, the EPA Office of Water establishes Maximum Contaminant Levels (MCLs). An MCL of 0.07 ppm has been established for 2,4-D in drinking water.

Tolerances Listed Under 40 CFR §180.142(b):

The tolerance listed in 40 CFR §180.142(b) is a time-limited tolerance established for 2,4-D in/on wild rice in connection with use of 2,4-D in MN under a Section 18 emergency exemption granted by EPA. The tolerance is set to expire on December 31, 2005. As adequate residue data are available on wild rice grown in MN, a permanent tolerance for rice, wild, grain should be established at 0.05 ppm under 40 CFR §180.142(c).

2. Tolerances to Be Proposed Under 40 CFR §180.142

Tolerances Needed Under 40 CFR §180.142(a):

The revised section will include all permanent tolerances for residues of 2,4-D, defined as residues of 2,4-D, both free and conjugated, determined as the acid. The section will include all plant commodities (excluding crop commodities exposed solely inadvertently), livestock commodities, fish, and shellfish at reassessed levels.

In addition, the available residue data indicate that new tolerances should be established for 2,4-D residues in/on the following commodities: almond hulls; aspirated grain fractions; barley bran and straw; oat straw; rice hulls; rye bran and straw; soybean forage, hay, and seeds; and wheat bran and straw.

Once adequate residue data become available, new tolerances should also be established for wheat hay. Wheat hay data will be translated to barley hay, millet hay, and oat hay.

Tolerances Needed Under 40 CFR §180.142(c):

Based on the available residue data, tolerances with regional use registrations should be established for wild rice grain at 0.05 ppm, reflecting the use of 2,4-D on wild rice grown in MN.

Tolerances Needed Under 40 CFR §180.142(d):

Tolerances for inadvertent 2,4-D residues in irrigated crops that have no registered, direct uses will be moved from paragraph §180.142(a)(3) to paragraph §180.142(d) and the commodity and crop group listings will be revised to the current EPA definitions.

Table 38. Tolerance Reassessment Summary for 2,4-D.

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Tolerance Listed Under 40 CFR §180.142 (ppm)</th>
<th>Reassessed Tolerance (ppm)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolerances Listed Under 40 CFR §180.142 (a) (1)</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commodity</td>
<td>Tolerance Listed Under 40 CFR §180.142 (ppm)</td>
<td>Reassessed Tolerance (ppm)</td>
<td>Comment</td>
</tr>
<tr>
<td>--------------------</td>
<td>---------------------------------------------</td>
<td>-----------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Apple</td>
<td>5</td>
<td>Revoke</td>
<td>A single tolerance should be established at 0.05 ppm under 180.142(a) for direct and inadvertent residues in/on the Fruit, pome, group 11.</td>
</tr>
<tr>
<td>Apricot</td>
<td>5</td>
<td>Revoke</td>
<td>Residues in/on apricots will be covered by the tolerance for direct and inadvertent residues in stone fruits at 180.142(a).</td>
</tr>
<tr>
<td>Fruit, citrus</td>
<td>5</td>
<td>3.0</td>
<td>A tolerance should be established in Fruit, citrus, group 10, recodified as 180.142(a), that will cover the preharvest use on citrus, the postharvest use on lemons in the U.S., the postharvest use on citrus imported into the U.S., and the inadvertent residues due to irrigation with treated water.</td>
</tr>
<tr>
<td>Pear</td>
<td>5</td>
<td>Revoke</td>
<td>A single tolerance should be established at 0.05 ppm under 180.142(a) for direct and inadvertent residues in/on the Fruit, pome, group 11.</td>
</tr>
<tr>
<td>Potato</td>
<td>0.2</td>
<td>0.40</td>
<td>Includes direct and inadvertent (irrigation) residues. Recodify as 180.142(a).</td>
</tr>
<tr>
<td>Quince</td>
<td>5</td>
<td>Revoke</td>
<td>Residues in/on quince will be included under the 0.05 ppm tolerance at 180.142(a) for direct and inadvertent residues in/on the Fruit, pome, group 11.</td>
</tr>
</tbody>
</table>

Tolerances Listed Under 40 CFR §180.142 (a) (2) ^2

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Tolerance Listed Under 40 CFR §180.142 (ppm)</th>
<th>Reassessed Tolerance (ppm)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barley, grain</td>
<td>0.5</td>
<td>2.0</td>
<td>The submitted data for wheat grain may be translated to barley grain. Recodify as 180.142(a).</td>
</tr>
<tr>
<td>Blueberry</td>
<td>0.1</td>
<td>Revoke</td>
<td>To be included under the 0.2 ppm Berries group 13 tolerance to be recodified as 180.142(a).</td>
</tr>
<tr>
<td>Corn, fodder</td>
<td>20</td>
<td>50.0</td>
<td>Residue data from the 7-day PHI. Recodify as 180.142(a). Corn, stover</td>
</tr>
<tr>
<td>Corn, forage</td>
<td>20</td>
<td>6.0</td>
<td>Residue data from the 7-day PHI. Recodify as 180.142(a).</td>
</tr>
<tr>
<td>Corn, fresh, sweet, kernel plus cob with husks removed</td>
<td>0.5</td>
<td>0.05</td>
<td>Recodify as 180.142(a).</td>
</tr>
<tr>
<td>Corn, grain</td>
<td>0.5</td>
<td>0.05</td>
<td>Residue data from 7-day PHI. Recodify as 180.142(a).</td>
</tr>
<tr>
<td>Cranberry</td>
<td>0.5</td>
<td>Revoke</td>
<td>To be included under the 0.2 ppm Berries group 13 tolerance to be recodified as 180.142(a).</td>
</tr>
<tr>
<td>Fruit, stone</td>
<td>0.2</td>
<td>0.05</td>
<td>Recodify as 180.142(a). This tolerance will now cover both direct and inadvertent residues. Fruit, stone, group 12</td>
</tr>
<tr>
<td>Grape</td>
<td>0.5</td>
<td>0.05</td>
<td>Residue data on grape are available for the entire U.S. Recodify as 180.142(a).</td>
</tr>
<tr>
<td>Grass, hay</td>
<td>300</td>
<td>300</td>
<td>Residue data from the 7-day posttreatment interval (PTI) for Grass, hay. Recodify as 180.142(a).</td>
</tr>
<tr>
<td>Commodity</td>
<td>Tolerance Listed Under 40 CFR §180.142 (ppm)</td>
<td>Reassessed Tolerance (ppm)</td>
<td>Comment</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------------------------------</td>
<td>----------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Grass, pasture</td>
<td>1,000</td>
<td>360</td>
<td>Recodify as 180.142(a). Residue data from the 0-day PTI. This new tolerance will now cover both direct and inadvertent residues. Grass, forage</td>
</tr>
<tr>
<td>Grass, rangeland</td>
<td>1,000</td>
<td>360</td>
<td></td>
</tr>
<tr>
<td>Millet, forage</td>
<td>20</td>
<td>25</td>
<td>The data for wheat forage, grain, and straw may be translated to millet forage, grain, and straw. The required wheat hay data will be translated to millet hay. Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues.</td>
</tr>
<tr>
<td>Millet, grain</td>
<td>0.5</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Millet, straw</td>
<td>20</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Nut</td>
<td>0.2</td>
<td>0.2</td>
<td>Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues. Nut, tree, group 14</td>
</tr>
<tr>
<td>Oat, forage</td>
<td>20</td>
<td>25</td>
<td>The data for wheat forage may be translated to oat forage. Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues.</td>
</tr>
<tr>
<td>Oat, grain</td>
<td>0.5</td>
<td>2.0</td>
<td>The data for wheat grain may be translated to oat grain. Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues.</td>
</tr>
<tr>
<td>Pistachio</td>
<td>0.2</td>
<td>0.05</td>
<td>Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues.</td>
</tr>
<tr>
<td>Rice</td>
<td>0.1</td>
<td>0.5</td>
<td>Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues. Rice, grain</td>
</tr>
<tr>
<td>Rice, straw</td>
<td>20</td>
<td>10</td>
<td>Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues.</td>
</tr>
<tr>
<td>Rye, forage</td>
<td>20</td>
<td>25</td>
<td>Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues. The data for wheat forage may be translated to rye forage.</td>
</tr>
<tr>
<td>Rye, grain</td>
<td>0.5</td>
<td>2.0</td>
<td>Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues. The data for wheat grain may be translated to rye grain.</td>
</tr>
<tr>
<td>Sorghum, fodder</td>
<td>20</td>
<td>0.2</td>
<td>Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues. Sorghum, stover</td>
</tr>
<tr>
<td>Sorghum, forage</td>
<td>20</td>
<td>0.2</td>
<td>Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues.</td>
</tr>
<tr>
<td>Sorghum, grain</td>
<td>0.5</td>
<td>0.2</td>
<td>Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues.</td>
</tr>
<tr>
<td>Sugarcane</td>
<td>2</td>
<td>0.05</td>
<td>Recodify as 180.142(a). Sugarcane, cane</td>
</tr>
<tr>
<td>Sugarcane, forage</td>
<td>20</td>
<td>Revoke</td>
<td>Sugarcane forage is no longer considered a significant livestock feed item.</td>
</tr>
<tr>
<td>Commodity</td>
<td>Tolerance Listed Under 40 CFR §180.142 (ppm)</td>
<td>Reassessed Tolerance (ppm)</td>
<td>Comment</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------------------------------</td>
<td>----------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Wheat, forage</td>
<td>20</td>
<td>25</td>
<td>Recodify as 180.142(a). This new tolerance will now cover both direct and inadvertent residues. The 14-day PHI residue data on wheat forage and grain will be used to support tolerances for residues in/on similar commodities of barley, millet, oats, and rye.</td>
</tr>
<tr>
<td>Wheat, grain</td>
<td>0.5</td>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>

**Tolerance Listed Under 40 CFR §180.142 (a)(3)**

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Tolerance Listed Under 40 CFR §180.142 (ppm)</th>
<th>Reassessed Tolerance (ppm)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avocado</td>
<td>0.1(N)</td>
<td>0.05</td>
<td>Recodify as 180.142(d).</td>
</tr>
<tr>
<td>Cottonseed</td>
<td>0.1(N)</td>
<td>0.05</td>
<td>Recodify as 180.142(d). Cotton, undelinted seed</td>
</tr>
<tr>
<td>Cucurbits</td>
<td>0.1(N)</td>
<td>0.05</td>
<td>Recodify as 180.142(d). Vegetable, cucurbit, group 9</td>
</tr>
<tr>
<td>Fruit, citrus</td>
<td>0.1(N)</td>
<td></td>
<td>Revoke Inadvertent residues will be covered by the crop group tolerance on citrus fruit at 180.142(a).</td>
</tr>
<tr>
<td>Fruit, pome</td>
<td>0.1(N)</td>
<td></td>
<td>Revoke Inadvertent residues will be covered by the crop group tolerance on pome fruit at 180.142(a).</td>
</tr>
<tr>
<td>Fruit, stone</td>
<td>0.1(N)</td>
<td></td>
<td>Revoke Revocation of one stone fruit tolerance is necessary to avoid duplication. Inadvertent residues will be covered by the stone fruit group tolerance at 180.142(a)(2) to be recodified as 180.142(a).</td>
</tr>
<tr>
<td>Grain, crop</td>
<td>0.1(N)</td>
<td></td>
<td>Revoke Separate tolerances in RACs of each grain will be individually established and recodified as 180.142(a) in/on grain, forage, fodder, stover, or hay, as applicable, to cover both direct and inadvertent residues. Upon formal Agency approval, a small grains subgroup tolerance may be established.</td>
</tr>
<tr>
<td>Grass, forage</td>
<td>0.1(N)</td>
<td></td>
<td>Revoke Inadvertent residues will be covered by the grass forage tolerance for direct residues to be recodified as 180.142(a).</td>
</tr>
<tr>
<td>Hop</td>
<td>0.1(N)</td>
<td>0.2</td>
<td>Inadvertent residues will be covered by the hop tolerance for direct residues upon establishment at 180.142(a) in response to PP#2E6352.</td>
</tr>
<tr>
<td>Leafy vegetables</td>
<td>0.1(N)</td>
<td>0.4</td>
<td>Establish separate tolerances for inadvertent residues in the Vegetable, leafy, except brassica, group 4 and Vegetable, brassica, leafy, group 5 at 0.4 ppm under the revised 180.142(d)</td>
</tr>
<tr>
<td>Legume, forage</td>
<td>0.1(N)</td>
<td>Group 7 - 0.2 Group 18 - 0.2</td>
<td>Establish separate tolerances for the Vegetable, foliage of legume, group 7 and Animal feed, nongrass, group 18 for inadvertent residues under 180.142(d).</td>
</tr>
<tr>
<td>Nut</td>
<td>0.1(N)</td>
<td></td>
<td>Revoke Inadvertent residues will be covered by the tolerance in the tree nuts crop group at 180.142(a)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Commodity</th>
<th>Tolerance Listed Under 40 CFR §180.142 (ppm)</th>
<th>Reassessed Tolerance (ppm)</th>
<th>Comment [Corrected Commodity Definition]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Root crop vegetables</td>
<td>0.1(N)</td>
<td>Group 1 - TBD</td>
<td>Additional data are required to determine inadvertent residues in sugar beet roots and tops to represent root and tuber vegetables. Establish separate tolerances in the Vegetable, bulb, group 3. When sugar beet data are received, establish separate tolerances in the Vegetable, root and tuber, group 1 and Vegetable, leaves of root and tuber, group 2. Recodify as §180.142(a).</td>
</tr>
<tr>
<td>Seed and pod vegetables</td>
<td>0.1(N)</td>
<td>0.05</td>
<td>Establish tolerance for inadvertent residues at 180.142(d) in the Vegetable, legume, group 6.</td>
</tr>
<tr>
<td>Small fruit</td>
<td>0.1(N)</td>
<td>0.2</td>
<td>The 0.2 ppm tolerance in the Berries group 13, to be recodified at §180.142(a), will also cover inadvertent residues. Inadvertent residues in/on blueberry and cranberry will also be covered by this group tolerance. Inadvertent residues in/on grape and strawberry will be covered by separate tolerances for direct uses on these crops §180.142(a).</td>
</tr>
<tr>
<td>Vegetable, fruiting</td>
<td>0.1(N)</td>
<td>0.05</td>
<td>Establish tolerance for inadvertent residues at 0.05 ppm in the Vegetable, fruiting, group 8 recodified under §180.142(d).</td>
</tr>
</tbody>
</table>

**Tolerance Listed Under 40 CFR §180.142 (a)(4)**

| Asparagus                       | 5                                            | 5.0                         | Recodify as §180.142(a). |

**Tolerance Listed Under 40 CFR §180.142 (a)(5)**

| Strawberry                      | 0.05                                         | 0.05                        | Recodify as §180.142(a). This tolerance will cover direct and inadvertent residues. |

**Tolerance Listed Under 40 CFR §180.142 (a)(6)**

| Crops in paragraph (c) of this section | 1.0                                          | Revoke                      | The tolerances to be established under paragraphs §180.142(a) and §180.142(d) will be sufficient to cover inadvertent residues in irrigated crops under the recodified §180.142(a)(6). |
| Crop groupings in paragraph (c) of this section | 1.0                                          | Revoke                      | The tolerances to be established under paragraphs §180.142(a) and §180.142(d) will be sufficient to cover inadvertent residues in irrigated crops under the recodified §180.142(a)(6). |
| Fish                            | 1.0                                          | 0.10                        | Residue data for fish and shellfish are from recent tests where fish and shellfish were exposed to 2,4-D under static conditions at 6.0 ppm (1.5x). Recodify to §180.142(a). |
| Shellfish                       | 1.0                                          | 1.0                         | |

**Tolerance Listed Under 40 CFR §180.142 (a)(8)**

<p>| Cattle, fat                     | 0.2                                          | 0.3                         | Recodify as §180.142(a). |
| Cattle, kidney                  | 2                                            | 4.0                         | Recodify as §180.142(a). |
| Cattle, meat                    | 0.2                                          | 0.3                         | Recodify as §180.142(a). |</p>
<table>
<thead>
<tr>
<th>Commodity</th>
<th>Tolerance Listed Under 40 CFR §180.142 (ppm)</th>
<th>Reassessed Tolerance (ppm)</th>
<th>Comment [Corrected Commodity Definition]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle, meat byproducts, except kidney</td>
<td>0.2</td>
<td>0.3</td>
<td>Recodify as §180.142(a).</td>
</tr>
<tr>
<td>Egg</td>
<td>0.05</td>
<td>Revoke</td>
<td>Category 3 of 40 CFR §180.6(a)(3) applies.</td>
</tr>
<tr>
<td>Goat, fat</td>
<td>0.2</td>
<td>0.3</td>
<td>Recodify as §180.142(a).</td>
</tr>
<tr>
<td>Goat, kidney</td>
<td>2</td>
<td>4.0</td>
<td>Recodify as §180.142(a).</td>
</tr>
<tr>
<td>Goat, meat</td>
<td>0.2</td>
<td>0.3</td>
<td>Recodify as §180.142(a).</td>
</tr>
<tr>
<td>Goat, meat byproducts, except kidney</td>
<td>0.2</td>
<td>0.3</td>
<td>Recodify as §180.142(a).</td>
</tr>
<tr>
<td>Hog, fat</td>
<td>0.2</td>
<td>Revoke</td>
<td>Category 3 of 40 CFR §180.6(a)(3) applies.</td>
</tr>
<tr>
<td>Hog, kidney</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hog, meat</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hog, meat byproducts, except kidney</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horse, fat</td>
<td>0.2</td>
<td>0.3</td>
<td>Recodify as §180.142(a).</td>
</tr>
<tr>
<td>Horse, kidney</td>
<td>2</td>
<td>4.0</td>
<td>Recodify as §180.142(a).</td>
</tr>
<tr>
<td>Horse, meat</td>
<td>0.2</td>
<td>0.3</td>
<td>Recodify as §180.142(a).</td>
</tr>
<tr>
<td>Horse, meat byproducts, except kidney</td>
<td>0.2</td>
<td>0.3</td>
<td>Recodify as §180.142(a).</td>
</tr>
<tr>
<td>Milk</td>
<td>0.1</td>
<td>0.05</td>
<td>Residues in milk increased linearly with dose; therefore, the 0.05 ppm tolerance will be adequate for the 1x dose level. Recodify as §180.142(a).</td>
</tr>
<tr>
<td>Poultry</td>
<td>0.05</td>
<td>Revoke</td>
<td>Category 3 of 40 CFR §180.6(a)(3) applies.</td>
</tr>
<tr>
<td>Sheep, fat</td>
<td>0.2</td>
<td>0.2</td>
<td>Recodify as §180.142(a).</td>
</tr>
<tr>
<td>Sheep, kidney</td>
<td>2</td>
<td>2.0</td>
<td>Recodify as §180.142(a).</td>
</tr>
<tr>
<td>Sheep, meat</td>
<td>0.2</td>
<td>0.2</td>
<td>Recodify as §180.142(a).</td>
</tr>
<tr>
<td>Sheep, meat byproducts, except kidney</td>
<td>0.2</td>
<td>0.2</td>
<td>Recodify as §180.142(a).</td>
</tr>
</tbody>
</table>

Tolerance Listed Under 40 CFR §180.142 (a)(9)

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Tolerance Listed Under 40 CFR §180.142 (a)(9) 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Tolerance Listed Under 40 CFR §180.142 (a)(10) 2

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Tolerance Listed Under 40 CFR §180.142 (a)(10) 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raspberry</td>
<td>1.0</td>
</tr>
<tr>
<td>Commodity</td>
<td>Tolerance Listed Under 40 CFR §180.142 (a)(11)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Soybean, seed</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Tolerance Listed Under 40 CFR §180.142 (a)(12)**

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Tolerance Listed Under 40 CFR §180.142 (a)(12)</th>
<th>Reassessed Tolerance (ppm)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugarcane bagasse</td>
<td>5</td>
<td>Revoke</td>
<td>Sugarcane bagasse is no longer considered a significant livestock feed item.</td>
</tr>
<tr>
<td>Sugarcane molasses</td>
<td>5</td>
<td>0.20</td>
<td>Maximum residue value is based on HAFT residues of 0.015 ppm in/on sugarcane and a 7x concentration factor for molasses. Recodify as §180.142(a). Sugarcane, molasses</td>
</tr>
<tr>
<td>Milled fractions derived from barley, oats, rye, and wheat to be ingested as animal feed or converted into animal feed</td>
<td>2</td>
<td>Revoke</td>
<td>Tolerances for direct and inadvertent residues of 2,4-D in barley, bran; rye, bran; and wheat, bran are to be established under revised 40 CFR 180.142(a). Tolerances in other small grain processed products are not necessary as residues do not concentrate upon processing.</td>
</tr>
</tbody>
</table>

**Tolerance Listed Under 40 CFR §180.142 (a)(13)**

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Tolerance Listed Under 40 CFR §180.142 (a)(13)</th>
<th>Reassessed Tolerance (ppm)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugarcane molasses</td>
<td>5</td>
<td>Revoke</td>
<td>The sugarcane molasses reassessed tolerance at §180.142(a)(12) will be recodified as §180.142(a). Duplication of tolerances is not necessary.</td>
</tr>
<tr>
<td>Milled fractions derived from barley, oats, rye, and wheat to be ingested as animal feed or converted into animal feed</td>
<td>2</td>
<td>Revoke</td>
<td>Tolerances for direct and inadvertent residues of 2,4-D in barley, bran; rye, bran; and wheat, bran are to be established under revised 40 CFR 180.142(a). Tolerances in other small grain processed products are not necessary as residues do not concentrate upon processing.</td>
</tr>
<tr>
<td>Potable water</td>
<td>0.1 (N)</td>
<td>Revoke</td>
<td>OPP no longer establishes tolerances in drinking water. EPA’s Office of Water has established an MCL for 2,4-D at 0.07 ppm.</td>
</tr>
</tbody>
</table>

**Tolerances Needed Under 40 CFR §180.142 (a); this list does not include recodifications, etc. from above**

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Tolerance Listed Under 40 CFR §180.142 (a)</th>
<th>Reassessed Tolerance (ppm)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almond hulls</td>
<td>None</td>
<td>0.10</td>
<td>Almond, hulls</td>
</tr>
<tr>
<td>Aspirated grain fractions</td>
<td>None</td>
<td>40</td>
<td>Based on HAFT residues of 0.038 ppm for corn grain and a 39x concentration factor, maximum expected residues would be 1.48 ppm in aspirated grain fractions (AGF) derived from corn grain. Based on HAFT residues of 3.24 ppm for wheat grain and a 11.2x concentration factor, maximum expected residues would be 36.3 ppm in AGF derived from wheat grain. As sorghum and soybeans uses are early-season uses, residue data on AGF were not generated for these crops. Establish tolerance in AGF at 40 ppm.</td>
</tr>
<tr>
<td>Commodity</td>
<td>Tolerance Listed Under 40 CFR §180.142 (ppm)</td>
<td>Reassessed Tolerance (ppm)</td>
<td>Comment</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------------------------------------</td>
<td>----------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Barley, hay</td>
<td>None</td>
<td>TBD</td>
<td>Data for wheat straw were translated to barley straw. Required wheat straw data will be translated to barley hay.</td>
</tr>
<tr>
<td>Barley, straw</td>
<td>None</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Barley, bran</td>
<td>None</td>
<td>4.0</td>
<td>Data for wheat bran were translated to barley bran.</td>
</tr>
<tr>
<td>Millet, hay</td>
<td>None</td>
<td>TBD</td>
<td>Required wheat straw data will be translated to millet hay.</td>
</tr>
<tr>
<td>Oat, hay</td>
<td>None</td>
<td>TBD</td>
<td>Data for wheat straw were translated to oat straw. Required wheat straw data will be translated to oat hay.</td>
</tr>
<tr>
<td>Oat, straw</td>
<td>--</td>
<td>50</td>
<td>Maximum residue value is based on HAFT residues of 0.425 ppm in/on oat grain and a 3.3x concentration factor for straw.</td>
</tr>
<tr>
<td>Rice, hulls</td>
<td>None</td>
<td>2.0</td>
<td>Maximum residue value is based on HAFT residues of 0.425 ppm in/on rice grain and a 3.3x concentration factor for hulls.</td>
</tr>
<tr>
<td>Rye, straw</td>
<td>None</td>
<td>50</td>
<td>Data for wheat straw were translated to rye straw.</td>
</tr>
<tr>
<td>Rye, bran</td>
<td>None</td>
<td>4.0</td>
<td>Data for wheat bran were translated to rye bran.</td>
</tr>
<tr>
<td>Soybean, forage</td>
<td>None</td>
<td>0.02</td>
<td>Adequate residue data are available to support permanent tolerances on soybean commodities.</td>
</tr>
<tr>
<td>Soybean, hay</td>
<td>None</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Soybean, seed</td>
<td>None</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Wheat, hay</td>
<td>None</td>
<td>TBD</td>
<td>Data are required on wheat hay.</td>
</tr>
<tr>
<td>Wheat, straw</td>
<td>None</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Wheat, bran</td>
<td>None</td>
<td>4.0</td>
<td>Maximum residue value is based on HAFT residues of 1.08 ppm in/on wheat grain (14-day PHI) and a 3.6x concentration factor for bran.</td>
</tr>
</tbody>
</table>

**Tolerance Listed Under 40 CFR §180.142 (b)**

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Tolerance</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild rice</td>
<td>0.1</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>Tolerance expires 12/31/05. Adequate data are available to establish a permanent tolerance with a regional registration to be recodified as §180.142(c) for Rice, wild, grain at 0.05 ppm.</td>
</tr>
</tbody>
</table>

**Tolerance Needed Under 40 CFR §180.142 (c)**

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Tolerance</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice, wild, grain</td>
<td>None</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>regional tolerance with use restricted to MN</td>
</tr>
</tbody>
</table>

**Tolerances Needed Under 40 CFR §180.142 (d)**

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Tolerance</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commodities and crop groups currently listed under paragraph (a)(3)</td>
<td>0.1 (N)</td>
<td>NA</td>
</tr>
</tbody>
</table>

1. Maximum residue of treated RAC sample(s) following application of 2,4-D formulations according to use patterns the Task Force II registrants intend to support for reregistration.
2. This subparagraph will be deleted and tolerances recodified under revised paragraph (a).
3. TBD = To be determined. Reassessment of tolerances(s) cannot be made at this time because additional data are required.
4. Tolerances listed under §180.142 (a)(3) for inadvertent residues will be recodified as either §180.142(a) or §180.142(d).
5. This paragraph will be reserved for future time-limited tolerances under Section 18 Emergency Exemptions.
6. Tolerances with regional use registration.
Paragraph (d) will contain tolerances for inadvertent residues (e.g., residues in irrigated crops) only, i.e., there is no registration for direct use in the U.S. If residues may result inadvertently as well as intentionally (direct, labeled treatment), the tolerance is codified at §180.142(a).

3. Codex Harmonization

The Codex Alimentarius Commission has established several maximum residue limits (MRLs) for residues of 2,4-D in/on various plant and animal commodities. The Codex MRLs are expressed in terms of 2,4-D per se. The expression of residues for Codex MRLs and U.S. tolerances is harmonized. A numerical comparison of the Codex MRLs and the corresponding reassessed U.S. tolerances is presented in Table 39.

Table 39. Codex MRLs and applicable U.S. tolerances for 2,4-D. Recommendations for compatibility are based on conclusions following reassessment of U.S. tolerances

<table>
<thead>
<tr>
<th>Codex Commodity, As Defined</th>
<th>Codex MRL (mg/kg)</th>
<th>Reassessed U.S. Tolerance, ppm</th>
<th>Recommendation And Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barley</td>
<td>0.5</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Blackberries</td>
<td>0.1</td>
<td>0.20</td>
<td>U.S. tolerance for Berries group 13</td>
</tr>
<tr>
<td>Citrus fruits</td>
<td>2.0</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Eggs</td>
<td>0.05 (*)</td>
<td>Revoked</td>
<td></td>
</tr>
<tr>
<td>Maize</td>
<td>0.05 (*)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Meat (from mammals other than marine mammals)</td>
<td>0.05 (*)</td>
<td>0.30</td>
<td>Meat, fat, and mbyp except kidney</td>
</tr>
<tr>
<td>Milk products</td>
<td>0.05 (*)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Milks</td>
<td>0.05 (*)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Oats</td>
<td>0.5</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Potato</td>
<td>0.2</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Raspberries, Red, Black</td>
<td>0.1</td>
<td>0.20</td>
<td>U.S. tolerance for Berries group 13</td>
</tr>
<tr>
<td>Rice</td>
<td>0.05 (*)</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Rye</td>
<td>0.5</td>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>Sorghum</td>
<td>0.05 (*)</td>
<td>0.20</td>
<td>Forage, grain, and stover=0.2</td>
</tr>
<tr>
<td>Vaccinium berries, including Bearberry</td>
<td>0.1</td>
<td>0.20</td>
<td>U.S. tolerance for Berries group 13</td>
</tr>
<tr>
<td>Wheat</td>
<td>0.5</td>
<td>2.0</td>
<td></td>
</tr>
</tbody>
</table>

(*) = At or about the limit of detection.

4. Residue Analytical Methods - Plants and Livestock (GLN 860.1340)

For the purpose of reregistration, adequate methods are available for data collection and the enforcement of plant commodity tolerances. The Pesticide Analytical Manual (PAM) Vol. II lists three GC methods (designated as Methods A, B, and C) with microcoulometric detection and one GC
method (designated as Method D) with electron capture detection (ECD). In a letter dated September 3, 1993 (CBRS No. 12270, DP Barcode D193335, 9/3/93, W. Smith), Task Force II indicated that the enforcement methods currently listed in PAM Vol. II are unsuitable for determining residues of 2,4-D in wheat and poultry commodities.

Plant Commodities: Task Force II submitted an adequate proposed GC/ECD enforcement method for plants (designated as EN-CAS Method No. ENC-2/93) which has been independently validated. Adequate radiovalidation data have been submitted and evaluated for the proposed enforcement method using samples from the wheat metabolism study. The proposed enforcement method or modifications of the enforcement method were used for data collection purposes.

Livestock Commodities: Task Force II submitted two separate (but essentially comparable) proposed enforcement methods (GC/ECD) for determination of 2,4-D in livestock commodities. Adequate radiovalidation data have been submitted for the method using samples of fat, kidney, and milk from the goat metabolism study and samples of eggs from the poultry metabolism study. The Agency concluded that the methods are adequate provided the registrants satisfy the following requests: (i) submit a revised method which combines the two methods into a single method; (ii) delete from the method all references to the use of diazomethane as a derivatizing agent; and (iii) provide complete raw data and sample calculations (including chromatograms showing peak areas, external standard linearity curves and associated data, standard calculations, etc.). Once an adequate revised method is submitted, the Agency will evaluate the tolerance method validation. Recently, it has been determined that the technology to generate diazomethane has advanced such that it is no longer considered to be a dangerous procedure; as a result, the use of diazomethane as a derivatizing agent is now considered acceptable.

E. Regulatory Rationale

The following is a summary of the rationale for managing risks associated with the use of 2,4-D. Where labeling revisions are warranted, specific language is set forth in the summary tables of Section V of this document.

1. Human Health Risk Management

   a. Residential Risk

      1) Residential risk summary

      A Margin of Exposure (MOE) of 1000 (10x for interspecies extrapolation, 10x for intraspecies variation, and 10x database uncertainty factor) is considered adequately protective for this assessment of residential risks. Residential handler risks are not of concern. All MOEs for post-application, oral exposure to children from playing on treated lawns meet or exceed 1000; therefore, post-application exposure to children is not of concern. Likewise, all adult acute/short term MOEs meet or exceed 1000, so post-application exposure is not of concern for adults.
As discussed below, potential risks were identified to individuals who swim in water treated with 2,4-D. Although the risk assessment is likely to be conservative, mitigation measures will be required.

2) Residential Post-application Mitigation

For residential, post-application exposures, when the calculated MOE of 1000 based on modeling is considered in conjunction with biomonitoring results, it is clear that the modeled short-term risks from post-application exposure are upper bound estimates. At one day post-treatment, the MOEs for the volunteers who wore shorts and no shoes ranged from 1400 to 35000 with the lowest MOE corresponding to the volunteer who removed his shirt during the exposure period. The MOEs for the remaining volunteers ranged from 24000 to 37000. The Agency has concluded that no further mitigation is needed for residential post-application exposures.

3) Residential Swimmer Mitigation

The acute MSWC of 9.8 ppm for exposures to 2,4-D acid or amine is greater than the proposed maximum application rate of 4.0 ppm, therefore, acute exposures to acid or amine are not of concern. The MSWC of 3.6 ppm for short-term exposures to acid or amine is also not of concern because some dissipation or dispersion is likely to occur which would cause the 7-day average of 2,4-D concentrations to be less than 3.6 ppm. Dissipation studies submitted to the Agency indicated that the half lives following pond and lake liquid treatments ranged from 3.2 days to 27.8 days which yield 7 day average concentrations of 1.9 ppm when the half life equals 3.2 days, to 3.6 ppm when the half life equals 27.8 days.

The MSWCs for 2,4-D BEE are less than the master label application rate of 4 ppm, but they are unlikely to be of concern for the following reasons:

- 2,4-D BEE degrades rapidly by abiotic hydrolysis in sterile water to form 2,4-D acid particularly when the pH is 7.5 or above.
- 2,4-D BEE degrades to 2,4-D acid by microbial hydrolysis with an average half life of 2.6 ± 1.8 hours at a bacterial concentration of 5 x 10^8 organisms per liter. Therefore, degradation of 2,4-D BEE to 2,4-D under typical environmental conditions will be rapid leading to significantly lower risk estimates because the 2,4-D acid has a lower rate of dermal absorption.
- Modeling predicts direct water application of 2,4-D BEE will yield surface water concentrations of 2,4-D BEE concentrations in the Agency standard pond of 624 ug/L for peak (24 hour average), 30 ug/L for the 21-day average, and 10 ug/L for the 60-day average.
- The existing label rates for 2,4-D BEE products are also lower than the master label rate.
Although the risk characterization above suggests that the risk estimates are conservative, a 24 hour post-application restriction on swimming is necessary to ensure the safety of children swimming in water treated with 2,4-D BEE.

b. Aggregate Risk

The Food Quality Protection Act amendments to the Federal Food, Drug, and Cosmetic Act (FFDCA, Section 408(b)(2)(A)(ii)) require “that there is a reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there is reliable information.” Aggregate exposure will typically include exposures from food, drinking water, residential uses of a pesticide, and other non-occupational sources of exposure.

1) Aggregate Risk Summary

For 2,4-D, EPA conducted acute, short-term, and chronic aggregate risk assessments using the reduced maximum application rate for residential turf (1.5 lbs ae/A). The aggregate risk assessment compares the Drinking Water Level of Comparison (DWLOC) for each scenario with the appropriate Estimated Drinking Water Concentration (EDWC) for the pesticide. The DWLOC is the maximum concentration in drinking water which, when considered together with food, and, if appropriate, residential exposure, does not exceed EPA’s level of concern. Generally, EDWCs that are less than the corresponding DWLOC are not of concern to the Agency.

It is important to note that the MCL for 2,4-D, established by EPA’s Office of Water under the Safe Drinking Water Act (SDWA), is 70 ug/L. To minimize the possibility that direct aquatic applications will result in drinking water concentrations in excess of the MCL, the Agency has worked with the 2,4-D Task Force and water quality specialists to develop appropriate label requirements for 2,4-D products registered for use to control aquatic weeds.

2) Acute Aggregate Risk

DWLOC Approach
Acute DWLOCs were calculated based upon acute dietary exposures. Acute residential exposures from swimming in treated water bodies or playing on treated turf were not included because exposures are unlikely to co-occur with acute dietary exposures. The acute DWLOCs are range from 432 to 1932 with the most sensitive population being females 13 to 49 years old. The EDWCs of 118 ug/liter for surface water and 15 ug/liter for groundwater are substantially less than the DWLOCs which means that the risks are not of concern.

Forward Calculation Approach
Acute aggregate risks were assessed by directly combining acute food exposures and estimates of acute water exposures. The acute aggregate risks and are not of concern because they are less than 100 percent of the aPAD. The highest risks (58 percent of the aPAD) are for females 13-49 years old because these risks are based upon the lower NOAEL of 25 mg/kg/day from a developmental study in
rats. Whereas, estimates of other population groups are based on a NOAEL of 67 mg/kg/day from an acute neurotoxicity study in rats.

3) Short-term Aggregate Risk

DWLOC Approach
Short-term aggregate risks assessments were conducted by calculating DWLOCs based upon short-term turf exposures, chronic food exposures and short-term endpoints. Short-term exposures from swimming in treated water bodies were not included because these exposures represent high-end unlikely scenarios. The short-term DWLOCs were calculated only for females 13-49 and children 1-6 because these population subgroups have the highest exposure and estimates calculated for these groups are protective of the other subgroups. The DWLOCs range from 24 to 36 ug/liter. The EDWCs range from 15 to 23 ug/liter. Since the DWLOCs are all greater than the EDWCs, the short term risks are not of concern.

Forward Calculation Approach
Short-term aggregate risks were assessed by aggregating short-term turf exposures, chronic food exposures and chronic water exposures. Short-term aggregate risk were calculated only for females 13-49 and children 1-6 because these population subgroups have the highest exposure and estimates calculated for these groups are protective of the other subgroups. The short-term aggregate MOEs indicate that the short term risks are not of concern because the MOEs equal or exceed the target MOE of 1000.

4) Chronic (Non-Cancer) Aggregate Risk

DWLOC Approach
Chronic DWLOCs were calculated based upon chronic dietary exposures. As there are no chronic residential exposures, residential exposures were not included in the chronic DWLOC calculations. The chronic DWLOCs are 46 ug/L or greater with the most sensitive populations being infants and children. The EDWCs, which range from 1.5 to 23 ug/L, are less than the DWLOCs which means that the risks are not of concern. It should be noted that the master label indicates that potable water consumption from a treated water body cannot begin until the 2,4-D concentration is 70 ug/L or below, therefore an annual average exposure at the MCL of 70 ug/L would not occur because dissipation would reduce the initial concentration of 70 ug/L to an annual average concentration of 11 ug/L.

Forward Calculation Approach
Chronic aggregate risks were assessed by aggregating chronic food exposures and chronic water exposures. The chronic aggregate risks are not of concern because they are less than 100 percent of the cPAD. The highest risks (38 percent of the cPAD) are for children 1-2 years old.
5) Aggregate Risk Mitigation

Given the reduced maximum application rate to residential lawns (1.5 lbs ae/A), the highest aggregate risks are the risks from short-term exposures, which include the turf exposure scenarios. For the most sensitive subpopulation (females 13-49) these risks meet the target MOE of 1000 and the turf exposure is the risk driver as it contributes 96 percent of the risk.

Whereas calculated risks just meet the Agency’s target MOE, it is important to note that the turf exposure estimate is based upon modeling and is greater than exposure measurements obtained from biomonitoring. As described in the human health assessment, the results of a biomonitoring study were used to calculate MOEs by assuming that all of the urinary 2,4-D measured in the 96 hours after the exposure period was the result of the turf exposure. This assumption is protective because 2,4-D exposures due to inhalation and due to food and water ingestion would be counted as dermal exposure. The biomonitoring results were adjusted by a factor of two to account for the SOP assumption of two hours of daily exposure vs one hour of exposure during the study, and a factor of 1.7 to account for an application rate of 1.5 lbs ae/acre vs 0.88 lb ae/acre applied during the study. At one day post-treatment, the MOEs for the volunteers who wore shorts and no shoes ranged from 1400 to 35000 with the lowest MOE corresponding to the volunteer who removed his shirt during the exposure period. The MOEs for the remaining volunteers ranged from 24000 to 37000. If the calculated MOE of 1000 based on modeling is considered in conjunction with the MOE calculated based on biomonitoring results, it is clear that the modeled short-term risks are upper bound estimates. The Agency has concluded that aggregate risks from acute, short-term and chronic exposures are not of concern. No further mitigation beyond reducing the maximum application rate from 2.0 to 1.5 lbs/ae per acre is needed.

c. Occupational Risk Mitigation

1) Handler Risk Mitigation

With the exception of mixing/loading wettable powder, the short-term and intermediate-term Margin of Exposure estimates (MOEs) exceed 100 with baseline attire (i.e., long-sleeved shirt, long pants, shoes plus socks) or single layer attire (i.e., long-sleeved shirt, long pants, shoes plus socks, gloves) and are not of concern. The MOEs for handling wettable powder are acceptable with engineering controls (i.e. water soluble bags). Water soluble bags will be required for wettable powder formulations.

2) Post-application Risk Mitigation

All short- and intermediate-term MOEs are above 100 on day zero. All occupational postapplication risk scenarios are below EPA’s level of concern. Products containing 2,4-D salt and ester forms as active ingredient with Worker Protection Standard (WPS) uses will require a re-entry interval (REI) of 12 hours. Because of acute eye irritation concerns, products containing 2,4-D acid and amine forms with WPS uses will require a REI of 48 hours and protective eyewear. The requirements for individual products will be finalized based on product-specific chemistry and acute
toxicity review. The exposure reduction program implemented in 1992 will be replaced with the personal protective equipment described in section V.D. of this document.

2. Environmental Risk Mitigation

The Agency has considered available information on 2,4-D’s toxicity, use areas, usage, fate properties, application methods, and formulations in calculating ecological risks. The resulting assessment suggests that the use of 2,4-D for aquatic weed control presents risk to aquatic organisms, while 2,4-D use on terrestrial sites presents greater potential risks to small mammals, birds, and non-target terrestrial plants, than to other plants and animals.

a. Birds

Acute Risk

Whereas the assessment of risk to birds from the terrestrial use of 2,4-D suggests risks of concern, the assessed exposures to 2,4-D are likely conservative in the following ways. Currently, Agency models do not account for the uptake of 2,4-D by plants and therefore assume that all non-dissipated pesticide applied to the field is present for exposure to organisms. In fact, many pesticides, including 2,4-D, are systemic and are absorbed by plants in the field and therefore, the current approach may overestimate the amount of 2,4-D available for exposure in terrestrial and aquatic systems.

For non-granular spray application, the highest acute avian RQ (3.5) was from the cranberry use-site scenario, for birds feeding on short grass. That assessment was based on a maximum application rate of 4 lbs ae/acre; however, the average application rate is 1.83 lbs ae/acre (see the Agency’s quantitative use assessment). If the modeled application rate was reduced to 1.83 lbs ae/acre for cranberries, and an assumption made that the resulting EEC will be reduced linearly, the RQ would be 1.6.

To determine the hazard associated with acute exposures to birds, the assessment has relied on two types of data, a suite of dietary studies and a suite of gavage studies. For avian acute exposures, the dietary studies result in non-definitive endpoints which are not appropriate for estimating risk. Therefore, the assessment has relied on the gavage studies to estimate avian acute risks. The Agency recognizes that this approach may overestimate risk to birds due to the fact that birds would not typically be expected to consume 2,4-D in this manner.

Chronic Risk

Potential chronic risks to birds is limited to the following use sites: non-cropland, forest, asparagus, and cranberry. The RQs for these sites range from one to slightly above one. Further characterization of these use sites by evaluating average application rates versus maximum application rates lower these RQs to below the LOCs.

Given the conservative assumptions in both exposure scenarios and hazard determinations, the Agency finds that the acute and chronic risks to birds from 2,4-D exposure are not of concern.
b. Mammals

Acute risk

All of the calculated RQs for mammalian acute risk for the non-granular use of 2,4-D were based on maximum labeled application rates. The EPA’s quantitative use assessment (EPA QUA) suggests that the average application rates for many crops are considerably less than the modeled maximum application rates. For non-granular spray application mammalian acute concerns, the highest RQ was 1.72 for use on asparagus for small mammals feeding on short grass based on a maximum application rate of 2 lbs ae/A applied two times a year; however, the average application rate was only 1.10 lbs ae/A (EPA QUA). If the modeled application rate was reduced to the reported average application rate of 1.10 lbs ae/A for asparagus, the RQ would be 1.08 which is still above the acute LOC of 0.5. However, asparagus is representative of a minor 2,4-D use, and risk to mammals from use of 2,4-D on asparagus would be minimal, given that fact.

To add context to the acute mammalian assessment, the effect of assuming an average application rate was determined. Major 2,4-D crops include pasture/rangeland, turf, wheat, corn, and soybeans. For pasture/rangeland, the highest acute RQ was 0.86 for small mammals feeding on short grass based on a maximum application rate of 4 lbs ae/A. However, the average application rate was only 0.62 lbs ae/A (BEAD QUA). If the modeled application rate was reduced to 0.62 lbs ae/A for pasture/rangeland, the resulting RQ is 0.31 which is below the acute LOC, but above the restricted use LOC of 0.2. Similar trends are noted for other major use sites.

Although the calculated RQ values still exceed the Agency’s level of concern when average applications rates are considered, the Agency has concluded that the benefits from 2,4-D use (including control of invasive and noxious weed species), taken together with the low toxicity of 2,4-D to humans, outweigh the concerns of toxicity to small mammals. No additional mitigation steps will be taken.

Chronic risk

Calculated chronic risks to mammals were greatest for small herbivores/insectivores. For 15 g mammalian herbivores/insectivores, chronic RQs based on maximum residues and mean residues ranged from <1 to 200 and <1 to 70, respectively. For major use sites, including rangeland/pasture, RQs were approximately 100. These chronic risk estimates are likely conservative as described below.

The chronic RQs calculated for mammalian herbivores/insectivores are based on conservative estimates of exposure that are not likely to occur in nature. In the example of pasture/rangeland, the chronic RQ of approximately 100 for maximum residues (35 for mean residues) was calculated based on an application rate of 2 lbs ae/A applied twice per year, at a 30 day interval. However, the EPA has determined that the average application rate on pasture/rangeland is only 0.62 lbs ae/A (EPA QUA). Moreover, information from several of the Agency’s state contacts indicate that a once per year application of less than 1 lb ae/A is typical (personal communications). As the typical rate is approximately 25% of the assessed rate, use of the typical rate would be expected to decrease the RQ for the pasture/rangeland scenario approximately four-fold, to approximately 25 for maximum residues and 9 for mean residues.

A second example of the conservative assumptions included in the assessment of exposure to mammalian herbivores/insectivores is the assumption that 100% of the long term diet is relegated to
single food types foraged only from treated fields. The assumption of 100% diet from a single food type may be realistic for acute exposures, but diets are likely to be more variable over longer periods of time. The risk assessment assumed that 100% of the small mammals’ diet consists of short grasses. Several published reports suggest that actual diets of small mammals are more varied, and would likely include invertebrates, worms, fungi, and seeds, in addition to plant matter.

Given the conservative assumptions in the exposure scenarios, the Agency finds that the risks identified in the risk assessment are likely to overestimate actual risks to mammals from 2,4-D applications. Based on information about average application rates and dietary patterns as described above, the Agency has concluded that actual 2,4-D exposures to mammals are likely to be significantly lower than those assessed but may still be above the chronic LOC for this screening level assessment. However, the Agency has concluded that the benefits from 2,4-D use (including control of invasive and noxious weed species), taken together with the low toxicity of 2,4-D to humans, outweigh the concerns of toxicity to small mammals. No additional mitigation is being required at this time.

c. Aquatic Organisms

Whereas the assessment of risk to aquatic organisms suggests risks of concern, the assessed exposures to 2,4-D are likely conservative as follows. Whereas the maximum labeled target concentration for control of aquatic weeds is 4 ppm, the typical target concentration is 2 ppm. A rate of 4 ppm is reserved for spot-treating new aquatic weed stands and hybrid weed species that tend to be less susceptible to 2,4-D. Per the product label, re-application of 2,4-D can occur after 21 days.

In the current assessment, the risks to aquatic organisms were estimated based on a 2,4-D application that resulted in a whole-reservoir concentration of 4 ppm. Treating 100% of the water body would likely result in a large amount of decaying plant life, thereby creating an oxygen-depleted environment that would most likely result in fish kills. To avoid that scenario, the current 2,4-D label advises that the applicator avoid treating more than 50% of a water body in a 21-day period. In actual practice, aquatic weeds that 2,4-D controls tend to grow near the shore of lakes, ponds, and reservoirs. As a result, generally a maximum of 20-30% of a water body is treated in a single application. Applying the typical rate of 2 ppm, and taking into account a typical maximum treated area of 30%, would decrease calculated RQs by approximately 6-fold.

While noting the potential risks to aquatic organisms from the direct application of 2,4-D for the control of aquatic weeds identified above, it is important to note the benefits gained through the direct application of 2,4-D to aquatic bodies, for the control of invasive species. The U.S Army Corps of Engineers (USACE) and state agencies have identified 2,4-D as an important tool for protecting water bodies from the invasion and establishment of some species of exotic nuisance vegetation. 2,4-D has a reputation as a selective and economical means to remove invasive plants, enhance the growth and recovery of desirable native vegetation, restore water quality, reduce sedimentation rates in reservoirs, and improve fish and wildlife habitat. 2,4-D products are used to control invasive weeds, such as Eurasian water milfoil (Myriophyllum spicatum) in the northern tier states and water hyacinth (Eichhornia crassipes) in the Gulf Coast states. Effective control of these plants can benefit public health with respect to reducing levels of mosquito habitat. In addition, according to USACE, no other product (or alternative technique) can control these plants in a more cost-effective manner (K. Getsinger, USACE, Public Comment; Docket ID# OPP-2004-0167-0053).
Given the typical application rates and treatment areas, and considering the beneficial aspects of using 2,4-D to control invasive plant species, the Agency concludes that the benefits from direct aquatic use of 2,4-D outweigh the risk concerns for aquatic organisms. No additional mitigation measures will be required at this time to address risk to aquatic organisms.

d. Non-target Insects

Risk to non-target insects do not exceed the Agency’s level of concern. Available data from a honey bee acute toxicity study indicated that technical 2,4-D is practically non-toxic to the honey bee. The potential for 2,4-D and its salts and esters to pose risk to pollinators and other beneficial insects is expected to be minimal.

e. Non-target Terrestrial Plants

Estimated RQs exceeded acute LOCs for both non-endangered and endangered terrestrial plants for non-granular and granular uses at many use sites. Consideration of average application rates did not result in exposure below LOCs. However, the exposure estimates used to develop the RQs were likely conservative, as follows.

In the exposure calculation for non-target aquatic plants and terrestrial plants in intermittently flooded areas, the major contributor is run-off from the application site. The run-off and leaching vulnerability schemes used in this assessment incorporate several conservative assumptions which are fully discussed in the ecological risk assessment. Also, it is likely that farm management practices would be in place to limit run-off, as run-off events are detrimental to the farm as a whole for reasons other than pesticide damage.

Whereas the risk assessments are likely conservative as described above, the Agency is concerned about the risk to non-target terrestrial plants from drift of 2,4-D during application. To address that concern, the Agency is implementing spray drift controls that will decrease the risk that 2,4-D will drift onto non-target plants.

f. Summary of Environmental Risk Mitigation

Characterization of the risks identified in the Agency’s screening level risk assessment suggests that risks from drift onto non-target plants exceeds the Agency’s level of concern. The Agency is implementing spray drift controls that will decrease the risk that 2,4-D will drift onto non-target plants.

F. Other Labeling Requirements

In order to be eligible for reregistration, various use and safety information will be included in the labeling of all end-use products containing 2,4-D. For the specific labeling statements and a list of outstanding data, refer to Section V of this RED document.

1. Endangered Species Considerations
The Agency has developed the Endangered Species Protection Program to identify pesticides whose use may cause adverse impacts on endangered and threatened species, and to implement mitigation measures that address these impacts. The Endangered Species Act requires federal agencies to ensure that their actions are not likely to jeopardize listed species or adversely modify designated critical habitat. To analyze the potential of registered pesticide uses that may affect any particular species, EPA uses basic toxicity and exposure data and considers ecological parameters, pesticide use information, geographic relationship between specific pesticide uses and species locations, and biological requirements and behavioral aspects of the particular species. Based on EPA’s screening level assessment for 2,4-D, RQs exceed levels of concern for mammals, birds, aquatic plants, and terrestrial plants. However, these findings are based solely on EPA’s screening level assessment and do not constitute “may affect” findings under the ESA. The Agency is requiring additional data to further characterize and refine its ecological and endangered species risk assessments. The 2,4-D Task Force has submitted a limited endangered species assessment on several crops for the Agency’s consideration. This assessment was generated using the FIFRA Endangered Species Task Force (FESTF) integrated management system (IMS).

2. Spray Drift Management

The Agency has been working closely with stakeholders to develop improved approaches for mitigating risks to human health and the environment from pesticide spray and dust drift. As part of the reregistration process, we will continue to work with all interested parties on this important issue. From its assessment of 2,4-D, as summarized in this document, the Agency concludes that certain drift mitigation measures are needed to address the risks from off-target drift for 2,4-D. Label statements implementing these measures are listed in the "spray drift management" section of the Labeling Changes Summary Table in section V.D. of this RED document. In the future, 2,4-D product labels may need to be revised to include additional or different drift label statements.

3. Consumer Labeling Initiative

The Consumer Labeling Initiative (CLI) is an effort among federal, state, and local government agencies, industry, environmental groups, and other interested parties working to improve product labels on residential pesticides in order to improve consumer understanding and compliance of consumer labels. The CLI Work Group of the Pesticide Program Dialogue Committee (PPDC) is working to revise consumer labels. In addition to the labeling changes presented in this RED, the Agency will leave open the possibility that changes to residential product labeling may occur as the result of the PPDC CLI.
V. What Registrants Need To Do

For 2,4-D technical grade active ingredient products, registrants need to submit the following items.

Within 90 days from receipt of the generic data call-in (DCI):

1. completed response forms to the generic DCI (i.e., DCI response form and requirements status and registrant’s response form); and

2. submit any time extension and/or waiver requests with a full written justification.

Within the time limit specified in the generic DCI:

1. cite any existing generic data which address data requirements or submit new generic data responding to the DCI.

Please contact Katie Hall at (703) 308-0166 with questions regarding generic reregistration and/or the DCI. All materials submitted in response to the generic DCI should be addressed:

By US mail:
Document Processing Desk (DCI/SRRD)  
Katie Hall  
US EPA (7508C)  
1200 Pennsylvania Ave., NW  
Washington, DC 20460

By express or courier service:
Document Processing Desk (DCI/SRRD)  
Katie Hall  
Office of Pesticide Programs (7508C)  
1801 S. Bell Street  
Arlington, VA 22202-4501

For products containing the active ingredient 2,4-D registrants need to submit the following items for each product.

Within 90 days from the receipt of the product-specific data call-in (PDCI):

1. completed response forms to the PDCI (i.e., PDCI response form and requirements status and registrant’s response form); and

2. submit any time extension or waiver requests with a full written justification.

Within eight months from the receipt of the PDCI:

1. two copies of the confidential statement of formula (EPA Form 8570-4);
(2) a completed original application for reregistration (EPA Form 8570-1). Indicate on the form that it is an “application for reregistration”;

(3) five copies of the draft label incorporating all label amendments outlined in Table 40 of this document;

(4) a completed form certifying compliance with data compensation requirements (EPA Form 8570-34);

(5) if applicable, a completed form certifying compliance with cost share offer requirements (EPA Form 8570-32); and

(6) the product-specific data responding to the PDCI.

Please contact Moana Appleyard at (703) 308-8175 with questions regarding product reregistration and/or the PDCI. All materials submitted in response to the PDCI should be addressed:

By US mail:
Document Processing Desk (PDCI/PRB)
Moana Appleyard
US EPA (7508C)
1200 Pennsylvania Ave., NW
Washington, DC 20460

By express or courier service only:
Document Processing Desk (PDCI/PRB)
Moana Appleyard
Office of Pesticide Programs (7508C)
Room 266A, Crystal Mall 2
1801 Bell Street
Arlington, VA  22202

A. Manufacturing Use Products

1. Additional Generic Data Requirements

The generic data base supporting the reregistration of 2,4-D for eligible uses has been reviewed and determined to be substantially complete. However the following data requirements are necessary to confirm the reregistration eligibility decision documented in this RED.

<table>
<thead>
<tr>
<th>Guideline Study Name</th>
<th>New OPPTS Guideline No.</th>
<th>Old Guideline No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aquatic field dissipation studies (Behavior of 2,4-D BEE under acidic</td>
<td>835.6200</td>
<td>164-2</td>
</tr>
<tr>
<td>to neutral aquatic conditions in a water/sediment system)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory volatility study (2,4-D IPE)</td>
<td>835.1410</td>
<td>163-2</td>
</tr>
<tr>
<td>Terrestrial field dissipation studies (2,4-D IPA, 2,4-D TIPA, 2,4-D DEA,</td>
<td>835.6100</td>
<td>164-1</td>
</tr>
<tr>
<td>2,4-D BEE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guideline Study Name</td>
<td>New OPPTS Guideline No.</td>
<td>Old Guideline No.</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------------</td>
<td>-------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Aquatic field dissipation studies in a rice use scenario (2,4-D IPA, 2,4-D TIPA,</td>
<td>835.6200</td>
<td>164-2</td>
</tr>
<tr>
<td>2,4-D DEA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aquatic field dissipation studies in an aquatic weed control scenario (2,4-D IPA,</td>
<td>835.6200</td>
<td>164-2</td>
</tr>
<tr>
<td>2,4-D TIPA, 2,4-D DEA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forest field dissipation studies (2,4-D IPA, 2,4-D TIPA, 2,4-D BEE, and 2,4-D DEA)</td>
<td>835.6300</td>
<td>164-3</td>
</tr>
<tr>
<td>Fish acute toxicity test, freshwater and marine with typical end-use product (TEP)</td>
<td>850.1075</td>
<td>72-1</td>
</tr>
<tr>
<td>(2,4-D BEE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oyster acute toxicity test with TEP (2,4-D BEE)</td>
<td>850.1025</td>
<td>72-3</td>
</tr>
<tr>
<td>Mysid acute toxicity test with TEP (2,4-D BEE)</td>
<td>850.1035</td>
<td>72-3</td>
</tr>
<tr>
<td>Penaid acute toxicity test with TEP (2,4-D BEE)</td>
<td>850.1045</td>
<td>72-3</td>
</tr>
<tr>
<td>Sediment and soil adsorption/desorption (2,4-D BEE granular formulation)</td>
<td>835.1230</td>
<td>163-1</td>
</tr>
<tr>
<td>Seedling Germination/Seedling Emergence</td>
<td>850.4225</td>
<td>123-1(a)</td>
</tr>
<tr>
<td>Vegetative Vigor</td>
<td>850.4250</td>
<td>123-1(b)</td>
</tr>
<tr>
<td>Non-target terrestrial plants - TEP representative testing from the acid and amine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>salts group, and representative testing from the ester group. The test products</td>
<td></td>
<td></td>
</tr>
<tr>
<td>should include the most common and most active surfactants and adjuvants which</td>
<td></td>
<td></td>
</tr>
<tr>
<td>affect the toxicity of the product. The registrants should consult with the Agency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>before finalizing which products to test.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The registrant must provide information on the proximity of Federally listed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>freshwater vascular plants, birds, mammals, and non-target terrestrial plants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(there are no listed estuarine/marine invertebrates) to the 2,4-D use sites. This</td>
<td></td>
<td></td>
</tr>
<tr>
<td>requirement may be satisfied in one of three ways: 1) having membership in the</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIFRA Endangered Species Task Force (Pesticide Registration [PR] Notice 2000-2); 2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>citing FIFRA Endangered Species Task Force data; or 3) independently producing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>these data, provided the information is of sufficient quality to meet FIFRA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>requirements. Registrants should consult with the Agency prior to fulfilling this</td>
<td></td>
<td></td>
</tr>
<tr>
<td>data requirement.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Human Health Effects Data Requirements

<table>
<thead>
<tr>
<th>Study</th>
<th>New OPPTS Guideline No.</th>
<th>Old Guideline No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental neurotoxicity study</td>
<td>870.6300</td>
<td>83-6</td>
</tr>
<tr>
<td>Subchronic inhalation toxicity study (28-day)</td>
<td>870.3465</td>
<td>82-4</td>
</tr>
<tr>
<td>Repeat two-generation reproduction study (using the most recent Agency protocol) addressing concerns for endocrine disruption (thyroid and immunotoxicity measures)</td>
<td>870.3800</td>
<td>83-4</td>
</tr>
</tbody>
</table>

### Product and Residue Chemistry Data Requirements

<table>
<thead>
<tr>
<th>Study</th>
<th>New OPPTS Guideline No.</th>
<th>Old Guideline No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crop field trials - wheat hay</td>
<td>860.1500</td>
<td>171-4k</td>
</tr>
</tbody>
</table>
B. End-Use Products

1. Additional Product-Specific Data Requirements

Section 4(g)(2)(B) of FIFRA calls for the Agency to obtain any needed product-specific data regarding the pesticide after a determination of eligibility has been made. Registrants must review previous data submissions to ensure that they meet current EPA acceptance criteria and if not, commit to conduct new studies. If a registrant believes that previously submitted data meet current testing standards, then the study MRID numbers should be cited according to the instructions in the Requirement Status and Registrants Response Form provided for each product.

2. Labeling for End-Use Products

Labeling changes are necessary to implement the mitigation measures outlined in Section IV above. Specific language to incorporate these changes is specified in Table 40.

C. Existing Stocks

Registrants may generally distribute and sell products bearing old labels/labeling for 12 months from the date of the issuance of this Reregistration Eligibility Decision document. Persons
other than the registrant may generally distribute or sell such products for 24 months from the date of
the issuance of this RED. However, existing stocks time frames will be established case-by-case,
depending on the number of products involved, the number of label changes, and other factors. Refer
to “Existing Stocks of Pesticide Products; Statement of Policy”; Federal Register; Volume 56, No.
D. Required Labeling Changes Summary Table

In order to be eligible for reregistration, all product labels must be amended to incorporate the risk mitigation measures outlined in Section IV. The following table describes how language on the labels should be amended.

<table>
<thead>
<tr>
<th>Description</th>
<th>Amended Labeling Language</th>
<th>Placement on Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>For all Manufacturing Use Products</td>
<td>“Only for formulation into an herbicide or plant growth regulator for the following use(s) [fill blank only with those uses that are being supported by MP registrant].”</td>
<td>Directions for Use</td>
</tr>
<tr>
<td></td>
<td>“Wettable powder formulations must be packaged in water-soluble packages.”</td>
<td></td>
</tr>
<tr>
<td>One of these statements may be added to a label to allow reformulation of the product for a specific use or all additional uses supported by a formulator or user group</td>
<td>“This product may be used to formulate products for specific use(s) not listed on the MP label if the formulator, user group, or grower has complied with U.S. EPA submission requirements regarding support of such use(s).”</td>
<td>Directions for Use</td>
</tr>
<tr>
<td></td>
<td>“This product may be used to formulate products for any additional use(s) not listed on the MP label if the formulator, user group, or grower has complied with U.S. EPA submission requirements regarding support of such use(s).”</td>
<td></td>
</tr>
<tr>
<td>Environmental Hazards Statements Required by the RED and Agency Label Policies</td>
<td>&quot;This chemical is toxic to fish and aquatic invertebrates. Do not discharge effluent containing this product into lakes, streams, ponds, estuaries, oceans, or other waters unless in accordance with the requirements of a National Pollution Discharge Elimination System (NPDES) permit and the permitting authority has been notified in writing prior to discharge. Do not discharge effluent containing this product to sewer systems without previously notifying the local sewage treatment plant authority. For guidance contact your State Water Board or Regional Office of the EPA.&quot;</td>
<td>Precautionary Statements</td>
</tr>
</tbody>
</table>

End Use Products Intended for Occupational Use
| PPE Requirements | Established by the RED\(^1\) for liquids, wettable powders formulated in water-soluble packages, and water-dispersible granules | “Personal Protective Equipment (PPE)“ Some materials that are chemical-resistant to this product are” (registrant inserts correct chemical-resistant material). “If you want more options, follow the instructions for category” [registrant inserts A,B,C,D,E,F,G,or H] “on an EPA chemical-resistance category selection chart.”

“All mixers, loaders, applicators, flaggers, and other handlers must wear:
- long-sleeved shirt and long pants,
- shoes and socks, plus
- chemical resistant gloves, when applying postharvest dips or sprays to citrus, applying with any handheld nozzle or equipment, mixing or loading, cleaning up spills or equipment, or otherwise exposed to the concentrate.
- chemical resistant apron when applying postharvest dips or sprays to citrus, mixing or loading, cleaning up spills or equipment, or otherwise exposed to the concentrate.

See engineering controls for additional requirements.” | Immediately following/below Precautionary Statements: Hazards to Humans and Domestic Animals |
|---|---|---|---|
| PPE Requirements | Established by the RED\(^1\) for granular formulations | “Personal Protective Equipment (PPE)“ All loaders, applicators, and other handlers must wear:
- long-sleeved shirt and long pants,
- shoes plus socks.” | Immediately following/below Precautionary Statements: Hazards to Humans and Domestic Animals |
<p>| User Safety Requirements | “Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washables exist, use detergent and hot water. Keep and wash PPE separately from other laundry.” | Precautionary Statements: Hazards to Humans and Domestic Animals immediately following the PPE requirements |</p>
<table>
<thead>
<tr>
<th>Engineering Controls for aerial applications</th>
<th>Enclosed Cockpits</th>
<th>Precautionary Statements: Hazards to Humans and Domestic Animals (Immediately following PPE and User Safety Requirements.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Engineering Controls:”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilots must use an enclosed cockpit that meets the requirements listed in the WPS for agricultural pesticides [40 CFR 170.240(d)(6)]”</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Engineering Controls for wettable powder formulations packaged in water-soluble packages</th>
<th>“Engineering Controls”</th>
<th>Precautionary Statements: Hazards to Humans and Domestic Animals (Immediately following PPE and User Safety Requirements.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Water-soluble packets when used correctly qualify as a closed loading system under the WPS. Mixers and loaders using water-soluble packets (1) must wear the PPE specified above for mixers and loaders and (2) must be provided, have immediately available for use in an emergency, such as a broken package, spill, or equipment breakdown a NIOSH-approved dust mist filtering respirator with MSHA/NIOSH approval number prefix TC-21C or a NIOSH-approved respirator with any N, R, P, or HE filter.”</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>User Safety Recommendations</th>
<th>“User Safety Recommendations”</th>
<th>Precautionary Statements under: Hazards to Humans and Domestic Animals immediately following Engineering Controls (Must be placed in a box.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Users should wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet.</td>
<td>Users should remove clothing/PPE immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing. If pesticide gets on skin, wash immediately with soap and water.</td>
<td></td>
</tr>
<tr>
<td>Users should remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing.”</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Environmental Hazard Statement for Terrestrial Uses | “This pesticide may be toxic to fish and aquatic invertebrates. Do not apply directly to water, to areas where surface water is present, or to intertidal areas below the mean high water mark except as noted on appropriate labels. Drift and runoff may be hazardous to aquatic organisms in water adjacent to treated areas. Do not contaminate water when disposing of equipment wash waters or rinsate.

This chemical has properties and characteristics associated with chemicals detected in groundwater. The use of this chemical in areas where soils are permeable, particularly where the water table is shallow, may result in groundwater contamination. Application around a cistern or well may result in contamination of drinking water or groundwater.” | Precautionary Statements immediately following the User Safety Recommendations |
| Environmental Hazard Statement for products used for aquatic weed control | “Fish breathe dissolved oxygen in the water and decaying weeds also use oxygen. When treating continuous, dense weed masses, it may be appropriate to treat only part of the infestation at a time. For example, apply the product in lanes separated by untreated strips that can be treated after vegetation in treated lanes has disintegrated. During the growing season, weeds decompose in a 2 to 3 week period following treatment. Begin treatment along the shore and proceed outwards in bands to allow fish to move into untreated areas. Waters having limited and less dense weed infestations may not require partial treatments.” | Precautionary Statements immediately following the User Safety Recommendations |
| Restricted-Entry Interval for products containing with directions for use within the scope of the WPS and containing 2,4-D acid or amine forms | “Do not enter or allow worker entry into treated areas during the restricted entry interval (REI) of 48 hours.” | Directions for Use, Under Agricultural Use Requirements Box |
| Restricted-Entry Interval for products containing with directions for use within the scope of the WPS and containing 2,4-D salt or ester forms | “Do not enter or allow worker entry into treated areas during the restricted entry interval (REI) of 12 hours.” | Directions for Use, Under Agricultural Use Requirements Box |
| Early Entry Personal Protective Equipment established by the RED for products containing 2,4-D acid or amine forms and with WPS uses | “PPE required for early entry to treated areas that is permitted under the Worker Protection Standard and that involves contact with anything that has been treated, such as plants, soil, or water is:
- coveralls,
- chemical-resistant gloves made of any water-proof material,
- shoes plus socks,
- protective eyewear.” | Directions for Use, Agricultural Use Requirements Box |
|---|---|---|
| Early Entry Personal Protective Equipment established by the RED for products containing 2,4-D salt or ester forms and with WPS uses | “PPE required for early entry to treated areas that is permitted under the Worker Protection Standard and that involves contact with anything that has been treated, such as plants, soil, or water is:
- coveralls,
- chemical-resistant gloves made of any water-proof material,
- shoes plus socks.” | Directions for Use, Agricultural Use Requirements Box |
<p>| Entry Restrictions for Granular Formulations with directions for use outside the scope of the WPS | “Do not enter or allow people (or pets) to enter the treated area until dusts have settled.” | If no WPS uses on the product, place the appropriate statement in the Directions for Use Under General Precautions and Restrictions. If the product also contains WPS uses, then create a NonAgricultural Use Requirements box as directed in PR Notice 93-7 and place the appropriate statement inside that box. |</p>
<table>
<thead>
<tr>
<th>Entry Restrictions for liquids, water-dispersible granules, and wettable powders formulated in water-soluble packages with directions for use outside the scope of the WPS</th>
<th>“Do not enter or allow people (or pets) to enter the treated area until sprays have dried.”</th>
<th>If no WPS uses on the product, place the appropriate statement in the Directions for Use Under General Precautions and Restrictions. If the product also contains WPS uses, then create a NonAgricultural Use Requirements box as directed in PR Notice 93-7 and place the appropriate statement inside that box.</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Application Restrictions for products primarily intended for occupational (professional) use</td>
<td>“Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application.”</td>
<td>Directions for Use under General Precautions and Restrictions</td>
</tr>
<tr>
<td>Use-Specific Application Restrictions</td>
<td>“Aquatic weed control”</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>(Note: The maximum allowable application rate must be listed as pounds or gallons of formulated product per surface acre, not just as pounds acid equivalent per surface acre.)</td>
<td>For all acids, salts, amines, and butoxyethanol ester forms used for aquatic weed control, the following statements must appear on the product label:</td>
<td></td>
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<tr>
<td></td>
<td>&gt; “Ditchbank application”</td>
<td></td>
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<tr>
<td></td>
<td>Postemergence:</td>
<td></td>
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<tr>
<td></td>
<td>Limited to 2 applications per season.</td>
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</tr>
<tr>
<td></td>
<td>Maximum of 2.0 lbs ae/acre per application.</td>
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<tr>
<td></td>
<td>Minimum of 30 days between applications.</td>
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<tr>
<td></td>
<td>Spot treatment permitted.</td>
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<tr>
<td></td>
<td>Do not use on small canals with a flow rate less than 10 cubic feet per second (CFS) where water will be used for drinking purposes. CFS may be estimated by using the formula below. The approximate velocity needed for the calculation can be determined by observing the length of time that it takes a floating object to travel a defined distance. Divide the distance (ft.) by the time (sec.) to estimate velocity (ft. per sec.). Repeat 3 times and use the average to calculate CFS.</td>
<td></td>
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<tr>
<td></td>
<td>Average Width (ft.) x Average Depth (ft.) x Average Velocity (ft. per sec.) = CFS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For ditchbank weeds:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not allow boom spray to be directed onto water surface.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Do not spray across stream to opposite bank.</td>
<td>Directions for Use Associated with the Specific Use Pattern</td>
</tr>
</tbody>
</table>
Use-Specific Application Restrictions

(Note: The maximum allowable application rate must be listed as pounds or gallons of formulated product per surface acre, not just as pounds acid equivalent per surface acre.)

For shoreline weeds:
Allow no more than 2 foot overspray onto water.”

> **Floating and Emergent Weeds**
Maximum of 4.0 lbs ae/surface acre per application.
Limited to 2 applications per season.
Minimum of 21 days between applications.
Spot treatments are permitted.
Apply to emergent aquatic weeds in ponds, lakes, reservoirs, marshes, bayous, drainage ditches, non-irrigation canals, rivers, and streams that are quiescent or slow moving.
Coordination and approval of local and state authorities may be required, either by letter of agreement or issuance of special permits for aquatic applications.

Water Use

1. Water for irrigation or sprays:

A. If treated water is intended to be used only for crops or non-crop areas that are labeled for direct treatment with 2,4-D such as pastures, turf, or cereal grains, the treated water may be used to irrigate and/or mix sprays for these sites at anytime after the 2,4-D aquatic application.

Directions for Use Associated with the Specific Use Pattern
Use-Specific Application Restrictions

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>B.</td>
<td>Due to potential phytotoxicity considerations, the following restrictions are applicable: If treated water is intended to be used to irrigate or mix sprays for plants grown in commercial nurseries and greenhouses; and other plants or crops that are not labeled for direct treatment with 2,4-D, the water must not be used unless one of the following restrictions has been observed:</td>
</tr>
<tr>
<td></td>
<td>i. A setback distance from functional water intake(s) of greater than or equal to 600 ft. was used for the application, or,</td>
</tr>
<tr>
<td></td>
<td>ii. A waiting period of 7 days from the time of application has elapsed, or,</td>
</tr>
<tr>
<td></td>
<td>iii. An approved assay indicates that the 2,4-D concentration is 100 ppb (0.1 ppm) or less at the water intake. Wait at least 3 days after application before initial sampling at water intake.</td>
</tr>
<tr>
<td>2.</td>
<td>Drinking water (potable water):</td>
</tr>
<tr>
<td>A.</td>
<td>Consult with appropriate state or local water authorities before applying this product to public waters. State or local agencies may require permits. The potable water use restrictions on this label are to ensure that consumption of water by the public is allowed only when the concentration of 2,4-D in the water is less than the MCL (Maximum Contaminant Level) of 70 ppb. Applicators should consider the unique characteristics of the treated waters to assure that 2,4-D concentrations in potable water do not exceed 70 ppb at the time of consumption.</td>
</tr>
</tbody>
</table>

Directions for Use Associated with the Specific Use Pattern
B. For floating and emergent weed applications, the drinking water setback distance from functioning potable water intakes is greater than or equal to 600 ft.

C. If no setback distance of greater than or equal to 600 ft. is used for application, applicators or the authorizing organization must provide a drinking water notification prior to a 2,4-D application to the party responsible for public water supply or to individual private water uses. Notification to the party responsible for a public water supply or to individual private water users must be done in a manner to assure that the party is aware of the water use restrictions when this product is applied to potable water.

The following is an example of a notification via posting, but other methods of notification which convey the above restrictions may be used and may be required in some cases under state or local law or as a condition of a permit.

**Example:**
Posting notification should be located every 250 feet including the shoreline of the treated area and up to 250 feet of shoreline past the application site to include immediate public access points. Posting must include the day and time of application. Posting may be removed if analysis of a sample collected at the intake 3 or more days following application shows that the concentration in the water is less than 70 ppb (100 ppb for irrigation or sprays), or after 7 days following application, whichever occurs first.
Use-Specific Application Restrictions

Text of notification: Wait 7 days before diverting functioning surface water intakes from the treated aquatic site to use as drinking water, irrigation, or sprays, unless water at functioning drinking water intakes is tested at least 3 days after application and is demonstrated by assay to contain not more than 70 ppb 2,4-D (100 ppb for irrigation or sprays). Application Date: _____ Time: _____

D. Following each application of this product, treated water must not be used for drinking water unless one of the following restrictions has been observed:

i. A setback distance from functional water intake(s) of greater than or equal to 600 ft. was used for the application, or,

ii. A waiting period of at least 7 days from the time of application has elapsed, or,

iii. An approved assay indicates that the 2,4-D concentration is 70 ppb (0.07 ppm) or less at the water intake. Sampling for drinking water analysis should occur no sooner than 3 days after 2,4-D application. Analysis of samples must be completed by a laboratory that is certified under the Safe Drinking Water Act to perform drinking water analysis using a currently approved version of analytical Method Number 515, 555, other methods for 2,4-D as may be listed in Title 40 CFR, Part 141.24, or Method Number 4015 (immunoassay of 2,4-D) from U.S. EPA Test Methods for Evaluating Solid Waste SW-846.

E. Note: Existing potable water intakes that are no longer in use, such as those replaced by a connection to a municipal water system or a potable water well, are not considered to be functioning potable water intakes.

Directions for Use Associated with the Specific Use Pattern
### Use-Specific Application Restrictions

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>F.</strong> Drinking water setback distances do not apply to terrestrial applications of 2,4-D adjacent to water bodies with potable water intakes.</td>
<td></td>
</tr>
</tbody>
</table>

### 3. Swimming (2,4-D butoxyethanol ester only):

**A.** Do not swim in treated water for a minimum of 24 hours after application.

**B.** Users must provide notification prior to performing a 2,4-D BEE application. Notification to the party responsible for the public swimming area or to individual private users must be done in a manner to assure that the party is aware of the water use swimming restrictions when this product is applied to water. The following is an example of a notification via posting, but other methods of notification which convey the above restrictions may be used and may be required in some cases under state or local law or as a condition of a permit.

**Example:**
Posting notification should be located every 250 feet including the shoreline of the treated area and up to 250 feet of shoreline past the application site to include immediate public access points.

**Text of Notification:** Do not swim in treated water for a minimum of 24 hours after application. Application Date: _____ Time: _____.

**4.** Except as stated above, there are no restrictions on using water from treated areas for swimming, fishing, watering livestock or domestic purposes.”

### Directions for Use Associated with the Specific Use Pattern

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>
Use-Specific Application Restrictions

(Note: The maximum allowable application rate must be listed as pounds or gallons of formulated product per acre-foot, not just as pounds acid equivalent per acre-foot.)

> **“Submersed Weeds**

Maximum of 10.8 lbs ae/per acre-foot per application.
Limited to 2 applications per season.
Apply to aquatic weeds in ponds, lakes, reservoirs, marshes, bayous, drainage ditches, non-irrigation canals, rivers, and streams that are quiescent or slow moving.
Do not apply within 21 days of previous application.
When treating moving bodies of water, applications must be made while traveling upstream to prevent concentration of 2,4-D downstream from the application.
Coordination and approval of local and state authorities may be required, either by letter of agreement or issuance of special permits for such use.

<table>
<thead>
<tr>
<th>Surface Area</th>
<th>Average Depth</th>
<th>For typical conditions - 2 ppm 2,4-D ae/acre-foot</th>
<th>For difficult conditions* - 4 ppm 2,4-D ae/acre-foot</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 acre</td>
<td>1 ft.</td>
<td>5.4 lbs</td>
<td>10.8 lbs</td>
</tr>
<tr>
<td></td>
<td>2 ft.</td>
<td>10.8 lbs</td>
<td>21.6 lbs</td>
</tr>
<tr>
<td></td>
<td>3 ft.</td>
<td>16.2 lbs</td>
<td>32.4 lbs</td>
</tr>
<tr>
<td></td>
<td>4 ft.</td>
<td>21.6 lbs</td>
<td>43.2 lbs</td>
</tr>
<tr>
<td></td>
<td>5 ft.</td>
<td>27.0 lbs</td>
<td>54.0 lbs</td>
</tr>
</tbody>
</table>

* Examples include spot treatment of pioneer colonies of Eurasian Water Milfoil and certain difficult to control aquatic species.

Directions for Use Associated with the Specific Use Pattern

Table 1. Amount of 2,4-D to Apply for a Target Subsurface Concentration
Use-Specific Application Restrictions

<table>
<thead>
<tr>
<th>Water Use:</th>
<th>Directions for Use Associated with the Specific Use Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Water Use:</strong></td>
<td><strong>Water for irrigation or sprays:</strong></td>
</tr>
<tr>
<td>1. Water for irrigation or sprays:</td>
<td>A. If treated water is intended to be used only for crops or non-crop areas that are labeled for direct treatment with 2,4-D such as pastures, turf, or cereal grains, the treated water may be used to irrigate and/or mix sprays for these sites at anytime after the 2,4-D aquatic application.</td>
</tr>
<tr>
<td>B. Due to potential phytotoxicity and/or residue considerations, the following restrictions are applicable:</td>
<td>B. If treated water is intended to be used to irrigate or mix sprays for unlabeled crops, non-crop areas or other plants not labeled for direct treatment with 2,4-D, the water must not be used unless one of the following restrictions has been observed:</td>
</tr>
<tr>
<td>i. A setback distance described in the Drinking Water Setback Table was used for the application, or,</td>
<td><strong>ii. A waiting period of 21 days from the time of application has elapsed, or,</strong></td>
</tr>
<tr>
<td>ii. A waiting period of 21 days from the time of application has elapsed, or,</td>
<td><strong>iii. An approved assay indicates that the 2,4-D concentration is 100 ppb (0.1 ppm) or less at the water intake. See Table 3 for the waiting period after application but before taking the initial sampling at water intake.</strong></td>
</tr>
</tbody>
</table>
### Use-Specific Application Restrictions

The potable water use restrictions on this label are to ensure that consumption of water by the public is allowed only when the concentration of 2,4-D in the water is less than the MCL (Maximum Contaminant Level) of 70 ppb. Applicators should consider the unique characteristics of the treated waters to assure that 2,4-D concentrations in potable water do not exceed 70 ppb at the time of consumption.

**B.** For submersed weed applications, the drinking water setback distances from functioning potable water intakes are provided in Table 2. Drinking Water Setback Distance (below).

**C.** If no setback distance from the Drinking Water Setback Table (Table 2) is to be used for the application, applicators or the authorizing organization must provide a drinking water notification and an advisory to shut off all potable water intakes prior to a 2,4-D application. Notification to the party responsible for a public water supply or to individual private water users must be done in a manner to assure that the party is aware of the water use restrictions when this product is applied to potable water. The following is an example of a notification via posting, but other methods of notification which convey the above restrictions may be used and may be required in some cases under state or local law or as a condition of a permit.

### Directions for Use Associated with the Specific Use Pattern
Use-Specific Application Restrictions

Example:
Posting notification should be located every 250 feet including the shoreline of the treated area and up to 250 feet of shoreline past the application site to include immediate public access points. Posting should include the day and time of application. Posting may be removed if analysis of a sample collected at the intake no sooner than stated in Table 3 (below) shows that the concentration in the water is less than 70 ppb (100 ppb for irrigation or sprays), or after 21 days following application, whichever occurs first.

Text of notification: Wait 21 days before diverting functioning surface water intakes from the treated aquatic site to use as drinking water, irrigation, or sprays, unless water at functioning drinking water intakes is tested no sooner than (insert days from Table 3) and is demonstrated by assay to contain not more than 70 ppb 2,4-D (100 ppb for irrigation or sprays).
Application Date: _____ Time: _____.

D. Following each application of this product, treated water must not be used for drinking water unless one of the following restrictions has been observed:

i. A setback distance described in the Drinking Water Setback Distance Table was used for the application, or,

ii. A waiting period of at least 21 days from the time of application has elapsed, or,
| Use-Specific Application Restrictions | iii. An approved assay indicates that the 2,4-D concentration is 70 ppb (0.07 ppm) or less at the water intake. Sampling for drinking water analysis should occur no sooner than stated in Table 3. Analysis of samples must be completed by a laboratory that is certified under the Safe Drinking Water Act to perform drinking water analysis using a currently approved version of analytical Method Number 515, 555, other methods for 2,4-D as may be listed in Title 40 CFR, Part 141.24, or Method Number 4015 (immunoassay of 2,4-D) from U.S. EPA Test Methods for Evaluating Solid Waste SW-846.  

E. Note: Existing potable water intakes that are no longer in use, such as those replaced by a connection to a municipal water system or a potable water well, are not considered to be functioning potable water intakes.  

F. Drinking water setback distances do not apply to terrestrial applications of 2,4-D adjacent to water bodies with potable water intakes. | Directions for Use Associated with the Specific Use Pattern |
3. Swimming (2,4-D butoxyethanol ester only):
A. Do not swim in treated water for a minimum of 24 hours after application.

B. Users must provide the following notification prior to performing a 2,4-D BEE application. Notification to the party responsible for the public swimming area or to individual private users must be done in a manner to assure that the party is aware of the water use swimming restrictions when this product is applied to water. The following is an example of a notification via posting, but other methods of notification which convey the above restrictions may be used and may be required in some cases under state or local law or as a condition of a permit.

Example:
Posting notification should be located every 250 feet including the shoreline of the treated area and up to 250 feet of shoreline past the application site to include immediate public access points.

**Text of Notification:** Do not swim in treated water for a minimum of 24 hours after application. Application Date: ______ Time: _____.

4. Except as stated above, there are no restrictions on using water from treated areas for swimming, fishing, watering livestock or domestic purposes.”

---

**Table 2. Drinking Water Setback Distance for Submersed Weed Applications**

<table>
<thead>
<tr>
<th>Application Rate and Minimum Setback Distance (feet) From Functioning Potable Water Intake</th>
<th>Directions for Use Associated with the Specific Use Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Sampling for Drinking Water Analysis After 2,4-D Application for Submersed Weed Applications

<table>
<thead>
<tr>
<th>1 ppm*</th>
<th>2 ppm*</th>
<th>3 ppm*</th>
<th>4 ppm*</th>
</tr>
</thead>
<tbody>
<tr>
<td>600</td>
<td>1200</td>
<td>1800</td>
<td>2400</td>
</tr>
</tbody>
</table>

* ppm acid equivalent target water concentration

<table>
<thead>
<tr>
<th>1 ppm*</th>
<th>2 ppm*</th>
<th>3 ppm*</th>
<th>4 ppm*</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>10</td>
<td>10</td>
<td>14</td>
</tr>
</tbody>
</table>

* ppm acid equivalent target water concentration"
Use-Specific Application Restrictions

(Note: The maximum allowable application rate must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.

<table>
<thead>
<tr>
<th align="left">“Asparagus”</th>
<th align="left">“Blueberry, low bush”</th>
</tr>
</thead>
<tbody>
<tr>
<td align="left">Permitted forms of 2,4-D include acid, salts, and amines.</td>
<td align="left"></td>
</tr>
<tr>
<td align="left">“The preharvest interval (PHI) is 3 days.</td>
<td align="left"></td>
</tr>
<tr>
<td align="left">Limited to 2 applications per crop cycle.</td>
<td align="left"></td>
</tr>
<tr>
<td align="left">Maximum of 2.0 lb ae/acre per application</td>
<td align="left"></td>
</tr>
<tr>
<td align="left">Minimum of 30 days between applications.</td>
<td align="left"></td>
</tr>
<tr>
<td align="left"></td>
<td align="left"></td>
</tr>
<tr>
<td align="left">Permitted forms of 2,4-D include acid, salts, and amines.</td>
<td align="left"></td>
</tr>
<tr>
<td align="left">“Postemergence:</td>
<td align="left"></td>
</tr>
<tr>
<td align="left">Limited to one postemergence application per year.</td>
<td align="left"></td>
</tr>
<tr>
<td align="left">Maximum of 0.0375 lbs ae/gallons of spray solution per application.</td>
<td align="left"></td>
</tr>
<tr>
<td align="left">Postharvest:</td>
<td align="left"></td>
</tr>
<tr>
<td align="left">Limited to one postharvest application per year.</td>
<td align="left"></td>
</tr>
<tr>
<td align="left">Maximum of 1.0 lbs ae/gallon spray solution per application.</td>
<td align="left"></td>
</tr>
<tr>
<td align="left">For spot or directed wipe treatment only.</td>
<td align="left"></td>
</tr>
<tr>
<td align="left">Apply only in non-bearing years.</td>
<td align="left"></td>
</tr>
<tr>
<td align="left">Use-Specific Application Restrictions</td>
<td align="left">“Blueberry, high bush”</td>
</tr>
<tr>
<td align="left">--------------------------------------</td>
<td align="left">------------------------</td>
</tr>
<tr>
<td align="left">(Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)</td>
<td align="left">Permitted forms of 2,4-D include acid, salts, and amines. “The preharvest interval (PHI) is 30 days. Postemergence and postharvest: Limited to 2 applications per year. Maximum of 1.4 lbs ae/acre per application.”</td>
</tr>
<tr>
<td align="left"></td>
<td align="left">“Cereal Grains (wheat, barley, millet, oats, and rye)”</td>
</tr>
<tr>
<td align="left"></td>
<td align="left">Permitted forms of 2,4-D include acid, salts, amines, and esters. “The preharvest interval (PHI) is 14 days. Postemergence: Limited to one postemergence application per crop cycle. Maximum of 1.25 lbs ae/acre per application. Preharvest: Limited to one preharvest application per crop cycle. Maximum of 0.5 lbs ae/acre per application. Limited to 1.75 lbs ae/acre per crop cycle.”</td>
</tr>
</tbody>
</table>
Other Application Restrictions (Risk Mitigation)

(Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)

<table>
<thead>
<tr>
<th>&quot;Citrus (growing fruit)&quot;</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Permitted form of 2,4-D is isopropyl ester.</td>
<td></td>
</tr>
<tr>
<td>“The preharvest interval (PHI) is 7 days.</td>
<td></td>
</tr>
<tr>
<td>- To increase fruit size on growing Navel oranges, Valencia oranges, and grapefruit: Limited to one application per crop cycle. Maximum of 45 grams ae per acre (0.1 lbs ae/acre).</td>
<td></td>
</tr>
<tr>
<td>- To reduce pre-harvest fruit drop on growing Navel oranges, Valencia oranges, and grapefruit: Limited to one application per crop cycle. Maximum rate of 200 ppm per application.</td>
<td></td>
</tr>
<tr>
<td>- To prevent pre-harvest drop of mature fruit and leaves on lemons, Navel oranges, Valencia oranges, and Tangelos: Limited to one application per crop cycle. Maximum rate of 24 ppm per application.”</td>
<td></td>
</tr>
</tbody>
</table>

Directions for Use Associated with the Specific Use Pattern
<table>
<thead>
<tr>
<th>Other Application Restrictions (Risk Mitigation)</th>
<th>Postharvest Citrus Treatment</th>
<th>Directions for Use Associated with the Specific Use Pattern</th>
</tr>
</thead>
</table>
| (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.) | Permitted form of 2,4-D is isopropyl ester.  
“Permitted application methods include dip or spray.  

Postharvest packing house application to lemons:  
Limited to one application per crop.  
Maximum rate of 500 ppm per application.” | |
<table>
<thead>
<tr>
<th>Other Application Restrictions (Risk Mitigation)</th>
<th>“Corn, field and pop”</th>
<th>Directions for Use Associated with the Specific Use Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)</td>
<td>Permitted forms of 2,4-D include acid, salts, amines, and esters. “Do not use treated crop as fodder for 7 days following application. The preharvest interval (PHI) is 7 days. Maximum of 3 lbs ae/acre per crop cycle. Preplant or preemergence: Limited to one preplant or preemergence application per crop cycle. Maximum of 1.0 lb ae/acre per application. Postemergence: Limited to one postemergence application per crop cycle. Maximum of 0.5 lb ae/acre per application. Preharvest: Limited to one preharvest application per crop cycle. Maximum of 1.5 lbs ae/acre per application.”</td>
<td></td>
</tr>
<tr>
<td>Other Application Restrictions (Risk Mitigation)</td>
<td>“Corn, sweet”</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td>(Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)</td>
<td>Permitted forms of 2,4-D include acid, salts, amines, and esters. “Do not use treated crop as fodder for 7 days following application. The preharvest interval (PHI) is 45 days. Minimum of 21 days between applications. Maximum of 1.5 lbs ae/acre per crop cycle.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Preplant or preemergence: Limited to one preplant or preemergence application per crop cycle. Maximum of 1.0 lb ae/acre per application.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postemergence: Limited to one postemergence application per crop cycle. Maximum of to 0.5 lb ae/acre per application.”</td>
<td></td>
</tr>
</tbody>
</table>

Directions for Use Associated with the Specific Use Pattern
<table>
<thead>
<tr>
<th>Other Application Restrictions (Risk Mitigation)</th>
<th>“Cranberries”</th>
<th>Directions for Use Associated with the Specific Use Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)</td>
<td>Permitted forms of 2,4-D include acid, salts, amines, and esters. “The preharvest interval (PHI) is 30 days.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dormant Season:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Limited to one application per crop cycle.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum of 4.0 lbs ae/acre per dormant season</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postemergence:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Limited to 2 applications per crop cycle.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum of 1.2 lbs ae/acre per postemergence application.”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>“Filberts”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Permitted forms of 2,4-D include acid, salts, and amines.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>“The preharvest interval (PHI) is 45 days.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimum of 30 days between applications.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Limited to 4 applications per year.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum of 1.0 lbs ae per 100 gallons of spray solution per application.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>“Fallowland (crop stubble on idle land, or postharvest to crops, or between crops)”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Permitted forms of 2,4-D include acid, salts, amines, and esters.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>“Plant only labeled crops within 29 days following application.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Limited to 2 applications per year.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maximum of 2.0 lbs ae/acre per application.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minimum of 30 days between applications.”</td>
<td></td>
</tr>
<tr>
<td>Other Application Restrictions (Risk Mitigation)</td>
<td>“Forestry (forest site preparation, forest roadsides, brush control, established conifer release, Christmas trees, reforestation areas)”</td>
<td>Directions for Use Associated with the Specific Use Pattern</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.) | Permitted forms of 2,4-D include acid, salts, amines, and esters.  
Broadcast application:  
Limited to 1 broadcast application per year.  
Maximum of 4.0 lbs ae/acre per broadcast application.  
Basal spray, Cut Surface - Stumps, and Frill:  
Limit of one basal spray or cut surface application per year.  
Maximum of 8.0 lbs ae per 100 gallons of spray solution.  
Injection:  
Limit to one injection application per year.  
Maximum of 2 ml of 4.0 lbs ae formulation per injection site.” | “Grapes”  
Permitted forms of 2,4-D include acid, salts, and amines.  
“For use only in California.  
The preharvest interval (PHI) is 100 days.  
Limited to 1 application per crop cycle.  
Maximum of 1.36 lbs ae/acre per application.” |
### Other Application Restrictions (Risk Mitigation)

(Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)

<table>
<thead>
<tr>
<th><strong>Grasses (pastures and rangeland not in agricultural production)</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Permitted forms of 2,4-D include acid, salts, amines, and esters.</td>
<td></td>
</tr>
<tr>
<td>“The preharvest interval (PHI) is 7 days (cut forage for hay).”</td>
<td></td>
</tr>
</tbody>
</table>

**Postemergence:**
- Limited to 2 applications per year.
- Maximum of 2.0 lbs ae/acre per application.
- Minimum of 30 days between applications.
- If grass is to be cut for hay, Agricultural Use Requirements for the Worker Protection Standard are applicable.
- For program lands, such as Conservation Reserve Program, consult program rules to determine whether grass or hay may be used. The more restrictive requirements of the program rules or this label must be followed.”

<table>
<thead>
<tr>
<th><strong>Hops</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Permitted forms of 2,4-D include acid and amines.</td>
<td></td>
</tr>
<tr>
<td>“The preharvest interval (PHI) is 28 days.</td>
<td></td>
</tr>
</tbody>
</table>

**Postemergence:**
- Limited to 3 applications per crop cycle.
- Maximum of 0.5 lb ae/acre per application.
- Maximum of 1.5 lbs ae/acre per crop cycle.
- Minimum of 30 days between applications.”
<table>
<thead>
<tr>
<th>Other Application Restrictions (Risk Mitigation)</th>
<th>“Non-Cropland (fencerows, hedgerows, roadsides, ditches, rights-of-way, utility power lines, railroads, airports, and industrial sites)”</th>
<th>Directions for Use Associated with the Specific Use Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)</td>
<td>Permitted forms of 2,4-D include acid, salts, amines, and esters. “Postemergence (annual and perennial weeds): Limited to 2 applications per year. Maximum of 2.0 lbs ae/acre per application. Minimum of 30 days between applications. Postemergence (woody plants): Limited to 1 application per year. Maximum of 4.0 lbs ae/acre per year. Applications to non-cropland areas are not applicable to treatment of commercial timber or other plants being grown for sale or other commercial use, or for commercial seed production, or for research purposes.”</td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Other Application Restrictions (Risk Mitigation)</th>
<th>“Pasture and Rangeland (established grass pastures, rangeland, and perennial grasslands not in agricultural production)”</th>
<th>Directions for Use Associated with the Specific Use Pattern</th>
</tr>
</thead>
</table>
| (Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.) | Permitted forms of 2,4-D include acid, salt, amines, and esters.  
“Do not cut forage for hay within 7 days of application.  
Postemergence:  
For susceptible annual and biennial broadleaf weeds: Use 1.0 lbs ae/acre per application.  
For moderately susceptible biennial and perennial broadleaf weeds: Use 1.0 to 2.0 lbs ae/acre per application.  
For difficult to control weeds and woody plants: Use 2.0 lbs ae/acre per application.  
Spot treatment: Use 2.0 lbs ae/acre.  
Maximum of two applications per year.  
Maximum of 4.0 lbs ae/acre per year.  
Minimum of 30 days between applications.  
If grass is to be cut for hay, Agricultural Use Requirements for the Worker Protection Standard are applicable.” | |
| “Pistachios” | Permitted forms of 2,4-D include acid, salts, and amines.  
“Do not cut orchard floor forage for hay within 7 days of application.  
The preharvest interval (PHI) is 60 days.  
Postemergence:  
Limited to 2 applications per year.  
Maximum of 2.0 lbs ae/acre per application.  
Minimum of 30 days between applications.” | |
<table>
<thead>
<tr>
<th>Other Application Restrictions (Risk Mitigation)</th>
<th>“Pome Fruits”</th>
<th>Directions for Use Associated with the Specific Use Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)</td>
<td>Permitted forms of 2,4-D include acid, salts, and amines. “The preharvest interval (PHI) is 14 days. Do not cut orchard floor forage for hay within 7 days of application.</td>
<td></td>
</tr>
<tr>
<td><strong>Postemergence:</strong></td>
<td>Limited to 2 applications per crop cycle. Maximum of 2.0 lbs ae/acre per application. Minimum of 75 days between applications.”</td>
<td></td>
</tr>
<tr>
<td>“Potatoes”</td>
<td>Permitted forms of 2,4-D include acid, salts, amines, and esters. “Only for use on potatoes intended for fresh market. The preharvest interval (PHI) is 45 days.</td>
<td></td>
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<tr>
<td><strong>Postemergence:</strong></td>
<td>Limited to 2 applications per crop cycle. Maximum of 0.07 lb ae/acre per application. Minimum of 10 days between applications.”</td>
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</tr>
</tbody>
</table>
## Other Application Restrictions (Risk Mitigation)

(Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)

### “Rice”
Permitted forms of 2,4-D include acid, salts, and amines.
“The preharvest interval (PHI) is 60 days.
Maximum of 1.5 lbs ae/acre per crop cycle.”

**Preplant:**
Limited to one preplant application per crop cycle.
Maximum of 1.0 lbs ae/acre per preplant application.

**Postemergence:**
Limited to one postemergence application per crop cycle.
Maximum of 1.5 lbs ae/acre per postemergence application.

### “Rice, wild”
Permitted forms of 2,4-D include acid, salts, and amines.
“For use in Minnesota only.
The preharvest interval (PHI) is 60 days.

**Postemergence:**
Limited to 1 application per crop cycle.
Maximum of 0.25 lb ae/acre per application.”

### Directions for Use
Associated with the Specific Use Pattern
<table>
<thead>
<tr>
<th><strong>Other Application Restrictions</strong>&lt;br&gt;(Risk Mitigation)</th>
<th><strong>“Sorghum”</strong>&lt;br&gt;Permitted forms of 2,4-D include acid, salts, amines, and esters.&lt;br&gt;“The preharvest interval (PHI) is 30 days.&lt;br&gt;Do not permit meat or dairy animals to consume treated crop as fodder or forage for 30 days following application.&lt;br&gt;&lt;br&gt;Postemergence (acid, salts, and amines):&lt;br&gt;Limited to 1 application per crop cycle.&lt;br&gt;Maximum of 1.0 lb ae/acre per application.&lt;br&gt;&lt;br&gt;Postemergence (esters):&lt;br&gt;Limited to 1 application per crop cycle.&lt;br&gt;Maximum of 0.5 lb ae/acre per application.”</th>
<th><strong>Directions for Use</strong>&lt;br&gt;Associated with the Specific Use Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Application Restrictions (Risk Mitigation)</td>
<td>“Soybeans”</td>
<td>Directions for Use Associated with the Specific Use Pattern</td>
</tr>
<tr>
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<tr>
<td>(Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)</td>
<td>Permitted forms of 2,4-D include acid, salts, amines, and esters.</td>
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<tr>
<td></td>
<td>“The maximum rate per crop cycle is 1.0 lb ae/acre.</td>
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<td></td>
<td>Preplant:</td>
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<td></td>
<td>Limited to 2 preplant applications per crop cycle.</td>
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<td></td>
<td>Maximum of 0.5 lb ae/acre per preplant application.</td>
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<td></td>
<td>&gt; Esters: Apply not less than 7 days prior to planting soybeans.</td>
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<tr>
<td></td>
<td>&gt; Amines, acid, salts: Apply not less than 15 days prior to planting soybeans.”</td>
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<tr>
<td></td>
<td>or</td>
<td></td>
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<td></td>
<td>“Preplant:</td>
<td></td>
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<tr>
<td></td>
<td>Limited to 1 application per crop cycle.</td>
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<tr>
<td></td>
<td>Maximum of 1.0 ae/acre per preplant application.</td>
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<tr>
<td></td>
<td>&gt; Esters: Apply not less than 15 days prior to planting soybeans.</td>
<td></td>
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<tr>
<td></td>
<td>&gt; Amines, acid, salts: Apply not less than 30 days prior to planting soybeans.”</td>
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<tr>
<td></td>
<td>“Stone Fruits”</td>
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<td></td>
<td>Permitted forms of 2,4-D include acid, salts, and amines.</td>
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<tr>
<td></td>
<td>“The preharvest interval (PHI) is 40 days.</td>
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<td></td>
<td>Do not cut orchard floor forage for hay within 7 days of application.</td>
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<td></td>
<td>Postemergence:</td>
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<td></td>
<td>Limited to 2 applications per crop cycle.</td>
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<td></td>
<td>Maximum of 2.0 lb ae/acre per application.</td>
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<tr>
<td></td>
<td>Minimum of 75 days between applications.”</td>
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<tr>
<td>Other Application Restrictions (Risk Mitigation)</td>
<td>“Strawberry”</td>
<td>Directions for Use Associated with the Specific Use Pattern</td>
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</tr>
<tr>
<td>(Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)</td>
<td>Permitted forms of 2,4-D include acid, salts, and amines. “Do not apply in California or Florida. Dormant or after last picking: Limited to 1 application per crop cycle. Maximum of 1.5 lbs ae/acre per application.”</td>
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<tr>
<td></td>
<td>“Sugarcane”</td>
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<td></td>
<td>Permitted forms of 2,4-D include acid, salts, and amines. “Do not harvest cane prior to crop maturity. Do not apply more than 4 lbs ae/acre per crop cycle. Preemergence: Limited to one application per crop cycle. Maximum of 2.0 lbs ae/acre per application. Postemergence: Limited to one application per crop cycle. Maximum of 2.0 lbs ae/acre per application.”</td>
<td></td>
</tr>
<tr>
<td>Other Application Restrictions (Risk Mitigation)</td>
<td>“Tree Nuts”</td>
<td>Directions for Use Associated with the Specific Use Pattern</td>
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<tr>
<td>(Note: The maximum allowable application rate and maximum allowable rate per year must be listed as pounds or gallons of formulated product per acre, not just as pounds acid equivalent per acre.)</td>
<td>Permitted forms of 2,4-D include acid, salts, and amines. “The preharvest interval (PHI) is 60 days. Do not cut orchard floor forage for harvest within 7 days of application. <strong>Postemergence:</strong> Limited to 2 applications per crop cycle Maximum of 2.0 lbs ae/acre per application. Minimum of 30 days between applications.”</td>
<td></td>
</tr>
<tr>
<td>“Turf, ornamental (golf courses, cemeteries, parks, sports fields, turfgrass, lawns and other grass areas)”</td>
<td>Permitted forms of 2,4-D include acid, salts, amines, and esters. <strong>“Postemergence:</strong> Limited to 2 applications per year. Maximum of 1.5 lbs ae/acre per application. The maximum seasonal rate is 3.0 lbs ae/acre, excluding spot treatments.”</td>
<td></td>
</tr>
<tr>
<td>“Turf, grown for seed or sod”</td>
<td>Permitted forms of 2,4-d include acid, salts, amines, and esters. <strong>“Limited to 2 applications per year.</strong> Maximum of 2.0 lbs ae/acre per application. Minimum of 21 days between applications.”</td>
<td></td>
</tr>
</tbody>
</table>
A variety of factors including weather conditions (e.g., wind direction, wind speed, temperature, relative humidity) and method of application (e.g., ground, aerial, airblast, chemigation) can influence pesticide drift. The applicator must evaluate all factors and make appropriate adjustments when applying this product.

**Droplet Size**

“When applying sprays that contain 2,4-D as the sole active ingredient, or when applying sprays that contain 2,4-D mixed with active ingredients that require a Coarse or coarser spray, apply only as a Coarse or coarser spray (ASAE standard 572) or a volume mean diameter of 385 microns or greater for spinning atomizer nozzles.”

“When applying sprays that contain 2,4-D mixed with other active ingredients that require a Medium or more fine spray, apply only as a Medium or coarser spray (ASAE standard 572) or a volume mean diameter of 300 microns or greater for spinning atomizer nozzles.”

**Wind Speed**

“Do not apply at wind speeds greater than 15 mph. Only apply this product if the wind direction favors on-target deposition and there are not sensitive areas (including, but not limited to, residential areas, bodies of water, known habitat for nontarget species, nontarget crops) within 250 feet downwind. If applying a Medium spray, leave one swath unsprayed at the downwind edge of the treated field.”
### Temperature Inversions

“If applying at wind speeds less than 3 mph, the applicator must determine if: a) conditions of temperature inversion exist, or b) stable atmospheric conditions exist at or below nozzle height. Do not make applications into areas of temperature inversions or stable atmospheric conditions.”

### Susceptible Plants

“Do not apply under circumstances where spray drift may occur to food, forage, or other plantings that might be damaged or crops thereof rendered unfit for sale, use or consumption. Susceptible crops include, but are not limited to, cotton, okra, flowers, grapes (in growing stage), fruit trees (foliage), soybeans (vegetative stage), ornamentals, sunflowers, tomatoes, beans, and other vegetables, or tobacco. Small amounts of spray drift that might not be visible may injure susceptible broadleaf plants.”

### Other State and Local Requirements

“Applicators must follow all state and local pesticide drift requirements regarding application of 2,4-D herbicides. Where states have more stringent regulations, they must be observed.”

### Equipment

“All aerial and ground application equipment must be properly maintained and calibrated using appropriate carriers or surrogates.”

**Additional requirements for aerial applications:**

“The boom length must not exceed 75% of the wingspan or 90% of the rotor blade diameter.”
“Release spray at the lowest height consistent with efficacy and flight safety. Do not release spray at a height greater than 10 feet above the crop canopy unless a greater height is required for aircraft safety. This requirement does not apply to forestry or rights-of-way applications.”

“When applications are made with a crosswind, the swath will be displaced downwind. The applicator must compensate for this by adjusting the path of the aircraft upwind.”

Additional requirements for ground boom application:

“Do not apply with a nozzle height greater than 4 feet above the crop canopy.”

Additional requirements for liquid products applied as a spray and containing an ester form of 2,4-D (e.g. 2,4-D butoxyethyl ester, 2,4-D ethylhexyl ester, 2,4-D isopropyl ester):

“2,4-D esters may volatilize during conditions of low humidity and high temperatures. Do not apply during conditions of low humidity and high temperatures.”

<table>
<thead>
<tr>
<th>End Use Products Intended for Residential Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application Restrictions</td>
</tr>
<tr>
<td>Entry Restrictions for liquids, water-dispersible granules, and wettable powders formulated in water-soluble packages</td>
</tr>
<tr>
<td>Entry Restrictions for granular formulations</td>
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<tr>
<td>---------------------------------------------</td>
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</tbody>
</table>
| Environmental Hazard Statement for Residential Use labels | “This pesticide is toxic to fish and aquatic invertebrates. Do not apply directly to water, to areas where surface water is present, or to intertidal areas below the mean high water mark except as noted on appropriate labels. Drift and runoff may be hazardous to aquatic organisms in water adjacent to treated areas. Do not contaminate water when disposing of equipment wash waters or rinsate.”
   This chemical has properties and characteristics associated with chemicals detected in groundwater. The use of this chemical in areas where soils are permeable, particularly where the water table is shallow, may result in groundwater contamination. Application around a cistern or well may result in contamination of drinking water or groundwater.” | Precautionary Statements immediately following the User Safety Recommendations |

1 PPE that is established on the basis of Acute Toxicity of the end-use product must be compared to the active ingredient PPE in this document. The more protective PPE must be placed in the product labeling. For guidance on which PPE is considered more protective, see PR Notice 93-7.

2 May be deleted for ready-to-use products.
VI. Appendicies
Appendix A. Table of 2,4-D Use Patterns Eligible for Reregistration (Case 0073)
## Appendix A. Use Patterns Subject to Reregistration for 2,4-D (Case 0073)

<table>
<thead>
<tr>
<th>Use Site</th>
<th>Formulation</th>
<th>Max. Single App. Rate</th>
<th>Unit</th>
<th>Max. # App. Per Crop Cycle/Year</th>
<th>Max. App. Rate Per Crop Cycle/Year</th>
<th>Min. Retreatment Interval (days)</th>
<th>Reentry Interval (REI)</th>
<th>Preharvest Interval (PHI)</th>
<th>Pregrazing Interval (PGI)</th>
<th>Preslaughtering Interval (PSI)</th>
<th>Restrictions/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aquatic weed control - Ditch bank application</td>
<td>Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid, Granular</td>
<td>2.0</td>
<td>Lbs ae/acre</td>
<td>2 per season</td>
<td>4.0 lbs ae/acre</td>
<td>30</td>
<td>NA</td>
<td>NA</td>
<td>See Label Changes Summary Table in 2,4-D RED.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aquatic weed control - floating and emergent weeds</td>
<td>Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid, Granular</td>
<td>4.0</td>
<td>Lbs ae/surface acre</td>
<td>2 per season</td>
<td>8.0 lbs ae/surface acre</td>
<td>21</td>
<td>NA</td>
<td>NA</td>
<td>Apply to aquatic weeds in ponds, lakes, reservoirs, marshes, bayous, drainage ditches, non-irrigation canals, rivers, and streams that are quiescent or slow moving. Coordination and approval of local and state authorities may be required, either by letter of agreement or issuance of special permits for such use. See Label Changes Summary Table in 2,4-D RED.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use Site</td>
<td>Formulation</td>
<td>Max. Single App. Rate</td>
<td>Unit</td>
<td>Max. # App. Per Crop Cycle/Year</td>
<td>Max. App. Rate Per Crop Cycle/Year</td>
<td>Min. Retreatment Interval (days)</td>
<td>Reentry Interval (REI)</td>
<td>Preharvest Interval (PHI)</td>
<td>Pregrazing Interval (PGI)</td>
<td>Preslaughtering Interval (PSI)</td>
<td>Restrictions/Comments</td>
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<tr>
<td>Aquatic weed control - submersed weeds</td>
<td>Wettable powder, Emulsifiable concentrate, soluble concentrate - liquid, soluble concentrate - solid, Granular</td>
<td>10.8</td>
<td>Lbs ae per acre-foot</td>
<td>2 per season</td>
<td>21.6 lbs ae per acre-foot per season</td>
<td>21</td>
<td>24 hour swimming restriction for 2,4-D BEE form</td>
<td>NA</td>
<td>Apply to aquatic weeds in ponds, lakes, reservoirs, marshes, bayous, drainage ditches, non-irrigation canals, rivers, and streams that are quiescent or slow moving. When treating moving bodies of water, applications must be made while traveling upstream to prevent concentration of 2,4-D downstream of the application. Coordination and approval of local and state authorities may be required, either by letter of agreement or issuance of special permits for such use. See Label Changes Summary Table in 2,4-D RED.</td>
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</tr>
<tr>
<td>Asparagus</td>
<td>Wettable powder, Emulsifiable concentrate, soluble concentrate - liquid, soluble concentrate - solid</td>
<td>2.0</td>
<td>Lbs ae/acre</td>
<td>2 per crop cycle</td>
<td>4.0 lbs ae/acre</td>
<td>30</td>
<td>2,4-D acid and amines -48 hours; 2,4-D salt and esters - 12 hours</td>
<td>NA</td>
<td>See Label Changes Summary Table in 2,4-D RED.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use Site</td>
<td>Formulation</td>
<td>Max. Single App. Rate</td>
<td>Unit</td>
<td>Max. # App. Per Crop Cycle/Year</td>
<td>Max. App. Rate Per Crop Cycle/Year</td>
<td>Min. Retreatment Interval (days)</td>
<td>Reentry Interval (REI)</td>
<td>Preharvest Interval (PHI) Pregrazing Interval (PGI) Preslaughtering Interval (PSI)</td>
<td>Restrictions/Comments</td>
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<tr>
<td>Blueberry, low bush</td>
<td>Wettable powder, Emulsifiable concentrate, soluble concentrate - liquid, soluble concentrate - solid</td>
<td>Postemergence: 0.0375</td>
<td>lbs ae per gallon spray solution per application</td>
<td>Postemergence: 1</td>
<td>0.0375 lbs ae per gallon spray solution</td>
<td>NA</td>
<td>NA</td>
<td>2,4-D acid and amines -48 hours; 2,4-D salt and esters - 12 hours</td>
<td>NA</td>
<td>Postharvest: For spot or directed wipe treatment only. Apply only in non-bearing years. See Label Changes Summary Table in 2,4-D RED.</td>
<td></td>
</tr>
<tr>
<td>Blueberry, high bush</td>
<td>Wettable powder, Emulsifiable concentrate, soluble concentrate - liquid, soluble concentrate - solid</td>
<td>1.4</td>
<td>Lbs ae/acre</td>
<td>2 per year</td>
<td>2.8 lbs ae/acre</td>
<td>NS</td>
<td>PHI - 30 days</td>
<td>2,4-D acid and amines -48 hours; 2,4-D salt and esters - 12 hours</td>
<td>See Label Changes Summary Table in 2,4-D RED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use Site</td>
<td>Formulation</td>
<td>Max. Single App. Rate</td>
<td>Unit</td>
<td>Max. # App. Per Crop Cycle/Year</td>
<td>Max. App. Rate Per Crop Cycle/Year</td>
<td>Min. Retreatment Interval (days)</td>
<td>Reentry Interval (REI)</td>
<td>Preharvest Interval (PHI)</td>
<td>Preslaughtering Interval (PSI)</td>
<td>Restrictions/Comments</td>
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<tr>
<td>Citrus, growing fruit</td>
<td>Emulsifiable concentrate</td>
<td>To increase fruit size on growing Navel oranges, Valencia oranges, and grapefruit: 0.1</td>
<td>To increase fruit size on growing Navel oranges, Valencia oranges, and grapefruit: lbs ae/acre</td>
<td>1 per crop cycle</td>
<td>same as max. single app. rate</td>
<td>NA</td>
<td>12 hours</td>
<td>PHI - 7 days</td>
<td>See Label Changes Summary Table in 2,4-D RED</td>
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<td></td>
<td></td>
<td>To reduce pre-harvest fruit drop on growing Navel oranges, Valencia oranges, and grapefruit: 200</td>
<td>To reduce pre-harvest fruit drop on growing Navel oranges, Valencia oranges, and grapefruit: ppm</td>
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<tr>
<td>Use Site</td>
<td>Formulation</td>
<td>Max. Single App. Rate</td>
<td>Unit</td>
<td>Max. # App. Per Crop Cycle/Year</td>
<td>Max. App. Rate Per Crop Cycle/Year</td>
<td>Min. Retreatment Interval (days)</td>
<td>Preharvest Interval (PHI)</td>
<td>Pregrazing Interval (PGI)</td>
<td>Preslaughtering Interval (PSI)</td>
<td>Restrictions/Comments</td>
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<tr>
<td>To prevent pre-harvest drop of mature fruit and leaves on lemons, Navel oranges, Valencia oranges, and Tangelos: 24</td>
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<td></td>
<td>1</td>
<td>same as max. single app. rate</td>
<td></td>
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<td></td>
<td>Application methods include dip or spray See Label Changes Summary Table in 2,4-D RED</td>
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<tr>
<td>Citrus, postharvest treatment</td>
<td>Emulsifiable concentrate</td>
<td>500 ppm</td>
<td>ppm</td>
<td>1</td>
<td>500 ppm</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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</tr>
<tr>
<td>Preplant or preemergence: 1.0</td>
<td>Preplant or preemergence: 1.0</td>
<td>Preemergence: 0.5</td>
<td>Preharvest: 1.5</td>
<td>Lbs ae/acre</td>
<td>3.0 lbs ae/acre</td>
<td>2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours</td>
<td>PHI - 7 days</td>
<td>PGI - 7 days</td>
<td>See Label Changes Summary Table in 2,4-D RED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preplant or preemergence: 1</td>
<td></td>
<td>Preemergence: 1</td>
<td>Preharvest: 1</td>
<td>Lbs ae/acre</td>
<td>NA</td>
<td>2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours</td>
<td>PHI - 7 days</td>
<td>PGI - 7 days</td>
<td>See Label Changes Summary Table in 2,4-D RED</td>
<td></td>
<td></td>
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<tr>
<td>Preemergence: 1</td>
<td></td>
<td>Preemergence: 1</td>
<td>Preharvest: 1</td>
<td>Lbs ae/acre</td>
<td>NA</td>
<td>2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours</td>
<td>PHI - 7 days</td>
<td>PGI - 7 days</td>
<td>See Label Changes Summary Table in 2,4-D RED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use Site</td>
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<td>Max. Single App. Rate</td>
<td>Unit</td>
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<td>Max. App. Rate Per Crop Cycle/Year</td>
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<td>Preharvest Interval (REI)</td>
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<td>Preslaughtering Interval (PSI)</td>
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<tr>
<td>Corn, sweet</td>
<td>Wettable powder, Emulsifiable concentrate, Granular, Soluble concentrate - liquid, Soluble concentrate - solid</td>
<td>Preplant or preemergence: 1.0 Postemergence: 0.5</td>
<td>Lbs ae/acre</td>
<td>Preplant or preemergence: 1 Postemergence: 1</td>
<td>1.5 lbs ae/acre per crop cycle</td>
<td>21</td>
<td>2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours</td>
<td>PHI - 45 days</td>
<td>PGI - 7 days</td>
<td>See Label Changes Summary Table in 2,4-D RED</td>
<td></td>
</tr>
<tr>
<td>Cranberries</td>
<td>Wettable powder, Emulsifiable concentrate, Granular, Soluble concentrate - liquid, Soluble concentrate - solid</td>
<td>Dormant season: 4.0 Postemergence: 1.2</td>
<td>Dormant season: lbs ae/acre per dormant season Postemergence: lbs ae/acre per postemergence application</td>
<td>Dormant season: 4 lbs ae/acre per dormant season Postemergence: 2.4 lbs ae/acre per postemergence application</td>
<td>NS</td>
<td>2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours</td>
<td>PHI - 30 days</td>
<td>See Label Changes Summary Table in 2,4-D RED</td>
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<tr>
<td>Filberts</td>
<td>Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid</td>
<td>1.0</td>
<td>lbs ae per 100 gallons of spray solution</td>
<td>4</td>
<td>4.0 lbs ae per 100 gallons of spray solution per year</td>
<td>30</td>
<td>2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours</td>
<td>PHI - 45 days</td>
<td>See Label Changes Summary Table in 2,4-D RED</td>
<td></td>
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</tr>
<tr>
<td>Use Site</td>
<td>Formulation</td>
<td>Max. Single App. Rate</td>
<td>Unit</td>
<td>Max. # App. Per Crop Cycle/Year</td>
<td>Max. App. Rate Per Crop Cycle/Year</td>
<td>Min. Retreatment Interval (days)</td>
<td>Reentry Interval (REI)</td>
<td>Preharvest Interval (PHI)</td>
<td>Pregrazing Interval (PGI)</td>
<td>Preslaughtering Interval (PSI)</td>
<td>Restrictions/Comments</td>
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<tr>
<td>Fallowland (crop stubble on idle land, or postharvest to crops, or between crops)</td>
<td>Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid</td>
<td>2.0</td>
<td>Lbs ae/acre</td>
<td>2 per year</td>
<td>4.0 lbs ae/acre per year</td>
<td>30</td>
<td>2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours</td>
<td>NS</td>
<td>Plant only label crops within 29 days following application. See Label Changes Summary Table in 2,4-D RED</td>
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<tr>
<td>Forestry (forest site preparation, forest roadsides, brush control, established conifer release, Christmas trees, reforestation areas)</td>
<td>Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid</td>
<td>Broadcast: 4.0 Basal spray, cut surface - stumps, frill: 8.0 Injection: 2</td>
<td>Broadcast: 1 per year</td>
<td>Broadcast: 4.0 lbs ae/acre per year Basal spray, cut surface - stumps, frill: lbs ae per 100 gallons of spray solution Injection: ml of 4.0 lbs ae formulation per injection site</td>
<td>NA</td>
<td>2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours</td>
<td>NA</td>
<td>See Label Changes Summary Table in 2,4-D RED</td>
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<tr>
<td>Grapes</td>
<td>Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid</td>
<td>1.36</td>
<td>Lbs ae/acre</td>
<td>1 per crop cycle</td>
<td>1.36 lbs ae/acre per year</td>
<td>NA</td>
<td>2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours</td>
<td>PHI - 100 days</td>
<td>For use in California only. Do not apply to grape foliage, shoots, or stems. See Label Changes Summary Table in 2,4-D RED</td>
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<td>Use Site</td>
<td>Formulation</td>
<td>Max. Single App. Rate</td>
<td>Unit</td>
<td>Max. # App. Per Crop Cycle/Year</td>
<td>Max. App. Rate Per Crop Cycle/Year</td>
<td>Min. Retreatment Interval (days)</td>
<td>Reentry Interval (REI)</td>
<td>Preharvest Interval (PHI)</td>
<td>Pregrazing Interval (PGI)</td>
<td>Preslaughtering Interval (PSI)</td>
<td>Restrictions/Comments</td>
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<tr>
<td>Grasses (pastures and rangeland not in agricultural production)</td>
<td>Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid</td>
<td>2.0</td>
<td>Lbs ae/acre</td>
<td>2 per year</td>
<td>4.0 lbs ae/acre per year</td>
<td>30</td>
<td>2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours</td>
<td>PHI - 7 days</td>
<td>Do not cut forage for hay within 7 days of application. If grass is to be cut for hay, Agricultural Use Requirements for the Worker Protection Standard are applicable. For program lands, such as Conservation Reserve Program, consult program rules to determine whether grass or hay may be used. The more restrictive requirements of the program rules or this label must be followed. See Label Changes Summary Table in 2,4-D RED</td>
<td></td>
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<tr>
<td>Hops</td>
<td>Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid</td>
<td>0.5</td>
<td>Lbs ae/acre</td>
<td>3 per crop cycle</td>
<td>1.5 lbs ae/acre per crop cycle</td>
<td>NS</td>
<td>2,4-D acid and amines - 48 hours</td>
<td>PHI - 28 days</td>
<td>See Label Changes Summary Table in 2,4-D RED</td>
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<td>Use Site</td>
<td>Formulation</td>
<td>Max. Single App. Rate</td>
<td>Max. # App. Per Crop Cycle/Year</td>
<td>Max. App. Rate Per Crop Cycle/Year</td>
<td>Min. Retreatment Interval (days)</td>
<td>Preharvest Interval (PHI)</td>
<td>Pregrazing Interval (PGI)</td>
<td>Preslaughtering Interval (PSI)</td>
<td>Restrictions/Comments</td>
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<tr>
<td>Non-Cropland (fenecrows, hedgerows, roadsides, ditches, rights-of-way, utility power lines, railroads, airports, and industrial sites)</td>
<td>Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid, Granular</td>
<td>Postemergence (annual and perennial plants): 2</td>
<td>Postemergence (woody plants): 4</td>
<td>4.0 lbs ae/acre</td>
<td>Postemergence (annual and perennial plants): 2</td>
<td>Postemergence (annual and perennial plants): 30 days</td>
<td>Postemergence (woody plants): 4</td>
<td>2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours</td>
<td>Applications to non-cropland areas are not applicable to treatment of commercial timber or other plants being grown for sale or other commercial use, or for commercial seed production, or for research purposes. See Label Changes Summary Table in 2,4-D RED.</td>
<td></td>
<td></td>
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<tr>
<td>Nut Orchards</td>
<td>Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid</td>
<td>2.0 lbs ae/acre</td>
<td>2 per year</td>
<td>4.0 lbs ae/acre per year</td>
<td>30</td>
<td>2,4-D acid and amines - 48 hours; 2,4-D salt - 12 hours</td>
<td>NS</td>
<td>Do not cut forage for hay within 7 days of application. See Label Changes Summary Table in 2,4-D RED.</td>
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<tr>
<td>Use Site</td>
<td>Formulation</td>
<td>Max. Single App. Rate</td>
<td>Unit</td>
<td>Max. # App. Per Crop Cycle/Year</td>
<td>Max. App. Rate Per Crop Cycle/Year</td>
<td>Min. Retreatment Interval (days)</td>
<td>Reentry Interval (REI)</td>
<td>Preharvest Interval (PHI)</td>
<td>Preslaughtering Interval (PSI)</td>
<td>Restrictions/Comments</td>
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<tr>
<td>Pasture and Rangeland (established grass pastures, rangeland, and perennial grasslands not in agricultural production)</td>
<td>Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid</td>
<td>2 per year</td>
<td>Lbs ae/acre</td>
<td>4.0 lbs ae/acre</td>
<td>30</td>
<td>2.4-D acid and amines - 48 hours; 2.4-D salt and esters - 12 hours</td>
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<td>Do not forage for hay within 7 days of application. For program lands, such as Conservation Reserve Program, consult program rules to determine whether grass or hay may be used. The more restrictive requirements of the program rules or this label must be followed. If grass is to be cut for hay, Agricultural Use Requirements for the Worker Protection Standard are applicable. See Label Changes Summary Table in 2,4-D RED.</td>
<td></td>
</tr>
<tr>
<td>Pome fruits</td>
<td>Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid</td>
<td>2 per crop cycle</td>
<td>Lbs ae/acre</td>
<td>4.0 lbs ae/acre</td>
<td>75</td>
<td>2.4-D acid and amines - 48 hours; 2.4-D salt - 12 hours</td>
<td></td>
<td>PHI - 14 days</td>
<td></td>
<td>Do not cut orchard floor forage for hay within 7 days of application. See Label Changes Summary Table in 2,4-D RED.</td>
<td></td>
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<tr>
<td>Use Site</td>
<td>Formulation</td>
<td>Max. Single App. Rate</td>
<td>Unit</td>
<td>Max. # App. Per Crop Cycle/Year</td>
<td>Max. App. Rate Per Crop Cycle/Year</td>
<td>Min. Retreatment Interval (days)</td>
<td>Preharvest Interval (PHI) Pregrazing Interval (PGI) Preslaughtering Interval (PSI)</td>
<td>Restrictions/Comments</td>
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<tr>
<td>Potatoes</td>
<td>Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid</td>
<td>0.07</td>
<td>Lbs ae/acre</td>
<td>2 per crop cycle</td>
<td>0.14 per crop cycle</td>
<td>10</td>
<td>2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours</td>
<td>PHI - 45 days Only for use on potatoes intended for fresh market. See Label Changes Summary Table in 2,4-D RED.</td>
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<tr>
<td>Rice</td>
<td>Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid</td>
<td>Preplant: 1.0</td>
<td>Lbs ae/acre</td>
<td>Preplant: 1 per crop cycle</td>
<td>1.5 lbs ae/acre per crop cycle</td>
<td>NA</td>
<td>2,4-D acid and amines - 48 hours; 2,4-D salt - 12 hours</td>
<td>PHI - 60 days See Label Changes Summary Table in 2,4-D RED.</td>
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<tr>
<td>Rice, wild</td>
<td>Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid</td>
<td>0.25</td>
<td>Lbs ae/acre</td>
<td>1 per crop cycle</td>
<td>0.25 lbs ae/acre per crop cycle</td>
<td>NA</td>
<td>2,4-D acid and amines - 48 hours; 2,4-D salt - 12 hours</td>
<td>PHI - 60 days For use in Minnesota only. See Label Changes Summary Table in 2,4-D RED.</td>
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<tr>
<td>Use Site</td>
<td>Formulation</td>
<td>Max. Single App. Rate</td>
<td>Unit</td>
<td>Max. # App. Per Crop Cycle/Year</td>
<td>Max. App. Rate Per Crop Cycle/Year</td>
<td>Min. Retreatment Interval (days)</td>
<td>Reentry Interval (REI)</td>
<td>Preharvest Interval (PHI)</td>
<td>Pregrazing Interval (PGI)</td>
<td>Preslaughtering Interval (PSI)</td>
<td>Restrictions/Comments</td>
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</tbody>
</table>
| Sorghum  | Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid | 1.0 | Lbs ae/acre | 1 per crop cycle | Postemergence (acid, salts, and amines): 1.0 | NA | 2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours | PHI - 30 days | Do not permit meat or dairy animals to consume treated crop as fodder or forage for 30 days following application. See Label Changes Summary Table in 2,4-D RED.
| Soybean  | Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid | 1.0 | Lbs ae/acre | 1 app. of 1.0 lbs ae/acre per crop cycle | 1.0 lbs ae/acre per crop cycle | NS | 2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours | - | 0.5 lbs ae/acre rate: >Esters: Apply not less than 7 days prior to planting soybeans. >Amines, acid, salts: Apply not less than 15 days prior to planting soybeans. 1.0 lb ae/acre rate: >Esters: Apply not less than 15 days prior to planting soybeans. >Amines, acid, salts: Apply not less than 30 days prior to planting soybeans. See Label Changes Summary Table in 2,4-D RED.
<p>| Use Site   | Formulation                                                                 | Max. Single App. Rate | Unit       | Max. # App. Per Crop Cycle/Year | Max. App. Rate Per Crop Cycle/Year | Min. Retreatment Interval (days) | Reentry Interval (REI) | Preharvest Interval (PHI) | Pregrazing Interval (PGI) | Preslaughtering Interval (PSI) | Restrictions/Comments |
|-----------|------------------------------------------------------------------------------|-----------------------|------------|--------------------------------|-----------------------------------|----------------------------------|------------------------|--------------------------|-----------------------------|----------------------------|-------------------------------|-------------------------|
| Stone fruits | Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid | 2.0 | Lbs ae/acre | 2 | 4.0 lbs ae/acre per crop cycle | 75 | 2,4-D acid and amines - 48 hours; 2,4-D salt - 12 hours | PHI - 40 days | Do not cut orchard floor forage for hay within 7 days of application. See Label Changes Summary Table in 2,4-D RED. |
| Strawberry | Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid | 1.5 | Lbs ae/acre | 1 | 1.5 lbs ae/acre per crop cycle | NA | 2,4-D acid and amines - 48 hours; 2,4-D salt - 12 hours | - | Do not apply in California or Florida. Apply in dormant stage or after last picking. See Label Changes Summary Table in 2,4-D RED. |
| Sugarcane | Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid | Preemergence: 2.0 | Lbs ae/acre | Preemergence: 1 | 4 lbs ae/acre per crop cycle | NS | 2,4-D acid and amines - 48 hours; 2,4-D salt - 12 hours | - | Do not harvest cane prior to crop maturity. See Label Changes Summary Table in 2,4-D RED. |</p>
<table>
<thead>
<tr>
<th>Use Site</th>
<th>Formulation</th>
<th>Max. Single App. Rate</th>
<th>Unit</th>
<th>Max. # App. Per Crop Cycle/Year</th>
<th>Max. App. Rate Per Crop Cycle/Year</th>
<th>Min. Retreatment Interval (days)</th>
<th>Preharvest Interval (PHI)</th>
<th>Pregrazing Interval (PGI)</th>
<th>Preslaughtering Interval (PSI)</th>
<th>Restrictions/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turf, ornamental (golf courses, cemeteries, parks, sports fields, turfgrass, lawns, and other grass areas)</td>
<td>Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid, Granular</td>
<td>1.5</td>
<td>Lbs ae/acre</td>
<td>2</td>
<td>3.0 lbs ae/acre per year, excluding spot treatments</td>
<td>NS</td>
<td>NS</td>
<td>-</td>
<td>See Label Changes Summary Table in 2,4-D RED.</td>
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<tr>
<td>Turf, grown for seed or sod</td>
<td>Wettable powder, Emulsifiable concentrate, Soluble concentrate - liquid, Soluble concentrate - solid, Granular</td>
<td>2.0</td>
<td>Lbs ae/acre</td>
<td>2</td>
<td>4.0 lbs ae/acre per crop cycle</td>
<td>21</td>
<td>2,4-D acid and amines - 48 hours; 2,4-D salt and esters - 12 hours</td>
<td>-</td>
<td>See Label Changes Summary Table in 2,4-D RED.</td>
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</tbody>
</table>
Appendix B. Data Supporting Guideline Requirements for the Reregistration of 2,4-D
## Appendix B

Data Supporting Guideline Requirements for the Reregistration of 2,4-D

<table>
<thead>
<tr>
<th>REQUIREMENT</th>
<th>Use Patterns</th>
<th>CITATION(S)</th>
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<tbody>
<tr>
<td><strong>PRODUCT CHEMISTRY</strong></td>
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<tr>
<td>New Guideline Number</td>
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<td>Product Identity and Composition</td>
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<td>830.1550</td>
<td>61-1</td>
<td>41219701, 41223801, 41926201, 43516401, 43516402, 43981801, 40808301, 41219601, 41055804, 41055805, 41220101, 41973501, 41055801, 41055802, 41220101, 41973501, 41067001, 41203301, 41123601, 41055809, 41055810, 41964401, 41055815, 41055816, 41978001, 44807001, 41055818, 41055819, 41055812, 41055813, 41961301, 41055806, 41055807, 41968301, 41015001, 42188601, 42786501, 40443301, 41224201</td>
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<td>830.1600</td>
<td>61-2A</td>
<td>Description of materials used to produce the product</td>
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<td>830.1620</td>
<td>61-2B</td>
<td>Description of production process</td>
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<td>41223801, 41637501, 41790601, 44149301, 44547901, 43516401, 40808301, 41246701, 41681901, 41796201, 41055804, 41496701, 41055801, 41496701, 41973501, 41067001, 41599401, 42537501, 44184201, 41055809, 41055815, 41055818, 41055812, 44584501, 44963803, 41055806, 44982101, 41015001, 42188601, 41376701, 40443301, 41224201</td>
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<td>41223801, 41790601, 44149301, 44547901, 43516401, 40808301, 41246701, 41681901, 41796201, 41055804, 41496701, 41055801, 41496701, 41973501, 41067001, 41599401, 42537501, 44184201, 41055809, 41055815, 41055818, 41055812, 44584501, 44963803, 41055806, 44982101, 41015001, 42188601, 41376701, 40443301, 41224201</td>
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## Appendix B

### Data Supporting Guideline Requirements for the Reregistration of 2,4-D

<table>
<thead>
<tr>
<th>REQUIREMENT</th>
<th>Use Patterns</th>
<th>CITATION(S)</th>
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<td>830.1670</td>
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<td>Preliminary Analysis</td>
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<tr>
<td>835.2410 161-3 Photodegradation on Soil</td>
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<td>2-Generation Reproduction - Rat A, B 00150557, 00163996, Repeat Study Required</td>
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<td>In vivo chromosome aberration A, B Mustonen, et al., 41478301, 42015704, 42015701, 42015707, 41409805, 41870102, 41409806, 41870103, 41478303, 42015701, 42015703, 42015706, 43930801, 41478302, 42015701, 42015702, 42015705</td>
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Appendix B
Data Supporting Guideline Requirements for the Reregistration of 2,4-D

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<td>Developmental Neurotoxicity</td>
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**OCCUPATIONAL/RESIDENTIAL EXPOSURE**

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<td>Estimation of Dermal Exposure at Outdoor Sites</td>
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<td>Estimation of Inhalation Exposure at Outdoor Sites</td>
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<td>875.2200</td>
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<td>Soil Residue Dissipation</td>
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**RESIDUE CHEMISTRY**

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<td>860.1300</td>
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<td>Livestock Metabolism</td>
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Blacktop and Linscott. (1968), Feung, et al. (1972), 41991503, 42423101, 42439701, 42615601, 43290501, 43496101
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Data Supporting Guideline Requirements for the Reregistration of 2,4-D

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<td>Storage Stability - Plant commodities</td>
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<td>171-4F</td>
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<td>Water, Fish, and Irrigated Crops - Irrigated Crops</td>
<td>00052597, 00139511, Datagap</td>
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## Appendix B

### Data Supporting Guideline Requirements for the Reregistration of 2,4-D

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<td>Meat, Milk, Poultry, Eggs - Milk and the Fat, Meat, and Meat Byproducts of Cattle, Goats, Hogs, Horses, and Sheep</td>
<td>A, B</td>
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<td>Crop Field Trials (Root and Tuber Vegetables Group - Potatoes)</td>
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<td>Crop Field Trials (Citrus - Grapefruits, Lemons, Oranges)</td>
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<td>Crop Field Trials (Pome Fruits Group - Apples, Pears, Quinces)</td>
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<td>Crop Field Trials (Stone Fruits Group - Cherry, Peach, Plum/Fresh Prune)</td>
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<td>Crop Field Trials (Berries Group - Blueberries, Raspberries)</td>
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# Appendix B

Data Supporting Guideline Requirements for the Reregistration of 2,4-D

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<td>Crop Field Trials (Tree Nut Group - Almond, Filbert, Pecan, Walnut)</td>
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<td>Crop Field Trials (Cereal Grains Group - Barley, grain; Corn, field, grain; Corn, sweet (K+CWHR); Millet, grain; Oats, grain; Rice, grain; Rice, wild, grain; Rye, grain; Sorghum, grain; Wheat, grain)</td>
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<td>860.1500 171-4K</td>
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<td>A, B</td>
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<td>Crop Field Trials (Forage, Fodder, and Straw of Cereal Grains Group - Barley, hay and straw; Corn, field, forage, and stover; Corn, sweet, forage and stover; Millet, forage, hay, and straw; Oat, forage, hay, and straw; Rice, straw; Rye, forage and straw; Sorghum, forage and stover; Wheat, forage, hay, and straw)</td>
<td>00036168, 00036171, 00059025, 00059027, 00021755, 00022622, 00025383, 00028385, 00030697, 00073273, 00075715, 00075724, 00102865, 00122723, 00139511, 43676801, 43686001, 43693702, 00059028, 00120057, 43747901, 43785901, 00102719, 00102889, 00120057, 43697801, 43718001, 43718002, 0004485, 00028317, 00028200, 00042288, 00061010, 00063507, 00090360, 00102712, 00120057, 00138635, 00144791, 00147047, 00147047, 00147047, 43665201, 43665202, 43676802, 43797901, 43797903, 44190301, 44190302, Datagap</td>
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<td>Crop Field Trials (Grass Forage, Fodder, and Hay Group - Grass (pastures and rangeland) forage and hay)</td>
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<td>Crop Field Trials (Miscellaneous Commodities - Asparagus; Aspirated Grain Fractions; Cranberries; Grapes; Hops; Pistachios; Strawberries; Sugarcane)</td>
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<td>Processed Food/Feed (Apples; Barley; Citrus; Corn, field; Grape; Oats; Potato; Prunes; Rice; Rye; Sorghum; Soybean; Sugarcane; Wheat)</td>
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Appendix C. Technical Support Documents
Appendix C. TECHNICAL SUPPORT DOCUMENTS

Additional documentation in support of this RED is maintained in the OPP docket, located in Room 119, Crystal Mall #2, 1801 South Bell Street, Arlington, VA. It is open Monday through Friday, excluding legal holidays, from 8:30 am to 4 pm.

The docket initially contained preliminary risk assessments and related documents as of June 23, 2004. Sixty days later the first public comment period closed. The EPA then considered comments, revised the risk assessment, and added the response to comments documents, preliminary mitigation strategies, and the revised risk assessments to the docket on January 12, 2005. The second sixty day public comment period closed on March 14, 2005. The 2,4-D Reregistration Eligibility Decision (RED), revised risk assessments, and response to comments documents were made available in the summer of 2005.

All documents, in hard copy form, may be viewed in the OPP docket room or downloaded or viewed via the Internet at the following site:

www.epa.gov/pesticides/reregistration

These documents include:

HED Documents:

1. 2,4-D. HED’s Revised Human Health Risk Assessment for the Reregistration Eligibility Decision (RED) Revised to Reflect Public Comments. PC Code 030001; DP Barcode D316597. May 12, 2005.

2. 2,4-D. Revised Acute and Chronic Dietary Exposure Assessments Including Proposed New Uses Hops and Potatoes for the Reregistration Eligibility Decision. April 18, 2005.


10. 2,4-D: Phase 3 Toxicology Chapter Revision. December 9, 2004.


EFED Documents:

1. Revised Environmental Fate and Effects Division Revised Preliminary Risk Assessment for the 2,4-Dichlorophenoxyacetic acid (2,4-D) Reregistration Eligibility Decision Document. October 28, 2004.


4. 2,4-D - Response to Public Comments from the San Francisco Department of the Environment on the EFED Science Chapter for the Reregistration Eligibility Decision Document. November 1, 2004.
Appendix D. Citations Considered to be Part of the Data Base Supporting the Reregistration Eligibility Decision (Bibliography) for 2,4-D
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Griffin, R. J.; Godfrey, V. B.; Kim, Y-C ; et al. (1997). Sex-Dependent Differences in the Disposition of 2,4-Dichlorophenoxyacetic Acid in Sprague-Dawley Rats, B6C3F1 Mice, and Syrian Hamsters. Drug Metabolism and Disposition. The American Society for Pharmacology and Experimental Therapeutics, Vol. 25, No. 9.


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Industry Task Force II on 2,4-D Research Data, “EPA/SRRD and 2,4-D Task Force Lawn and Turf Application Rate”, May 2, 2005.

Maroni et al./Chapter 6-Phenoxyacetate Herbicides, Toxicology 143 (2000), 77-83.


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U.S. EPA, August 23, 2002, Master Label for the Reregistration of 2,4-Dichlorophenoxyacetic Acid Uses Supported by the 2,4-D Industry and IR-4.
2,4-D Bibliography

U.S. EPA, March 18, 2003, Maximum Application Rates for 2,4-D Risk Assessments

U.S. EPA, May 1, 2003, 2,4-D Report of Hazard Identification And Review Committee; Author: Linda Taylor, Ph.D., TXR NO. 0051866

U.S. EPA, January 14, 2004, Review of 2,4-D Incident Reports; Authors: Jerome Blondell, Ph.D. and Monica Hawkins, M.P.H., DP Barcode D297233.


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Cancer Epidemiology Review References


2,4-D Bibliography


2,4-D Bibliography


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Re-evaluation of the Lawn and Turf Uses of (2,4-Dichlorophenoxy) acetic acid [2,4-D], Pest Management Regulatory Agency, Health Canada, 21 February 2005.

Environmental Fate and Effects References


Kennedy, I. and Mahoney, M. Revised Tier 1 Estimates for Drinking Water Concentrations Resulting from Triclopyr Use for Aquatic Weed Control. EFED Memorandum dated June 17, 2002.


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Holley, R.W. (1952) Studies of the fate of radioactive 2,4-Dichlorophenoxyacetic acid in bean plants: II. A water-soluble transformation product of 2,4-D. Archives of Biochemistry and Biophysics 35(? ):171-175. (Also in unpublished submission received Sep 16, 1968 under 8F0676; submitted by Dow Chemical U.S.A., Midland, Mich.; CDL:092090-X)


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00025338 Klausen-Rogers, G.; Renfrow, J.; Slater, L.; et al. (1970) Residue Results: Dicamba. (Unpublished study received Jan 15, 1973 under 1F1131; submitted by Velsicol Chemical Corp., Chicago, Ill.; CDL: 090907-F)


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Bjerke, E.L.; Ervick, D.K.; Stymiest, C.; et al. (1973) A Residue Study of the Disappearance of Picloram and 2,4-Dichlorophenoxy-acetic acid in Small Grain following Application of Tordon Herbicide: GH-C 683. (Unpublished study received Jul 3, 1975 under 6F1653; prepared in cooperation with South Dakota State Univ. and others, submitted by Dow Chemical Co., Indianapolis, Ind.; CDL:094498-C)

00036169
Southwick, L.; Hartman, G.P.; Stritzke, J.; et al. (1975) A Residue Study of Pieloram and 2,4-D in Oats and Barley following Post- emergence Application of Tordon(R) 202 Herbicide: GHP-912. (Unpublished study received Jul 3, 1975 under 6F1653; prepared in cooperation with Univ. of Montana and others, submitted by Dow Chemical Co., Indianapolis, Ind.; CDL:094498-D)
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00036171 Bjerke, E.L.; Dietrich, I.; Baker, L.O.; et al. (1975) A Residue Study of Picloram and 2,4-D in Wheat and Barley following Post-emergence Application of Tordon 22K Weed Killer plus Formula 40 Herbicide: GH-C 821. (Unpublished study received Jul 3, 1975 under 6F1653; prepared in cooperation with Univ. of Montana and Montana State Univ., submitted by Dow Chemical Co., Indianapolis, Ind.; CDL:094498-F)


00043759 Sikka, H.C. (1976) Fate of 2,4-D in Fish and Blue Crabs: Contract No. DACW39-74-C-0068. (Syracuse Research Corp. for U.S. Army, Office of the Chief of Engineers, Environmental Characterization Branch, MESL, Waterways Experiment Station, unpublished study; CDL:099544-D)
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Appendix E. Generic Data Call-In
Appendix E.

The generic data call-in will be posted at a later date.
Appendix F.  Product Specific Data Call-In
Appendix F.

The product specific data call-in will be posted at a later date.
Appendix G. EPA’s Batching of 2,4-D Products for Meeting Acute Toxicity Data Requirements for Reregistration
Appendix G.

The batching of 2,4-D products for meeting acute toxicity data requirements for reregistration will be posted at a later date.
Appendix H. List of Registrants Sent This Data Call-In
Appendix H.

A list of registrants sent this data call-in will be posted at a later date.
Appendix I. List Of Available Related Documents And Electronically Available Forms
Appendix I. LIST OF AVAILABLE RELATED DOCUMENTS AND ELECTRONICALLY AVAILABLE FORMS

Pesticide Registration Forms are available at the following EPA internet site:

http://www.epa.gov/opprd001/forms/

Pesticide Registration Forms (These forms are in PDF format and require the Acrobat reader)

**Instructions**

1. Print out and complete the forms. (Note: Form numbers that are bolded can be filled out on your computer then printed.)

2. The completed form(s) should be submitted in hardcopy in accord with the existing policy.

3. Mail the forms, along with any additional documents necessary to comply with EPA regulations covering your request, to the address below for the Document Processing Desk.

DO NOT fax or e-mail any form containing 'Confidential Business Information' or 'Sensitive Information.'

If you have any problems accessing these forms, please contact Nicole Williams at (703) 308-5551 or by e-mail at williams.nicole@epa.gov.

The following Agency Pesticide Registration Forms are currently available via the internet: at the following locations:

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**Pesticide Registration Kit**  [www.epa.gov/pesticides/registrationkit/](http://www.epa.gov/pesticides/registrationkit/)

Dear Registrant:

For your convenience, we have assembled an online registration kit which contains the following pertinent forms and information needed to register a pesticide product with the U.S. Environmental Protection Agency's Office of Pesticide Programs (OPP):

1. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA) as Amended by the Food Quality Protection Act (FQPA) of 1996.

2. Pesticide Registration (PR) Notices
   a. 83-3 Label Improvement Program—Storage and Disposal Statements
   b. 84-1 Clarification of Label Improvement Program
   c. 86-5 Standard Format for Data Submitted under FIFRA
   d. 87-1 Label Improvement Program for Pesticides Applied through Irrigation Systems (Chemigation)
   e. 87-6 Inert Ingredients in Pesticide Products Policy Statement
   f. 90-1 Inert Ingredients in Pesticide Products; Revised Policy Statement
   g. 95-2 Notifications, Non-notifications, and Minor Formulation Amendments
   h. 98-1 Self Certification of Product Chemistry Data with Attachments (This document is in PDF format and requires the Acrobat reader.)

Other PR Notices can be found at [http://www.epa.gov/opppmsdl/PR_Notices](http://www.epa.gov/opppmsdl/PR_Notices)

3. Pesticide Product Registration Application Forms (These forms are in PDF format and will require the Acrobat reader).
   a. EPA Form No. 8570-1, Application for Pesticide Registration/Amendment
   b. EPA Form No. 8570-4, Confidential Statement of Formula
   c. EPA Form No. 8570-27, Formulator's Exemption Statement
   d. EPA Form No. 8570-34, Certification with Respect to Citations of Data
   e. EPA Form No. 8570-35, Data Matrix

4. General Pesticide Information (Some of these forms are in PDF format and will require the Acrobat reader).
   a. Registration Division Personnel Contact List
   b. Biopesticides and Pollution Prevention Division (BPPD) Contacts
   c. Antimicrobials Division Organizational Structure/Contact List
   d. 53 F.R. 15952, Pesticide Registration Procedures; Pesticide Data Requirements (PDF format)
   e. 40 CFR Part 156, Labeling Requirements for Pesticides and Devices (PDF format)
   f. 40 CFR Part 158, Data Requirements for Registration (PDF format)
   g. 50 F.R. 48833, Disclosure of Reviews of Pesticide Data (November 27, 1985)
Before submitting your application for registration, you may wish to consult some additional sources of information. These include:

1. The Office of Pesticide Programs' website.

2. The booklet "General Information on Applying for Registration of Pesticides in the United States", PB92-221811, available through the National Technical Information Service (NTIS) at the following address:

   National Technical Information Service (NTIS)  
   5285 Port Royal Road  
   Springfield, VA  22161

   The telephone number for NTIS is (703) 605-6000.

3. The National Pesticide Information Retrieval System (NPIRS) of Purdue University's Center for Environmental and Regulatory Information Systems. This service does charge a fee for subscriptions and custom searches. You can contact NPIRS by telephone at (765) 494-6614 or through their website.

4. The National Pesticide Telecommunications Network (NPTN) can provide information on active ingredients, uses, toxicology, and chemistry of pesticides. You can contact NPTN by telephone at (800) 858-7378 or through their website: ace.orst.edu/info/nptn.

The Agency will return a notice of receipt of an application for registration or amended registration, experimental use permit, or amendment to a petition if the applicant or petitioner encloses with his submission a stamped, self-addressed postcard. The postcard must contain the following entries to be completed by OPP:

   • Date of receipt;
   • EPA identifying number; and
   • Product Manager assignment.

Other identifying information may be included by the applicant to link the acknowledgment of receipt to the specific application submitted. EPA will stamp the date of receipt and provide the EPA identifying file symbol or petition number for the new submission. The identifying number should be used whenever you contact the Agency concerning an application for registration, experimental use permit, or tolerance petition.

To assist us in ensuring that all data you have submitted for the chemical are properly coded and assigned to your company, please include a list of all synonyms, common and trade names, company experimental codes, and other names which identify the chemical (including "blind" codes used when a sample was submitted for testing by commercial or academic facilities). Please provide a chemical abstract system (CAS) number if one has been assigned.

Documents Associated with this RED

The following documents are part of the Administrative Record for this RED document and may be included in the EPA's Office of Pesticide Programs Public Docket. Copies of these documents are not available electronically, but may be obtained by contacting the person listed on the respective Chemical Status Sheet.

PREPUBLICATION COPY NOTICE:

On April 7, 2012, the Director for the Office of Pesticide Programs at the U.S. Environmental Protection Agency signed the attached Federal Register document entitled:

2,4-D; Order Denying NRDC's Petition to Revoke Tolerances

This is a prepublication version of the document that EPA is submitting for publication in the Federal Register. While the Agency has taken steps to ensure the accuracy of this prepublication version of the document, it is not the official version of the document for purposes of further administrative proceedings in connection with this action. Please refer to the official version of the document that will appear in a forthcoming Federal Register publication.

Please note that the Order is effective upon publication in the Federal Register. The 60 day period for filing objections and requests for a hearing on this Order runs from the date of publication in the Federal Register and not the date of pre-publication release.

Once the official version of the document publishes in the Federal Register, the advance publication version of the document posted on the internet will be replaced with a link to the document that published in the Federal Register. At that time, you will also be able to access the on-line docket for this document at http://www.regulations.gov under Docket ID# EPA-HQ-OPP-2008-0877. You can then use EPA’s electronic docket and comment system at http://www.regulations.gov, to access the index listing of the contents of the docket, to submit or view public comments, and to access those documents in the docket that are available electronically.

For further information about the docket, please consult the ADDRESSES section in the front of the Federal Register document or go to http://www.epa.gov/dockets/.
ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA-HQ-OPP-2008-0877; FRL-9344-1]

2,4-D; Order Denying NRDC's Petition to Revoke Tolerances

AGENCY: Environmental Protection Agency (EPA).

ACTION: Order

SUMMARY: In this Order, EPA denies a petition requesting that EPA revoke all pesticide tolerances for 2,4-dichlorophenoxyacetic acid (2,4-D) under section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA). The petition was filed on November 6, 2008, by the Natural Resources Defense Council.

DATES: This Order is effective [insert date of publication in the Federal Register].

Objections and requests for hearings must be received on or before [insert date 60 days after this order is published in the Federal Register], and must be filed in accordance with the instructions provided in 40 CFR part 178 (see also Units I.B and I.C. of the SUPPLEMENTARY INFORMATION.)

ADDRESSES: EPA has established a docket for this action under docket identification (ID) number EPA-HQ-OPP-2008-0877. All documents in the docket are listed in the docket index available at http://www.regulations.gov. Although listed in the index, some information is not publicly available, e.g., Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Certain other material, such as
copyrighted material, is not placed on the Internet and will be publicly available only in hard copy form. Publicly available docket materials are available either in the electronic docket at http://www.regulations.gov, or, if only available in hard copy, by appointment at One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA, between 9:00 a.m. to 3 p.m., Monday through Friday, excluding legal holidays. To schedule an appointment, call (703) 305-5805.

FOR FURTHER INFORMATION CONTACT: Cathryn Britton, Pesticide Re-evaluation Division, Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; telephone number: (703) 308-0136; fax number: (703) 308-8005; email address: britton.cathryn@epa.gov.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

In this document EPA denies a petition by the Natural Resources Defense Council (NRDC) to revoke pesticide tolerances. This action may also be of interest to agricultural producers, food manufacturers, or pesticide manufacturers. Potentially affected entities may include, but are not limited to:

- Crop production (North American Industrial Classification System (NAICS) code 111), e.g., agricultural workers; greenhouse, nursery, and floriculture workers; farmers
- Animal production (NAICS code 112), e.g., cattle ranchers and farmers, dairy cattle farmers, livestock farmers.
- Food manufacturing (NAICS code 311), e.g. agricultural workers; farmers; greenhouse, nursery, and floriculture workers; ranchers; pesticide applicators.
• Pesticide manufacturing (NAICS code 32532), e.g. agricultural workers; commercial applicators; farmers, greenhouse, nursery, and floriculture workers; residential users.

This listing is not intended to be exhaustive, but rather provides a guide for readers regarding entities likely to be affected by this action. Other types of entities not listed in this unit could also be affected. NAICS codes have been provided to assist you and others in determining whether this action might apply to certain entities. If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under FOR FURTHER INFORMATION CONTACT.

B. Can I File an Objection or Hearing Request?

Under section 408(g) of FFDCA, any person may file an objection to any aspect of this order and may also request a hearing on those objections. You must file your objection or request a hearing on this order in accordance with the instructions provided in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number EPA-HQ-OPP-2008-0877 in the subject line on the first page of your submission. All objections and requests for a hearing must be in writing, and must be received by the Hearing Clerk on or before [insert date 60 days after date of publication in the Federal Register]. Addresses for mail and hand delivery of objections and hearing requests are provided in 40 CFR 178.25(b).

In addition to filing an objection or hearing request with the Hearing Clerk as described in 40 CFR part 178, please submit a copy of the filing that does not contain CBI for inclusion in the public docket that is described in ADDRESSES. Information not marked confidential pursuant to 40 CFR part 2 may be disclosed publicly by EPA.
without prior notice. Submit this copy, identified by docket ID number EPA-HQ-OPP-2008-0877, by one of the following methods:

- **Federal eRulemaking Portal: http://www.regulations.gov.** Follow the on-line instructions for submitting comments.


- **Delivery:** OPP Regulatory Public Docket (7502P), Environmental Protection Agency, Rm. S-4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. Deliveries are only accepted during the Docket Facility's normal hours of operation (8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays). Special arrangements should be made for deliveries of boxed information. The Docket Facility telephone number is (703) 305-5805.

C. What Should be Included in Objections?

The objection stage is the second stage in the multi-stage petition process under FFDCA section 408. This multi-stage process is initiated by a petition requesting establishment, modification, or revocation of a tolerance. In the petition, the petitioner has the opportunity to make its best case for why its request should be granted. Notice and comment on the petition gives interested parties the chance to express views or provide information on the subject matter of the petition.

Once EPA makes a decision on a petition, and publishes its decision in the **Federal Register**, the second stage of the petition process is triggered. At this point, parties who disagree with EPA’s decision, whether it is a decision to grant or deny the
petition, may file objections with EPA to the decision made. The objection stage gives parties a chance to seek review of EPA’s decision before the Agency. This is an opportunity for parties to contest the conclusions EPA reached and the determinations underlying those conclusions. As an administrative review stage, it is not an opportunity to raise new issues or arguments or present facts or information that was available earlier. On the other hand, parties must do more than repeat the claims in the petition. The objection stage is the opportunity to challenge EPA’s decision on the petition. An objection fails on its face if it does not identify aspects of EPA’s decision believed to be in error and explain why EPA’s decision is incorrect.

This two-stage process ensures that issues are fully aired before the Agency and a comprehensive record is compiled prior to judicial review. The sequential nature of the petition and objection process is essential for two reasons. The availability of administrative review before EPA gives EPA, as well as other parties, an opportunity to clearly define and articulate the complex science, policy, and legal issues involved in tolerance decisions. The two-stage process also is designed to make the administrative process as efficient as possible while still providing parties an opportunity for an adjudicatory hearing if needed. In the first stage, EPA is given the opportunity to resolve the issues raised by petition through a process similar to informal notice-and-comment rulemaking. Only material, factual issues that remain disputed following this first stage may be raised in a hearing request. Under this scheme, hearings, if needed, can focus on the key areas of factual dispute. Of course, the first stage of the petition process can only serve its winnowing function if parties are restricted at the second (objection) stage from raising new issues.
II. Background

A. What Action is the Agency Taking?

On November 6, 2008, the Natural Resources Defense Council (NRDC) filed with EPA a petition that, among other things, requested that EPA revoke all tolerances for the pesticide 2,4-dichlorophenoxyacetic acid (2,4-D) established under section 408 of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a (Ref. 1). NRDC claims that EPA’s conclusion outlined in the 2005 Reregistration Eligibility Decision (RED) for 2,4-D, which allowed 2,4-D to be reregistered and its tolerances retained, was based on a risk assessment that was deficient in regard to the toxicity of 2,4-D and the amount of human exposure to the chemical. Specific to 2,4-D tolerances, NRDC asserts that EPA failed to incorporate information on the endocrine disrupting effects of 2,4-D into its human health risk assessments; EPA disregarded data on neurotoxicity related to 2,4-D; EPA disregarded information showing that 2,4-D is mutagenic; EPA ignored data showing that dermal absorption of 2,4-D is enhanced by alcohol consumption, sunscreen, and DEET; and that EPA ignored the exposure of 2,4-D via breast milk to infants. Numerous studies are cited in the petition that NRDC claims supports its assertions. EPA has reviewed all of the studies cited by NRDC.

In this order, EPA is denying NRDC’s petition to revoke 2,4-D’s tolerances in full. Many of NRDC’s claims fail to state a sufficient ground for revocation and instead merely critique the manner in which the risk assessment underlying the 2,4-D RED was conducted. Those claims that do allege relevant statutory grounds for revocation EPA finds to be without merit. The other aspects of NRDC’s petition not concerning the 2,4-D tolerances are addressed in another EPA action.
B. What is the Agency's Authority for Taking this Action?

Under section 408(d)(4) of the FFDCA, EPA is authorized to respond to a section 408(d) petition to revoke tolerance either by issuing a final rule revoking the tolerances, issuing a proposed rule, or issuing an order denying the petition. (21 U.S.C. 346a(d)(4)).

III. Statutory and Executive Order Reviews

A. FFDCA/FIFRA and Applicable Regulations

1. In general. EPA establishes maximum residue limits, or “tolerances,” for pesticide residues in food and feed commodities under section 408 of the FFDCA. (21 U.S.C. 346a). Without such a tolerance or an exemption from the requirement of a tolerance, a food containing a pesticide residue is “adulterated” under section 402 of the FFDCA and may not be legally moved in interstate commerce. (21 U.S.C. 331, 342). Monitoring and enforcement of pesticide tolerances are carried out by the U.S. Food and Drug Administration (FDA) and the U.S. Department of Agriculture (USDA). Section 408 was substantially rewritten by the Food Quality Protection Act of 1996 (FQPA), which added the provisions discussed below establishing a detailed safety standard for pesticides, additional protections for infants and children, and the estrogenic substances screening program. (Public Law 104–170, 110 Stat. 1489 (1996)).

EPA also regulates pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), (7 U.S.C. 136 et seq). While the FFDCA authorizes the establishment of legal limits for pesticide residues in food, FIFRA requires the approval of pesticides prior to their sale and distribution, (7 U.S.C. 136a(a)), and establishes a registration regime for regulating the use of pesticides. FIFRA regulates pesticide use in conjunction with its registration scheme by requiring EPA review and approval of
pesticide labels and specifying that use of a pesticide inconsistent with its label is a violation of federal law. (7 U.S.C. 136j(a)(2)(G)).

2. Safety standard for pesticide tolerances. A pesticide tolerance may only be promulgated or left in effect by EPA if the tolerance is “safe.” (21 U.S.C. 346a(b)(2)(A)(i)). This standard applies when responding both to petitions to establish and petitions to revoke tolerances. “Safe” is defined by the statute to mean that “there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.” (21 U.S.C. 346a(b)(2)(A)(ii)). Section 408 includes numerous provisions directing how EPA should quantitatively assess the risks of pesticides in determining whether a tolerance meets the safety standard. For example, section 408 either authorizes or requires EPA to consider safety factors appropriate to use of animal experimentation data, 21 U.S.C. 346a(b)(2)(D)(ix), aggregate and cumulative exposures to the pesticide in question and other related substances, 21 U.S.C. 346a(b)(2)(D)(v) and (vi), anticipated or actual pesticide residue levels as compared to the maximum levels permitted by tolerances, 21 U.S.C. 346a(b)(2)(E), and the percentage of crops that bear pesticide residues, 21 U.S.C. 346a(b)(2)(F). See 21 U.S.C. 346a(b)(2)(B)(iv) (limiting an exception to the safety standard to pesticides posing risks that do not exceed “10 times the yearly risk” allowed under the safety standard).

Risks to infants and children are given special consideration. Providing additional protection to infants and children was a particular focus of the FQPA. Section 408(b)(2)(C) requires EPA to make a specific determination regarding the safety of tolerances to infants and children and to consider, among other things, information
“concerning the special susceptibility of infants and children to the pesticide chemical residues . . . .” (21 U.S.C. 346a(b)(2)(C)(i)(II) and (ii)(II)). This provision also creates a presumptive additional safety factor for the protection of infants and children. Specifically, it directs that “[i]n the case of threshold effects, ... an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children.” (21 U.S.C. 346a(b)(2)(C)). EPA is permitted to “use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children.” (Id.). Due to Congress’ focus on both pre- and post-natal toxicity, EPA has interpreted this additional safety factor as pertaining to risks to infants and children that arise due to pre-natal exposure as well as to exposure during childhood years. For convenience’s sake, the legal requirements regarding the additional safety margin for infants and children in section 408(b)(2)(C) are referred to throughout this Order as the “FQPA safety factor for the protection of infants and children” or simply the “FQPA safety factor.”

3. Procedures for establishing, amending, or revoking tolerances. Tolerances are established, amended, or revoked by rulemaking under the unique procedural framework set forth in the FFDCA. Generally, a tolerance rulemaking is initiated by the party seeking to establish, amend, or revoke a tolerance by means of filing a petition with EPA. (See 21 U.S.C. 346a(d)(1)). EPA publishes in the Federal Register a notice of the petition filing and requests public comment. (21 U.S.C. 346a(d)(3)). After reviewing the petition, and any comments received on it, EPA may issue a final rule establishing,
amending, or revoking the tolerance, issue a proposed rule to do the same, or deny the petition. (21 U.S.C. 346a(d)(4)).

Once EPA takes final action on the petition by establishing, amending, or revoking the tolerance or denying the petition, any party may file objections with EPA to EPA’s decision on the petition and seek an evidentiary hearing on those objections. (21 U.S.C. 346a(g)(2)). Objections and hearing requests must be filed within 60 days. (Id.). The statute provides that EPA shall “hold a public evidentiary hearing if and to the extent the Administrator determines that such a public hearing is necessary to receive factual evidence relevant to material issues of fact raised by the objections.” (21 U.S.C. 346a(g)(2)(B). EPA regulations make clear that hearings will only be granted where it is shown that there is “a genuine and substantial issue of fact,” the requestor has identified evidence “which, if established, resolve one or more of such issues in favor of the requestor,” and the issue is “determinative” with regard to the relief requested. (40 CFR 178.32(b)). Further, a party may not raise issues in objections unless they were part of the petition and an objecting party must state objections to the EPA decision and not just repeat the allegations in its petition. *Corn Growers v. EPA*, 613 F.2d 266 (D.C. Cir. 2010), cert. denied, 131 S. Ct. 2931 (2011). EPA’s final order on the objections is subject to judicial review. (21 U.S.C. 346a(h)(1)).

4. *Tolerance reassessment and FIFRA reregistration.* The FQPA required that EPA reassess the safety of all pesticide tolerances existing at the time of its enactment. (21 U.S.C. 346a(q)). EPA was given 10 years to reassess the approximately 10,000 tolerances in existence in 1996. In this reassessment, EPA was required to review existing pesticide tolerances under the new “‘reasonable certainty that no harm will
result” standard set forth in section 408(b)(2)(A)(ii). (21 U.S.C. 346a(b)(2)(A)(ii)). This reassessment was substantially completed by the August 3, 2006 deadline. Tolerance reassessment was generally handled in conjunction with a similar program involving reregistration of pesticides under FIFRA. (7 U.S.C. 136a–1). Reassessment and reregistration decisions were generally combined in a document labeled a Reregistration Eligibility Decision (RED).

5. Estrogenic substances screening program. Section 408(p) of the FFDCA creates the estrogenic substances screening program. This provision directed EPA to “develop a screening program to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect, as the Administrator may designate.” This screening program must use “appropriate validated test systems and scientifically relevant information.” (21 U.S.C. 346a(p)(1)).

Pursuant to the Administrator’s discretionary authority, EPA adopted a two-tiered screening and testing strategy and expanded the EDSP to include the androgen and thyroid hormonal pathways and ecological effects. (63 FR 71542, 71544, December 28, 1998). The first tier involves screening “to identify substances that have the potential to interact with the endocrine system” and the second tier involves testing “to determine whether the substance causes adverse effects, identify the adverse effects caused by the substance, and establish a quantitative relationship between the dose and the adverse effect.” (Id. at 71545). Tier 1 screening is limited to evaluating whether a substance is “capable of interacting with” the endocrine system, and is “not sufficient to determine whether a chemical substance may have an effect in humans that is similar to an effect
produced by naturally occurring hormones.” (Id. at 71550). Based on the results of Tier 1 screening, EPA will decide whether Tier 2 testing is needed. Importantly, “[t]he outcome of Tier 2 is designed to be conclusive in relation to the outcome of Tier 1 and any other prior information. Thus, a negative outcome in Tier 2 will supersede a positive outcome in Tier 1.” (Id. at 71554-71555).

In 2008, after an extensive validation process, including peer review of individual assays, EPA notified the public of the EDSP proposed Tier 1 battery of screening assays in a Federal Register Notice issued January 24, 2008 (73 FR 4216). EPA submitted the proposed battery for peer review by FIFRA Scientific Advisory Panel (SAP). A final report of the peer review is available. (Ref. 2). EPA announced the issuance of orders for Tier 1 Screening on October 21, 2009 for 67 chemicals including 2,4-D. (74 FR 54422, 54425). With regard to endocrine effects on humans, EPA has designated the 1998 rat two generation reproduction study (870.3800) as the applicable Tier 2 study for the Endocrine Disruptor Screening Program. In this reproduction study, potential hormonal effects can be detected through behavioral changes, ability to become pregnant, duration of gestation, signs of difficult or prolonged parturition, apparent sex ratio (as ascertained by anogenital distances) of the offspring, feminization or masculinization of offspring, number of pups, stillbirths, gross pathology and histopathology of the vagina, uterus, ovaries, testis, epididymis, seminal vesicles, prostate, and any other identified target organs. EPA concluded that the rat two-generation reproduction study is valid for the identification and characterization of reproductive and developmental effects, including those due to endocrine disruption, based on the long history of its use, the endorsement of
the 1998 test guideline by the FIFRA SAP, and acceptance by member countries of the Organisation for Economic Cooperation and Development (OECD).

In addition to the 1998 test guideline for the mammalian two-generation reproductive toxicity study, EPA has proposed the new OECD test guideline for the extended one-generation reproductive toxicity study as an alternate EDSP Tier 2 test. The extended one-generation reproductive toxicity study was not only designed to provide the traditional spectrum of information from a reproductive study, but was also enhanced to evaluate reproductive and developmental endpoints associated with the endocrine, nervous, and immune systems in male and female adult rodents and offspring at birth, weaning, and puberty, which may not necessarily be covered in other 40 CFR part 158 test guideline studies.

EPA has received all required final study reports and data from the Tier 1 battery of tests for 2,4-D. (Refs. 3, 4, 5, 6, 7, 8, and 9). EPA waived the in vivo mammalian Tier 1 tests for 2,4-D due to the availability of a newly-submitted extended one generation reproduction study with 2,4-D. (Ref. 10). The submitted EDSP Tier 1 assays will be considered with regard to potential ecological effects and the need for Tier 2 in vivo studies for effects in wildlife. Although the submitted Tier 1 in vitro studies may inform EPA on mechanistic issues in mammalian systems (e.g., whether 2,4-D can bind to the estrogen or androgen receptor in mammals), the studies will not affect EPA’s conclusions on the quantitative endocrine risks posed by 2,4-D for humans given the availability of the extended one-generation reproduction study (an in vivo study in rats) that comprehensively examined the risks to human health from 2,4-D’s interaction with endocrine system endpoints. (See discussion in Unit VII.A.1.c.).
B. EPA Risk Assessment for Tolerances--Policy and Practice

1. The safety determination--risk assessment. To assess risk of a pesticide tolerance, EPA combines information on pesticide toxicity with information regarding the route, magnitude, and duration of exposure to the pesticide. The risk assessment process involves four distinct steps:

- Identification of the toxicological hazards posed by a pesticide;
- Determination of the "Level of Concern (LOC)" with respect to human exposure to the pesticide;
- Estimation of human exposure to the pesticide; and
- Characterization of risk posed to humans by the pesticide based on comparison of human exposure to the LOC.

a. Hazard identification. In evaluating toxicity or hazard, EPA reviews toxicity data, typically from studies with laboratory animals, to identify any adverse effects on the test subjects. Where available and appropriate, EPA will also take into account studies involving humans, including human epidemiological studies. For most pesticides, the animal toxicity database usually consists of studies investigating a broad range of endpoints including gross and microscopic effects on organs and tissues, functional effects on bodily organs and systems, effects on blood parameters (such as red blood cell count, hemoglobin concentration, hematocrit, and a measure of clotting potential), effects on the concentrations of normal blood chemicals (including glucose, total cholesterol, urea nitrogen, creatinine, total protein, total bilirubin, albumin, hormones, and enzymes such as alkaline phosphatase, alanine aminotransferase and cholinesterases), and behavioral or other gross effects identified through clinical observation and measurement.
EPA examines whether adverse effects are caused by different durations of exposure ranging from short-term (acute) to long-term (chronic) pesticide exposure and different routes of exposure (oral, dermal, inhalation). Further, EPA evaluates potential adverse effects in different age groups (adults as well as fetuses and juveniles). (Ref. 11 at 8-10).

EPA also considers whether the adverse effect has a threshold—a level below which exposure has no appreciable chance of causing the adverse effect. For effects that have no threshold, EPA assumes that any exposure to the substance increases the risk that the adverse effect may occur.

b. LOC/dose-response analysis. Once a pesticide's potential hazards are identified, EPA determines a toxicological LOC for evaluating the risk posed by human exposure to the pesticide. In this step of the risk assessment process, EPA essentially evaluates the levels of exposure to the pesticide at which effects might occur in the toxicity studies. An important aspect of this determination is assessing the relationship between exposure (dose) and response (often referred to as the dose-response analysis). EPA follows differing approaches to identifying a LOC for effects that only occur above a threshold (“threshold effects”) and those for which a threshold dose cannot be determined (“non-threshold effects”). Because EPA identified only threshold effect risks for 2,4-D, only EPA’s risk assessment procedures for threshold risks are discussed in this Order.

In examining the dose-response relationship for a pesticide's threshold effects, EPA evaluates an array of toxicity studies on the pesticide. Two critical parts of this evaluation involve identification of a quantitative dose level(s) from these studies to be used in assessing the pesticide’s safety to humans (referred to as the Point of Departure).
and selection of appropriate safety factors for translating the results of toxicity studies in relatively small groups of animals or humans to the overall human population, including major identifiable subgroups of consumers. The Point of Departure is used in conjunction with identified safety factors to calculate a Level of Concern for a pesticide.

i. **Point of Departure.** A Point of Departure (POD) is the dose serving as the ‘starting point’ in extrapolating a risk to the human population. In selecting the POD, EPA first evaluates all relevant available toxicity data and conducts a weight of the evidence analysis, considering consistency, reproducibility, temporal and dose concordance, and biological plausibility of the effects reported. EPA then selects a value from a dose-response curve that is at the low end of the observable data (the no observed adverse effect level, or NOAEL, the lowest-observed adverse effect level, or LOAEL, or an extrapolated benchmark dose) as the POD. Doses in toxicology studies are generally expressed in terms of milligrams of the test substance per kilogram of body weight of the test subject per day (mg/kg/day). EPA will make separate determinations as to the Points of Departure for both short and long exposure periods as well as for the different routes of exposure (oral, dermal, and inhalation).

ii. **Safety factors.** It has long been a standard risk assessment practice, to use numerical factors – variously referred to over time as either uncertainty or safety factors.

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1 Different terminology has been used to label factors used in calculating safe doses of chemical substances. At first, they were frequently referred to as “safety” factors. The terminology has evolved over the decades, however, such that what was once generally called a safety factor has come to be generally referred to as an uncertainty factor. (Ref. 12 at A-3). The rationale for the change was that although the use of such factors does promote safety, the factors actually address uncertainty issues (e.g., uncertainty about the differences in sensitivities of animals and humans, uncertainty concerning variation in human sensitivities, uncertainty created by missing data, etc.). The FQPA reintroduced
in conjunction with experimental toxicity data in assessing risk to humans. The two most common safety/uncertainty factors are the factors used to address the potential difference in sensitivity between humans and experimental animals (i.e., inter-species sensitivity) and within the human population (i.e., intra-species sensitivity). Generally a factor of tenfold (10X) is used as a default for both the inter-species and intra-(human) species safety factors. When EPA bases its POD on a dose level from experimental animal data, it will generally use both factors so that it accounts both for the fact that it is extrapolating a dose level in animals to humans and that there may be a wide variation in human response to the compound. This would result in a total safety factor of 100X because each factor indicates that the potential variations addressed constitute a multiple of 10X. When EPA bases its POD on a dose level from human data, only the intra-species factor would be needed because EPA is not extrapolating a dose used in an animal study.

In addition to the inter- and intra-species factors, risk assessors also apply “additional” or “modifying” safety/uncertainty factors based on specific circumstances related to the toxicity data, particularly with regard to deficiencies in that data. Additional factors are applied to address: (1) An absence of critical toxicity data; (2) the failure of a study to identify a NOAEL; (3) the necessity of using a sub-chronic data to choose a POD for estimating chronic risk; and (4) results in a study that suggest the inter- or intra-species factors may not be sufficient. Generally, a safety factor value of 10X or

the term “safety” factors with its reference to a “margin of safety.” Subsequent to the passage of FQPA, the Office of Pesticide Programs has used the terms safety factor and uncertainty factor interchangeably.
3X (which is considered to be one-half of 10X on the logarithmic scale) is used to address these concerns.

EPA’s safety/uncertainty factor practice with regard to pesticides was altered to a degree by the Food Quality Protection Act (FQPA). (Ref. 12). That Act established a presumptive additional “safety” factor of 10X to protect infants and children. The additional factor was designed to account for the completeness of the toxicity and exposure databases and the potential for pre- and post-natal toxicity. EPA has interpreted this legislation as both a “codification and expansion” of prior EPA practice with regard to additional safety/uncertainty factors. (Ref. 12 at A-4 – A-5). It codified EPA’s prior practice by requiring the additional presumptive factor to address toxicity data completeness issues (i.e., absence of a particular study, a NOAEL in a completed study, or chronic data). These traditional additional uncertainty factors became FQPA safety factors for the protection of infants and children. EPA concluded that Congress had not intended EPA to double-up on safety factors by, for example, applying an “additional” uncertainty factor due to missing data, and apply a FQPA safety factor as well to address the same missing data. (Ref. 12 at A-5). Congress expanded EPA’s prior practice by providing that the additional FQPA safety factor for the protection of infants and children was designed to address not just toxicity data deficiencies but exposure data deficiencies as well and by its emphasis on protecting against potential pre- and post-natal toxicity. In theory, EPA could have, prior to the enactment of the FQPA, used an “additional” or “modifying” factor to address health risks to children not otherwise protected by the inter-species, intra-species, or data deficiency safety factors, but use of such a factor was
not common. The FQPA also modified the status quo by making the additional safety factor for infants and children presumptive in nature.

The narrowly-focused and highly-prescriptive nature of the FQPA safety factor provision has created some practical problems for EPA in integrating the new statutory requirements with pesticide risk assessment approaches and, more generally, with Agency risk assessment practices. As noted above, the FQPA essentially codified EPA’s prior risk assessment practice as to “additional” uncertainty factors and it expanded the use of additional uncertainty factors into new areas. The FQPA, however, did not speak to use of traditional (non-additional) uncertainty factors. Thus, the end result was that some uncertainty factors for FFDCA pesticides remained unaffected by the new statutory requirements (the inter- and intra-species factors), some uncertainty factors became FQPA safety factors (additional uncertainty factors that addressed toxicity data deficiencies), and some safety factors that either had previously never existed or were at least extremely rare were created as a statutory phenomenon (a factor to address exposure data base deficiencies and a factor to address potential pre- and post-natal toxicity). This selective inter-weaving of statutory requirements with Agency science policy made FFDCA risk assessments for pesticides unique compared to general Agency risk assessment practice.

Pesticide risk, however, is not regulated under a single statute. Risks to workers or the environment from pesticide use are regulated by EPA under FIFRA not the FFDCA. Further, EPA may address risks posed by pesticide contamination of the environment under several other statutes, including the Safe Drinking Water Act, 42 U.S.C. 300f et seq., the Resource Conservation and Recovery Act, 42 U.S.C. 6901 et
seq., and the Comprehensive Environmental Response, Compensation, and Liability Act, 42 U.S.C. 9601 et seq. Prior to enactment of the FQPA’s specific provisions on pesticide risk assessment, a pesticide risk assessment performed by EPA’s Office of Pesticide Programs under the aegis of FFDCA section 408 could generally be easily translated for use by the Office of Pesticide Programs under FIFRA, or by the other media offices within EPA for use under other statutes. However, once pesticide risk assessment under the FQPA became not simply a matter of good scientific practice but was channeled by explicit statutory requirements, it became incumbent upon the Office of Pesticide Programs to prepare its FFDCA pesticide risk assessments in a manner that clearly delineated what aspects of the assessment were driven solely by science and what aspects primarily by FQPA statutory requirements. Specifically, the Office of Pesticide Programs had to be transparent with regard to whether it was relying on FQPA safety factors based on unique FQPA requirements (exposure database deficiencies and potential pre- and post-natal toxicity) or FQPA safety factors that are essentially a codification of prior general EPA “additional” safety/uncertainty factor practice.

EPA addressed these “transparency” issues at length in its 2002 policy statement on the FQPA safety factor. To clarify how the FQPA safety factor provision left a portion of prior safety/uncertainty practice unchanged, codified another portion, and also expanded the use of safety factors, EPA explained the overlap between the FQPA safety factor and “additional” safety factors in depth and included the following figure to graphically illustrate the issue:
With regard to providing transparency on the FQPA safety factor decisions, EPA took two steps. First, it adopted a new term, the “special” FQPA safety factor, for children safety factors that were based solely on the new FQPA requirements. Second, it adopted the approach of calculating two different safe doses for a pesticide: One that excluded any “special” FQPA safety factors and one that included them. (See discussion of reference doses and population-adjusted doses in Unit III.B.1.b.iii, below).

Introducing the new terminology on FQPA safety factors into long-established safety factor practice has proved challenging. EPA staff frequently drafted documents that (1) claimed no FQPA safety factor was needed but applied an additional uncertainty factor to address the completeness of the data base or reliance on a LOAEL; or (2) treated the...
“special” FQPA safety factor as the only type of FQPA safety factor. Such misstatements did not substantively change risk assessment outcomes but they did raise the confusion level on an already complex topic. Eventually, EPA determined that the term “special” FQPA safety factor caused more problems than it solved and abandoned it. However, EPA has retained the approach of continuing to calculate both a safe dose with, and without, what was once referred to as “special” FQPA safety factors.

(iii). Level of Concern. By Level of Concern (LOC), EPA means a numerical value that separates exposures that would generally be regarded as raising health concerns from those that do not. The POD (see Unit III.B.1.b.i. above) is used in estimating and describing the LOC; however, the LOC is expressed differently depending on whether the risk assessment addresses dietary or non-dietary exposures. The use of different approaches is due to the fact that non-dietary exposure assessments often involve combining exposures from multiple pathways.

For dietary risks, EPA uses the POD to calculate an acceptable LOC that is referred to as a reference dose (RfD). The RfD is calculated by dividing the POD by all applicable safety or uncertainty factors with one exception (see below). (Ref. 12 at 4-11). Safety/uncertainty factors are divided separately and sequentially into the POD. Thus, for example, if the POD is 1 milligram/kilogram/day (mg/kg/day) and there are two applicable 10X safety/uncertainty factors, then the reference dose would be 0.01 mg/kg/day (i.e., 1 mg/kg/day divided twice by 10). For convenience’s sake, safety factors are often combined by multiplying them by each other. This product when divided into the POD would, of course, produce the same result as sequential division. For reduction of a safety factor, a similar process is followed. For example, if a safety
factor is to be reduced by half, this is done by taking the square root of the factor rather than dividing by two. See 73 FR 42683, 42696 (July 23, 2008).

In implementing FFDCA section 408, EPA's Office of Pesticide Programs, also calculates a variant of the RfD referred to as a Population Adjusted Dose (PAD). A PAD is the RfD divided by any portion of the FQPA safety factor that does not correspond to one of the traditional additional safety factors used in general Agency risk assessments. (Ref. 12 at 13-16). As noted above, the reason for calculating PADs is so that other parts of the Agency, which are not governed by FFDCA section 408, can, when evaluating the same or similar substances, easily identify which aspects of a pesticide risk assessment are a function of the particular statutory commands in FFDCA section 408. Today, RfDs and PADs are generally calculated for both acute and chronic dietary risks although traditionally RfDs and PADs were only calculated for chronic risks. RfDs/PADs for acute and chronic risks will generally have different Points of Departure (because they are generally based on studies of different duration) and may be based on different safety factors as well depending on the characteristics of the studies relied on in choosing the POD. For example, if the study used to pick the POD for acute risk identified a NOAEL but the study used for chronic risk did not, any additional safety factor used to address this lack of a NOAEL in calculating the RfD/PAD for chronic risk would not be applicable to the acute RfD/PAD derivation.

For non-dietary, and combined dietary and non-dietary, risk assessments of threshold effects, the toxicological LOC is not expressed as an RfD/PAD but rather in terms of an acceptable (or target) Margin of Exposure (MOE) between human exposure and the POD. The "margin" that is being referred to in the term MOE is the ratio between
human exposure and the POD which is calculated by dividing human exposure into the POD. An acceptable MOE is generally considered to be a margin at least as high as the product of all applicable safety factors for a pesticide. For example, if a pesticide needs a 10X factor to account for potential inter-species differences, 10X factor for potential intra-species differences, and 10X factor for the FQPA children's safety provision, the safe or target MOE would be a MOE of at least 1,000. What that means is that for the pesticide in the example to meet the safety standard, human exposure to the pesticide would generally have to be at least 1,000 times smaller than the POD. Like RfD/PADs, specific target MOEs are selected for exposures of different durations and routes. For non-dietary exposures, EPA typically examines short-term, intermediate-term, and long-term exposures. Additionally, target MOEs may be selected based on both the duration of exposure and the various routes of non-dietary exposure--dermal, inhalation, and oral. Target MOEs for a given pesticide can vary depending on the characteristics of the studies relied upon in choosing the POD for the various duration and route scenarios.

c. Estimating human exposure. Risk is a function of both hazard and exposure. Thus, equally important to the risk assessment process as determining the hazards posed by a pesticide and the toxicological LOC for those hazards is estimating human exposure. Under FFDCA section 408, EPA is concerned not only with exposure to pesticide residues in food but also exposure resulting from pesticide contamination of drinking water supplies and from use of pesticides in the home or other non-occupational settings. (See 21 U.S.C. 346a(b)(2)(D)(vi)). Additionally, EPA must take into account non-occupational exposure from "other related substances." (Id.).
i. Exposure from food. There are two critical variables in estimating exposure in food: (1) The types and amount of food that is consumed; and (2) the residue level in that food.

Consumption is estimated by EPA based on scientific surveys of individuals' food consumption in the United States conducted by the USDA. (Ref. 11 at 12). Information on residue values comes from a range of sources including crop field trials; data on pesticide reduction (or concentration) due to processing, cooking, and other practices; information on the extent of usage of the pesticide; and monitoring of the food supply. (Id. at 17).

In assessing exposure from pesticide residues in food, EPA, for efficiency's sake, follows a tiered approach in which it, in the first instance, assesses exposure using the worst case assumptions that 100 percent of the crop or commodity in question is treated with, or exposed to, the pesticide and 100 percent of the food from that crop or commodity contains pesticide residues at the tolerance level. (Id. at 11). When such an assessment shows no risks of concern, a more complex risk assessment is unnecessary. By avoiding a more complex risk assessment, EPA's resources are conserved and regulated parties are spared the cost of any additional studies that may be needed. If, however, a first tier assessment suggests there could be a risk of concern, EPA then attempts to refine its exposure assumptions to yield a more realistic picture of residue values through use of data on the percent of the crop or commodity actually treated with, or exposed to, the pesticide and data on the level of residues that may be present on the treated crop or commodity. These latter data are used to estimate what has been traditionally referred to by EPA as "anticipated residues." More information on refining
estimates of pesticide exposure can be found at Ref.1; 70 FR 46706, 46732, August 10, 2005).

ii. Exposure from water. EPA may use either or both field monitoring data and mathematical water exposure models to generate pesticide exposure estimates in drinking water. Monitoring and modeling are both important tools for estimating pesticide concentrations in water and can provide different types of information. Monitoring data can provide estimates of pesticide concentrations in water that are representative of specific agricultural or residential pesticide practices and under environmental conditions associated with a sampling design. Although monitoring data can provide a direct measure of the concentration of a pesticide in water, it does not always provide a reliable estimate of exposure because sampling may not occur in areas with the highest pesticide use, and/or the sampling may not occur when the pesticides are being used.

In estimating pesticide exposure levels in drinking water, EPA most frequently uses mathematical water exposure models. EPA's models are based on extensive monitoring data and detailed information on soil properties, crop characteristics, and weather patterns. (69 FR 30042, 30058-30065, May 26, 2004). These models calculate estimated environmental concentrations of pesticides using laboratory data that describe how fast the pesticide breaks down to other chemicals and how it moves in the environment. These concentrations can be estimated continuously over long periods of time, and for places that are of most interest for any particular pesticide. Modeling is a useful tool for characterizing vulnerable sites, and can be used to estimate peak concentrations from infrequent, large storms.
iii. Exposure from residential use of pesticides. Residential assessments examine exposure to pesticides in non-occupational or residential settings (e.g., homes, parks, schools, athletic fields or any other areas frequented by the general public). Exposures to pesticides may occur to persons who apply pesticides or to persons who enter areas previously treated with pesticides. Such exposures may occur through oral, inhalation, or dermal routes.

Residential assessments are conducted through examination of significant exposure scenarios (e.g., children playing on treated lawns or homeowners spraying their gardens) using a combination of generic and pesticide-specific data. To regularize this process, OPP has prepared Standard Operating Procedures (SOPs) for conducting residential assessments on a wide array of scenarios that are intended to address all major possible means by which individuals could be exposed to pesticides in a non-occupational environment (e.g. homes, schools, parks, athletic fields, or other publicly accessible locations). The SOPs identify relevant generic data and construct algorithms for calculating exposure amounts using these generic data in combination with pesticide-specific information. The generic data generally involve survey data on behavior patterns (e.g., activities conducted on turf and time spent on these activities) and transfer coefficient data. Transfer coefficient data measure the amount of pesticide that transfers from the environment to humans from a defined activity (e.g., hand contact with a treated surface or plant). Specific information on pesticides can include information on residue levels as well as information on environmental fate such as degradation data.

d. Risk characterization. The final step in the risk assessment is risk characterization. In this step, EPA combines information from the first three steps (hazard
identification, LOC/dose-response analysis, and human exposure assessment) to quantitatively estimate the risks posed by a pesticide. Separate characterizations of risk are conducted for different durations of exposure. Additionally, separate and, where appropriate, aggregate characterizations of risk are conducted for the different routes of exposure (dietary and non-dietary).

For threshold risks, EPA estimates risk in one of two ways. Where EPA has calculated a RfD/PAD, risk is estimated by expressing human exposure as a percentage of the RfD/PAD. Exposures lower than 100 percent of the RfD/PAD are generally not of concern. Alternatively, EPA may express risk by comparing the MOE between estimated human exposure and the POD with the acceptable or target MOE. As described previously, the acceptable or target MOE is the product of all applicable safety factors. To calculate the actual MOE for a pesticide, estimated human exposure to the pesticide is divided into the POD. In contrast to the RfD/PAD approach, higher MOEs denote lower risk. Accordingly, if the target MOE for a pesticide is 100, MOEs equal to or exceeding 100 would generally not be of concern. As a conceptual matter, the RfD/PAD and MOE approaches are fundamentally equivalent. For a given risk and given exposure of a pesticide, if exposure to a pesticide were found to be acceptable under an RfD/PAD analysis it would also pass under the MOE approach, and vice-versa.

2. EPA policy on the FQPA safety factor for the protection of infants and children. As the previous brief summary of EPA's risk assessment practice indicates, the use of safety factors plays a critical role in the process. This is true for traditional 10X safety factors to account for potential differences between animals and humans when
relying on studies in animals (inter-species safety factor) and potential differences among humans (intra-species safety factor) as well as the FQPA's additional 10X safety factor.

In applying the FQPA safety factor provision, EPA has interpreted it as imposing a presumption in favor of applying an additional 10X safety factor. (Ref. 12 at 4, 11). Thus, EPA generally refers to the additional 10X factor as a presumptive or default 10X factor. EPA has also made clear, however, that this presumption or default in favor of the additional 10X is only a presumption. The presumption can be overcome if reliable data demonstrate that a different factor is safe for children. (Id.). In determining whether a different factor is safe for children, EPA focuses on the three factors listed in FFDCA section 408(b)(2)(C)--the completeness of the toxicity database, the completeness of the exposure database, and potential pre- and post-natal toxicity. In examining these factors, EPA strives to make sure that its choice of a safety factor, based on a weight-of-the-evidence evaluation, does not understate the risk to children. (Id. at 24-25, 35).

IV. 2,4-D Regulatory Background

2,4-D is a phenoxy herbicide, plant growth regulator, and fungicide that has been used in the United States since the mid 1940s. It comes in multiple chemical forms and is currently found in approximately 600 end-use products registered for agricultural, residential, industrial, and aquatic uses. It is formulated primarily as an amine salt in an aqueous solution or as an ester in an emulsifiable concentrate. There are 85 tolerances for 2,4-D listed in the Code of Federal Regulations.

1. Special review based on human carcinogenicity. On September 22, 1986, the Agency issued a preliminary notification of Special Review of 2,4-D because of concerns for epidemiological links of 2,4-D to non-Hodgkin’s lymphoma from both occupational
and residential exposure. In 1987, EPA requested that the FIFRA SAP examine the evidence bearing on 2,4-D’s carcinogenicity. The Panel concluded that the present data for animals and humans were inadequate for determining carcinogenicity and that 2,4-D should be classified under Group D of EPA’s cancer guidelines -- Not Classifiable as to Human Carcinogenicity. (Refs. 13 and 14). Based upon findings that existing data did not support a link between 2,4-D and carcinogenicity, the Agency published a proposed decision Not to Initiate Special Review on March 23, 1988 (53 FR 9590) and deferred a final decision until reregistration.

To further address the potential link of non-Hodgkin’s lymphoma to 2,4-D exposure, a joint Science Advisory Board (SAB)/SAP Special Joint Committee was convened to review available epidemiological and other data on 2,4-D. In 1994, the Committee 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.” (Ref. 15). In 1997, EPA re-examined the weight of the evidence on cancer taking into account two new cancer bioassays in mice and rats. (Ref. 16). These new bioassays showed no statistically significant tumor response in either species. Although EPA concurred with the Joint Committee’s recommendation to classify 2,4-D under Group D, EPA requested further histopathological examinations of mouse and rat tissue from previously conducted studies to further inform its decision. These exams showed no evidence to alter the prior findings, and on March 16, 1999, the Agency notified the 2,4-D Task Force that the EPA would continue to classify 2,4-D under Group D. (Ref. 17).

Since the March 16, 1999 decision, the Agency has twice reviewed epidemiological studies linking cancer to 2,4-D exposure during the reregistration
process of 2,4-D. In the first review, completed January 14, 2004, EPA concluded there was no additional evidence that would implicate 2,4-D as a cause of cancer. (Ref. 14).

The second review of available epidemiological studies occurred in response to comments received during development of the 2,4-D RED. EPA’s report, dated December 8, 2004, found that none of the more recent epidemiological and animal studies supported a conclusion that 2,4-D was a likely human carcinogen. (Ref. 15).

Because the Agency determined that the existing data did not support a conclusion that links human cancer to 2,4-D exposure, it decided not to initiate a Special Review of 2,4-D in 2007. (72 FR 44510, August 8, 2007).

A part of this cancer assessment was the review of data bearing on 2,4-D’s potential mutagenicity. EPA has consistently found that these data do not support classification of 2,4-D as a carcinogen. This view was concurred in by the Joint Committee of SAB/SAP.

2. **FFDCA tolerance reassessment and FIFRA pesticide reregistration.** As required by the Food Quality Protection Act of 1996, EPA reassessed the safety of the 2,4-D tolerances under the safety standard established in the FQPA. In the June 2005 RED for 2,4-D, EPA evaluated the human health risks associated with all registered uses of 2,4-D and determined that there is a reasonable certainty that no harm will result from aggregate non-occupational exposure to the pesticide chemical residue. (Refs. 18 and 19).

In making this determination, EPA considered dietary exposure from food and drinking water and all other non-occupational sources of pesticide exposure for which there is reliable information. The Agency concluded that with the adoption of the risk mitigation measures identified in the 2,4-D RED, all of the tolerances for 2,4-D meet the safety
standard as set forth in section 408(b)(2)(D) of the FFDCA. Therefore, the tolerances established for residues of 2,4-D were considered reassessed as safe under section 408(q) of FFDCA.

At the time of 2,4-D reregistration, there were no available studies on 2,4-D that adequately assessed its endocrine disruption potential, and the Agency determined that a repeat 2-generation reproduction study should be conducted to evaluate comparative thyroid effects in young and adult animals as well as the gonads and reproductive/developmental endpoints more thoroughly. The 2,4-D RED indicated that a new reproduction study using the revised 2-generation reproduction study protocol and measurement of additional parameters was needed to address these data gaps. EPA also required submission of a developmental neurotoxicity study. Although these data were needed, EPA concluded that the toxicology database was adequate for identification of doses and endpoints of concern for risk assessments. The values selected for risk assessments were protective of all observed adverse effects. Additionally, EPA retained the additional FQPA 10X safety factor for the protection of infants and children to address the uncertainty raised by the missing data. Finally, 2,4-D toxicity generally occurs at doses above renal saturation, i.e., doses above which the excretory processes could readily eliminate the chemical; the Agency’s risk assessment regulated at doses below this level. Consequently, the Agency had high confidence that the risk assessment did not underestimate risks from exposure to 2,4-D.

On February 28, 2006, EPA issued a data call-in for 2,4-D that, among other things, required submission of the reproduction and developmental neurotoxicity studies mentioned above. In February, 2010, in response to the data call-in, the Industry Task
Force II on 2,4-D Research Data submitted a state-of-the-science extended one-generation reproduction toxicity study to fulfill these requirements. The 2,4-D extended one-generation reproductive toxicity study included a detailed assessment of endocrine endpoints (thyroid, estrus cyclicity, sexual maturation (animals were observed for delays in vaginal opening and preputial separation), andrology, and ovarian staging), in addition to reproductive function, developmental neurotoxicity, and immunotoxicity endpoints.

3. More recent actions. EPA has conducted a number of rulemakings with respect to 2,4-D tolerances since completion of tolerance reassessment. In July, 2005, EPA established new 2,4-D tolerances on hops, soybeans, and wild rice. (70 FR 43298, July 27, 2005). This action was based on the safety determination in the 2,4-D tolerance reassessment. No comments were received. In June 2007, EPA proposed numerous changes to the 2,4-D tolerances to implement determinations made in the 2,4-D tolerance reassessment (72 FR 31221). These proposed changes included modification of the chemical terms used in the tolerance expression, the amendment of various tolerance levels, and removal of certain tolerances. No comments relevant to 2,4-D tolerances were received and EPA finalized the tolerance actions on September 12, 2007 (72 FR 52013). 2,4-D tolerances have been modified three times since 2007. In 2008, minor changes were made to correct errors in the 2007 rulemaking. (73 FR 53732, September 17, 2008). NRDC commented on the proposal for these changes but did not raise any new information that had not been addressed in response to their comments on the RED. In 2009, EPA modified the 2,4-D tolerance for cranberries. No comments were received. (74 FR 48408, September 23, 2009). In 2011, a tolerance for teff was established, for which EPA received no significant comments. (76 FR 55814, September 9, 2011).
Additionally, in response to an application to amend the 2,4-D FIFRA registration, EPA, in 2011, re-examined the risks of 2,4-D. That re-examination took into account the newly submitted extended one-generation reproduction toxicity study evaluating 2,4-D’s potential for causing endocrine, neurotoxic, or immunotoxic effects. As part of that risk assessment, EPA re-evaluated the decision to retain the FQPA safety factor. Because the FQPA safety factor had previously been retained due to the absence of data on endocrine and neurotoxic effects and those data requirements had been met, EPA determined that the 10X FQPA safety factor should be removed. (Refs. 20 and 21).

V. The Petition to Revoke Tolerances

NRDC filed a petition dated November 6, 2008 (petition), requesting, among other things, that EPA revoke all 2,4-D tolerances. (Ref. 1). In response to EPA’s publication of the petition pursuant to section 408(d) of the FFDCA, NRDC submitted a comment in support of its petition. (Ref. 22). The petition asserts that EPA’s conclusion outlined in the 2005 2,4-D RED, allowing 2,4-D to be reregistered and its tolerances retained, was based on incorrect information and assumptions related to the toxicity of 2,4-D and the amount of human exposure to the chemical. Specific to tolerances, the petition asserts that EPA failed to incorporate information on the endocrine disrupting effects of 2,4-D into its human health risk assessments; EPA disregarded data on neurotoxicity related to 2,4-D; EPA disregarded information showing that 2,4-D is mutagenic; EPA ignored data showing that dermal absorption of 2,4-D is enhanced by alcohol consumption, sunscreen, and DEET; and that EPA ignored the exposure of infants to 2,4-D via breast milk. Numerous studies are cited in the petition that NRDC says supports their assertions. EPA has reviewed all of the studies submitted by NRDC.
NRDC also relies, in part, on portions of its comments submitted on the 2,4-D RED in support of its petition. (Ref. 1 at 11; Refs. 23 and 24).

VI. Public Comment

EPA published notice of the petition for comment on December 24, 2008 (73 FR 79100). EPA received approximately 500 comments on the petition. The vast majority of the comments were against the petition, and many discussed the importance of 2,4-D to various industries, including forestry, grains, landscaping, and minor use crops. (See e.g., Ref. 25). These issues, however, are irrelevant to the safety determination under FFDCA section 408. Two of the comments opposing the petition, from the Industry Task Force on 2,4-D Research Data II (Task Force), and National Council for Air and Stream Improvement (NCASI), provided detailed comments on the petition and on the studies cited in the petition. (Refs. 26 and 27). The Task Force and NCASI cited additional studies during the comment period for EPA to consider in its response to the petition.

Twenty-three comments were in support of the petition and agreed with NRDC that 2,4-D’s tolerances should be revoked. Most of the comments that were in support of the petition assert in a general way that 2,4-D is “unsafe,” but provide little or no reasoning for this conclusion. Two of the comments in support of the petition, one from Beyond Pesticides and a combined comment from the New York State Department of Health and New York State Department of Environmental Conservation, identified additional studies for EPA consideration. (Refs. 28 and 29). Additionally, the comment from Beyond Pesticides asserts that EPA ignored evidence that EPA endangers children by removing the FQPA 10X safety factor; and EPA has failed to perform a cumulative
assessment for 2,4-D and other phenoxy herbicides. Finally, NRDC submitted as a comment additional material in support of its petition. (Ref. 22).

**VII. Ruling on Petition**

This Order addresses NRDC’s petition to revoke 2,4-D tolerances. EPA has divided NRDC’s grounds for revocation into two main categories – toxicology and exposure - and addressed separately each claim under these categories. Each specific claim of NRDC is summarized in Unit VII immediately prior to EPA’s response to the claim.

This Order also constitutes a response to the comments received during the public comment period on the petition as they relate to NRDC’s arguments for revoking tolerances. Below are the Agency’s responses to NRDC’s assertions and the related public comments. Detailed reviews of the studies cited by NRDC and commenters can be found in the docket. (Ref. 30).

*A. Toxicology*

NRDC has raised four toxicological issues regarding the safety of 2,4-D: Endocrine disruption, neurotoxicity, mutagenicity, and impacts on body weight. Each of these issues are addressed below.

1. *Endocrine Disruption—*a. NRDC Claims. In support of their petition, NRDC cites several studies that it says, “…establish the dangerous endocrine disrupting effects of 2,4-D and underscore the need for EPA to consider these impacts in its assessment of the health impacts of 2,4-D.” (Ref. 1 at 2). NRDC asks EPA to incorporate information on the endocrine disrupting effects of 2,4-D into its human health risk assessments. (Id. at 2).
Specifically, NRDC cites several studies, discussed below, that it contends show that 2,4-D is an endocrine disruptor. (Id. at 4-5). NRDC quotes a portion of the 2,4-D RED, which states: “Based on currently available toxicity data, there is evidence of the endocrine-disrupting effects of 2,4-D on mammals. However, no specific measures of such effect have been attempted” and a statement that when the EDSP is underway, 2,4-D may be subject to additional screening or testing. (Id. at 5-6). NRDC argues that EPA has relied on the delay in conducting the EDSP to neglect analyzing the endocrine effects of 2,4-D despite the existence of “an entire category of existing scientific studies demonstrating adverse health effects.” (Id. at 6). It uses atrazine as an example of a case where EPA has considered endocrine disrupting effects in the absence of the formal screening program. The atrazine example, according to NRDC, shows that EPA cannot claim that the existing studies on endocrine disrupting effects cannot be considered in human health risk assessments. NRDC states that “EPA should have quantitatively incorporated these studies and these effects in its risk assessment of 2,4-D.” (Id.).

b. Public comments. In its comments, Beyond Pesticides supports NRDC’s petition to cancel all 2,4-D product registrations due to the alleged wealth of relevant scientific information available that indicates that 2,4-D is a potential endocrine disruptor. (Ref. 28 at 3). Beyond Pesticides cites additional studies to those cited by NRDC. (Id. at 3-4).

The 2,4-D Task Force, in its comments, disputes NRDC’s claim that 2,4-D is an endocrine disruptor. (Ref. 26 at 11-18). Specifically, the Task Force argues that NRDC’s assertions that 2,4-D has been shown to be a potent endocrine disruptor are not supported by the weight of the evidence surrounding 2,4-D’s potential for endocrine
disrupting effects. The Task Force disagrees with NRDC’s contention that EPA ignored endocrine disrupting effects given that the Agency issued a data call-in for a study that assesses thyroid, gonadal, reproductive and other endocrine-sensitive endpoints and while awaiting the study imposed an additional 10X uncertainty factor to account for the data gap. (Id. at 11-12). The Task Force provided detailed comments on each of the studies cited by NRDC disputing NRDC’s conclusions.

Additionally, National Council for Air and Stream Improvement (NCASI), in its comments, takes issue with NRDC’s characterization of various studies indicating that 2,4-D was an endocrine disruptor. (Ref. 27 at 2-3). NCASI indicates that studies cited by NRDC to support their claim for endocrine disruption concerns are not consistent with other studies of 2,4-D estrogenicity. (Id. at 3).

c. *EPA response.* With regard to endocrine effects, NRDC argues that EPA should revoke the 2,4-D tolerances because EPA failed to properly assess 2,4-D’s endocrine effects in the RED risk assessment. For example, NRDC contends that “[r]ecent studies [ ] establish the dangerous endocrine disrupting effects of 2,4-D and underscore the need for EPA to consider these impacts in its assessment of the health impacts of 2,4-D.” (Ref. 1 at 4). NRDC concludes this portion of its petition by asserting that “given the studies suggesting that 2,4-D has the potential to cause endocrine disrupting effects, EPA should have quantitatively incorporated these studies and these effects in its risk assessment of 2,4-D.” (Id. at 6).

These claims by NRDC do not allege sufficient grounds for revocation of the 2,4-D tolerances. The statutory standard for revocation of a pesticide tolerance is that the tolerance is not “safe.” 21 U.S.C. 346a(b)(2)(A)(i). “Safe” is defined by the statute to
mean that “there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.” 21 U.S.C. 346a(b)(2)(A)(ii). As explained in Unit II.B., EPA has implemented this safety standard, consistent with the statute, by a quantitative risk assessment process that (1) identifies the harms or toxic effects caused by the pesticide, (2) ascertains the safe level of exposure as to those harms; and (3) determines whether aggregate exposure to the pesticide exceeds that safe level. Thus, safety is not simply a question of a pesticide’s potential to cause harm but an issue involving a combination of factors including the pesticide’s potential harms, the pesticide’s potency (i.e., at what exposure levels will it cause harm), and the level of human exposure to the pesticide.

The flaw in NRDC’s petition with regard to its endocrine claim is that it addresses only 2,4-D’s potential harm and not 2,4-D’s safety. NRDC claims that 2,4-D has the “potential to cause endocrine disrupting effects . . . [and] EPA should have quantitatively incorporated [this information on 2,4-D’s harmful effects] in its risk assessment of 2,4-D.” While the reference to endocrine effects clearly addresses the first element of the risk assessment process – identification of a harm or toxic effect — NRDC’s assertion that EPA should quantitatively incorporate the endocrine studies cited by NRDC in its risk assessment falls far short of addressing the other elements of the risk assessment process. NRDC does not allege that quantitative incorporation of the studies it cites would alter EPA’s prior conclusion regarding the safe exposure level for 2,4-D. Yet, unless NRDC claims that the safe level of exposure should be lowered, it has no basis to argue that the toxicity data on endocrine effects it cites indicate a lack of safety. At best,
NRDC is asking EPA to take a revised look at the toxicity of 2,4-D. Yet, the ground for tolerance revocation is a lack of safety. Accordingly, NRDC’s claim that the 2,4-D tolerance should be revoked due to 2,4-D’s endocrine effects is denied due to a failure to make a proper claim for revocation by, at the very least, alleging facts that, if proven, would meet the statutory standard for revocation.

Despite the inadequacy of petitioners’ endocrine claims, EPA has examined the evidence cited by petitioners in light of the most current toxicity data on 2,4-D for the purpose of evaluating whether the evidence raises sufficient grounds for concern that EPA should consider initiating action that might lead to revocation of the 2,4-D tolerances.

To the extent data were available, EPA examined 2,4-D’s potential for endocrine disruption in the 2005 RED. However, as noted there, EPA was handicapped in this evaluation due to the fact that the otherwise acceptable two-generation rat reproduction study conducted with 2,4-D did not adequately address endocrine concerns. Although several toxicity studies required under 40 CFR part 158 involve an examination of organs or endpoints related to endocrine disruption, the rat reproduction study is the most critical of these required studies. In fact, the two-generation rat reproduction study, as described in the 1998 EPA guideline, has been designated as the study that will be used in Tier 2 of the EDSP for evaluating mammalian endocrine effects. As mentioned above, EPA issued a data call-in for a two-generation reproduction study in rats to address this data gap. In response to the data call-in, the Task Force submitted an extended one-generation reproductive toxicity study to fulfill this requirement. The 2,4-D extended one-generation study examined endocrine disruption as well as developmental neurotoxicity.
and developmental immunotoxicity. This extended one-generation reproductive toxicity study was conducted in accordance with OECD guidelines and is considered a state-of-the-science study with regard to examining these toxicological and endocrine effects.

As to endocrine effects, the extended one-generation reproduction study examined: Potential effects on parental male and female reproductive function, offspring survival and growth including endocrine and systemic toxicity parameters such as estrous cyclicity (female adult rats and offspring); sperm parameters; anogenital distance; nipple retention; puberty onset (vaginal opening and balano-preputial separation); adrenal weight, thyroid/parathyroid gland weight, pituitary gland weight, testes and ovarian weight, thyroid hormone effects; and histopathology of a wide range of tissues including the thyroid, adrenal, pituitary, testes, and ovary. (Refs. 31 and 32). The endpoints examined in the extended one-generation reproduction study meet or exceed the specifications in the latest guideline (1998) for the two-generation reproduction study. (Ref. 33). Specifically, this extended one-generation study included evaluation of sperm parameters and thyroid assays across various age groups, which are not part of the two-generation study. The main design difference between an extended one-generation study and a two-generation study is that the latter study is run for a full two generations no matter what results are seen in the first generation. On the other hand, an extended one-generation study is not continued into the second generation if triggers on the key endpoints do not indicate there is a potential concern. This design eliminates the needless destruction of animals, but does not reduce the scientific value of the data.

The extended one-generation study for 2,4-D showed no treatment-related effects on potential estrogenic effects or androgen-sensitive endpoints (no adverse effects on
anogenital distance, nipple retention, age at vaginal opening, estrous cycle length or pattern, mating, fertility, time to mating, gestation length, pre-implantation loss, number of corpora lutea, sperm parameters, ovarian follicle counts, and reproductive organ weights and histopathology; no evidence of hyposadias, ectopic tests, or treatment-related testicular prostate or seminal vesicle histopathology). Anti-androgenic effects in terms of decreased male reproductive organ weights were observed in some animals but they were not statistically significant and were associated with decreased body weight. No treatment-related effects on reproductive organ histopathology were observed. Slight effects were seen in the thyroid (increases or decreases in thyroid weight and in T3, T4, and TSH hormones in some animals) but no dose response relationship was shown. These effects were more significant at the highest dose tested but still were considered adaptive and not adverse (i.e., the thyroid responded to insult and corrected itself) due to the fact that this dose exceeded the renal saturation level. Accordingly, the highest dose was considered a No Observed Adverse Effect Level (NOAEL) for thyroid effects.

Overall, the effects observed at the lowest doses in the extended one-generation reproductive study for both the parental rats and offspring were not based on endocrine–related endpoints but on nephrotoxicity manifested as increased kidney weights, and degenerative lesions in the proximal convoluted tubules in the main study in the first-generation adult rats (P1 generation; 45.3 mg/kg bw/day); kidney toxicity manifested as increased kidney weights and increased incidence of degeneration of the proximal convoluted tubules in the adult offspring (F1 adults; 55.6/46.7 (M/F) mg/kg/day); and decreased body weight observed in the male pup offspring (F1, Set 1a males, PND 28-69; 76.6 mg/kg/day) (see discussion in Unit VII.A.4.e.). The NOAEL for parents and
offspring for these effects is approximately 20 mg/kg/day, (Ref. 32), which is greater than the NOAEL of 5 mg/kg/day from a rat chronic toxicity study that was used as the POD in assessing chronic dietary, long-term dermal, and long-term inhalation in the human health risk assessment supporting the 2,4-D RED. (Ref. 18). In that chronic study, the effects seen at the LOAEL of 75 mg/kg/day were decreased body-weight gain and food consumption, alteration in hematology and clinical chemistry parameters, decreased T4, glucose, cholesterol, and triglycerides. The use of the NOAEL from the chronic rat study as the POD in the RED risk assessment is protective of chronic effects identified in the extended one-generation study.

The NOAEL found in the extended one-generation reproductive study is also similar to the NOAEL of 15 mg/kg/day seen in a rat subchronic oral toxicity study and used to identify a POD for subchronic effects in the RED. (Ref. 18 at 22). The effects seen at the LOAEL of 100 mg/kg/day in the rat subchronic study were decreased body weight/body-weight gain, alterations in some hematology [decreased platelets (both sexes)] and clinical chemistry [decreased T3 (females) and T4 (both sexes)] parameters, and cataract formation. This study was used for the intermediate incidental oral and intermediate dermal and inhalation assessments. Again, the NOAEL in the extended one-generation study is greater than the NOAEL chosen as a POD for subchronic effects, and therefore, the RED assessment is protective of any subchronic effects identified in the extended one-generation study.

As noted above, EPA concluded that this study showed no adverse effects on endocrine endpoints. Accordingly, the extended one-generation reproduction study’s
comprehensive examination of 2,4-D’s potential effect on the endocrine system provides no indication that EPA should consider initiating action to revoke 2,4-D tolerances.

Nothing in the data cited by NRDC or other commenters contradicts this conclusion. For the most part, the data relied upon by NRDC address whether 2,4-D is capable of interacting with the endocrine system. The studies do not provide quantitative information appropriate for use in risk assessment or the quantitative information they provide shows that EPA’s risk assessment is protective of endocrine effects. Many of the studies cited by NRDC were studies conducted to investigate 2,4-D’s mechanism of action and involved testing at a single high dose designed to ensure effects were seen. In rats, although 2,4-D is readily absorbed in the blood, it is not metabolized but removed from the blood by the kidneys and rapidly excreted through the urine. Once the dose of 2,4-D in rats exceeds about 50 mg/kg/day, however, the kidney (renal) clearance mechanism is overwhelmed and 2,4-D builds up in the body resulting in toxic effects. The toxic effects seen at doses above the renal saturation level are generally not seen at lower doses. EPA has assessed the risk of 2,4-D based on the dose levels below the renal saturation level at which adverse effects occur.

NRDC first cites a study in fish (Xie (2005)) that it contends shows that 2,4-D has “relatively potent estrogenic effects in fish.” (Ref. 1 at 4 and Ref. 34). As an initial matter, a study in fish would carry little weight regarding a safe tolerance level when compared to a study in mammals such as the extended one-generation reproduction study in rats. Additionally, EPA does not regard the Xie study as reliable due to a failure to identify the sex of the fish used. The study reported that 7-day exposure of rainbow trout juveniles to 1.64 mg/L 2,4-D (active or formulated product undetermined) produced a 93-
fold increase in plasma vitellogenin compared to untreated fish. This was a significant difference from the untreated control. Six fish were used per test concentration, and they were described as “juvenile rainbow trout (standard length: 11.5 ± 2.2 cm) provided by the California Department of Fish and Game Mojave River Hatchery (Victorville, California)” with no reference to their sex or specific age information. However, the sex of the fish is significant with regard to vitellogenin levels. Male fish generally maintain null or very low levels of vitellogenin in their natural state. In the presence of endocrine disruptors, male fish will have significant levels of vitellogenin in their blood. Female fish will have naturally increasing levels of vitellogenin as they approach maturity and maintain those levels upon maturation. Given the sample size and a failure to identify the sex of the fish, the results seen may be a result of unbalanced numbers of male and female fish in the control and treated groups. Several other difficulties with the Xie study, including the failure to identify a biologically significant effect on vitellogenin, are noted in the comments of the Task Force and NCASI.

NRDC next relies on two studies (Rawlings (1998) and Charles (1996)), which it alleges show that 2,4-D causes hormone suppression in animals. (Refs. 35 and 36). In the Rawlings study, 2,4-D treatment resulted in a significant (p <0.05) decrease in serum T4 concentrations compared to control. No other significant effects were noted for serum cortisol, insulin, estradiol, LH pulse frequency (mean and amplitude), mean serum FSH, progesterone, or gross signs of toxicity or body weight change. In the absence of a quantifiable relationship between serum T4 concentration and effects upon survival, growth, or reproduction, the results of this study do not evidence an adverse effect that could be incorporated directly into the Agency risk assessment process. The Charles
study reports on a subchronic study in rats and was submitted to EPA and relied upon in the RED risk assessment. The study identified a NOAEL of 15 mg/kg/day and a LOAEL of 100 mg/kg/day. The effects seen at 100 mg/kg/day did include thyroid effects such as decreased thyroxine, increased thyroid weight, and hypertrophy of follicular cells. These effects were seen at a dose (100 mg/kg/day) that was well above the renal saturation level and the NOAEL from the study was used to set the safe dose for subchronic exposures to 2,4-D and is protective of effects occurring at higher dose levels. (Ref. 18 at 36).

NRDC also cites several studies (Liu (1996), Kim (2005), Kim (2002)) which it claims show that 2,4-D can result in effects on testicular cells and the prostate. (Refs. 37, 38, and 39). Liu is an *in vitro* study investigating possible mechanisms of action in relation to Leydig cell adenomas and peroxisome proliferation. 2,4-D was one of the peroxisome proliferators evaluated in the study. Kim (2005) also is an *in vitro* study investigating potential androgenic mechanisms. EPA could not evaluate the Kim (2002) study because it is written in Korean and not available to EPA in English. The Task Force argues that the 2002 study is irrelevant because it involved doses above the renal saturation level and thus the 2005 study, which was designed to investigate the effects in the 2002 study, is of limited value given the high dosing in the 2002 study. Liu also appears to have shown statistically significant effects for 2,4-D on production of estradiol only at very high doses. In any event, EPA has adequate data in living animals regarding 2,4-D’s potential to affect testicular cells or the prostate. There is an adequate/guideline cancer study in rats that dosed at levels of 5, 75, and 150 mg/kg/day (2-year study); there were no effects observed in the prostate, including no tumors. In fact, there was no increase in any tumor type in either the rat or mouse. (Ref. 19 at 29). There are
numerous studies in the rat of varying duration, and no effects on the prostate have been observed. In the studies available for the 2005 RED, effects on the testes and ovary were identified, hence the request for the two-generation rat reproduction study. The extended one-generation reproductive study is now available and it assessed the prostate. There were no effects on prostate weight and no histopathology findings in the prostate or other male accessory sex organs.

Finally, NRDC argues that studies have shown that 2,4-D causes abnormalities in the estrus cycle (Duffard (1995)), lowers sperm counts and causes other sperm abnormalities (Lerda (1991)), and results in birth defects (Garry (1996)). (Refs. 40, 41, and 42). NRDC has only cited an abstract of the Duffard study, which provides little information. It is clear, however, that the Duffard study used a single dose (70 mg/kg/day) that was at or above the renal clearance level. Garry (1996) investigated the hypothesis that offspring of pesticide applicators might have increased risks of birth anomalies. Although the initial study found an apparent linkage between an area of high phenoxy use and birth anomalies, a more detailed cross-sectional analysis of this area showed no statistically significant correlations between phenoxy use and excess adverse birth or neurodevelopmental effects. (Ref. 43). Lerda (1991) reported an apparent link between exposures to 2,4-D in 32 male applicators and reproductive effects (spermatogenesis). However, these results have little weight for assessing 2,4-D risk because Lerda (1991) did not describe the nature of applicators’ exposures in sufficient detail to show that 2,4-D was the causal agent and, if so, the level of that exposure. For example, Lerda (1991) lacked information on the timing/duration of exposure relative to sampling, the use of protective clothing/equipment, the possible presence of
manufacturing contaminants given timeframe of study, and exposures to other pesticides. On the other hand, as noted above, the extended one-generation reproduction study assessed 2,4-D’s potential impact on the estrous cycle and sperm counts/abnormalities, and no adverse effects were found in these parameters.

Beyond Pesticides, in commenting on the petition, cited Garry (2001) and Malysheva (1997), in addition to studies referenced by NRDC, as supporting NRDC’s claim that 2,4-D is an endocrine disruptor. (Refs. 44 and 45). Garry (2001) indicated serum luteinizing hormone (LH) values were correlated with urinary 2,4-D levels in humans, but follicle-stimulating hormone and free and total testosterone were not. Garry (2001) also found 2,4-D levels were not correlated with chromosome aberration frequency in humans but that chromosome aberration frequencies were correlated with the total volume of herbicides applied, including products other than 2,4-D and the use of adjuvants. This study is of limited value because of the small sample size, as noted by the authors, and because it is not clear what other pesticides the individuals were exposed to and how specific components of adjuvant products in the pesticide may have impacted the findings.

According to Beyond Pesticides, the Malysheva (1997) study found that the thyroid glands of laboratory rats were sensitive to 2,4-D as decreases in the thyroid gland transport and hormone production functions, and impairment of hormone iodination in the thyroid were observed after acute exposure. However, no information on the study was presented and the cited article is in Russian and no translation was available. Thyroid function was fully evaluated in the extended one-generation reproduction study. As noted above, the extended one-generation reproduction study examined 2,4-D’s
potential thyroid effects and established a NOAEL for such effects demonstrating that EPA’s prior risk assessment was protective.

In sum, the data cited by NRDC, Beyond Pesticides, and NYDOH do not support changing the quantitative endpoints for assessing the risk posed by 2,4-D for potential endocrine effects given the equivocal results in the studies cited and/or the high doses involved in the studies. Further, the recently-completed extended one-generation reproduction study that was specifically designed to evaluate such effects for the purpose of assessing human risks does not indicate that existing Points of Departure for assessing 2,4-D risks are under protective. Accordingly, EPA concludes that NRDC’s petition does not raise sufficient grounds for concern that EPA should consider initiating action that might lead to revocation of the 2,4-D tolerances.

2. Neurotoxicity--a. NRDC Claims. NRDC asserts that “the neurotoxic and anti-thyroid effects of 2,4-D make it highly likely that fetuses, infants, and children will be more susceptible to long-term adverse health effects from exposure to this chemical.” (Ref. 1 at 7). It cites several studies that it claims provide evidence that postnatal exposures to 2,4-D during the critical period for development of the infant brain raise serious scientific concerns. The cited studies by the same group of authors report alterations on the neurotransmitters systems (catecholamine, indoleamine), marked depression in locomotor activity, and moderate circling towards the right side following exposure to 2,4-D via the diet, during gestation, and/or postnatally. NRDC also cites a study reporting decreased serotonin levels were found in various areas of the brain following direct injection of 2,4-D into the brain. Impairment of normal deposition of myelin in the developing brain was reported following exposure via the milk or direct
subcutaneous exposure. Several studies were cited to show potential effects of 2,4-D on the brain of neonatal rats exposed lactationally. (Id.).

b. Public comments. The New York State Department of Health (NYS DOH) submitted comments in support of the NRDC petition, stating that various toxicological findings associated with 2,4-D in EPA’s RED document are weak. (Ref. 29 at 1). The RED, for example, identified specific adverse health effects of concern, including developmental neurotoxicity and endocrine disruption, and required further studies from the registrants to evaluate these effects. NYS DOH identifies additional studies for the Agency to consider. (Id.).

Beyond Pesticides, in its comments, argues that EPA has underestimated 2,4-D’s potential neurotoxic effects, and cites studies which it says show changes to maternal behavior in rats, along with increased catecholamine levels and a drastic decrease in indolamine levels. (Ref. 28 at 3).

The 2,4-D Task Force submitted comments arguing that the studies cited by NRDC do not provide credible or substantive evidence that 2,4-D causes developmental neurotoxicity at exposure levels or routes of administration relevant to humans. (Ref. 26 at 18-21). It notes that in response the reregistration data call-in issued for 2,4-D, the 2,4-D Task Force agreed to conduct an extended one-generation reproduction study in rats of 2,4-D in the diet. The Task Force points out that this study would include assessment of developmental neurotoxicity endpoints, and states that at the time it was preparing comments, there were no dose-related statistically significant indications of developmental neurotoxicity related to 2,4-D exposures, even at dose levels demonstrated to be well above the renal clearance threshold in rat dams and pups. (Id. at 4).
c. Agency response. NRDC requests revocation of 2,4-D tolerances because (1) “[t]he neurotoxic and anti-thyroid effects of 2,4-D make it highly likely that fetuses, infants, and children will be more susceptible to long-term adverse health effects from exposure to this chemical;” and (2) data cited in the petition “provide evidence that postnatal exposures to 2,4-D during the critical period for development of the infant brain raise serious scientific concerns.” (Ref. 1 at 7). However, such claims, as discussed in Unit VII.A.1.c., have the same flaw as NRDC’s endocrine arguments: The fact that the young are more susceptible to adverse effects of a pesticide or that data on a pesticide raise “serious scientific concerns” do not amount to a showing that aggregate exposure to the pesticide is unsafe, the standard for revoking tolerances. That the young may be more sensitive to a pesticide than adults may be irrelevant to the safety determination if both the young and adults have aggregate exposures below the safe dose. Similarly, that exposure to a pesticide in high dose testing may result in serious effects does not show that aggregate actual exposure to the pesticide, as opposed to exposure levels in laboratory testing, is unsafe. Again, NRDC has failed to address all the steps in the risk assessment process necessary to a safety determination. As with its endocrine claim, NRDC has done no more than allege 2,4-D has the potential to cause harm. Accordingly, NRDC’s claim that the 2,4-D tolerance should be revoked due to 2,4-D’s neurotoxic effects is denied due to a failure to allege facts sufficient to meet the statutory standard for revocation.

Despite the inadequacy of petitioners’ neurotoxicity claims, EPA has examined the evidence cited by petitioners for the purpose of evaluating whether the evidence
raises sufficient grounds for concern regarding 2,4-D that EPA should consider initiating action that might lead to revocation of the 2,4-D tolerances.

In the 2005 RED, EPA identified neurotoxic effects in the acute and subchronic neurotoxicity studies as well as other studies. These effects included clinical signs (e.g., ataxia, tremors, decreased motor activity) as well as neuropathology (e.g., retinal degeneration); however, these effects were only seen at doses above the level of saturation of renal clearance. Given these neurotoxic effects, EPA issued a data call-in for a developmental neurotoxicity study and retained the FQPA safety factor for the protection of infants and children in the absence of that data. To address this data gap, the Task Force submitted an extended one-generation reproduction study with a developmental neurotoxicity component.

The extended one-generation reproductive toxicity study on 2,4-D assessed developmental neurotoxicity at three dose levels up to the saturation level for renal clearance. (Ref. 31). The potential for neurotoxic effects was assessed using numerous parameters. First, the study used a Functional Observation Battery (FOB) to evaluate whether there were clinical signs of neurotoxicity. This FOB included cage-side, hand-held, and open-field observations of behavior, and measurements of body weight, rectal temperature, grip performance, and landing foot splay. Second, the study used an automated system for measuring motor activity. Third, the study assessed the startle response to auditory stimuli. Finally, a neuropathological exam was conducted on the brain (including the cerebrum, thalamus/hypothalamus, cerebellum and medulla), spinal cord, dorsal root ganglia, dorsal and ventral roots, peripheral nerves, and skeletal muscle. The examination of the brain included assessment of brain weight and gross
measurements, microscopic measurements (morphometrics), and brain myelin. There were no treatment-related adverse effects on any of the numerous parameters assessed across life stages, which included multiple neurotoxicity-related endpoints similar to those in the studies cited by NRDC (e.g., an assessment of motor activity, myelination, and maternal behavior). Thus, the extended one-generation reproduction study, in conjunction with all of the other data bearing on neurotoxicity, supports EPA’s risk assessment of 2,4-D and provides no indication that EPA should consider initiating action to revoke 2,4-D tolerances.

The studies relied upon by NRDC in the portion of its petition addressing neurotoxicity do not suggest that EPA has not protected against potential neurotoxic effects of 2,4-D. Similar to its approach to endocrine effects, NRDC appears to take the position that the mere fact that 2,4-D could have a neurotoxic effect shows that it is unsafe. Consistent with this approach, NRDC, for the most part, relies on mechanism of action studies that involve a single, high dose as opposed to risk assessment studies designed to investigate a chemical’s dose response relationship across a wide range of doses. NRDC relies on the following 2,4-D studies: A study in fish showing adverse brain effects (Ton (2006)); a study in rats showing delays in brain development and abnormal behavior patterns (Evangelista (1995)); a study in rats showing neurotoxic effects on the basal ganglia in the brain (Bortolozzi (2001)); and three studies that appear to show impairment of normal deposition of myelin in the developing brain (Rosso (2000); Duffard (1996); Konjuh (2008)). (Refs. 46, 47, 48, 49, 50, and 51). Each of these studies, however, either involve testing at levels above the renal saturation dose or use routes of exposure or methodology inappropriate to human risk assessment or both.
Ton (2006) was a research study investigating the use of zebrafish as a screening assay for identifying whether a chemical has the potential for neurotoxic effects and requires further testing in mammalian systems. For 2,4-D, appropriate testing in mammals is available, including a developmental neurotoxicity study in rats. Further, Ton only found potential neurotoxic effects at dose levels exceeding the dose concentration that is lethal to 50 percent for zebrafish (referred to as the LC\textsubscript{50} (lethal concentration)). Other limitations in this study are outlined in the Task Force’s comments. (Ref. 26 at 18-19).

Evangelista (1995) used doses of 50 and 100 mg/kg/day of 2,4-D. These doses meet or exceed the renal saturation level. Further compromising interpretation of this study is the fact that the identified neurotoxic effects were only detected when exposure to 2,4-D was combined with doses of amphetamine. NRDC also inaccurately describes this study as involving young rats when, in fact, adult animals were tested.

Bortolozzi (2001) investigated potential neurotoxic effects of 2,4-D by directly injecting 2,4-D into different brain areas of rats. Such a methodological approach is not useful for risk assessment because it does not correspond to the routes of exposure for humans to 2,4-D and, as noted, appropriate route of exposure studies are available for 2,4-D. Further, the Task Force described the doses in the study as being 40- to 100-fold greater than the concentration in the brain after systemic treatment.

Rosso (2000), Duffard (1996), and Konjuh (2008) each involved testing at 70 or 100 mg/kg/day. These doses exceed the renal saturation level. Other limitations in these studies are detailed in the Task Force’s comments. (Ref. 26 at 20-21).
Other studies cited by NRDC and Beyond Pesticides that address neurotoxicity have similar weaknesses. Ferri (2007), Garcia (2004), and Garcia (2008) used doses exceeding the renal saturation level. Sturtz (2008) found effects on maternal care but these effects were not duplicated in the extended one-generation reproduction study and the effects were not associated with any adverse effects in the pups.

Studies cited by the New York State Department of Health in comments are similar to the NRDC studies in that they are studies investigating mechanism of toxicity and were conducted at doses exceeding the renal saturation level.

In sum, EPA does not disagree with NRDC that 2,4-D, if administered at high enough doses, may result in neurotoxic effects in animals. However, the data regarding neurotoxicity relied upon by NRDC, or cited by commenters, does not indicate that the existing Points of Departure for evaluating 2,4-D risks are underprotective. Similarly, the extended one-generation reproduction study confirms the protectiveness of the existing Points of Departure as to neurotoxic effects. Accordingly, EPA concludes that NRDC’s petition does not raise sufficient grounds for concern that EPA should consider initiating action that might lead to revocation of the 2,4-D tolerances.

3. Mutagenicity--a. NRDC claims. NRDC claims that in comments submitted to EPA on the 2004 human health risk assessment for 2,4-D risk assessment, it pointed out that EPA disregarded a number of studies that highlight the mutagenicity and genotoxicity of 2,4-D. (Ref. 1 at 7). NRDC states that at the time of the RED, EPA responded that it was under no obligation to consider these studies because "positive findings are always confined to samples of 2,4-D formulations and not the pure substance.” (Id. at 7). NRDC claims EPA’s response in 2005 was deficient first because
nothing confines EPA only to consider studies that examine the pure substance (that is, the active ingredient). Second, recent studies involving just the active ingredient do indeed confirm the mutagenicity and cytotoxicity findings of the studies ignored by EPA. In light of these points, NRDC argues that EPA should not allow the continued use of 2,4-D.

NRDC also cited four studies it claims confirm the mutagenicity and cytotoxicity of 2,4-D. (Id. at 8). Two of these were published since the EPA RED was finalized and two were published shortly beforehand but were not cited in the risk assessment. Three of these studies examined just the active ingredient 2,4-D, while the third used a commercial 2,4-D product containing a mixture of 2,4-D and various inert ingredients. NRDC states that these results must be considered in determining whether users of these products are being exposed to potential toxicity.

NRDC also argues that apart from these new data, the discussion of the carcinogenicity and mutagenicity of 2,4-D that was provided by EPA in the 2004 risk assessment was inadequate because EPA failed to acknowledge numerous additional positive genotoxicity studies in the peer-reviewed scientific literature that together indicate that 2,4-D formulations are likely to be cytotoxic and mutagenic. (Id. at 9). According to NRDC, research in the open scientific literature have reported oxidant effects of 2,4-D, indicating the potential for cytotoxicity or genotoxicity. NRDC argues that another finding that may provide a unifying explanation of some of the data on 2,4-D and lymphoma is that the herbicide may increase lymphocyte replication. (Id.)

b. Public comments. The 2,4-D Task Force submitted comments stating that 2,4-D is not mutagenic. (Ref. 26 at 4). The Task Force claims that for reregistration, 2,4-D acid,
plus eight different 2,4-D derivatives have been tested in a battery of mutagenicity tests which are comprised of a total of 28 studies. All of these studies were negative (non-mutagenic). (Id. at 22). While the Task Force acknowledges that some positive mutagenicity studies occur, it argues that the weight of the evidence overwhelmingly supports a conclusion of minimal or no concern for mammalian mutagenicity for 2,4-D. The Task Force notes that several inherent characteristics of 2,4-D suggest that there is a very low potential for it to cause mutagenic effects: The half-life of 2,4-D in humans is less than 12 hours; 2,4-D does not metabolize or transform; 2,4-D is excreted unchanged; and it does not accumulate. (Id. at 23).

Beyond Pesticides submitted comments to support the petition by NRDC requesting the cancellation of all 2, 4-D product registrations and the revocation of all tolerances, stating that the Agency underestimated 2,4-D’s mutagenic effects. (Ref. 28 at 1). Beyond Pesticides cites a study on plants which shows the induction and frequency of certain point mutations by 2,4-D (and dicamba), suggesting that these point mutations are important as they are frequently associated with various types of cancer. Beyond Pesticides also cites a study which they claim indicates 2,4-D is cytotoxic and induces apoptosis via direct effect on mitochondrial membranes. (Id. at 2-3).

NCASI, in its comments, asserts that the overwhelming weight of evidence indicates that 2,4-D is neither mutagenic nor genotoxic. NCASI states that tests of mutagenicity and genotoxicity are important in this context as indicators of the potential for carcinogenicity. They point out that the International Commission for Protection Against Environmental Mutagens and Carcinogens, categorization of a chemical as genotoxic is not an a priori indication of a health hazard. They note that there is a large
body of evidence and broad scientific consensus that 2,4-D is not a carcinogen. (Ref. 27 at 4)

c. Agency response. NRDC’s petition argues that the 2,4-D tolerances should be revoked on several grounds related to mutagenicity. First, NRDC claims that EPA did not adequately address NRDC’s comments on the RED risk assessment regarding 2,4-D’s mutagenicity and that subsequent data confirm the accuracy of NRDC’s comments. NRDC argues that “[i]n light of these points, EPA should not allow the continued use of 2,4-D.” (Ref. 1 at 7). Second, NRDC asserts that “the discussion of the carcinogenicity and mutagenicity of 2,4-D that EPA does provide in the [RED] risk assessment is wholly inadequate.” (Id. at 8). NRDC argues that this inadequate discussion led to EPA “failing to assess fully the risk of cancer in humans from [2,4-D] exposure and failing to protect humans from this risk adequately.” (Id. at 10)

These assertions do not, however, provide a sufficient basis for revoking the 2,4-D tolerances. The ground for seeking revocation of a tolerance is a showing that the pesticide is not “safe.” Claiming that EPA improperly conducted its reassessment of the 2,4-D tolerances by failing to consider certain data bearing on its decision on mutagenicity or carcinogenicity does not amount to a showing that the tolerance is unsafe. Neither is the allegation that 2,4-D is a mutagen or the derivative claim that EPA’s failure to adequately consider mutagenicity data results in its “failing to assess fully the risk of cancer” sufficient to show that the 2,4-D tolerances are unsafe. As explained in Unit VII.A.1.c., with regard to its endocrine and neurotoxic claims, to properly assert grounds for revocation of a tolerance, NRDC must allege facts showing that aggregate exposure to 2,4-D poses an unsafe mutagenic risk. That, it has not done.
As to mutagenicity, NRDC merely alleges that 2,4-D can cause mutagenic harm. As to carcinogenicity, NRDC’s claims are even more amorphous. It argues that because EPA failed to consider 2,4-D’s alleged mutagenic effects, it thereby failed to “assess fully,” and adequately protect against, 2,4-D’s cancer risks. As to neither mutagenicity nor cancer has NRDC addressed what the safe level of exposure to 2,4-D is for humans or alleged that the exposure levels of humans to 2,4-D exceed this safe level. Accordingly, NRDC’s claim that the 2,4-D tolerance should be revoked due to 2,4-D’s mutagenic effects or its failure to assess 2,4-D’s cancer risk in light of these mutagenic effects are denied due to a failure to make a proper claim for revocation by, at the very least, alleging facts that, if proven, would meet the statutory standard for revocation.

Despite the inadequacy of petitioners’ mutagenicity claims, EPA has examined the evidence cited by petitioners for the purpose of evaluating whether the evidence raises sufficient grounds for concern regarding 2,4-D that EPA should consider initiating action that might lead to revocation of the 2,4-D tolerances.

EPA requires the submission of mutagenicity data on pesticides to assess a pesticide’s potential to cause heritable mutations that may contribute to cancer or other genetic diseases. (Refs. 52 and 53). Mutagenicity analysis has been directed primarily at investigating the mechanism of action with regard to toxic endpoints, particularly cancer. (Refs. 54 and 55). It should be noted that EPA’s data requirements on mutagenicity have evolved over the years. Whereas earlier data requirements identified a wide range of genotoxicity tests, EPA’s current testing requirements focus on tests for mutagenic effects, i.e., heritable changes in DNA that could potentially lead to disease. It is important to point out that genotoxicity assays include any kind of study that evaluates
cellular functions involving gene damage, or interference with gene replication and repair. Mutagenic effects are a subset of genotoxic ones. The difference between the terms “genotoxicity” and “mutagenicity” is that “genotoxicity pertains to all types of DNA damage (including mutagenicity), whereas mutagenicity pertains specifically to mutation induction at the gene and chromosome levels.” (Ref. 56). Importantly, “[w]hile genotoxic effects may be transient, mutagenic effects are persistent.” (Id.). So unlike mutagenic effects which are generally non-repairable, and permanent, other genotoxic effects generally do not exhibit these same traits. Consequently, non-heritable genotoxic effects do not necessarily lead to adverse effects in a whole organism, and, for the same reason, are also not a reliable predictor of such effects. While genotoxicity data can help to inform an understanding of the adverse outcome pathway for a chemical, by themselves, EPA does not accord much weight in risk assessment to genotoxicity data that fail to show heritable effects.

EPA’s current data regulations require, as to mutagenicity testing, a bacterial reverse mutation assay, an in vitro mammalian cell assay, and an in vivo cytogenetics test. 40 CFR 158.500(d). The recommended study guidelines indicate a preference for tests directed at identifying not merely genotoxicity but mutagenic effects in terms of gene mutation or chromosomal aberrations. (40 CFR 158.500(d) (test notes 31 and 32); (Refs. 57, 58, 59, 60, and 61). Omitted from the data regulations is the former requirement pertaining to “other genotoxic effects . . . [such as] numerical chromosome aberrations, direct DNA damage and repair, mammalian cells transformation, target organ/cell analysis.” 40 CFR 158.340(a) and (b)(22) (2007). The bacterial reverse mutation assay (commonly known as the Ames test) is designed to detect point mutations
in genetic material. As the guideline indicates: “Point mutations are the cause of many human genetic diseases and there is substantial evidence that point mutations in oncogenes and tumour suppressor genes of somatic cells are involved in tumour formation in humans and experimental animals.” (Ref. 57). For the *in vitro* mammalian cell assay, the guidelines recommend either individual assays directed at detecting gene mutations, (Ref. 58), or structural chromosome aberrations, or both endpoints in a single assay. (Ref. 59). For an *in vivo* cytogenetics test, the regulations recommend either an assay for the detection of structural chromosome aberrations in bone marrow cells of animals, usually rodents, (Ref. 60), or an assay for the detection of cytogenetic damage which results in the formation of micronuclei containing lagging chromosome fragments or whole chromosomes. (Ref. 61). Between the *in vitro* and *in vivo* tests, the latter carry the greater weight in assessing mutagenic potential because *in vitro* tests do not capture how a living body responds to a toxic insult, including its ability to detoxify putative mutagens and genotoxicants. (Ref. 54 at 2-34; and Ref. 62).

EPA has a large body of mutagenicity and genotoxicity data for 2,4-D. Those data show little to no concern for heritable mutagenic effects in mammals but some evidence supporting 2,4-D’s potential to cause genotoxic effects. More specifically, these data show: (1) that 2,4-D is negative in bacterial mutation assays; (2) some positive results for mutagenicity in assays in yeast, plants, and insects; (3) negative results for mutagenicity in *in vivo* studies in animals; and (4) mixed results for mutagenic and genotoxic results in *in vitro* tests in mammalian cells. EPA summarized the results in the last formal cancer assessment for 2,4-D in 1997 as follows:

The mutagenic potential of 2,4-D has been extensively evaluated in a range of *in vivo* and *in vitro* assays that have included tests with human
cells. Ames tests, with and without metabolic activation, were consistently negative. Negative results were also seen in a mouse bone marrow micronucleus and UDS assays in rat hepatocytes. Conflicting results were obtained in *Drosophila*; positive effects were seen in larvae, while negative results were seen in adults after feeding or injection. Conflicting results were also seen in *in vitro* mammalian cell cytogenetics assays; 2,4-D was negative for structural chromosomal damage up to an insoluble level but positive in the presence of metabolic activation at high doses. The positive evidence, however, tends to be weak and generally not supported by the data from *in vivo* cytogenetic assays. 2,4-D also was nonactive in mammalian cell DNA repair assays. Overall, the pattern of responses observed in both *in vivo* and *in vitro* tests indicated that 2,4-D was not mutagenic (although some cytogenetic effects were seen).

(Ref. 16 at 17).

Mutagenicity was considered as part of the weight of the evidence determination on cancer. EPA concluded that 2,4-D should be classified under Category D – Unclassifiable as to Human Carcinogenicity. This determination was based primarily on the finding that in the two most recent rodent studies there were no compound-related statistically significant increases in tumors in either rats or mice and the conclusion that epidemiology data failed to show a cause-and-effect relationship between 2,4-D exposure and cancer. The weak evidence on genotoxicity was not sufficient to outweigh the absence of positive findings on tumor development in rodent carcinogenicity studies or epidemiology studies. Similar conclusions on mutagenic (and carcinogenic) potential of 2,4-D have been reached by independent science review panels. In 1994, a joint committee of EPA’s SAB and SAP concluded that:

The conflicting cytogenetic results do not provide evidence for genotoxicity of 2,4-D. Studies with positive results have significant experimental deficiencies as noted above, thus limiting the value of these studies for assessing genotoxicity. Therefore, although there are serious data deficiencies, the currently available evidence suggests that 2,4-D is non-genotoxic. The lack of genotoxicity may reduce the concern for potential carcinogenicity of 2,4-D, but it is recognized that not all carcinogens are necessarily genotoxic.
(Ref. 15 at 19) (See Refs. 13 and 14 (earlier meeting of the FIFRA SAP disagreeing with EPA’s conclusion that there was limited evidence supporting a carcinogenic designation for 2,4-D and instead concluding that 2,4-D should be classified no higher than Category D because evidence was only equivocal)).

Since the 1997 EPA cancer assessment, the 2,4-D registrant has submitted a series of mutagenicity tests with 2,4-D and its various metabolites. The tests included bacteria mutation assays, and *in vitro* mammalian assays investigating gene mutation and chromosomal aberrations. These tests were uniformly negative. Further, in its comments on the petition, the Task Force offers a plausible hypothesis for the predominantly negative findings for 2,4-D in mutagenicity testing. The Task Force notes that 2,4-D does not metabolize or transform in the body and is rapidly excreted in an unchanged form. This lack of reactivity supports a conclusion of low mutagenic potential.

NRDC in its petition has cited a number of positive mutagenicity and genotoxicity studies. Taken together, these studies do not have a significant effect on the balance of the weight of evidence on mutagenicity and genotoxicity as summarized by EPA in its last cancer assessment.

Studies cited by NRDC and Beyond Pesticides do not significantly add to the weight of evidence supporting a mutagenicity conclusion for several reasons. First, NRDC only referenced one *in vivo* study (Madrigal-Bujaidar (2001)) and that study only looked at a genotoxic, as opposed to a mutagenic, endpoint (sister chromatid exchange). (Ref. 63). Further diminishing the weight of this study is the fact that the authors described it as only showing “weak positive results,” and concluded that given the "moderate genotoxic effect produced by 2,4-D, . . . the hazard for the general population
appears to be small.” (Id.). Second, many of the studies cited by NRDC looked only at DNA damage (sister chromatid exchange), (Refs. 64 and 65), not mutagenic effects, and at least two of these studies showed marginal positive results at best (Arias (2003, 2007)). (Refs. 66 and 67). Although two studies cited by NRDC did show a mutagenic (chromosomal aberration) response in an in vitro mammalian cell assay, (Zeljezic (2004); Venkov (2000)), two other in vitro studies were either negative (Figg (2000) (authors conclude findings do not support a “genotoxic pathway”) or marginal (Holland (2002)). (Refs. 68, 69, 70, 71, and 72). As noted above, conflicting results in in vitro testing for 2,4-D was previously recognized by EPA. Other tests (Tuschl (2003); Bukowska (2003)) showed cytotoxicity but studies on cytotoxicity alone do not provide evidence of genotoxicity. (Refs. 73 and 74). Finally, NRDC and Beyond Pesticides cited studies confirming EPA’s earlier conclusion regarding positive mutagenic effects in yeast and insects (Venkov (2000); Tripathy 1993). (Refs. 75 and 76). Such studies are entitled to less weight compared to mammalian studies, particularly in vivo mammalian studies. Finally, NRDC’s arguments regarding the reported oxidant effects of 2,4-D do not change the weight of evidence as to 2,4-D’s cancer classification because the primary evidence on cancer – rodent carcinogenicity studies and human epidemiology data – do not support a positive cancer finding.

Accordingly, EPA concludes that NRDC’s claim concerning mutagenicity does not raise sufficient grounds for concern that EPA should consider initiating action that might lead to revocation of the 2,4-D tolerances.

4. Body weight. a. NRDC claim. In a section of its petition addressing exposure to 2,4-D through maternal milk, NRDC argues that EPA chose an incorrect POD for
addressing short-term oral exposure and should “redo the short-term oral risk assessment . . .” (Ref. 1 at 11). NRDC cites a study conducted in rats by Sturtz (2006) which identified 15 mg/kg/day as a LOAEL based on “adverse effects on breastmilk composition and on bodyweight in offspring . . . .” (Id.; Ref. 77) NRDC contrasts this value with the 25 mg/kg/day NOAEL that EPA used as the POD in assessing short-term oral risk.

b. Public comments. The Task Force responded that the results in the Sturtz (2006) study were not replicated in a recent study performed under Good Laboratory Practice conditions. (Ref. 26 at 27 and Ref. 78). In this study, according to the Task Force, 2,4-D significantly decreased pup body weights at dose levels above the renal saturation level but not at lower levels.

c. Agency response. NRDC’s request on pup body weight is for EPA to “redo” the short-term oral risk assessment using a lower POD based on a LOAEL rather than a NOAEL. Although this argument, like NRDC’s other claims as to 2,4-D toxicity, appears to state an insufficient basis, on its face, for revoking the 2,4-D tolerances, EPA concludes that it is qualitatively different than NRDC’s claims regarding endocrine disruption, neurotoxicity, and mutagenicity. Those claims did not address the statutory standard for revocation. Although not clearly articulated by NRDC, EPA can piece together a sufficient allegation supporting revocation with regard to NRDC’s body weight claim: Namely, that, if EPA recalculated 2,4-D short-term risk using a revised POD of a LOAEL of 15 mg/kg/day, it would find that short-term aggregate exposure to 2,4-D exceeds the safe level.
Nonetheless, while EPA has interpreted NRDC’s allegation on body weight as a legally sufficient ground for revocation, EPA denies NRDC’s claim on body weight because the cited evidence does not support NRDC’s allegation. EPA disagrees with NRDC’s allegation that EPA has misidentified the POD for adverse effects on pup body weight. The recent extended one-generation rat reproduction study comprehensively evaluated effects on pup body weights from pre- and post-natal exposures to 2,4-D. (Refs. 31). In this study, intended doses were: 5 mg/kg/day for the low dose; 15 mg/kg/day for a mid dose; and 40 mg/kg/day for males and 30 mg/kg/day for females for a high dose. Actual calculated doses in post-natal pups following weaning (PND 21) were considerably higher with four of the five subsets within the study (Sets 1a, 1b, 2a, and 2b) receiving almost double the intended dose for the post-lactation period. Actual doses can differ from intended doses when experimental animals consume different amounts of food than projected. Body weights were tracked for all pups in the study from PNDs 1-21. There were between 24 and 28 litters per dose group with roughly 10 pups per litter which translates to roughly 250 pups per dose group. Looking across all pups in the study, no statistically significant body weight decreases were seen for males or females at any dose level for PND 1-21. A smaller subset of pups (Set 1a – 20 pups per dose), was specifically examined as to general toxicity effects including body weight effects. In that subset, statistically significant effects were seen in the high dose group for males generally between PNDs 28 and 69. No statistically significant body weight effects were seen in males at the low or mid doses or at the high dose prior to PND 28. No statistically significant body weight effects were seen in females at any dose on any day. Other subsets (Sets 1b, 2a, 2b, and 3) for which dosing continued past at least PND
55 showed no statistically significant decrease in body weight at the conclusion of the study. Similar results were found in an earlier two-generation study with 2,4-D. (Refs. 79 and 80). In that study, the intended doses were: 5 mg/kg/day for the low dose; 20 mg/kg/day for a mid dose; and 80 mg/kg/day for a high dose. Actual calculated doses in post-natal pups after weaning were 7-14 mg/kg/day, 26-48 mg/kg/day, and 76-133 mg/kg/day. Body weight effects were seen at the mid-dose at PND 28 and at the high dose. No effects on body weight were observed prior to weaning at the mid-dose. Additionally, in the range-finding study for the extend one-generation reproduction study, similar effects regarding pup body weight were seen – namely, statistically significant body weight decrements were only observed at the high dose ((1,000 ppm) 123 mg/kg/day for males (calculated on PND 35) and (800 ppm) 121 mg/kg/day for females (calculated on PND 35)). (Ref. 78).

The Sturtz (2006) study reports decreases in body weight gain or absolute body weight at doses as low as 15 mg/kg/day on PNDs 6 through 16. These results are not consistent with the prior two-generation reproduction study and were not replicated by either the range-finding study for the extended one-generation reproduction study or the one-generation study itself. Moreover, there are several reasons to give the Sturtz (2006) study less weight than the results of the other three studies. First, the extended one-generation and two-generation study were conducted under EPA’s Good Laboratory Practice Standards regulations, see 40 CFR part 160, and all underlying data for these

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2 The study does not make clear whether it was reporting decrements in body weight gain (the amount of weight gained between designated time periods) or absolute body weight. Body weight is generally regarded as the more important measure because decrements in body weight gain, which is a calculated value and may be misleading, may occur even though the pup is otherwise within normal body weight levels.
studies are available for review. Further, the extended one-generation study is considered state-of-the-science because it considered the toxicokinetic profile of 2, 4-D as it makes its way from the mother to the offspring, as well as a variety of other endpoints that are considered more sensitive than body weight (e.g., hormones, hematology, clinical chemistry, etc). The toxicokinetic aspect is particularly important because, based on the toxicokinetic profile, the doses in the extended one-generation reproduction study were adjusted during the lactational period to prevent excessive dosing both to the maternal rat and to the pups during early lactation and due to a “double exposure” when pups are both nursing and starting to consume diet (as in the case on PND 16). Adjustments to the diet were also performed in the Sturtz study, although the procedures used were different and may, to some extent, explain the results in the Sturtz study compared to the extended one-generation reproduction study. Second, the Sturtz (2006) study does not show a clear dose response effect. Although there is a greater effect on body weight comparing the lowest and highest doses, the body weight effects are essentially the same in the lowest two doses despite significant differences in the doses and that same phenomena is seen with regard to the highest two doses. Third, the extended one-generation reproduction study examined a much larger sample of pups. Roughly four times as many pups were evaluated in the extended one-generation reproduction study from PNDs 1 - 21 compared to the Sturtz study, and the Sturtz study evaluated no pups after PND 16. Finally, NRDC infers that the Sturtz study identified an “adverse effect” on the composition of maternal milk. However, changes in the composition in maternal milk may provide an explanation for effects seen in the pups but do not constitute an adverse effect independent of effects in the pups.
Thus, to the extent NRDC’s petition argues that the Sturtz study showed the 2,4-D tolerances to be unsafe, that claim is denied.

B. Exposure

1. Aggregate exposures and risk -- residential use--a. NRDC claims. In its petition, NRDC restates its comments submitted in 2002 and 2004 concerning the Agency’s aggregate assessment (Ref. 1 at 11). In its comments submitted in 2002 and 2004, NRDC claims that EPA failed to conduct adequate aggregate risk assessment due to outstanding data gaps and missing information, and that EPA did not consider exposure through drift, migration of contaminated soil, or residential track-in exposures. (Refs. 23 and 24). In its comments, NRDC cites two studies (Nishioka (1996 and 2001)) in support of these comments that pertain to track-in exposures. (Refs. 81 and 82).

b. Public comments. There were no public comments received on this issue.

c. Agency response. In addition to the generalized claims regarding inadequate assessment of aggregate exposure in the RED risk assessment, NRDC does specifically allege that “[t]he use of 2,4-D in and around the home could itself exceed appropriate risk levels if properly calculated.” (Ref. 24 at 28). If the evidence adduced by NRDC substantiates this point - the Nishioka studies (1996 and 2001) - this claim would be sufficient grounds for revocation of 2,4-D tolerances.

In response to NRDC’s claims regarding the level of 2,4-D exposure from residential use, the Agency reviewed both Nishioka studies (1996 and 2001) to ascertain if the risk assessment completed for 2,4-D was protective. (Ref. 83 at 13).

Residential exposure to 2,4-D results from its use on turf in residential environments. In the RED risk assessment this use pattern was evaluated using a
screening level methodology that considers direct contact by toddlers with treated turf. Toddlers are considered the most highly exposed group in the population to turf uses because their behavior patterns (e.g., playing on turf, mouthing of hands and other objects) lead to both increased dermal and non-dietary ingestion exposures. The screening methodology assumes that these behaviors co-occur and also aggregates exposures from the pesticide in food and water. For 2,4-D, this screening methodology did not indicate a risk of concern even taking into account that the RED risk assessment retained the full 10X FQPA safety factor due to missing data on pre- and post-natal toxicity.  

Dusts are thought by some to possibly contribute more than negligible levels to potential exposures in indoor environments but a methodology has not been developed which definitively establishes a link between levels in dust with a clearly defined exposure pathway. This construct was discussed extensively at a 2009 meeting of the FIFRA SAP related to the revisions of the EPA’s Standard Operating Procedures for Residential Exposure Assessment. (Ref. 84). The conclusions of that panel were that insufficient information is currently available to definitively link residues in dusts to specific exposure pathways. Nonetheless, to examine whether 2,4-D contamination of indoor dust might significantly alter the RED risk assessment, EPA considered how the indoor residue values in the Nishioka studies would affect the risk assessment. EPA assumed for screening purposes that toddlers consume 100 mg/day of dust containing the highest 2,4-D concentration found in Nishioka studies (67 micrograms/gram (µg/g)). The

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3 In 2011, EPA removed the FQPA safety factor because the data gaps were filled by submission of the extended one-generation rat reproduction study.
2,4-D levels in dust in the Nishioka studies were generally much lower than 67 µg/g (e.g., 1996 maximum is 4.85 µg/g, and 2001 median is 10 µg/g). The value of 100 mg/day for dust consumption is drawn from the EPA’s Child Specific Exposure Factors Handbook (Ref. 85), and is the same value assumed for soil consumption. This value was also used in the Nishioka studies. Additional conservatisms in this screening assessment are the assumptions that (1) exposures from dust residues are assumed despite the uncertainties noted in the 2009 FIFRA SAP Report; and (2) 2,4-D residues do not decline over time even though 2,4-D is known to dissipate quickly. (Ref. 84 at 26 and Ref. 86). Based on these assumptions, margins of exposure range from approximately 32,000 to 150,000 depending upon whether the duration of exposure considered is acute-, short- or intermediate-term. (Ref. 30 at 66). As such, use of this highest dust concentration value would not impact the findings of the current risk assessment. If it is further assumed that dusts persist in impacted residences in such a way that ingestion of the highest concentration would occur in a chronic exposure pattern and that the highest noted concentration in dust would never dissipate, which is counter-intuitive given how 2,4-D is used and its known rapid dissipation characteristics, risks are still not of concern. In such situations, dust would be the predominant source for chronic exposures but margins of exposure still would exceed 11,000 based on the chronic dietary POD (5 mg/kg/day). (Ref. 30 at 66). It should also be noted that Nishioka (1996) indicated that such exposures could be chronic in nature after a single application of 2,4-D, but this is viewed by EPA as unlikely due to a lack of empirical information to support such a supposition. Nishioka (1996) projected that 2,4-D would be found in residential carpet dust up to 1 year later based on short-term track-in sampling. However, the value estimated by
Nishioka (0.5 µg/g) is two orders of magnitude less than the value used in the extremely conservative assessments described above. Given that these unrealistic and high-end assumptions yield MOEs greater than 10,000, EPA concludes that the cited data do not support NRDC’s allegation that “[t]he use of 2,4-D in and around the home could itself exceed appropriate risk levels if properly calculated.” To the contrary, even assessing exposure using unrealistic, high-end values for 2,4-D, levels in dust indicates that residential dust exposures to 2,4-D are a relatively minor exposure. NRDC’s claim regarding track-in exposures is denied.

Finally, it should be noted that the Agency is currently in the process of evaluating the state of the science related to the exposure pathways from indoor dust as illustrated by the SAP review of residential methods and an additional review related to exposures from volatilization. Additionally, EPA is developing more definitive methods focused on addressing and characterizing potential exposures from chemical trespass. These efforts were recently described in a 2011 meeting of the Pesticide Program Dialogue Committee. (Ref. 87). Once final, any potential modifications to methods impacting residential risk assessment will be accounted for in the upcoming registration review process for 2,4-D.

2. Exposure through maternal milk-- a. NRDC claims. NRDC asserts that EPA failed to include any lactational exposure in its aggregate risk assessment, although it was aware of research demonstrating the potential exposure to 2,4-D from maternal milk. (Ref. 1 at 11). NRDC cites several studies involving lactational exposure to show potential effects of 2, 4-D on the brain of neonatal rats exposed lactationally. (Id.). The cited studies provide an assessment of the levels of 2, 4-D attained in the milk of the
dams and in the plasma and brain of the pups. NRDC also cites studies that it claims “confirm the lactational exposure and identify adverse effects in the offspring.” (Id.)

b. Public comments. In its comments, the Industry Task Force disputes NRDC’s allegation that EPA failed to address 2,4-D exposure from maternal milk. (Ref. 26 at 24-27). The Task Force comments that EPA was aware, when conducting the aggregate risk assessment, that 2,4-D may be present in maternal milk because of the results of animal feeding studies using exaggerated doses of 2,4-D. Further, the Task Force argues that NRDC’s claim that EPA failed to include any lactational exposure in its aggregate risk assessment is not correct. According to the Task Force, the Agency used half the limit of detection (LOD) for milk value in its 2005 risk assessment because no detectable residues were found in milk samples over several years of Pesticide Data Program (PDP) monitoring. Thus, the Task Force asserts that EPA assumed that 2,4-D would be present in milk at 0.004 ppm for both acute and chronic exposure (despite it being non-detectable in PDP sampling). (Id. at 26).

The Task Force states that large doses of 2,4-D administered in the Sturtz et al (2000) study cited by NRDC render the study uninformative for human health risk assessment. (Id. at 24). The Task Force cites biomonitoring data from farm families to support its contention that EPA’s exposure estimates are reasonable. (Id. at 25).

c. EPA’s response. Initially, EPA would note that the studies NRDC cited to support its claim that 2,4-D exposure through maternal milk causes adverse effects were considered together with other studies cited by NRDC pertaining to toxicity issues. See Unit VII.A. above.
With regard to human exposure to 2,4-D through maternal milk, NRDC alleges that such exposure occurs and was ignored by EPA despite the fact that it could result in “potentially significant exposures.” As discussed in Unit VII.A.1.c., this ground for objection is denied because (1) the standard for revocation is that the tolerance is unsafe not that there are “potentially significant exposures” that should be included in an aggregate assessment; and (2) NRDC presents no evidence to support its assertion that potentially significant exposures were excluded from EPA’s risk assessment. Accordingly, NRDC’s claim that the 2,4-D tolerance should be revoked due to exposure to 2,4-D in human breast milk is denied due to a failure to allege facts sufficient to meet the statutory standard for revocation and a failure to support the allegations that are made.

Despite the inadequacy of petitioners’ claim regarding 2,4-D exposure in human breast milk, EPA has examined the evidence cited by petitioners for the purpose of evaluating whether the evidence raises sufficient grounds for concern regarding 2,4-D that EPA should consider initiating action that might lead to revocation of the 2,4-D tolerances.

NRDC is incorrect in asserting that EPA assumed that humans are not exposed to 2,4-D through maternal milk. To the contrary, EPA assumed, in its RED risk assessment, that all milk – whether animal or human – contained 2,4-D at levels that may be present in cow’s milk. This is an extremely conservative assumption as it pertains to human breast milk.

Residues in various food forms of cow’s milk (e.g., milk fat, nonfat milk solids, etc.) have been accounted for in the dietary exposure assessment based on monitoring data from the USDA Pesticide Data Program (PDP). There were no detections of 2,4-D
in any samples, so EPA assumed that all milk contains half the detection limit for 2,4-D. (Ref. 19 at 47). This is a very conservative assumption as it pertains to human breast milk because 2,4-D levels in human breast milk are expected to be significantly lower than residues in cow’s milk. Exposure of dairy cattle to pesticides are generally significantly higher than humans as residues in cows’ key feed items, such as grass forage, are generally much higher than in human foods. As to 2,4-D, this is certainly the case given that the 2,4-D tolerances for grass (hay) and grass (forage) are 300 and 360 ppm, respectively, while 2,4-D tolerances for various human foods are all much lower -- in the single digits or less than 1 ppm (40 CFR 180.142). Grass hay and forage can constitute 60 percent of the diets of beef and dairy cattle. (Ref. 88).

Accordingly, EPA concludes that NRDC’s claim regarding exposure to 2,4-D through human breast milk does not raise sufficient grounds for concern that EPA should consider initiating action that might lead to revocation of the 2,4-D tolerances.

3. Dermal absorption—a. NRDC claims. NRDC asserts that in the final risk assessment, the dermal absorption factor used by EPA (10 percent) was too low. Specifically, NRDC claims that the EPA failed to address the possibility of enhanced dermal absorption of 2,4-D due to the potentially interacting factors of alcohol consumption and application of sunscreen, and/or the insect repellent DEET. (Ref. 1 at 12; Ref. 22 at 1). In its exposure comments on the RED, which NRDC incorporates in its petition, NRDC argued that EPA should increase its dermal absorption factor to at least 14 percent based on a human dermal absorption study by Moody (1992). (Ref. 24 at 16 and Ref. 89). NRDC claimed that such an adjustment of the dermal absorption factor would result in post-application exposures for toddlers exceeding the LOC. (Ref. 24 at
16). In addition, NRDC claims that the Agency did not sufficiently address that using rubber gloves when applying 2,4-D does not afford adequate dermal protection and the effect of 2,4-D soaking into clothing. (Ref. 1 at 13).

b. Public comments. In its comments, the Task Force disagrees with NRDC’s allegation regarding enhanced dermal absorption due to the interacting factors of alcohol consumption, sunscreen, and DEET. The Task Force argues that the study on which EPA relied to estimate dermal absorption, Feldmann and Maibach (1974), used “extreme” conditions. (Ref. 26 at 28 and Ref. 90). According to the Task Force, in this study 2,4-D was applied with acetone which denatures skin and allows for increased absorption. Additionally, the Task Force noted that the skin was not protected and not washed for 24 hours to allow maximum absorption. That study showed absorption of 5.8 percent. The Task Force also cites a recent article, Ross (2005), which summarized numerous dermal absorption studies with 2,4-D. (Ref. 91). According to the Task Force, this study concluded that the available studies showed remarkable agreement and strongly supported the conclusion in the Feldmann and Maibach study.

The Task Force also commented on other issues related to dermal exposure such as the use of rubber gloves by agricultural workers. Those comments are not relevant to the FFDCA portion of NRDC’s petition and are thus addressed elsewhere.

c. EPA’s response. For the purposes of responding to the portion of NRDC’s petition that requests EPA to revoke tolerances, EPA will respond to issues related to residential exposure here. Concerns about occupational exposures will be addressed elsewhere.
Unlike most of NRDC’s other claims, as to dermal absorption, NRDC alleges grounds that if substantiated would provide grounds for revoking the 2,4-D tolerances. As summarized above, NRDC alleges that EPA has understated dermal absorption and adjustment of dermal absorption factor to the degree supported by Moody (1992) would show a risk of concern (i.e., a lack of safety). (Ref. 24 at 16). In the petition, NRDC’s focus shifts from the Moody study to a series of in vitro studies investigating the effect of the use of sunscreen and alcohol on 2,4-D dermal absorption. NRDC argues that these studies show that EPA has underestimated dermal absorption. The various combinations of in vitro results appear to indicate that dermal absorption was enhanced by up to a factor of about 2.5 while most tested scenarios indicate a factor of 2 or less. (Refs. 92, 93, 94 and 95). One study used human skin and the results suggest a factor of up to 3 depending upon sunscreen ingredient tested. (Ref. 92). NRDC also claims that use of the pesticide Deet increases dermal absorption of 2,4-D. Here, NRDC turns back to the Moody study but that study actually concluded that “Deet had no significant effect on total cumulative palmar permeability to this herbicide [2,4-D].” (Ref. 89 at 245).

EPA believes that its use of a 10 percent dermal absorption value for 2,4-D is protective. EPA’s conclusion is supported by an extensive set of high quality human research results. Ross (2005) notes that “the degree of uncertainty and variability associated with human dermal absorption for 2,4-D is better defined than for virtually any other pesticide . . . .” (Ref. 91 at 84). EPA principally relied on an in vivo human study which showed average human dermal absorption at 5.8 percent. (Ref. 90). EPA also considered four other in vivo human studies. (Refs. 89, 96, 97 and 98). These studies involved 8 separate trials using a total of 34 participants and had an average dermal
absorption value of 5.7 percent. (Ref. 91 at 84, Table 2)  To account for potential variability EPA chose a value of 10 percent.

There are several factors that support reliance on these data and demonstrate the reasonableness of EPA’s choice of a 10 percent dermal absorption factor.  First, the data relied upon by EPA are from *in vivo* human studies.  NRDC, with one exception, has cited only to *in vitro* data. EPA generally does not rely on *in vitro* dermal absorption data without corroboration from *in vivo* testing. The critical limitations with *in vitro* dermal absorption testing, such as the lack of an intact vasculature, make it an uncertain guide for risk assessment.  The Moody study (1992) did involve *in vivo* human testing but the results of this study were similar to the higher values seen in the human *in vivo* studies considered by EPA.  In fact, if the Moody study results from the trial combining 2,4-D and DEET are included in the overall average of dermal absorption from the human studies, the average absorption only increases from 5.7 percent to 6.4 percent. (Ref. 30).

Second, the studies considered by EPA involved exposure conditions that varied based on application site (forearms, hands), topical dose rates (1.7 to 1,100 µg/cm²), form (acid or salt), application media (water, ethanol, acetone), and exposure time.  As noted, the overall average dermal absorption value for all of these data combined (N=34), regardless of design, was 5.7 percent. Examination of these variables, particularly the use of different application vehicles and different anatomical sites, is likely to have captured much of the variability measured in the sunscreen and alcohol *in vitro* studies. On this latter point, it is worth noting that NRDC placed particular emphasis on the potential additive effect of sunscreen and alcohol. Yet, the relevant study on this point found that the effect from both sunscreen and alcohol to be no higher than a factor of 2.9 and that
was only with an extremely high alcohol dose. (Ref. 92). At the lowest alcohol dose
tested in the study, the researchers actually concluded that alcohol had an inhibitory
effect on dermal absorption. This low dose, when converted to human consumption
amounts, is the equivalent of 7 ounces of 100 proof liquor for women and just slightly
less than 9 ounces for men. Third, the data considered by EPA was developed by
different researchers at different laboratories. The reproducibility of results across these
studies gives them enhanced reliability. As Ross (2005) notes: “Multiple human studies
conducted on the forearm and hand provide remarkably consistent results, especially
considering the studies were performed years apart in time, at different laboratories by
different personnel on totally different human subjects.” (Ref. 91 at 84). On the other
hand, the in vitro studies cited by NRDC all were conducted by the same group of
researchers. Finally, the value chosen by EPA for dermal absorption was nearly twice the
average value seen in human testing.

Providing further support for the reasonableness of EPA’s assumption on dermal
absorption are exposure monitoring studies (including epidemiological analyses,
environmental measurements, and methodological analyses) cited by NRDC and
commenters. (Ref. 30 at 65-69). In fact, many of these studies report exposure levels
that are similar to or far below exposures estimated by EPA. For example, NRDC cited
results from Lerda (1991), (Ref. 99), prior to the RED, which are similar to those
predicted in the 2005 EPA risk assessment for applicators wearing normal work clothing.
Current labels require the use of protective clothing and gloves. NRDC also cited median
urinary values in children reported by Morgan (2008), (Ref. 100), which are lower than
those used to establish risk estimates in the 2005 risk assessment. Other data cited in
comments, such as Alexander (2007), (Ref. 101), cited by the 2,4-D Task Force, (Ref. 26 at 30), indicate values much lower than values that would reflect a risk concern for both applicators and their family members according to the 2005 assessment. (Ref. 19 at 57-60).

Accordingly, NRDC’s claim regarding dermal absorption is denied.

EPA is currently involved in processes to refine many of its exposure assessment inputs (http://www.epa.gov/pesticides/science/handler-exposure-data.html) and to establish better methods for the consideration of epidemiological research into the regulatory process. (See Ref. 102). The Agency is also re-evaluating pesticide risks on a cyclical basis under its registration review process. Given these two efforts, the Agency will further evaluate research related to 2,4-D during registration review. The Agency has also been actively participating in epidemiological research efforts such as the Agricultural Health Study and, as part of this process, will pursue additional information related to 2,4-D and the potential for health effects in potentially exposed populations.

C. Additional Issues Raised in Public Comments

Some comments raised issues beyond the scope of NRDC’s petition. For example, Beyond Pesticides, in its comments, claimed that EPA was not justified in removing the FQPA safety factor and had failed to address cumulative effects from 2,4-D and other chlorophenoxy pesticides. (Ref. 28 at 5-6). It is not appropriate for EPA to consider these comments in support of the petition because they have not been subject to the public comment process which is critical to the EPA’s administrative review of the petition under section 408(d).

VIII. Statutory and Executive Order Reviews
This action, denies a petition to revoke tolerances, is in the form of an order and not a rule. (21 U.S.C. 346a(f)(1)(C)). Under the Administrative Procedure Act (APA), orders are expressly excluded from the definition of a rule. (5 U.S.C. 551(4)). Accordingly, the regulatory assessment requirements imposed on a rulemaking do not apply to this action, as explained further in the following discussion.

A. Executive Order 12866 and Executive Order 13563

Because this order is not a “regulatory action” as that term is defined in Executive Order 12866 entitled “Regulatory Planning and Review” (58 FR 51735, October 4, 1993), this action is not subject to review by the Office of Management and Budget (OMB) under Executive Orders 12866 and 13563 entitled “Improving Regulation and Regulatory Review” (76 FR 3821, January 21, 2011).

B. Paperwork Reduction Act

This action does not contain any information collections subject to OMB approval under the Paperwork Reduction Act (PRA), 44 U.S.C. 3501 et seq.

C. Regulatory Flexibility Act

Since this order is not a rule under the APA (5 U.S.C. 551(4)), and does not require the issuance of a proposed rule, the requirements of the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 et seq.) do not apply.

D. Unfunded Mandates Reform Act; and Executive Orders 13132 and 13175

This order denies a petition to revoke tolerances; it does not alter the relationships or distribution of power and responsibilities established by Congress in the preemption provisions of section 408(n)(4) of FFDCA. As such, the Agency has determined that this action will not have a substantial direct effect on States or tribal governments, on the
relationship between the national government and the States or tribal governments, or on the distribution of power and responsibilities among the various levels of government or between the Federal Government and Indian tribes. Thus, the Agency has determined that Executive Order 13132 entitled “Federalism” (64 FR 43255, August 10, 1999) and Executive Order 13175 entitled “Consultation and Coordination with Indian Tribal Governments” (65 FR 67249, November 9, 2000) do not apply to this order. In addition, this order does not impose any enforceable duty or contain any unfunded mandate as described under Title II of the Unfunded Mandates Reform Act (UMRA) (2 U.S.C. 1531-1538).

E. Executive Orders 13045, 13211 and 12898

As indicated previously, this action is not a “regulatory action” as defined by Executive Order 12866. As a result, this action is not subject to Executive Order 13045, entitled “Protection of Children from Environmental Health Risks and Safety Risks”, (62 FR 19885, April 23, 1997) and Executive Order 13211 entitled “Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use”, (66 FR 28355, May 22, 2001). In addition, this order also does not require any special considerations under Executive Order 12898 entitled “Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations” (59 FR 7629, February 16, 1994).

F. National Technology Transfer and Advancement Act

This action does not involve any technical standards that would require Agency consideration of voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act (NTTAA), (15 U.S.C. 272 note).
IX. Congressional Review Act

The Congressional Review Act, 5 U.S.C. 801 et seq. does not apply because this action is not a rule as that term is defined in 5 U.S.C. 804(3).

X. References

1. Petition of Natural Resources Defense Council to Revoke All Tolerances and Cancel All Registrations for the Pesticide 2,4-D (November 6, 2008).

2. Office of Prevention, Pesticides and Toxic Substances, EPA, Memorandum from Elizabeth Resek to Jim Downing, “Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held on March 25-26, 2008 to review and consider the Endocrine Disrupter Screening Program (EDSP) Proposed Tier 1 Screening Battery.” (June 11, 2008).


5. Schisler, M.; LeBaron, M.; Visconti, N. (2011) (Endocrine Disruptor Screening Program): Evaluation of 2,4-dichlorophenoxyacetic Acid (2,4-D) in an in vitro
Androgen Receptor Binding Assay. Project Number: 111111/OCR. Unpublished study prepared by Exponent, Inc. and The Dow Chemical Co. 91p. MRID 48614301.


10. Office of Chemical Safety and Pollution Prevention, EPA, Memorandum from Greg Ackerman to Katie Weyrauch, “2, 4-Dichlorophenoxyacetic Acid (2,4-D) - Report of the Endocrine Disruptor Review Team - Test Order #: EDSP–031001-120” (December 20, 2010).


15. EPA, An SAB Report: Assessment of Potential 2,4-D Carcinogenicity. Review of the Epidemiological and Other Data on Potential Carcinogenicity of 2,4-D by the SAB/SAP Joint Committee. (March 22, 1994).

16. EPA, Carcinogenicity Peer Review (4th) of 2,4-Dichlorophenoxyacetic acid (2,4-D). (January 29, 1997).


18. Office of Prevention, Pesticides and Toxic Substances, EPA, Reregistration Eligibility Decision for 2,4-D (June 2005).
19. Office of Prevention, Pesticides and Toxic Substances, EPA, Memorandum from Timothy C. Dole to Katie Hall, “2,4-D. HED's Revised Human Health Risk Assessment for the Reregistration Eligibility Decision (RED) Revised to Reflect Public Comments. PC Code 030001; DP Barcode D316597” (May 12, 2005).

20. Office of Chemical Safety and Pollution Prevention, EPA, Memorandum from Alexandra LaMay to Michael Walsh, “Petition for the Establishment of a New Formulation of 2,4-D Choline on Herbicide Tolerant Field Corn Containing the Aryloxyalkanoate Dioxygenase-1 (ADD-1) Gene. (October 27, 2011).


22. NRDC, “Supplement To The Natural Resources Defense Council Petition To Revoke All Tolerances And Cancel All Registrations For The Pesticide 2,4 D” (February 23, 2009).

23. Boston Women’s Health Book Collective, et al., Objections to the establishment of a tolerance for pesticide chemical residues of 2,4-D. OPP 301219. (May 7, 2002).


26. Industry Task Force II on 2,4-D Research Data, “Comments on The Natural Resource Defense Council’s Petition to Revoke All Tolerances and Cancel All Registrations for the Pesticide 2,4-D” (February 23, 2009).


28. Beyond Pesticides, “Re: Petition to Revoke all Tolerances and Cancel all Registrations for the Pesticide 2,4-Dichlorophenoxyacetic Acid (2,4-D); Docket Number: EPA-OPP-2008-0877” (February 23, 2009).


30. Office of Chemical Safety and Pollution Prevention, EPA, Memorandum from Linda Taylor, Nancy McCarroll, and Khin Swe Oo to Joel Wolf, “2,4-D: Evaluation of Data Identified in NRDC Petition and Associated Documents” (March 27, 2012).


32. Office of Chemical Safety and Pollution Prevention, EPA, Memorandum from Linda Taylor to Katie Weyrauch, “2,4-D: Revised Executive Summary of the Data Evaluation record of the Extended 1-Generation Reproduction Study” (June 1, 2011).


68. Office of Pesticide Programs, EPA, Reevaluation of the Genetic Toxicology Profile on 2,4-D (December 12, 2011).


73. Tuschl, H.; Schwab, C. Cytotoxic effects of the herbicide 2,4-dichlorophenoxyacetic acid in HepG2 cells. *Food and Chemical Toxicology* 41:385-393, 2003.


77. Sturtz, N.; Bongiovanni, B., et al. Detection of 2,4-dichlorophenoxyacetic acid in rat milk of dams exposed during lactation and milk analysis of their major components. *Food and Chemical Toxicology* 44:8-16, 2006.


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92. Brand, R.M.; McMahon, L., et al. (2007) Transdermal absorption of the herbicide 2,4-dichlorophenoxyacetic acid is enhanced by both ethanol consumption and sunscreen application. *Food and Chemical Toxicology* 45:93-97.


List of Subjects

Environmental protection, Agricultural commodities, Pesticides and pests.

Dated: 4/7/12

[Signature]

Director, Office of Pesticide Programs.
IARC Monographs evaluate DDT, lindane, and 2,4-D

Lyon, France, 23 June 2015 - The International Agency for Research on Cancer (IARC), the specialized cancer agency of the World Health Organization, has evaluated the carcinogenicity of the insecticides gamma-hexachlorocyclohexane (lindane) and dichlorodiphenyltrichloroethane (DDT) and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D).

After thoroughly reviewing the latest available scientific literature, a Working Group of 26 experts from 13 countries convened by the IARC Monographs Programme classified the insecticide lindane as carcinogenic to humans (Group 1). There was sufficient evidence in humans for the carcinogenicity of lindane for non-Hodgkin lymphoma (NHL). The insecticide DDT was classified as probably carcinogenic to humans (Group 2A), based on sufficient evidence that DDT causes cancer in experimental animals and limited evidence of its carcinogenicity in humans. Epidemiological studies found positive associations between exposure to DDT and NHL, testicular cancer, and liver cancer. There was also strong experimental evidence that DDT can suppress the immune system and disrupt sex hormones. However, overall there was no association between breast cancer and DDT levels measured in samples of blood or fat.

The herbicide 2,4-D was classified as possibly carcinogenic to humans (Group 2B), based on inadequate evidence in humans and limited evidence in experimental animals. There is strong evidence that 2,4-D induces oxidative stress, a mechanism that can operate in humans, and moderate evidence that 2,4-D causes immunosuppression, based on in vivo and in vitro studies. However, epidemiological studies did not find strong or consistent increases in risk of NHL or other cancers in relation to 2,4-D exposure.

A summary of the final evaluations is available online in The Lancet Oncology, and the detailed assessments will be published as Volume 113 of the IARC Monographs.

Lindane has been used extensively for insect control, including in agriculture and for treatment of human lice and scabies. High exposures have occurred among agricultural workers and pesticide applicators; however, the use of lindane is now banned or restricted in most countries. Large epidemiological studies of agricultural exposures in the USA and Canada showed a 60% increased risk of NHL in those exposed to lindane.

DDT was introduced for the control of insect-borne diseases during the Second World War and was later applied widely to eradicate malaria and in agriculture. Although most uses of DDT were banned from the 1970s, DDT and its breakdown products are highly persistent and can be found in the environment and in animal and human tissues throughout the world. Exposure to DDT still occurs, mainly through diet. The remaining and essential use of DDT is for disease vector control, mainly for malaria. This use is strictly restricted under the Stockholm Convention.

Since its introduction in 1945, 2,4-D has been widely used to control weeds in agriculture, forestry, and urban and residential settings. Occupational exposures to 2,4-D can occur during manufacturing and application, and the general population can be exposed through food, water, dust, or residential application, and during spraying.
Note to the Editor:

What does the classification mean in terms of risk?
The classification indicates the strength of the evidence that a substance or agent causes cancer. The Monographs Programme seeks to identify cancer hazards, meaning the potential for the exposure to cause cancer. However, it does not indicate the level of risk associated with exposure. The cancer risk associated with substances or agents assigned the same classification may be very different, depending on factors such as the type and extent of exposure and the strength of the effect of the agent.

What is the difference between risk and hazard?
The IARC Monographs Programme evaluates cancer hazards but not the risks associated with exposure. An agent is considered a cancer hazard if it is capable of causing cancer under some circumstances. Risk measures the probability that cancer will occur, taking into account the level of exposure to the agent. The distinction between hazard and risk is important, and the Monographs Programme identifies cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

Read the IARC Monographs Q&A

For more information, please contact

Véronique Terrasse, Communications Group, at +33 (0)4 72 73 83 66 or terrassev@iarc.fr
or Dr Nicolas Gaudin, IARC Communications, at com@iarc.fr

The International Agency for Research on Cancer (IARC) is part of the World Health Organization. Its mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships. If you wish your name to be removed from our press release e-mailing list, please write to com@iarc.fr.