UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: 27-SEP-2017

SUBJECT: 2,4-D. Revised Human Health Risk Assessment for Registration Review

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As part of Registration Review, the Pesticide Re-evaluation Division (PRD) of the Office of Pesticide Programs (OPP) has requested that the Health Effects Division (HED) evaluate the hazard data and conduct dietary (food and drinking water), residential, aggregate, and occupational exposure assessments to estimate the risks to human health that may result from the currently registered uses of 2,4-D.

This memorandum serves as HED's draft human health risk assessment, and supersedes the previous 2016 risk assessment (D424052). This revised risk assessment incorporates the findings of a toxicology systematic literature review (D441132), a Tier II epidemiology report focusing on non-cancer effects (D442486), and a Tier II epidemiology report focusing on carcinogenic effects (D441161). These findings did not alter the toxicological endpoints, points of departure, or overall risk conclusions of the previous risk assessment.

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1.0 Executive Summary

2,4-Dichlorophenoxyacetic acid (2,4-D) is an alkylchlorophenoxy herbicide used to control a variety of broadleaf weeds. It is used on several agricultural crops, on non-agricultural areas such as turf, and aquatic areas. 2,4-D is also registered for use on hybrid field corn and soybean containing the inserted aryloxyalkanoate dioxygenase-1 (AAD-1) gene. Expression of the AAD-1 protein encoded by the AAD-1 gene results in a trait that increases the herbicide tolerance of field corn and soybean to 2,4-D via increased metabolism through a pathway involving the metabolite 2,4-dichlorophenol (2,4-DCP). The residue of concern for non-transgenic crop and livestock tolerances is 2,4-D, while for transgenic crops, the residue of concern also includes the metabolite 2,4-DCP. Tolerances are established in a variety of food and feed, fish, and livestock commodities (40 CFR §180.142). In addition to 2,4-D acid, the other active ingredients in the 2,4-D case are its choline, sodium, and amine salts and its esters (see Appendix A for a complete list).

Hazard Assessment: The 2,4-D toxicology database is complete and sufficient for the quantification and characterization of a wide variety of toxic effects, including potential carcinogenic, mutagenic, developmental, reproductive, neurotoxic, and immunotoxic effects. There are no outstanding toxicity data requirements for 2,4-D. A toxicology systematic review of the open literature was conducted for 2,4-D, and did not identify any information that would alter the current human health risk assessment conclusions.

2,4-D is a phenoxy herbicide and a plant growth regulator. Since toxicity following exposure of rats and dogs to the amine salts and esters of 2,4-D was similar to that observed following 2,4-D acid exposure, the acid has been selected as being representative of all members of the 2,4-D registration review case including 2,4-D acid, the sodium, choline, and amine salts, and esters.

The toxicity profile of 2,4-D shows that the principal toxic effects are changes in the kidney, thyroid, liver, adrenal, eye, and ovaries/testes in the rat following exposure to 2,4-D *via* the oral route at dose levels above the threshold of saturation of renal clearance. No systemic toxicity was observed in rabbits following repeated exposure *via* the dermal route at dose levels up to the limit dose. Neurotoxicity was observed in the acute neurotoxicity study in rats at the high dose. In an extended 1-generation reproductive toxicity study in rats, reproductive toxicity, developmental neurotoxicity, and immunotoxicity were not observed, and the thyroid effects observed at dose levels up to/approaching renal saturation were considered treatment-related, although not adverse. Maternal and developmental toxicities were observed only at high dose levels exceeding the threshold of saturation of renal clearance. There are clearly established NOAELs and LOAELs for the population of concern, and the points of departure (POD) selected for risk assessment are protective of any susceptibility. There are no residual uncertainties for pre- and/or postnatal toxicity. HED recommends that the 10X FQPA Safety Factor (for the protection of infants and children) be reduced to 1X. The various forms of 2,4-D are not acutely (lethal) toxic *via* the oral, dermal, and inhalation routes, and are not dermal irritants or dermal sensitizers. Some, but not all, forms of 2,4-D are severe eye irritants. 2,4-D has been classified as a Category D chemical, i.e., not classifiable as to human carcinogenicity.

Dietary (Food and Water) Exposure and Risk: Acute and chronic aggregate (food + dietary drinking water) exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 3.16. This software uses 2003-2008 food consumption data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA).

The estimated drinking water concentrations (EDWCs) were modeled using the Surface Water Concentration Calculator (SWCC) for surface water and Pesticide Root Zone Model for GroundWater (PRZM-GW). For groundwater, monitoring data are available that report a maximum concentration of 14.89 µg/L which exceeds modeled predictions. For surface water, the acute (peak) and 1-in-10 year annual average modeled concentrations are 298 and 34.5 µg/L, respectively and were used in the acute and chronic analyses, respectively.

The acute and chronic dietary exposure assessment assumed tolerance-level residues, except for transgenic soybeans and cotton (for which a value higher than the tolerance was used to account for the 2,4-DCP metabolite), 100% crop treated (CT) for all commodities, empirical and default processing factors as appropriate, and incorporated the drinking water estimates described above. The resulting acute food plus drinking water risk estimates are not of concern to HED (≤100% of the acute population adjusted dose, aPAD) at the 95th percentile of the exposure distribution for the general population and all population subgroups. The acute risk estimate for children 1 to 2 years old (the subgroup with the greatest exposure) was 23% of the aPAD at the 95th percentile of exposure. The chronic risk estimates are not of concern to HED for the general population and all population subgroups. The most highly exposed population was children 1 to 2 years old, utilizing 20% of the chronic PAD (cPAD).

Residential Exposure and Risk Assessment: There are registered uses of 2,4-D on turf including lawns, golf courses and parks as well as aquatic uses; therefore, residential handler exposure and post-application exposure to treated turf and aquatic sites is possible. There is no potential hazard *via* the dermal route for 2,4-D; therefore, the handler assessment included only the inhalation route of exposure, and the post-application assessment included the incidental oral route of exposure and episodic ingestion of granules. The residential handler and post-application risk estimates are not of concern for 2,4-D for all scenarios and all routes of exposure [i.e., margins of exposure (MOEs) ≥ level of concern (LOC) of 300 for inhalation and 100 for incidental oral). Residential handler MOEs range from 5,500 to 130,000, and residential post-application MOEs range from 640 to 410,000.

Non-Occupational Spray Drift Exposure and Risk: The residential post-application exposure assessment for the registered use as direct application to turf is protective of potential deposition on turf from spray drift for the registered uses of 2,4-D. For the direct application to turf, there were no incidental oral risk estimates that were of concern (i.e., all MOEs ≥ LOC of 100).

Volatilization/Residential Bystander: The potential exposure to vapor phase 2,4-D residues emitted from treated fields for the registered uses of 2,4-D has been evaluated in this assessment. Volatilization modeling was completed using the Probabilistic Exposure and Risk model for FUMigants (PERFUM) as well as chemical-specific flux data. The flux data indicate that volatilization of 2,4-D from treated crops does occur and could result in bystander exposure to vapor phase 2,4-D; however, results of PERFUM modeling indicate that airborne concentrations are negligible, and risk estimates are not of concern even at the edge of the treated fields. In addition, the Agency assessed bystander volatilization inhalation exposure using available ambient air monitoring data, which indicated no risk estimates of concern (MOEs range from 820,000 to 1,900,000).

Aggregate Risk Estimates: The acute aggregate risk assessment includes only food and water exposure. The resulting acute food plus drinking water risk estimates are not of concern to HED (≤100% aPAD) at the 95th percentile of the exposure distribution for the general population and all population subgroups. The short-term aggregate risk assessment includes food, water, and residential exposure. The resulting short-term aggregate risks are not of concern to HED (MOEs > level of concern (LOC) of 100) for adults and children. There are no intermediate-term or longer term residential exposures to 2,4-D; therefore the intermediate-term aggregate risk assessment is not required. The chronic aggregate risk assessment includes only food and water exposure. The chronic food plus drinking water risk estimates are not of concern to HED for the general population and all populations subgroups.

Occupational Exposure and Risk Assessment: Occupational handlers may be exposed to 2,4-D during mixing/loading and applying of products containing 2,4-D. In addition, there may be post-application exposure to treated crops or use sites after application. However, since there is no potential hazard *via* the dermal route for 2,4-D, the occupational handler assessment included only the inhalation route of exposure. Occupational handler inhalation risk estimates were of concern for some scenarios assuming a respirator is not worn (current labels do not require respirators). For some scenarios where applicable, the addition of a respirator resulted in risk estimates that were not of concern. However, aerial application of granular formulations to some use sites, assuming enclosed cockpits (i.e., engineering controls), did result in risk estimates of concern. All end-use products should be checked to ensure the appropriate PPE is on labels considering both product-specific acute toxicity data and any risks of concern identified in this assessment. Restricted entry intervals (REIs) vary across labels (e.g., 12 hours versus 48 hours). All end-use products should be checked to ensure the appropriate REI based on the technical grade active ingredient acute toxicity requirements. These requirements may vary since each 2,4-D form might have a different acute toxicity profile, in addition to the potential presence of other active ingredients in a product.

***Review of Human Research*:** This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their inhalation exposure. Appendix provides additional information on the review of human research used to complete the 2,4-D risk assessment. There is no regulatory barrier to continued reliance on these

studies, and all applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied.

2.0 HED Recommendations

2.1 Data Deficiencies

None.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

Adequate analytical methods are available for data collection and the enforcement of plant commodity tolerances. An adequate GC/ECD enforcement method for plants (designated as EN-CAS Method No. ENC-2/93) was submitted, which has been independently validated and radiovalidated. An enforcement method was submitted for determination of 2,4-D in livestock commodities, which has been adequately radiovalidated. The methods have been submitted to FDA for inclusion in PAM II. The 10/1997 edition of FDA PAM Volume I, Appendix I indicates that 2,4-D is partially recovered (50-80%) using Multiresidue Methods Section 402 E1 and 402 E2.

For multiresidue method analysis, 2,4-D is documented to be well-recovered through the QuEChERS (Quick, Easy, Cheap, Effective, Rugged, and Safe) streamlined extraction method[1].

2.2.2 International Harmonization

U.S. permanent tolerances (listed in 40 CFR §180.142) plus Mexican, Canadian, and Codex maximum residue levels (MRLs) are summarized in Appendix F. Mexico adopts U.S. tolerances and/or Codex MRLs for its export purposes. The U.S., Canadian, and Codex residue definitions are harmonized (parent only). For most raw agricultural commodities, the established tolerances/MRLs for the U.S., Canada, and Codex are harmonized; however, there are commodities for which the levels are not harmonized. Commodities that are not harmonized include: cattle, kidney; goat, kidney; horse, kidney; milk; sheep, kidney; berries (crop group 13); and citrus fruit (crop group 10). The kidney and milk tolerances are not harmonized because different livestock diets were followed in establishing these 2,4-D tolerances prior to the 2008 revision of the Table 1 feedstuffs (D287660, W. Hazel, 2004). Harmonization of the U.S. tolerance on fruit, citrus, group 10 is acceptable with the Canada as the U.S. citrus residue data do not exceed the Canadian MRL of 2.0 ppm (D221853, D. Miller, 07/08/1996). Harmonization of the U.S tolerance on berry, group 13 is acceptable with Codex as the representative crops of raspberries and highbush blueberries do not exceed the Codex MRL of 0.10 ppm (CB No. 4684, F. Troghrol, 03/03/1989 and D235983, W. Hazel, 03/01/2004)).

[1] http://quechers.cvua-stuttgart.de/pdf/acidicpesticides.pdf

2.2.3 Recommended Tolerances

Permanent tolerances have been established in 40 CFR §180.142 for the residues of 2,4-D (2,4-dichlorophenoxyacetic acid), both free and conjugated in/on various raw agricultural commodities ranging from 0.02 ppm to 360 ppm with the following definition:

"Tolerances are established for residues of the herbicide, plant regulator, and fungicide 2,4-D, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels is to be determined by measuring residues of 2,4-D (2,4-dichlorophenoxyacetic acid), both free and conjugated, determined as the acid".

Cotton undelinted seed has an indirect/inadvertent residue tolerance at 0.05 ppm in section (d), however, based on recently submitted cotton studies and the OECD calculation procedure, HED concluded that the undelinted cotton seed tolerance should be increased to 0.08 ppm and moved to the general section (a) in the 40 CFR. HED has also concluded that a tolerance for 2,4-D residues on cotton gin by-product should be established at 1.5 ppm under 180.142 (a). The recently submitted processing study confirms that the processed cotton commodities of refined oil, hull, and meal do not require separate tolerances because residues of parent compound, 2,4-D in the cotton RAC were non-detectable (<0.01 ppm) even when exaggerated application rates were used; therefore, quantifiable residues of the parent compound 2,4-D are not likely in cotton processed commodities (D493777, K. King, 01/04/2016).

2.2.4 Revisions to Established Tolerances

A summary of the established and HED-recommended tolerances for residues of 2,4-D can be found in Appendix F.

HED previously recommended for the following tolerance revisions which need to be included in 40 CFR §180.142:

- Establishment of a tolerance of 50 ppm for residues of 2,4-D in/on wheat hay, barley hay, millet hay and oat hay under 40 CFR §180.142(a) (D340921, T. Goodlow, 10/18/07).
- Establishment of a tolerance of 0.1 ppm for residues of 2,4-D on strawberries, grapes, and Crop Groups 11 (pome fruit) and 12 (stone fruit) (D336596, T. Goodlow, 4/16/07).
- HED recommends that the undelinted cotton seed tolerance be increased to 0.08 ppm and moved to the general section (a) in the 40 CFR. HED also recommends that a tolerance for 2,4-D residues on cotton gin byproducts be established at 1.5 ppm under 180.142 (a) (D426371, K.King, 01/04/2016).

The recommended harmonization of the U.S. tolerances with the Canadian MRL on citrus fruit crop group 10 and the Codex MRL for berry crop group 13 require revision of 40 CFR §180.142(a) as follows:

Berry, group 13 ..... 0.10 ppm

Fruit, citrus, group 10.....2.0 ppm

2.3 Label Recommendations

No label recommendations have been identified. A summary of the risk estimates has been provided, and shows that there are risk estimates of concern for registered uses of 2,4-D based on the use information and label-required personal protective equipment (i.e., no respirator).

3.0 Introduction

3.1 Chemical Identity

Table 3.1. Test Compound Nomenclature.

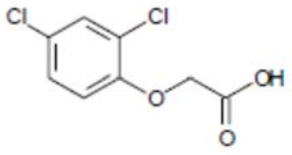
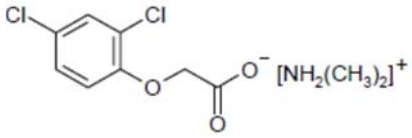
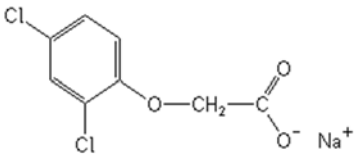
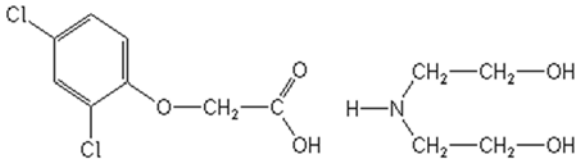
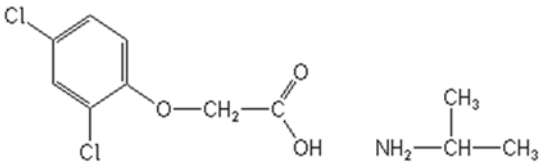
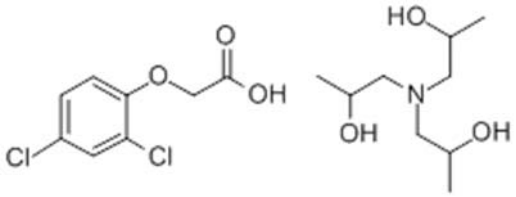
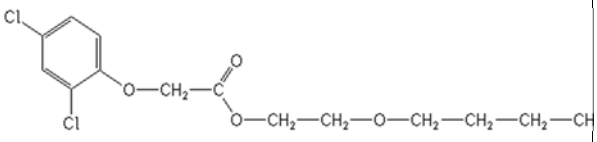
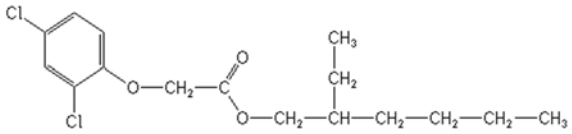
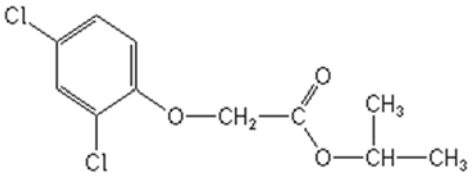
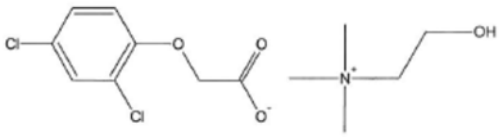
2,4-Dichlorophenoxyacetic acid (2,4-D) IUPAC name: (2,4-dichlorophenoxy)acetic acid CAS name: 2-(2,4-dichlorophenoxy)acetic acid CAS #: 94-75-7 PC Code: 030001 	**2,4-D dimethylamine salt (DMA)** IUPAC name: (2,4-dichlorophenoxy)acetic acid - dimethylamine (1:1) CAS name: 2-(2,4-dichlorophenoxy)acetic acid compound with N-methylethanamine (1:1) CAS #: 2008-39-1 PC Code: 030019 
2,4-D sodium salt (Na) IUPAC name: sodium (2,4-dichlorophenoxy)acetate CAS name: sodium 2-(2,4-dichlorophenoxy)acetate CAS #: 2702-72-9 PC Code: 030004 	**2,4-D diethanolamine salt (DEA)** IUPAC name: (2,4-dichlorophenoxy)acetic acid - 2,2′-iminodiethanol (1:1) CAS name: 2-(2,4-dichlorophenoxy)acetic acid compound with 2,2′-iminobis[ethanol] (1:1) CAS #: 5742-19-8 PC Code: 030016 

Table 3.1. Test Compound Nomenclature.	
2,4-D, isopropylamine salt (IPA) IUPAC name: (2,4-dichlorophenoxy)acetic acid - isopropylamine (1:1) CAS name: 2-(2,4-dichlorophenoxy)acetic acid compound with 2-propanamine (1:1) CAS #: 5742-17-6 PC Code: 030025 	**2,4-D, triisopropanolamine salt (TIPA)** IUPAC name: 1-[bis(2-hydroxypropyl)amino]propan-2-ol; 2-(2,4-dichlorophenoxy)acetic acid CAS #: 32341-80-3 PC Code: 030035 
2,4-D, butoxyethyl ester or 2,4-D, butoxyethanol ester (BEE) IUPAC name: 2-butoxyethyl (2,4-dichlorophenoxy)acetate CAS name: 2-butoxyethyl 2-(2,4-dichlorophenoxy)acetate CAS #: 1929-73-3 PC Code: 030053 	**2,4-D, 2-ethylhexyl ester (2-EHE)** IUPAC name: (RS)-2-ethylhexyl (2,4-dichlorophenoxy)acetate CAS name: 2-ethylhexyl 2-(2,4-dichlorophenoxy)acetate CAS #: 1928-43-4 PC Code: 030063 
2,4-D, isopropyl ester (IPE) IUPAC name: isopropyl (2,4-dichlorophenoxy)acetate CAS name: 1-methylethyl 2-(2,4-dichlorophenoxy)acetate CAS #: 94-11-1 PC Code: 030066 	**2,4-D choline** IUPAC name: 2-hydroxy-N,N,N-trimethylethanaminium (2,4-dichlorophenoxy)acetate CAS name: Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, 2-(2,4-dichlorophenoxy)acetic acid hydroxide (1:1:1) CAS #: 1048373-72-3 PC Code: 051505 

3.2 Physical/Chemical Characteristics

The vapor pressure of 2,4-D acid is 1.4 x 10^{-7} mm Hg at 25°C. The pKa of 2,4-D is 2.73; this indicates that 2,4-D will exist primarily in anion form in the environment; therefore, significant volatilization from moist soil and water surfaces is not anticipated because anions are not expected to volatilize[2].

[2] http://webwiser.nlm.nih.gov/getSubstanceData.do?substanceId=108&displaySubstanceName=24-D&STCCID=&UNNAID=&selectedDataMenuItemID=81

2,4-D is non-persistent ($t_{1/2}$=6.92 days) in terrestrial (aerobic) environments, moderately persistent ($t_{1/2}$=45 days) in aerobic aquatic environments, and highly persistent ($t_{1/2}$= 321 days) in anaerobic aquatic environments. Because 2,4-D will be anionic under most environmental conditions, it is expected to be mobile (K_{oc}=76.02) in soil and aquatic environments.

Available physical/chemical properties of the various forms of 2,4-D are provided in Appendix G.

3.3 Pesticide Use Pattern

The active ingredient 2,4-D, including its choline, sodium, and amine salts, and esters, are herbicides registered for preplant, preemergence, postemergence or preharvest use on a variety of agricultural crops. 2,4-D can also be used as a post-harvest treatment on lemons. In addition, 2,4-D can be used in aquatic sites; irrigation and ditchbanks; established grass pastures, rangeland, and perennial grasslands not in agricultural production (such as Conservation Reserve Program); turfgrass (including golf courses, cemeteries, parks, sports fields, and lawns); grass grown for seed and sod farms; non-cropland (such as fencerows, hedgerows, roadsides, ditches, rights-of-way, utility power lines, railroads, airports, industrial sites, and other non-crop areas); and forest site preparation, forest roadsides, brush control established conifer release (including christmas trees).

2,4-D is also registered for use on hybrid field corn and soybean containing the inserted aryloxyalkanoate dioxygenase-1 (AAD-1) gene. Expression of the AAD-1 protein encoded by the AAD-1 gene results in a trait that increases the herbicide tolerance of field corn and soybean to 2,4-D via increased metabolism through a pathway involving the metabolite 2,4-dichlorophenol (2,4-DCP).

The currently registered formulations include liquids (including ready-to-use), granulars, and wettable powders packaged in water soluble packets. The 2,4-D RED specifically required that risks from handling wettable-powder products be mitigated by requiring wettable powder products to be packaged in water-soluble packaging. Maximum single application rates range from 0.07 to 5 lb acid equivalent (ae)/A, and 0.0002 to 1.5 lb ae/gallon. Possible application equipment includes aerial, groundboom, airblast, aerosol can, backpack sprayer, belly grinder, injector, manually-pressurized handwand, mechanically-pressurized handwand, rotary spreader, tractor-drawn spreader, and trigger spray bottle.

A full summary of the use sites, including maximum application rates, is provided in Appendix B.

3.4 Anticipated Exposure Pathways

Humans may be exposed to 2,4-D in food and drinking water, since 2,4-D may be applied directly to growing crops and application may result in 2,4-D reaching surface and ground water

sources of drinking water. There are residential uses of 2,4-D, so humans may be exposed to 2,4-D in residential or non-occupational settings, including during pesticide application as well as potential for post-application exposure. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. There is a potential for post-application exposure for workers re-entering treated fields.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.archives.gov/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

2,4-D is a phenoxy herbicide and a plant growth regulator. Since toxicity following exposure of rats and dogs to the amine salts and esters of 2,4-D was similar to that observed following 2,4-D acid exposure, the acid form has been selected as being representative of all members of the 2,4-D Registration Review case including 2,4-D acid, the sodium, choline, and amine salts, and esters.

4.1 Toxicology Studies Available for Analysis

The toxicology database on 2,4-D is complete and sufficient for assessing the toxicity and characterizing the hazard of 2,4-D. The toxicology studies for 2,4-D are summarized in Appendix C. The database includes the following studies.

- Subchronic: 21-day dermal toxicity (rabbit), 90-day oral toxicity (rat), 13-week oral (diet) toxicity (dog), 13-week oral (capsule) toxicity (dog), 28-day inhalation toxicity (rat)
- Developmental toxicity: developmental toxicity (rat), developmental toxicity (rabbit)
- Reproduction: 2-generation reproduction study (rat); an extended 1-generation reproductive toxicity study (rat)
- Chronic: combined oral chronic toxicity/carcinogenicity (rat), carcinogenicity (mouse), chronic oral toxicity (dog)
- Neurotoxicity: acute neurotoxicity (rat), subchronic neurotoxicity (rat), developmental neurotoxicity (rat)
- Other: immunotoxicity study (rat), thyroid assessment (rat), mutagenicity battery, metabolism (rat)

The studies available for consideration of 2,4-D toxicity provide a comprehensive database, with routes of administration that are consistent with potential exposure scenarios. Additionally, there are 90-day oral toxicity (dog and rat), 21-day dermal toxicity (rabbit), and developmental toxicity (rat and rabbit) studies available on the amine salts and esters of 2,4-D, which show a similar toxicity profile as to that observed following exposure to 2,4-D.

Recently, a systematic review of the toxicology open literature was conducted for 2,4-D in order to identify studies that could potentially impact the human health risk assessment. This review did not identify any information that would alter the current human health risk assessment conclusions on 2,4-D (Memo, L. Taylor and C. Schlosser, D441132).

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

2,4-D is well absorbed orally (85%-94%), undergoes limited metabolism, and is eliminated quickly from the body primarily unchanged (73%-91%) in the urine by active saturable renal transport. The observed dose-dependent, non-linear pharmacokinetics of 2,4-D is primarily due to the saturation of this renal secretory transport system. This saturation results in elevated plasma concentrations of 2,4-D that are associated with toxicity. The main target organ for 2,4-D is the kidney, where the highest tissue levels are found. There is a gender-based difference in the renal clearance of 2,4-D in adult rats whereby males show a greater ability to clear 2,4-D relative to females. Additionally, toxicokinetic studies conducted in pregnant rats show that 2,4-D is transferred through maternal milk to the pups. 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. Based on data obtained from the open literature[3], the calculation of relevant pharmacokinetic parameters for 2,4-D in different species shows that renal clearance, volume of distribution, and plasma half-life of 2,4-D correlate with body weight (allometric scaling) for the mouse, rat, pig, calf, and human, but not the dog (Figure 1 below). The dog shows a lower than expected renal clearance and a longer than expected plasma half-life compared to the other species. The calculated renal clearance in dogs is about an order of magnitude lower than the values expected from allometric scaling for the other species. This finding is consistent with oral toxicity data

[3] Timchalk, C. Toxicology 200 (2004), 1-19.

(MRID 45840901), which show that the dose where saturation occurs in the dog (5 mg/kg) is about an order of magnitude lower than in the rodent (50 mg/kg).

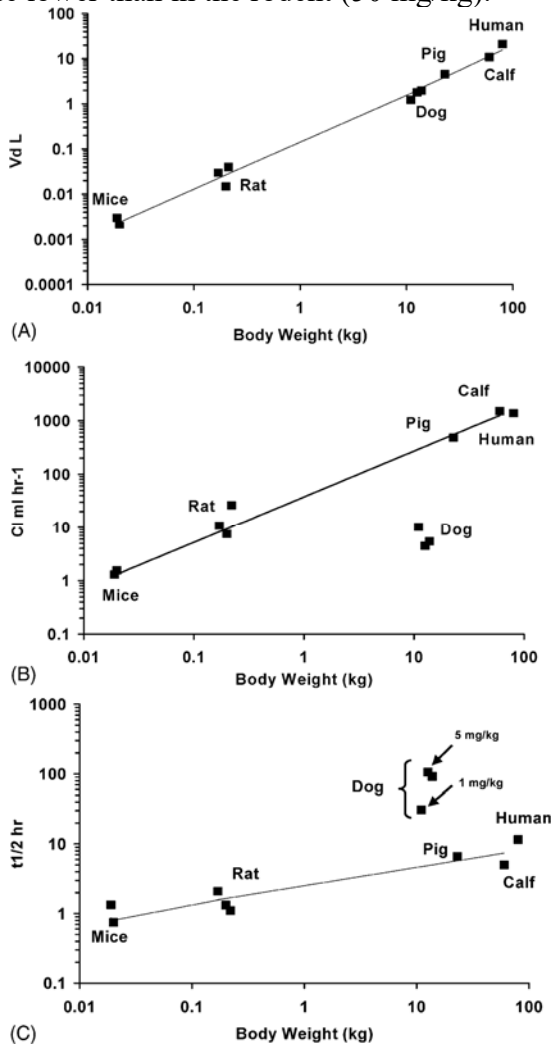


Figure 1. Correlation between volume of distribution (A), renal clearance (B), and plasma half-life (C) of 2,4-D with body weight (allometric scaling). From Timchalk, Toxicology 200 (2004), 1-19.

4.2.1 Dermal Absorption

There is an extensive set of high quality human *in vivo* dermal absorption data available, and a dermal absorption factor of 10% has been used previously. However, quantification of dermal risk is not required since there was no hazard identified in the 21-day dermal toxicity study at the limit dose, as discussed in Section 4.5.1 (Dose-Response Assessment).

4.3 Toxicological Effects

Following oral exposure to 2,4-D at dose levels above the threshold of saturation of renal clearance (50 mg/kg/day), toxic effects are observed in the rat on the kidneys, thyroid, and liver, which include changes in organ weight, clinical chemistry parameters and hormone levels, and histopathological alterations. Additional organs affected include the adrenals, testes and ovaries, and the eye (organ weight effects and histopathological alterations). Following repeated oral exposure, 2,4-D has been shown to accumulate in renal proximal tubules through the action of a saturable, metabolically active renal organic anion transporter (OATI) (Berndt and Koschier, 1973; Hasegawa, *et al*., 2003; Hook *et al.*, 1974). The OATI transporter plays a critical role in the dose-dependent systemic renal clearance of 2,4-D in rats, and is saturated at oral gavage and dietary doses of approximately 50 mg/kg, resulting in distinct nonlinear toxicokinetic (TK) behavior (Gorzinski *et al.*, 1987; Saghir *et al.,* 2006; Timchalk, 2004; van Ravenzwaay *et al.*, 2003). It is to be noted that the OATI is the primary transporter responsible for renal clearance of 2,4-D in humans, also (Nozaki *et al.,* 2007).

In the dog, the kidneys, thyroid gland, and testis are target organs following exposure *via* the oral (diet and capsule) route at dose levels above the threshold of saturation of renal clearance. Effects in dogs were observed at lower dose levels (10-fold lower) than those observed in rodents, and this effect is attributed to the dog's limited capacity to eliminate 2,4-D and other organic acids. This decreased capacity of the dog to eliminate organic acids results in higher blood levels in the dog relative to those found in the rat and, consequently, effects are seen at lower dose levels in the dog than in the rat. Data (allometric parameter scaling) demonstrate that the pharmacokinetics in the dog are markedly different than in the rat, humans, and mice, as shown in Figure 1, above (Timchalk, 2004). Consequently, the rat is a better predictor than the dog of the potential toxicity of 2,4-D to humans.

No systemic toxicity was observed in rabbits following repeated exposure *via* the dermal route at dose levels up to the limit dose [1000 mg/kg/day]. Following inhalation exposure, histopathological findings in the larynx (squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells) were observed in rats of both sexes at lower dose levels than systemic effects. These portal-of-entry effects are the basis of the POD for inhalation exposure and protective of all other effects in the database.

In the developmental toxicity study in rats, the developmental effects (skeletal malformations) occurred at the same dose level as the maternal effects, although the findings in the maternal rat are minimal (decreased body weight gain). However, the dose level where the effects occurred (75 mg/kg/day) exceeds the threshold of saturation of renal clearance, and based on the extensive toxicology database on 2,4-D, effects on the maternal kidney would have been observed had they been assessed. However, in order not to stress the maternal animal, these types of examinations, which would compromise interpretation of the study, are not performed in the developmental studies. In the rabbit, clinical signs (ataxia, decreased motor activity, loss of righting reflex, cold extremities) and decreased body weight gain were observed in the maternal animal at the high dose (90 mg/kg/day); additionally, there were two abortions at the high dose. In the rat 2-generation reproductive toxicity study, decreased maternal body weights, and offspring deaths

and skeletal variations were observed at the high dose level (75 mg/kg/day), which exceeds the threshold of saturation of renal clearance.

Neurotoxicity, as evidenced by the increased incidence of in-coordination and slight gait abnormalities (forepaw flexing or knuckling), was observed following oral exposure to rats during the FOB assessment in the acute neurotoxicity study in rats. Relative forelimb grip strength was significantly increased in rats of both sexes at the high-dose level in the subchronic neurotoxicity study, although there was no treatment-related change in absolute grip strength Additionally, an increased incidence of bilateral retinal degeneration was observed in the high-dose females. Developmental neurotoxicity and developmental immunotoxicity were not observed in the extended 1-generation reproduction toxicity study in rats, and the findings in the thyroid were considered adaptive.

2,4-D is classified as "not classifiable as to human carcinogenicity", based upon bioassays in rats and mice that showed no statistically significant tumor response in either species. HED has also completed a systematic literature review focused on carcinogenic effects to ensure the Agency's assessment of carcinogenicity for 2,4-D captured all pertinent scientific data to date (Memo, A. Aldridge, D441161). The epidemiology review found that, overall, there was little substantive evidence to suggest a clear associative or causal relationship between exposure to 2,4-D and cancer including non-Hodgkin lymphoma (NHL) in several cohort and case-control studies including the AHS (Agricultural Health Study).

2,4-D is not acutely (lethal) toxic *via* the oral, dermal, and inhalation routes, is not a dermal irritant or a dermal sensitizer, but it is a severe eye irritant. Similar results were observed for the amine salts and esters, although the esters are not severe eye irritants.

As noted above, in Section 3.3, 2,4-D is registered for use on hybrid field corn and soybean containing the inserted aryloxyalkanoate dioxygenase-1 (AAD-1) gene, and expression of the AAD-1 protein encoded by the AAD-1 gene results in a trait that increases the herbicide tolerance of field corn and soybean to 2,4-D via increased metabolism through a pathway involving the metabolite 2,4-dichlorophenol (2,4-DCP). There are adequate toxicity data available on 2,4-DCP, which suggest that 2,4-DCP is less toxic than 2,4-D (i.e., higher dose levels are tolerated). Both the rat National Toxicology Program (NTP) carcinogenicity and mouse NTP carcinogenicity studies (1989) on 2,4-DCP are negative for carcinogenicity. In the 2-generation reproduction study on 2,4-DCP, the NOAEL for effects on offspring is 2000 ppm (134 mg/kg/day), based on a slight decrease in the number of pups, delayed eye opening in both sexes and generations, and slight (≤1 day) delays in sexual maturation at 543 mg/kg/day. The reproductive toxicity NOAEL is 2000 ppm (134 mg/kg/day, based on decreased number of implantation sites (F1 parental/F2 offspring) at the LOAEL of 543 mg/kg/day. Developmental toxicity was not observed in the rat. Since 2, 4-DCP is less toxic than 2,4-D, comparing 2,4-DCP exposure to 2,4-D endpoints is protective for risk assessment purposes.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

HED recommends that the 10X FQPA Safety Factor (for the protection of infants and children) be reduced to 1X. An FQPA Safety Factor of 1X is appropriate for the following reasons:

The toxicity database is complete and adequate to assess safety for infants and children. There is evidence of increased susceptibility in the rat developmental toxicity study and in the rat 2-generation reproduction study; however, these studies have clearly defined NOAELs/LOAELs, and the points of departure used in the risk assessment are below where these findings occur and are protective. There are acute and subchronic neurotoxicity studies, a developmental neurotoxicity study, a detailed evaluation of thyroid function across life stages, and a developmental immunotoxicity study on 2,4-D. The exposure assessment will not underestimate children's exposure to 2,4-D. Further details may be found in the following sections.

4.4.1 Completeness of the Toxicology Database

The toxicology database for 2,4-D is complete. Acceptable rat and rabbit developmental toxicity studies, a rat 2-generation reproduction study, an extended 1-generation rat reproduction toxicity study (F1 offspring evaluated for potential effects on the nervous system, immune system, reproductive and endocrine systems, thyroid function, and other systemic toxicity parameters), and acute, subchronic, and developmental neurotoxicity studies in rats are available.

4.4.2 Evidence of Neurotoxicity

Evidence of neurotoxicity was observed in the acute neurotoxicity study in rats, as evidenced by an increase in the incidence of in-coordination and slight gait abnormalities (forepaw flexing or knuckling) during the FOB assessment at the high dose in both sexes. In the subchronic neurotoxicity study, relative forelimb grip strength was significantly increased in rats of both sexes at the high-dose level, although there was no treatment-related change in absolute grip strength. Clinical signs of neurotoxicity (decreased motor activity, ataxia, loss of righting reflex, extremities cold to the touch) were observed in maternal rabbits in the developmental toxicity study. Developmental neurotoxicity was not observed in the developmental neurotoxicity cohort of the Extended One Generation Reproductive Toxicity study (EOGRTS) in rats. Neuropathological effects were not observed in any study.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

There is evidence of increased susceptibility following *in utero* exposure to 2,4-D in the rat developmental toxicity study, and following *in utero* and/or pre-/post-natal exposure in the rat 2-generation reproduction study at dose levels that exceed renal saturation. There is no evidence of increased susceptibility following *in utero* exposure to 2,4-D in the rabbit developmental toxicity study or following *in utero* and/or pre-/post-natal exposure in the rat extended 1-generation reproduction toxicity study.

2,4-D has been evaluated for potential developmental effects in the rat and rabbit. Maternal toxicity included decreased body weight gains in the rat study at the same dose level where developmental effects (occurrence of skeletal malformations) were observed. Maternal toxicity in the rabbit included decreased body weight gain, clinical signs of toxicity (decreased motor activity, ataxia, loss of righting reflex, extremities cold to the touch), and abortions, the latter being indicative of developmental toxicity. Decreased maternal body weight gains were observed in the rat 2-generation reproduction study at a dose that exceeded renal saturation and resulted in reduced viability of the F1 pups. As discussed previously, kidney effects would have been expected in the maternal animal had examination of the kidney been performed in these studies, and the findings are not considered evidence of susceptibility. There are clearly established NOAELs and LOAELs for the population of concern, there are no data gaps in the toxicology database, and the points of departure (POD) are protective of susceptibility.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. The dietary exposure estimates are unrefined and reflect primarily tolerance-level residue in food, 100% CT, and upper-bound drinking water estimates based on modeling. These assumptions and refinements are detailed in the Section 5.4.1. Additionally, HED does not believe that non-occupational exposure estimates are underestimated. The assumptions are detailed in Section 6.0.

4.5 Toxicity Endpoint and Point of Departure Selections

4.5.1 Dose-Response Assessment

A detailed description of the toxicity studies used for selecting toxicity endpoints and points of departure for various exposure scenarios is presented in the appendix. The available hazard database is adequate to characterize any potential for prenatal or postnatal risk for infants and children.

An acute dietary endpoint for females 13+ was selected from the developmental toxicity study in rats with a NOAEL of 25 mg/kg/day. At the study LOAEL of 75 mg/kg/day, fetal skeletal malformations (14^{th} rudimentary ribs) were observed. A 100X uncertainty factor was applied to account for inter- and intra-species variability resulting in an acute reference dose (RfD) of 0.25 mg/kg/day.

An acute dietary endpoint for the general population, including infants and children, was selected from the acute neurotoxicity study in rats with a NOAEL of 67 mg/kg/day. At the study LOAEL of 225 mg/kg/day, an increased incidence of incoordination and slight gait abnormalities (forepaw flexing or knuckling) and decreased motor activity were observed. A 100X uncertainty factor was applied to account for inter- and intra-species variability resulting in an acute reference dose (RfD) of 0.67 mg/kg/day.

The chronic dietary endpoint was selected from the extended one-generation reproduction toxicity (EOGRT) study in rats with a NOAEL of 21 mg/kg/day. This robust study assessed several durations of exposure and life stages and included a thorough assessment of the F1 offspring for potential effects on the nervous system, immune system, reproductive and endocrine systems, thyroid function, and other systemic toxicity parameters. At the study LOAEL of 55.6/46.7 mg/kg/day, kidney toxicity, manifested as increased kidney weights and increased incidence of degeneration of the proximal convoluted tubules, was observed and decreased body weight in pups was observed throughout lactation. A 100X uncertainty factor was applied to account for inter- and intra-species variability resulting in a chronic reference dose (cRfD) of 0.21 mg/kg/day.

Short-term and intermediate-term incidental oral endpoints for risk assessment were selected from the extended one-generation reproduction toxicity study in rats with a NOAEL of 21 mg/kg/day. At the study LOAEL of 55.6/46.7 mg/kg/day, kidney toxicity, manifested as increased kidney weights and increased incidence of degeneration of the proximal convoluted tubules, was observed and decreased body weight in pups was observed throughout lactation. A 100X uncertainty factor was applied to account for inter- and intra-species variability.

Short-term and intermediate-term inhalation endpoints for risk assessment were selected from the route-specific 28-day inhalation toxicity study in rats with a LOAEL of 0.05 mg/L/day. At the study LOAEL of 0.05 mg/L/day, squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx, which was not totally resolved following a 4-week recovery period, were observed. Human Equivalent Concentrations (HEC)/Human Equivalent Doses (HED) for residential and occupational scenarios were calculated and details are listed in Appendix D. A NOAEL for portal-of-entry effects was not determined. A 3X uncertainty factor was applied to account for inter-species variability (to account for the PD differences), a 10X uncertainty factor was applied to account for intra-species variability, and a 10X $UF_{LOAEL \rightarrow NOAEL}$ was applied to account for the lack of a NOAEL. Although there was no assessment of the thyroid in the inhalation study, the rat extended 1-generation reproduction toxicity (oral) study performed an assessment of the thyroid for several age groups at dose levels up to/approaching renal saturation. The changes in thyroid hormones observed, along with thyroid histopathological findings, were considered treatment-related, although not adverse. The lack of an assessment of the thyroid in the inhalation study is considered inconsequential because the portal of entry endpoint is protective of potential thyroid effects expected to occur at higher concentrations; *i.e.,* at doses that exceed the level of renal clearance. Portal-of-entry effects were observed at all dose levels, and an additional 10X uncertainty factor is applied to the LOAEL to obtain an extrapolated NOAEL used for the inhalation risk assessments. The use pattern indicates that dose levels required to exceed the renal clearance mechanism would not be attained following human inhalation exposure.

No quantification of dermal risk is required. Although the dermal toxicity study did not evaluate developmental endpoints, (1) there was no dermal or systemic toxicity observed following repeated dermal applications to rabbits at the Limit Dose (1000 mg/kg/day); (2) there was no quantitative susceptibility observed in the developmental or reproductive toxicity studies; (3) the

use of a 10% human dermal absorption factor (DAF) with the oral developmental LOAEL of 90 mg/kg/day established in the rabbit developmental toxicity study yields a dermal equivalent dose (DED) of 900 mg/kg/day, which is numerically similar to the high-end dermal NOAEL (1000 mg/kg/day) in the dermal rabbit study; (4) the use of the 10% human DAF with the oral developmental LOAEL of 75 mg/kg/day established in the rat developmental study yields a DED of 750 mg/kg/day; (5) the developmental findings in the rat and rabbit occurred at oral dose levels exceeding renal clearance, and clear NOAELs were obtained (dermal equivalent doses of 250 and 300 mg/kg/day); (6) although there was no assessment of the thyroid in the dermal study, the rat extended 1-generation reproduction toxicity (oral) study performed an assessment of the thyroid for several age groups at dose levels up to/approaching renal saturation. The changes in thyroid hormones (↓ T_3 and T_4 with ↑TSH levels) observed, along with thyroid histopathological findings, were considered treatment-related, although not adverse (NOAEL for thyroid effects is ≈40 mg/kg/day; dermal equivalent dose of 400 mg/kg/day); and (7) the use pattern indicates that dose levels required to exceed the renal clearance mechanism would not be attained following human dermal exposure.

4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

No quantification of dermal risk is required. Oral and inhalation endpoints are not the same, and thus should not be combined.

4.5.3 Cancer Classification and Risk Assessment Recommendation

The Cancer Peer Review Committee (CPRC; TXR No. 0050017, dated January 29, 1997) classified 2,4-D as "not classifiable as to human carcinogenicity", based upon bioassays in rats and mice that showed no statistically significant tumor response in either species. HED has also completed a systematic literature review focused on carcinogenic effects to ensure the Agency's assessment of carcinogenicity for 2,4-D captured all pertinent scientific data to date (Memo, A. Aldridge, D441161). The epidemiology review found that, overall, there was little substantive evidence to suggest a clear associative or causal relationship between exposure to 2,4-D and cancer including NHL in several cohort and case-control studies including the AHS.

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

The points of departure, uncertainty factors, and toxicity endpoints are presented in the following table.

Table 4.5.4.1 Summary of Toxicological Doses and Endpoints for 2,4-D for Use in Dietary and Occupational and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-49 years old)	Developmental NOAEL = 25 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	aRfD=aPAD = 0.25 mg/kg/day	Developmental Toxicity Study – rat MRID 00130407, 00130408 (1983) Developmental LOAEL = 75 mg/kg/day based on fetal skeletal abnormalities (14th rudimentary ribs)
Acute Dietary (General Population, including Infants and Children)	NOAEL = 67 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	aRfD=aPAD = 0.67 mg/kg/day	Acute Neurotoxicity Study – rat MRID 43115201 (1994) LOAEL = 227 mg/kg/day based on slight gait abnormalities (forepaw flexing and knuckling) and increased incidence of incoordination.
Chronic Dietary (All Populations)	NOAEL= 21 mg/kg/day	UF_A=10x UF_H=10x FQPA SF = 1x	cRfD =cPAD= 0.21 mg/kg/day	Extended 1-generation reproduction (Crl:CD(SD) rat) MRID 47972101 (2010) Parental LOAEL=800/600 ppm (males 55.6 mkd; females 46.7 mkd), based on kidney toxicity manifested as increased kidney weights and increased incidence of degeneration of the proximal convoluted tubules and for offspring based on decreased body weight observed throughout lactation.
Incidental Oral Short- and Intermediate-Term (1-30 days and 1-6 months)	NOAEL = 21 mg/kg/day	UF_A= 10x UF_H=10x FQPA SF= 1x	Residential LOC for MOE = 100	Extended 1-generation reproduction (Crl:CD(SD) rat) MRID 47972101 (2010) LOAEL=800/600 ppm (males 55.6 mkd; females 46.7 mkd), based on kidney toxicity manifested as increased kidney weights and increased incidence of degeneration of the proximal convoluted tubules, and for offspring based on decreased body weight observed throughout lactation.
Dermal (All durations)	No potential hazard *via* the dermal route, based on the lack of systemic effects following repeat dermal exposure of rabbits at dose levels up to 1000 mg/kg/day. Although developmental toxicity was not assessed in the dermal study, clear NOAELs (dermal equivalent doses of 250 and 300 mg/kg/day) were determined; the developmental effects occurred at dose levels that exceed renal clearance mechanism (dermal equivalent doses of 750 and 900 mg/kg/day); dose levels required to exceed the renal clearance mechanism would not be attained following dermal exposure to humans.			

Table 4.5.4.1 Summary of Toxicological Doses and Endpoints for 2,4-D for Use in Dietary and Occupational and Non-Occupational Human Health Risk Assessments				
Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Inhalation (all durations)	LOAEL = 0.05 mL/kg/day HEC=0.013 mg/L/day[A] (bystander) HED=1.76 mg/kg/day[B] (residential handler) HEC= 0.056 mg/L/day[C] (occupational) HED= 5.29 mg/kg/day[D] (occupational handler, depending on scenario)	UF_A = 3X UF_H = 10X UF_L = 10X	Residential and Occupational LOC for MOE = 300	Subchronic inhalation toxicity study (SD CD rat) MRID 47398701 (2008) LOAEL = 0.05 mg/L/day, based on portal-of-entry effects (squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx); not totally resolved following a 4-week recovery period.
Cancer (oral, dermal, inhalation)	Classification: Group D – not classifiable as to human carcinogenicity			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

[A] Residential bystander HEC (portal of entry endpoint) = rat POD * daily duration adjustment * weekly duration adjustment * RDDR = 0.05 mg/L * (6 hrs/24 hrs) * (5 days/7 days) * Tracheobronchial RDDR (1.49) = 0. 013 mg/L

[B] Residential handler HED (portal of entry endpoint) = rat POD * RDDR * human specific conversion factor * human daily duration = 0.05 mg/L* RDDR (1.49) * 11.8 L/hr/kg * 2 hrs = 1.76 mg/kg/day

[C] Occupational HEC (portal of entry endpoint) = rat POD * daily duration adjustment * weekly duration adjustment * RDDR = 0.05 mg/L * (6 hrs/8 hrs) * (5 days/5 days) * Tracheobronchial RDDR (1.49) = 0.056 mg/L

[D] Occupational handler HED (portal of entry endpoint) = HEC * human specific conversion factor * daily duration * relative activity factor = HEC (0.056 mg/L) * 11.8 L/hr/kg * 8 hrs = 5.29 mg/kg/day

4.6 Endocrine Disruption

As required by FIFRA and the Federal Food, Drug, and Cosmetic Act (FFDCA), EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic, and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity.

These studies include endpoints that may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision for 2,4-D, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), 2,4-D is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[4] and includes some pesticides scheduled for Registration Review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

2,4-D is on List 1 for which EPA has received all the required Tier 1 assay data. The Agency has reviewed all of the assay data received for the appropriate List 1 chemicals and the conclusions of those reviews are available in the chemical-specific public dockets (see EPA-HQ-OPP-2012-0330). For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[5]

5.0 Dietary Exposure and Risk Assessment

5.1 Metabolite/Degradate Residue Profile

[4] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.
[5] http://www.epa.gov/endo/

5.1.1 Summary of Plant and Animal Metabolism Studies

The residue chemistry database is adequate. Adequate metabolism studies are available for both non-transgenic crops and 2,4-D tolerant field corn and soybean.

The requirements for livestock metabolism are fulfilled. Adequate goat and hen metabolism studies are available, and the metabolism of 2,4-D is similar in both species. Based on the available data, the Agency determined that the residue of concern in livestock for the tolerance expression and for risk assessment is 2,4-D, free and conjugated, determined as the acid (Memo, T. Jimerson, 10/13/04, D309452, TXR. No. 0052264).

5.1.2 Summary of Environmental Degradation

According to the 2005 RED (Memo, T. Dole, 5/12/05, D316597), the major route of degradation is aerobic microbial metabolism, therefore, 2,4-D is non-persistent ($t_{1/2}$=6.92 days) in terrestrial (aerobic) environments, moderately persistent ($t_{1/2}$=45 days) in aerobic aquatic environments, and highly persistent ($t_{1/2}$= 321 days) in anaerobic aquatic environments. Because 2,4-D will be ionized under most environmental conditions, it is expected to be mobile (K_{oc}=76.02) in soil and aquatic environments.

In six aquatic field dissipation studies, 2,4-D was the predominant residue. There are three major degradates identified in the submitted environmental fate studies for 2,4-D: 1,2,4-benezenetriol, 2,4-dichlorophenol (2,4-DCP), and chlorohydroquinone (CHQ). The Agency determined that residues other than 2,4-D are not of risk concern in water due to low occurrence under environmental conditions, comparatively low toxicity, or a combination thereof（Memo, T. Jimerson, 10/13/04, D309452, TXR. No. 0052264）. Therefore, estimated drinking water concentrations (EDWCs) for human health are based on 2,4-D acid.

5.1.3 Comparison of Metabolic Pathways

An acceptable 2,4-D metabolism study in rats is available (MRID 41737302). 2,4-D is well absorbed orally, undergoes limited metabolism, and is eliminated quickly from the body primarily unchanged in the urine. Parent 2,4-D was the major metabolite found in the urine, accounting for 72.9 - 90.5% of the administered dose. 2,4-DCP was not observed as a major metabolite in the rat metabolism study.

In non-transgenic crops, milk, tissue, and poultry, the primary residue is parent 2,4-D. 2,4-DCP is a minor metabolite in non-transgenic plants, milk, fat, and eggs. It was determined that 2,4-DCP is not of concern at the levels expected in non-transgenic crops and livestock tissue, and considering the lower toxicity of 2,4-DCP compared to 2,4-D. 2,4-D is more readily metabolized into 2,4-DCP in transgenic corn and soybean than in non-transgenic corn and soybean.

5.1.4 Residues of Concern Summary and Rationale

HED's MARC determined that the residue of toxicological concern to be included in non-transgenic crop and livestock tolerances and in dietary risk assessments (food and water) is 2,4-D, both free and conjugated, determined as the acid (Memo, T. Jimerson, 10/13/04, D309452, TXR. No. 0052264). For 2,4-D-tolerant field corn and soybean, the metabolite 2,4-DCP was also included as a residue of concern for dietary risk assessment purposes as there are greater amounts of 2,4-DCP found in tolerant crops compared to non-tolerant crops. Since 2,4-DCP is less toxic than 2,4-D, comparing 2,4-DCP residues to 2,4-D endpoints would be protective for risk assessment purposes (Memo, A. LaMay, 10/27/11, D394981).

Table 5.1.4 Summary of Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression

Matrix		Residues included in Risk Assessment	Residues included in Tolerance Expression
Plants	Primary Crop	Parent (2,4-D)	Parent (2,4-D)
	Rotational Crop	Parent (2,4-D)	Parent (2,4-D)
	Transgenic Corn and Soybean	2,4-D and 2,4-DCP	Parent (2,4-D)
Livestock	Ruminant	Parent (2,4-D)	Parent (2,4-D)
	Poultry	Parent (2,4-D)	Parent (2,4-D)
Drinking Water		Parent (2,4-D)	Not Applicable

2,4-D is 2,4-Dichlorophenoxyacetic acid, and 2,4-DCP is 2,4-dichlorophenol.

5.2 Food Residue Profile

HED has previously evaluated field residue data depicting the magnitude of 2,4-D residues of concern in/on all registered crops. Quantifiable residues were found in crops, with 2,4-D acid generally found as the major component of the total residue in non-transgenic crops, and 2,4-D acid and the metabolite, 2,4-DCP, being major components in transgenic crops.

Tolerance residues were used for a conservative dietary exposure estimate. HED has evaluated residue data pertaining to the potential for concentration of 2,4-D residues of concern in processed commodities. Concentration of residues was observed in regulated commodities processed from citrus fruits, sugarcane, and wheat grain. The data indicated that residues of 2,4-D and 2,4-DCP may concentrate in aspirated grain fractions (AGF) and cotton meal.

5.3 Water Residue Profile

The dietary analyses incorporated the drinking water estimates provided by the Environmental Fate and Effects Division (EFED). The estimated drinking water concentrations (EDWCs) were derived using the Surface Water Concentration Calculator (SWCC) for surface water and Pesticide Root Zone Model for GroundWater (PRZM-GW). For groundwater, monitoring data are available that report a maximum concentration of 14.89 µg/L which exceeds modeled predictions. For surface water, the acute (peak) and 1-in-10 year annual average concentrations are 298 and 34.5 µg/L, respectively (D4332483, F. Khan, 04/13/2016). EFED indicated that the estimated drinking water concentration for the acute assessment should be 298 ppb, the 1-in-10 year annual peak exposure based on the MS corn scenario. The chronic assessment should use the 1-in-10 year annual mean value of 34.5 ppb.

While higher water concentrations were estimated from the direct aquatic use and the use on rice, it should be noted that the master label includes potable water use restrictions, "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." Therefore, these water concentrations were not recommended for use in the dietary risk assessment.

Table 5.3. Estimated Surface Water and Groundwater Concentrations for 2,4-D[A]

Drinking Water Source	Peak Exposure (µg a.e. /L)	Annual Mean Exposure (a.e. µg/L)	30 year Mean Exposure (a.e. µg/L)
Surface water (SWCC Model)	298[B]	34.5[B]	23.4[C]
Groundwater	14.89[D]		

[A] Acid equivalent
[B] 1-in-10-year Concentrations are based on LA sugarcane scenario for ground application
[C] 30-year mean Concentration is based on LA sugarcane scenario for aerial application
[D] Maximum 2,4-D concentration detected in groundwater (USEPA 2004, D286666)

5.4 Dietary Risk Assessment

Acute and chronic aggregate (food + dietary drinking water) exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 3.16. This software uses 2003-2008 food consumption data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA).

5.4.1 Description of Residue Data Used in Dietary Assessment

The acute and chronic analyses assumed tolerance level residues (2,4-D only) for all commodities (excluding transgenic soybean and cotton commodities; see below). For transgenic

soybean, the combined 2,4-D and 2,4-DCP residues were used for the acute and chronic dietary analyses since the combined residues found in tolerant soybean were greater than the tolerance of parent only for soybean.

For transgenic cotton, a combined 2,4-D and 2,4-DCP residue value of 0.15 ppm was used in the acute and chronic dietary assessment for cotton seed oil. That value incorporated the empirical processing factors for 2,4-D and 2,4-DCP for cottonseed oil; the 2,4-DCP processing factor is 0.4x and for 2,4-D is assumed to be 1x.

For transgenic field corn, as the combined residues of 2,4-D and 2,4-DCP found in transgenic field corn food items are less than the tolerances of parent only in non-transgenic field corn, using field corn tolerance-level values for 2,4-D in the acute and chronic dietary analyses are protective of residues of 2,4-D and 2,4-DCP in transgenic field corn.

It was assumed that 100% of all crops had been treated. DEEM (ver. 7.81) default processing factors were assumed for all relevant processed commodities.

5.4.2 Percent Crop Treated Used in Dietary Assessment

Percent crop treated (%CT) data were not applied to the acute and chronic assessments; 100% CT was assumed for all commodities, including transgenic crops, in both analyses.

5.4.3 Acute Dietary Risk Assessment

The resulting acute food plus drinking water risk estimates are not of concern to HED (≤100% aPAD) at the 95th percentile of the exposure distribution for the general population and all population subgroups. The resulting acute risk estimate for children 1 to 2 years old, the subgroup with the greatest exposure, was 23% of the aPAD at the 95th percentile of the exposure (see Table 5.4.6). The acute dietary assessment is unrefined; to further refine the 2,4-D dietary exposure and risk estimates, %CT or monitoring data, if available, could be used.

5.4.4 Chronic Dietary Risk Assessment

The resulting chronic food plus drinking water risk estimates are not of concern to HED for the general population and all population subgroups. The most highly exposed population was children 1 to 2 years old utilizing 20% of the cPAD (see Table 5.4.6). The chronic dietary assessment is unrefined; to further refine the 2,4-D dietary exposure and risk estimates, %CT or available monitoring data, if available, could be used.

5.4.5 Cancer Dietary Risk Assessment

A cancer dietary exposure and risk assessment was not conducted because 2,4-D is classified as “not classifiable as to human carcinogenicity”.

5.4.6 Summary Table

Table 5.4.6. Results of (Food and Drinking Water) **Exposure and Risk for 2,4-D**				
Population Subgroup	**Acute Dietary (95th Percentile)**		**Chronic Dietary**	
	Dietary Exposure (mg/kg/day)	**% aPAD**	**Dietary Exposure (mg/kg/day)**	**% cPAD**
General U.S. Population	0.050595	7.6	0.012899	6.1
All Infants (<1 year old)	0.067674	10	0.010864	5.2
Children 1-2 years old*	**0.154238**	**23**	**0.041792**	**20**
Children 3-5 years old	0.119812	18	0.035063	17
Children 6-12 years old	0.068628	10	0.019362	9.2
Youth 13-19 years old	0.050316	7.5	0.012037	5.7
Adults 20-49 years old	0.041872	6.3	0.010090	4.8
Adults 50+ years old	0.035334	5.3	0.009466	4.5
Females 13-49 years old	0.041783	17	0.009727	4.6

*The subpopulation(s) with the highest risk estimates

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are registered residential uses of 2,4-D for use on ornamental turf, including lawns, parks, sports fields, and golf courses, as well as aquatic uses.

6.1 Residential Handler Exposure

There are registered 2,4-D products for use in residential sites (e.g., lawns and turf) that do not require the use of personal protective equipment (PPE), and these labels have been considered in the residential assessment for 2,4-D. As the aquatic use product labels include PPE requirements, and state that coordination and approval of local and state authorities and/or permits may be required prior to application, those applications are assumed to be made only by occupational applicators, as is consistent with HED's Aquatic Use SOP (November 2015).

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

- mixing/loading/applying liquid to lawns/turf with hose-end sprayer,
- mixing/loading/applying ready-to-use liquids or wettable powders (WP) in water soluable packets (WSP) to lawns/turf with hose-end sprayer,
- mixing/loading/applying liquids or WP in WSP to lawns/turf with manually-pressurized handwand,
- mixing/loading/applying liquids or WP in WSP to lawns/turf with backpack, and
- mixing/loading/applying granules to lawns/turf with push-type spreader or belly grinder.

Residential Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the residential handler risk assessments. Each assumption and factor is detailed below.

Application Rate:
The maximum application rates for lawns/turf are provided in Appendix B.

Unit Exposures and Area Treated or Amount Handled:
Unit exposure values and estimates for area treated or amount handled were taken from HED's 2012 Residential SOPs.

Exposure Duration:
Residential handler exposure is expected to be short-term in duration. Intermediate-term exposures are not likely because of the intermittent nature of applications by homeowners.

Residential Handler Non-Cancer Exposure and Risk Estimate Equations
The algorithms used to estimate exposure and dose for residential handlers can be found in the 2012 Residential SOPs.

Combining Exposures/Risk Estimates:
There is no potential hazard *via* the dermal route for 2,4-D. Only inhalation risk estimates were quantitatively assessed.

Summary of Residential Handler Non-Cancer Exposure and Risk Estimates
The residential handler margins of exposure (MOEs) range from 5,500 to 130,000 (LOC = 300). All scenarios are not of concern for 2,4-D (MOEs are greater than the LOC of 300 for inhalation).

Table 6.1.1. Residential Handler Non-cancer Exposure and Risk Estimates for 2,4-D Use on Turf/Lawns.

Exposure Scenario		Inhalation Unit Exposure (mg/lb ai)	Maximum Application Rate[1]	Area Treated or Amount Handled Daily[2]	Inhalation	
					Dose (mg/kg/day)[3]	MOE[4] (LOC = 300)
Mixer/Loader/Applicator						
Liquid	Hose-end sprayer	0.022	1.5 lb ae/acre	0.5 acres	0.00021	8,500
Ready-to-use or WP in WSP		0.034			0.00032	5,500
Liquid or WP in WSP	Manually-pressurized handwand	0.018	0.012 lb ae/gallon	5 gallons	0.000014	130,000
WP in WSP	Backpack					
Liquid		0.14			0.00011	17,000
Granule	Push-type spreader	0.0026	1.5 lb ae/acre	0.5 acres	0.000024	72,000
	Belly Grinder	0.039	0.000028 lb ae/ft^2	1200 ft^2	0.000016	110,000

1 Based on registered labels.
2 Based on HED's 2012 Residential SOPs (http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).

3 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ae/acre or lb ae/gal or lb ae/sq. ft.) × Area Treated or Amount Handled (A/day or gallons/day or sq. ft./day) ÷ BW (80 kg).
4 Inhalation MOE = Inhalation POD (1.76 mg/kg/day) ÷ Inhalation Dose (mg/kg/day). Bolded MOEs are less than the level of concern.

6.2 Post-Application Exposure

There is potential for post-application exposure for individuals as a result of being in an environment that has been previously treated with 2,4-D. The quantitative exposure/risk assessment for residential post-application exposures is based on the following scenarios:

- Incidental ingestion (i.e., hand-to-mouth, object-to-mouth, soil ingestion exposure) from contact with treated turf (children 1 < 2 years old only),
- Episodic granular ingestion on treated turf (children 1 < 2 years old only), and
- Incidental ingestion of water during recreational swimming (both adults and children 3 < 6 years old).

Inhalation exposure from swimming is expected to be negligible, especially when compared to ingestion. Furthermore, 2,4-D will exist primarily in anion form in the environment; therefore, significant volatilization from water surfaces is not anticipated because anions are not expected to volatilize in significant amounts. Post-application inhalation exposure from treated turf is expected to be minimal due to the combination of low vapor pressure for chemicals typically used as active ingredients in outdoor residential pesticide products (vapor pressure of 2,4-D = 1.4 x 10^{-7} mmHg at 25C) and the dilution in outdoor air.

Assessment of post-application exposure to turf treated with liquid formulations is protective of exposure to solid formulations since many of the inputs used for liquid products are more conservative than for granular products.

The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs. These lifestages are not the only lifestages that could be potentially exposed for these post-application scenarios; however, the assessment of these lifestages is health protective for the exposures and risk estimates for any other potentially exposed lifestages.

Residential Post-application Exposure for Turf Use

Residential Post-application Exposure Data and Assumptions for Turf Use
A series of assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. Each assumption and factor is detailed in the 2012 Residential SOPs.

Chemical-specific Turf Transferable Residue (TTR) Data
There are three turf transferable residue studies available for 2,4-D: MRIDs 45033101, 44655703, and 44655702. These studies have been reviewed (D410012, D410013, D410014)

and determined to be acceptable for risk assessment purposes. The studies included analysis for various forms of 2,4-D, including the acid, esters and salts. A summary of each study is provided in the corresponding ORE memo (Memo, K. Lowe, 11/15/2016, D436660). The highest predicted Day 0 TTR value is 0.284 µg/cm^2 (from MRID 44655703, Treatment 3, North Carolina, application rate of 1.786 lb ae/acre). For risk assessment purposes, this residue value is scaled to the maximum registered 1.5 lb ae/acre application rate; therefore, the residue value for risk assessment is 0.24 µg/cm^2 on Day 0. No additional TTR data are required for 2,4-D.

Residential Post-application Non-Cancer Exposure and Risk Equations

The algorithms used to estimate residential post-application exposure and dose can be found in the 2012 Residential SOPs.

Combining Exposure and Risk Estimates

There is no potential hazard *via* the dermal route for 2,4-D. Only incidental oral risk estimates were quantitatively assessed. The incidental oral scenarios (i.e., hand-to-mouth and object-to-mouth) should be considered inter-related and it is likely that they occur interspersed amongst each other across time. Combining these scenarios would be overly-conservative because of the conservative nature of each individual assessment. The episodic granular ingestion scenario is not combined as this exposure would not occur as a result of routine behavior and is considered an episodic event related to poisoning. Therefore, no post-application exposure scenarios were combined for children 1 < 2 years old.

Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates for Turf Use

The residential post-application risk estimates are not of concern for 2,4-D (MOEs range from 640 to 410,000 and are greater than the LOC of 100) for all incidental oral scenarios.

Table 6.2.1. Residential Post-application Non-cancer Exposure and Risk Estimates for 2,4-D.

Lifestage	Post-application Exposure Scenario		Application Rate[a]	TTR[b]	Dose (mg/kg/day)[c]	MOE (LOC = 100)[d]
	Use Site	Route of Exposure				
1 to <2 years	Turf	Hand-to-Mouth	1.5 lb ae/acre	0.24 ug/cm^2	0.033	640
		Object-to-Mouth			0.001	21,000
		Soil Ingestion		NA	5.1x10-5	410,000
		Episodic Granular Ingestion	1.37% ai		0.06	1,100[e]

a. Based on registered labels.
b. TTR based on chemical-specific data submitted (MRIDs 45033101, 44655703, and 44655702). The highest TTR value from study (0.28 µg/cm^2) was adjusted for difference in application rates (1.79 lb ae/A in study and max registered rate for 2,4-D of 1.5 lb ae/A).
c. Dose equations can be found in the Residential SOPs.
d. MOE = POD (mg/kg/day) / Dose (mg/kg/day), where the incidental oral POD = 21 mg/kg/day and the acute dietary POD (used for the episodic ingestion scenario) = 67 mg/kg/day.
e. Ingestion of granules is considered episodic in nature; MOE was calculated using the acute dietary endpoint and POD.

Residential Post-application Exposure for Aquatic Use

2,4-D can be used for aquatic weed control of surface and submerged weeds. Although many treatments are applied to aquatic areas where recreational swimming is not likely to occur, some subsurface treatments are made at recreational lakes. As a result, individuals can be exposed to 2,4-D residues in water by entering these areas if they have been previously treated. A 24-hour

swimming restriction was also added to the master label according to the RED. Of the possible post-application exposures, swimming in treated water is considered by HED to be worse case and is used as a surrogate for all other possible post-application exposures from aquatic uses. The extent of exposure during recreational swimming is assumed to be short-term in duration. Risk estimates were calculated for post-application incidental oral ingestion while swimming in treated lakes or ponds. Inhalation exposure from swimming is expected to be negligible, especially in comparison to ingestion. Furthermore, 2,4-D will exist primarily in anion form in the environment; therefore, significant volatilization from water surfaces is not anticipated because anions are not expected to volatilize in significant amounts.

Adults and children 3 < 6 years old are considered the index lifestages for the aquatic exposure scenario as it is assumed that younger children (i.e., < 3 years old) won't spend as much time swimming in lakes/ponds. Older children (6 to <11 years old and 11 to <16 years old) may spend slightly more time swimming on average, but the differences in other inputs (e.g., body weight, body surface area, inhalation rates) offset the higher exposure time input. The exposures estimated for children 3 to <6 years old are anticipated to be protective of older children engaging in similar activities.

Residential Post-application Exposure Data and Assumptions for Aquatic Use

A series of assumptions and exposure factors served as the basis for completing the residential post-application risk assessment for the swimmers scenario. These assumptions are outlined in HED's Aquatic SOP (November 2015).

Residential Post-application Non-Cancer Exposure and Risk Equations

The algorithms used to estimate residential post-application exposure and dose can be found in the November 2015 Aquatic SOP.

Summary of Residential Post-application Exposure and Risk Estimates for Aquatic Use

Table 6.2.2 presents the post-application incidental oral MOE values calculated for adults and children 3 to <6 years old after aquatic applications of 2,4-D. Post-application risk estimates range from 8,000 to 84,000 and do not exceed HED's level of concern for any of the scenarios assessed.

Table 6.2.2. Residential Post-application Non-cancer Exposure and Risk Estimates for 2,4-D (Swimmer Scenario)

Lifestage	Cw = Chemical concentration in water (mg/L)[a]	Ingestion rate (L/hr)	Exposure time (hr/day)	Absorbed Dose (mg/kg/day)[b]	Ingestion MOE[c] (LOC = 100)
Adult	4	0.05	0.1	0.00025	84,000
3 to <6 years old		0.05	0.25	0.00263	8,000

a. Maximum concentration in water = 4 mg/L (4 ppm) based on maximum application rate for aquatic weed control: 10.8 lb ae/acre-foot. It is possible that the concentration may exceed this value immediately after application before mixing. However it is conservative to assume exposure to this concentration for a short-term duration (1 to 30 days) as well as considering the 24-hour swimming restriction on the master label.

b. Dose (mg/kg/day) = Cw (mg/L) * Ingestion rate (L/hr) * Exposure time (hr/day) / Body weight (80 kg for adults and 19 kg for children 3 to <6 years).

c. MOE = POD (21 mg/kg day) / Dose (mg/kg/day).

6.3 Residential Risk Estimates for Use in Aggregate Assessment

Table 6.3.1 reflects the residential risk estimates that are recommended for use in the aggregate assessment for 2,4-D. It should be noted that inhalation exposures are not included in the aggregate assessment since effects from the inhalation route are not systemic, and post-application episodic granular ingestion exposures following applications to lawns and turf are not included in the aggregate assessment as this exposure would not occur as a result of routine behavior and is considered an episodic event related to poisoning.

- The recommended residential exposure for use in the adult and Children 3 to <6 years aggregate assessments reflects incidental oral exposure from post-application exposure swimmer scenario.
- The recommended residential exposure for use in the children 1 to <2 years old aggregate assessment reflects hand-to-mouth exposures from post-application turf scenario (i.e., post-application exposure to turf applications).

Table 6.3.1. Recommendations for the Residential Exposures for the 2,4-D Aggregate Assessment.

Lifestage	Exposure Scenario	Dose (mg/kg/day)[1]				MOE[2]			
		Dermal	Inhalation	Oral	Total	Dermal	Inhalation	Oral	Total
Adult	Post-application incidental oral ingestion of water (swimmer)	N/A	N/A	0.00025	0.00025	N/A	N/A	84,000	84,000
Child 3 to <6 years				0.00263	0.00263			8,000	8,000
Child 1 to <2 years	Post-application hand-to-mouth exposure from treated turf			0.033	0.033			640	640

1 Dose = the highest dose for each applicable lifestage of all residential scenarios assessed. Total = dermal + inhalation + incidental oral (where applicable).

2 MOE = the MOEs associated with the highest residential doses. Total = 1 ÷ [(1/Dermal MOE) + (1/Inhalation MOE) + (1/Incidental Oral MOE)], where applicable.

7.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

7.1 Application Site Flux Assessment

The potential exposure to bystanders from vapor phase 2,4-D residues emitted from treated fields has been evaluated for the registered uses of 2,4-D. Such exposure depends on two main factors: 1) the rate at which these chemicals come off a treated field (described as the off-gassing, emission or flux) and 2) how those vapors are dispersed in the air over and around the treated field. Volatilization can occur during the application process or thereafter. It can result from aerosols evaporating during application, while deposited sprays are still drying (e.g., possibly via co-distillation), or after as dried deposited residues volatilize.

This assessment employs approaches EPA has used previously to assess inhalation exposures to fumigant pesticides[6] and is also consistent with the recommendations of the December 2009 Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP)[7] meeting on the scientific issues associated with field volatilization of conversional (semi-volatile) pesticides.

Flux Data

Flux data for 2,4-D were submitted and reviewed by the Agency[8]. The study measured the flux rates of 2,4-D ethylhexyl ester (EHE), 2,4-D dimethylamine salt (DMA salt) and the 2,4-D choline salt. These flux data are protective of all the forms of 2,4-D, covering both the ester and salt forms. Trials were conducted based on the following three scenarios:

1) Treatments of the three forms were applied to tilled bare soil plots in Fowler, IN and to mature soybeans approximately 30 cm high with 80% canopy in Farmland, IN;
2) Treatments of the three forms plus a formulation with 2,4-D choline plus glyphosate were applied to growing soybeans approximately 12-15 cm high with 15% canopy cover in Little Rock, AR; and
3) Treatments of the three forms plus a formulation with 2,4-D choline plus glyphosate were applied to cotton plants approximately 50 cm high with 40% canopy in Ty Ty, GA.

Air samplers were placed in a wheel and spoke design at 5 and 15 meters from each treated field edge. Samplers were placed at a height of 30 cm in Fowler, at 50 cm in Farmland, at 15 cm in Little Rock, and at 50 cm in Ty Ty. A summary of application timing, area treated, and application rates is provided in Table 7.1.

Table 7.1. Summary of application methods and rates for 2,4-D.

Site	Field	Treatment	Time of Application (Date (mm/dd/yy) and Start Time)	Area Treated (acres)	Reported Application Rate (kg ae/ha)	Calculated Application Rate (lb ae/acre)
1 (Fowler, Indiana)	1	2,4-D choline (GF-2654)	9/10/2010 8:35 AM	4.27 (1.73 ha)	5.64	5.04
	2	2,4-D DMA	9/10/2010 10:07 AM	4.25 (1.72 ha)	2.94	2.63
	3	2,4-D EHE	9/10/2010 8:54 AM	0.62 (0.25 ha)	1.12	1
2 (Farmland, Indiana)	1	2,4-D choline (GF-2654)	8/7/2010 9:30 AM	5.8 (2.35 ha)	4.48	4
	2	2,4-D DMA	8/7/2010 10:00 AM	5.8 (2.35 ha)	2.24	2
	3	2,4-D EHE	8/7/2010 10:35 AM	0.62 (0.25 ha)	1.12	1

[6] U.S. EPA 2004d. FIFRA Science Advisory Panel Meeting Minutes - Fumigant Bystander Exposure Model Review: Probabilistic Exposure and Risk Model for Fumigants (PERFUM) Using Iodomethane as a Case Study. Available at http://www.epa.gov/scipoly/sap/meetings/2004/august1/august2425minutes.pdf

[7] U.S. EPA 2009. FIFRA Science Advisory Panel Meeting Minutes - Scientific Issues Associated with Field Volatilization of Conventional Pesticides. Available at http://www.epa.gov/scipoly/sap/meetings/2009/december/120309meetingminutes.pdf

[8] MRID 48862902. Field Volatility of Different 2,4-D Forms. June 15, 2012. Dow AgroSciences LLC.

Table 7.1. Summary of application methods and rates for 2,4-D.						
Site	Field	Treatment	Time of Application (Date (mm/dd/yy) and Start Time)	Area Treated (acres)	Reported Application Rate (kg ae/ha)	Calculated Application Rate (lb ae/acre)
3 (Little Rock, Arkansas)	1	2,4-D choline (GF-2654)	7/12/2011 6:38 AM	5.43 (2.2 ha)	4.48	4
	2	2,4-D choline + glyphosate DMA (GF-2726)	7/12/2011 7:50 AM	5.51 (2.23 ha)	9.19	8.21
	3	2,4-D DMA	7/12/2011 8:50 AM	5.43 (2.20 ha)	0.46	0.41
	4	2,4-D EHE	7/12/2011 9:40 AM	0.59 (0.24 ha)	0.46	0.41
4 (Ty Ty, Georgia)	1	2,4-D choline + glyphosate DMA (GF-2726)	8/16/2011 7:30 AM	5.48 (2.22 ha)	8.85	7.9
	2	2,4-D choline (GF-2654)	8/16/2011 8:52 AM	5.48 (2.22 ha)	4.48	4
	3	2,4-D DMA	8/16/2011 7:33 AM	5.48 (2.22 ha)	0.46	0.41
	4	2,4-D EHE	8/16/2011 8:58 AM	0.64 (0.26 ha)	0.46	0.41

Flux was calculated using the indirect method based on the study design. Flux rates are adjusted to the maximum registered application rates for each form from the application rates in the flux study. This type of adjustment is done routinely for this type of data and analyses.

Volatilization Modeling and Risk Assessment

Volatilization modeling for a single day was completed using Probabilistic Exposure and Risk model for FUMigants (PERFUM). There are a variety of factors that potentially affect the emission rates of 2,4-D and subsequent offsite transport including: field condition (bare soil, growing or mature crop canopy), field parameters (soil type, moisture, etc.), formulation type, meteorological conditions, and application scenario (rate, method). To the extent possible, based on the limited information available and a lack of intentional statistical design to quantitatively evaluate such factors, the impact of these variables was considered. Flux estimates from all monitored trials, a number of field sizes, and various meteorological data were used with PERFUM to estimate risk based on the 2,4-D field volatility study. The PERFUM modelling results are based on Bradenton, FL; Yakima, WA; Flint, MI; and Ventura, CA weather datasets which have been used in the past for other volatilization analyses and represent a range of conditions including those which have consistently provided the highest risk estimates. The results of this analysis have been summarized for a 40, 80, and 120 acre field using the flux data submitted and each source of weather data. The short-term residential inhalation endpoint was used in the volatilization assessment; it is a conservative assumption to compare the Day 1 volatilization exposure to a short-term HEC. Furthermore, a 6-hour exposure averaging period was used in the model; it is a conservative assumption to compare the 6 hour average exposure from the model to the HEC calculated for 24 hours of exposure especially since the 6 hour exposure period used as the basis for the comparison represents the peak emissions period after application.

All of the files associated with the use of PERFUM in this assessment can be provided upon request. These files could be used to examine the detailed input and output files for each permutation of the model completed for this analysis.

Volatilization Risk Estimates

The field volatility study suggests that volatilization of 2,4-D from treated crops does occur and could result in bystander exposure to vapor phase 2,4-D; however, results of PERFUM modeling indicate that airborne concentrations are negligible, and even at the edge of the treated fields, risk estimates are not of concern. The maximum registered application rates for 2,4-D DMA, 2-EHE, and choline were assessed. There were no whole field or maximum field buffers necessary based on PERFUM analysis for any field size (i.e., risks were acceptable at all percentiles of exposure at the edge of a treated field). All modeling results regardless of geographical location, acreage, buffer type, or percentile resulted in recommended buffers of 0 feet.

7.2 Ambient Air Monitoring Assessment

There is an available ambient air monitoring study conducted in Minnesota by the Pesticide Action Network North America (PANNA). The Agency has developed a preliminary bystander volatilization inhalation exposure assessment for 2,4-D using the currently available inhalation toxicity and the PANNA air monitoring data.

Ambient air monitoring typically is focused on characterizing the airborne pesticide levels within a localized airshed or community structure of some definition (e.g., city, township, or municipality). This type of monitoring effort also can be focused on capturing chronic background levels or other temporal characteristics of interest such as focusing on seasonal pesticide use patterns. Typically, samples are taken for 24 consecutive hours and collected at the same site over an extended period of time (e.g., several weeks or months). In contrast to application site air monitoring, information on the precise timing and location of pesticide applications are rarely collected in ambient air monitoring studies. However, this does not mean that an application did not occur near an ambient sampler during the monitoring period.

The PANNA study[9] monitored for airborne pesticides between June 2006 and August 2009 in central Minnesota. Drift Catcher sampling devices were stationed in 19 locations, usually on porches, in windows, or in yard areas. A total of 340 field samples were taken, and residues of one or more pesticides were detected in 224 of the samples. 2,4-D was found in samples from three sites in 2008: Frazee Sites D and E and Perham Site A. Of the 29 field samples from these sites, 2,4-D was detected in 21 (72%). Time-weighted average concentrations at the sites ranged from 7 to 17 ng/m^3, and the maximum concentration observed was 115 ng/m^3 (Sample "Mud",

[9] http://www.panna.org/sites/default/files/TechReport_MN-Drift_May2012-2.pdf

collected at Site Frazee D on July 19–20, 2008). The detection limit for 2,4-D was 8 ng/sample (equivalent to an air concentration of 3 ng/m^3 for a 24-hour sample at a 2.0 L/min flow rate).

Table 7.2 provides 2,4-D volatilization risk estimates for each site. The comparison of the mean air concentration values against the short-/intermediate-term HEC is a reasonable match of the toxicological effect and exposure profile. This arithmetic mean comparison was completed to represent the potential for a seasonal exposure profile. Even with the conservative use of the short-/intermediate-term endpoint to evaluate peak exposures from the ambient monitoring, none of the samples resulted in risk estimates of concern.

Table 7.2. Residential Bystander: Preliminary Volatilization Risk Analysis for 2,4-D from Ambient Air Monitoring Data.									
Study	**Year of Study**	**Sampler/Site Location**	**Number of samples[a]**	**Duration of samples**	**Duration of sampling period**	**Maximum Air Concentration (mg/m^3)**	**Arithmetic Mean Air Concentration (mg/m^3)**	**Single-Day MOEs[b] (LOC = 300)**	**Short-/intermediate-term MOEs[c] (LOC = 300)**
Ambient Air Monitoring									
Pesticide Drift Monitoring in Minnesota (PANNA)	June 26–July 29, 2008	Frazee Site D	13 (10 less than the LOQ)	24-hour	1 month	1.15E-04	1.62E-05	120,000	820,000
	June 27–July 28, 2008	Frazee Site E	11 (8 less than the MDL)			5.60E-05	1.05E-05	240,000	1,300,000
	June 27–July 28, 2008	Perham Site A	5 (5 less than the LOQ)			7.00E-06	7.00E-06	1,900,000	1,900,000

a. For non-detects, assumed ½ Method Detection Limit (MDL) of 8 ng/sample – 3 ng/m^3 (1.5 ng/m^3). For samples less than the LOQ (15 ng/m^3), assumed ½ the LOQ (7 ng/m^3).
b. Single Day MOE = Steady-state HEC (13.3 mg/m^3) / Study maximum air concentration (ng/m^3). LOC = 300.
c. Steady-state MOE = Steady-state HEC (13.3 mg/m^3) / Study arithmetic mean air concentration (mg/m^3). LOC = 300.

Ambient Air Monitoring/Post-application Inhalation Risk Characterization

The 2,4-D bystander volatilization inhalation exposure assessment compares the maximum and average air concentrations detected in the available monitoring studies to the short-/intermediate-term HEC for residential bystanders, as no acute HEC is available for 2,4-D. The comparison of the peak ambient concentrations against the short-/intermediate-term endpoint is a conservative representation of a potential resident of an agricultural area where 2,4-D is being applied in multiple field locations.

Some of the limitations and considerations that have been identified that should be considered in the interpretation of these results include:

- Most of the data used in this preliminary assessment are 24-hour air samples. When these data are used, an assumption is made that an individual is exposed to the same air concentration for 24-hours every day. However, this is not always the case as real world time-activity data indicate that many parts of the population move from site to site on a daily basis (e.g., go to work and back).

- This assessment is only representative of outdoor concentrations at locations similar to the monitoring sites (i.e., the exposure and risk estimates assume an individual is outdoors all the time). It does not take into account potential effects of air conditioning systems and similar air filtration systems which could potentially reduce air concentrations of 2,4-D indoors. The assessment assumes that indoor concentrations will be no greater than outdoor concentrations and may potentially be lower.

- The residential bystander estimated exposure should not be included in the human health risk assessment aggregate due to the fact that this is only a preliminary assessment and is not considered a refined assessment for the reasons noted above. There are limitations associated with the available air monitoring data, such as the fact that most are air sampling and measurement techniques do not distinguish between aerosols and vapors. In addition, as noted in the above bullet, this assessment assumes residents are outdoors during the entire exposure duration.

8.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (*e.g.*, children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to

prevent them.[10] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

Several 2,4-D products have existing labels for use on turf, thus it was considered whether the risk assessment for that use may be considered protective of any type of exposure that would be associated with spray drift. The currently registered maximum single application rate of 2,4-D for low bush blueberries is 5 lb ae/A. The highest degree of spray drift noted for any application method immediately adjacent to a treated field (Tier 1 output from the aerial application using fine to medium spray quality) results in a deposition fraction of 0.26 of the application rate. A quantitative spray drift assessment for 2,4-D is not required because the maximum application rate to a crop/target site multiplied by the adjustment factor for drift of 0.26 is less than the maximum direct spray residential turf application rate (1.5 lb ai/A)[11] for any 2,4-D products. The turf post-application MOEs have been previously assessed, are based on the revised SOPs for Residential Exposure Assessment (i.e., see above in Section 6.2), and are not of concern.

9.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

9.1 Acute Aggregate Risk

The acute aggregate risk assessment includes only food and water exposure. The acute food plus drinking water risk estimates are not of concern to HED (≤100% aPAD) at the 95th percentile of the exposure distribution for the general population and all population subgroups. Refer to section 5.4.3 for a detailed discussion of the acute dietary assessment.

9.2 Short-Term Aggregate Risk

The short-term aggregate risk assessment includes food, water, and residential exposure. The resulting short-term aggregate risks are not of concern to HED (MOEs > LOC of 100) for adults and children.

[10] This approach is consistent with the requirements of the EPA's Worker Protection Standard which, when included on all labels, precludes direct exposure pathways.
[11] 5 lb ai/A x 0.26 ≤ 1.5 lb ai/A

Table 9.2. Short-Term Aggregate Risk Calculations.							
Population	NOAEL (mg/kg/day)	LOC[1]	Max Allowable Exposure (mg/kg/day)[2]	Average Food and Water Exposure (mg/kg/day)[3]	Residential Exposure (mg/kg/day)[4]	Total Exposure (mg/kg/day)[5]	Aggregate MOE (food, water, and residential)[6]
Adult	21	100	0.21	0.010090	0.00025	0.010340	2000
Child (3 -5 years old)	21	100	0.21	0.035063	0.00263	0.037693	560
Child (1 - 2 years old)	21	100	0.21	0.0414792	0.033	0.074479	280

[1] LOC = inter- and intra- species uncertainty factors totaling 100.
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC.
[3] Average Food and Water Exposure (mg/kg/day) = chronic dietary exposure from Table 5.4.6; adults = 20-49 year old.
[4] Residential Exposure = Highest exposure; see Table 6.3.1.
[5] Total Exposure = Avg Food & Water Exposure + Residential Exposure.
[6] Aggregate MOE = NOAEL (mg/kg/day) ÷ Total Exposure (mg/kg/day).

9.3 Intermediate-Term Aggregate Risk

Intermediate-term residential exposures are not likely because of the intermittent application of 2,4-D by homeowners.

9.4 Chronic Aggregate Risk

The chronic aggregate risk assessment includes only food and water exposure. The chronic food plus drinking water risk estimates are not of concern to HED for the general population and all population subgroups. Refer to section 5.4.4 for a detailed discussion of the chronic dietary assessment.

9.5 Cancer Aggregate Risk

2,4-D has been classified as a Category D chemical, i.e., not classifiable as to human carcinogenicity. A quantitative cancer risk assessment is not required.

10.0 Cumulative Exposure/Risk Characterization

2,4-D is a member of the alkylphenoxy herbicide class of pesticides. This class also includes MCPA, 2,4-DB, and 2,4-DP. 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 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 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/.

11.0 Occupational Exposure/Risk Characterization

11.1 Short-/Intermediate-Term Handler Risk

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the registered uses. The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

- Mixing/loading liquids, granulars or WP in WSP for aerial applications,
- Mixing/loading liquids or WP in WSP for groundboom applications,
- Mixing/loading liquids for airblast applications,
- Mixing/loading liquids, granulars or WP in WSP for aquatic application via boat boom / solid spreader,
- Mixing/loading liquids for tree injection,
- Mixing/loading liquids or WP in WSP for backpack applications,
- Mixing/loading liquids or WP in WSP for mechanically-pressurized handgun applications,
- Mixing/loading granulars for tractor-drawn spreader applications,
- Applying sprays or granulars via aerial equipment,
- Applying sprays via groundboom equipment,
- Applying sprays via airblast equipment,
- Applying sprays or granulars via boat boom or solid spreader equipment,
- Applying sprays via mechanically-pressurized handgun,
- Applying granulars via tractor drawn spreader,
- Applying ready-to-use (RTU) liquids via trigger-spray bottle,
- Applying RTU pressurized liquid via aerosol can,
- Applying liquids via tree injection,
- Flagging for aerial applications,
- Mixing/loading/applying liquids via trigger-spray bottle, backpack, manually-pressurized handwand, mechanically-pressurized handgun,
- Mixing/loading/applying WSP via backpack, manually-pressurized handwand, mechanically-pressurized handgun,
- Loading/applying granulars via backpack, rotary spreader, belly grinder,
- Mixing/loading for automated post-harvest treatments, and
- Mixing/loading/applying for direct spray post-harvest treatments.

Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below on an individual basis.

Application Rate:
The registered maximum single application rates were used in this assessment and are provided in Appendix B.

Unit Exposures: It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the AHETF database, the Outdoor Residential Exposure Task Force (ORETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[12]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[13].

Area Treated or Amount Handled:
Most of the assumptions for area treated or amount handled were pulled from the Exposure Science Advisory Council Policy #9 or the Post-Harvest Treatment Policy (23-MAR-2012), and are listed in the risk summary table in Appendix H for the various scenarios.

For the number of trees treated per day for injection scenarios, information from the 2008 acephate occupational/residential exposure assessment was used (Memo, M. Lloyd, 14-May-2008, D348935). In that assessment, HED received information from RD that for professional applicators, the number of trees treated per day ranged from 10 to 20 trees depending on the type of product (micro-infusion vs macro-infusion). The specific type of product for 2,4-D is unclear, therefore, HED used the assumption of 20 trees/day as a conservative assumption.

A formal assumption for the number of trigger-spray bottles used per day was also not available for assessing spot applications to trees in rights-of-ways and forestry use sites (e.g., hack and squirt scenarios); therefore, HED assumed 10 32-oz trigger-spray bottles could be used per day.

Exposure Duration:
HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. Exposure duration is determined by multiple factors, including the exposed population, the use site, the pest pressure triggering the use of the pesticide, and the cultural practices surrounding that use site. For most agricultural uses, it is reasonable to believe that occupational handlers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region).

For 2,4-D, based on the registered uses, short- and intermediate-term exposures are anticipated for the following reasons: (1) the product can be applied multiple times per year (2) the product can be applied to multiple application sites and (3) there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks.

[12] Available: http://www2.epa.gov/sites/production/files/2015-09/documents/handler-exposure-table-2015.pdf
[13] Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

Mitigation/Personal Protective Equipment: Product labels vary with respect to work attire and levels of personal protective equipment, from some labels not providing any specifications to others requiring use of chemical-resistant gloves, protective eyewear, coveralls, and chemical-resistant headgear. As previously described, dermal toxicity was not identified so dermal risks are not quantified in this section. Dermal exposure-related work attire and PPE should therefore be considered in the context of end-use-product acute toxicity requirements. Inhalation exposure is assessed assuming no respiratory protection and then, when risks of concern might indicate a need for them, assessed assuming different types of respirators. Respiratory protection requirements, beyond end-use-product acute toxicity requirements, should be considered for certain scenarios as described in this section.

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations
The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in the corresponding ORE memo (Memo, K. Lowe, 11/15/2016, D436660).

Combining Exposures/Risk Estimates:
There is no potential hazard *via* the dermal route for 2,4-D; therefore, only occupational handler inhalation exposures are quantitatively assessed.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates
Occupational handler inhalation risk estimates of concern were identified for some scenarios at the current label recommended PPE (i.e., no respirator). A summary of the occupational handler scenarios and associated risk estimates is provided in Appendix H.

Risk estimates of concern for the following scenarios were identified with no respirator, but are mitigated with the use of a PF5 respirator (current labels do not require a respirator):

- Mixing/loading granulars for aerial application to the following use sites:
  - Non-cropland @4 lb ae/A
  - Aquatic sites @ 10.8 lb ae/A-ft
  - Field corn/popcorn @ 1.5 lb ae/A
  - Field corn/popcorn, sweet corn, grain or forage sorghum @ 1 lb ae/A
- Mixing/loading granulars for solid spreader application to aquatic sites @ 10.8 lb ae/A-ft
- Applying sprays using mechanically-pressurized handgun to ROW sites @ 0.4 lb ae/gallon
- Mixing/loading/applying WSP using backpack to turf @ 1 lb ae/gallon

Risk estimates of concern for the following scenarios were identified with no respirator, but are mitigated with the use of a PF10 respirator (current labels do not require a respirator):

- Mixing/loading/applying liquids or WSP using mechanically-pressurized handgun to orchard floors @ 1.5 lb ae/gallon

Risk estimates of concern for the following scenarios were identified with engineering controls (i.e., enclosed cockpit):

- Aerial application of granulars to the following use sites:
  - Cranberries and non-cropland areas @ 4 lb ai/A
  - Aquatic areas @ 10.8 lb ae/acre-ft

- Field corn/popcorn @ 1.5 lb ae/A
- Field corn/popcorn, sweet corn, grain or forage sorghum @ 1 lb ae/A

11.2 Short-/Intermediate Term Post-Application Risk

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

11.2.1 Dermal Post-application Risk

Occupational Post-application Dermal Exposure

There is no potential hazard *via* the dermal route for 2,4-D; therefore, a quantitative occupational post-application dermal risk assessment was not completed.

In accordance with the updated Part 158 data requirements (2007), one or more DFR studies are required when a pesticide has residential or occupational uses that could result in post-application dermal exposure. A DFR study is not required for 2,4-D at this time since there is no potential hazard via the dermal route for 2,4-D.

Restricted Entry Interval

The REIs specified on the registered labels are based on the acute toxicity of the forms of 2,4-D present as the active ingredient. The acute toxicity data indicate that the various forms of 2,4-D are not very toxic (Toxicity Category III) via the oral, dermal or inhalation routes of exposure. The available data show the various forms of 2,4-D to be slightly irritating to the skin and not skin sensitizers. Although the ester forms are not eye irritants, the acid and salt forms are considered to be severe eye irritants. Acute toxicity of 2,4-D amine salts and esters are virtually identical to that of 2,4-D acid (see Appendix C). REIs should be reconciled with the acute toxicity-based requirements under 40 CFR 156.208 (c) (2).

11.2.2 Inhalation Post-application Risk

Foliar/Field Applications

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The agency has

evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for 2,4-D.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the agency's risk assessments.

Post-Harvest Applications

During automated treatments, dermal and inhalation exposure is anticipated for workers performing sorting, culling, and packing tasks. Since the workers experience exposure following the treatment, this is technically "post-application" exposure; however, unlike other post-application activities (e.g., harvesting, scouting, etc.), this treatment is not governed by the Worker Protection Standard (WPS) and potential re-entry intervals (REIs). Additionally, for workers in the warehouse or packaging facility not directly involved in the automated treatment process, there is potential for indirect inhalation exposure.

Occupational inhalation risk estimates for sorters/packers in a post-harvest treatment facility are not of concern (i.e., MOEs ≥ LOC of 300) with no respirator. In addition, risk estimates for workers exposed in a post-harvest treatment warehouse are not of concern (i.e., MOEs ≥ LOC of 300). A summary of risk estimates is provided in Table 11.2.1.1.

Table 11.2.1.1. Occupational Post-application Non-Cancer Exposure and Risk Estimates for 2,4-D.

Crop	Activities	Max Application Rate	Inhalation Unit Exposures (µg/% ai) Baseline	Inhalation Dose (mg/kg/day)[2] Baseline	Short-term/Intermediate-term MOE[3]
Citrus	Sorters	0.05% ai (in solution)	6,720	0.0042	1,300
	Packers		6,760		
	Ambient Air Exposure		307	0.0002	27,000

1 Application Rate: 500 ppm = 0.05% ai solution.
2 Daily Inhalation Dose = [UE (unit exposure ug/ % ai) × AR (% ai in solution) ÷ [CF (1000 ug/mg) x BW (80 kg)]
3 MOE = POD (5.29 mg/kg/day) / Daily Inhalation Dose (mg/kg/day).

12.0 Public Health and Pesticide Epidemiology Data

A review of medical case studies found that most of the accidental poisonings were exposed to low doses of 2,4-D and were not fatal. Although patients suffered from neurological, respiratory, liver, and kidney dysfunctions; they usually responded to prompt and effective treatment. In rare occupational exposure cases although 2,4-D is considered to be of low toxicity, muscle weakness, difficulty in breathing and peripheral neuropathy have been reported. Most of the high dose exposure cases (intentionally or unintentionally) had, significant depression of the central nervous system (coma), liver dysfunction, myotonia, respiratory muscles damage leading to acute respiratory failure, cardiac muscles damage leading to irregular heart rhythms, myoglobin

released from damaged muscle cells leading to kidney failure, and even fatal outcome in several cases.

A review of incident in IDS, NPIC, SENSOR-Pesticides and California PISP by HED found that the acute health effects reported for 2,4-D are consistent among the databases queried. These health effects primarily include neurological, respiratory, dermal and gastrointestinal effects. HED did not identify any aberrant effects outside of those anticipated. These effects are generally mild/minor to moderate and resolve rapidly.

The available incident data from NPIC, SENSOR-Pesticides and California PISP suggest that most of the reported 2,4-D incidents involve off-target drift exposure. In IDS the most commonly reported exposure scenario is residential application followed by residential post-application exposure.

Occupational incidents account for nearly half of all reported incidents involving 2,4-D in SENSOR-Pesticides and California PISP (46% and 49% respectively). However, in both of these databases there is a slight majority of residential 2,4-D case reports (54% and 51% respectively). Both SENSOR-Pesticides and PISP reported that most occupational incidents occurred while conducting routine work, including fieldwork. Overall (for occupational and non-occupational cases combined), both SENSOR-Pesticides and PISP report off-target drift as the most common cause of cases involving 2,4-D.

The IDS incident trend for 2,4-D, from 2005 to 2014, was reviewed. These incidents are primarily non-occupational cases. The 2,4-D incidents have fluctuated over the time period evaluated, but appear to be trending down over the last three years.

A systematic review focused on non-carcinogenic effects relative to 2,4-D exposure was conducted, and published studies investigating the association of 2,4-D with non-carcinogenic health outcomes were reviewed (Memo, A. Aldridge, D442486). Overall, the epidemiology review found that there was little substantive evidence to suggest a clear causal relationship between exposure to 2,4-D and non-carcinogenic health outcomes investigated in the studies.

HED has also completed a systematic literature review focused on carcinogenic effects to ensure the Agency's assessment of carcinogenicity for 2,4-D captured all pertinent scientific data to date (Memo, A. Aldridge, D441161). The epidemiology review found that, overall, there was little substantive evidence to suggest a clear associative or causal relationship between exposure to 2,4-D and cancer including NHL in several cohort and case-control studies including the AHS. The Agency will continue to monitor the epidemiology for 2,4-D, and if a concern is triggered, additional analysis will be conducted.

13.0 References

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Toghrol, F. 03/03/89, CB No. 4684. PP#9E3704: 2,4-D (Geographical Restriction, MN only) in Raspberries. EPS Reg. No. 50534-13. Evaluation of Residue Data and Analytical Methodology. (MRID No.408814-00, and 01 DEB# 4684).

Appendix A. 2,4-D Active Ingredients in Case No. 0073

Active ingredient name		PC code
2,4-D acid	Acid	030001
2,4-D sodium salt	Na	030004
2,4-D diethanolamine salt	DEA	030016
2,4-D, dimethylamine salt	DMA	030019
2,4-D, isopropylamine salt	IPA	030025
2,4-D, triisopropanolamine salt	TIPA	030035
2,4-D, butoxyethyl ester or 2,4-D, butoxyethanol ester	BEE	030053
2,4-D, 2-ethylhexyl ester	2-EHE	030063
2,4-D, isopropyl ester	IPE	030066
2,4-D choline salt	Choline	051505

Appendix B. Summary of Use Directions for 2,4-D

Summary of Directions for Use of 2,4-D										
Use Site	Chemical	Application Timing	Application Type	Application Equipment	Formulation	Maximum Application Rate	Max Number Applications per Season	Max. Seasonal Application Rate	PHI (days)	REI (hours)
Agricultural Crops										
Asparagus	Acid, DMA, TIPA, IPA, DEA	After cutting; Apply on actively growing weeds.	Broadcast	Aerial, Groundboom	WP/WSP or Liquid	2 lb ae/A	2	4 lb ae/A	3	12 - 48 (depending on label)
Blueberries - Low Bush	Acid, DMA, TIPA, IPA, DEA	Postharvest; Make directed application to cut hardwoods in row middles in summer or fall after harvest.	Directed, Ground Wipe or Spot Application	Wick or directed boom sprayer (groundboom), Handheld (mechnically-pressurized handgun)	WP/WSP or Liquid	1.0 lb ae/10 gallons of oil (assume 50 gal/A = 5 lb ae/A)	1	1.0 lb ae/10 gallons of oil	NA	12 - 48 (depending on label)
		Postemergence; Make directed wipe or spot applications when weed tops are above the crop.				Wiper solution containing 0.0375 lbs ae/gal (assume 100 gal/A = 3.75 lb ae/A)	1	Wiper solution containing 0.0375 lbs ae/gal		
Blueberries - High Bush	Acid, DMA, TIPA, IPA, DEA	Post harvest; Make directed application to row middles in summer or fall after harvest.	Directed, Ground Wipe or Spot Application	Wick or directed boom sprayer (groundboom)	WP/WSP or Liquid	1.4 lb ae	2	2.8 lb ae	30	12 - 48 (depending on label)
		Postemergence; Make directed or shielded application in the spring.								

Summary of Directions for Use of 2,4-D										
Use Site	Chemical	Application Timing	Application Type	Application Equipment	Formulation	Maximum Application Rate	Max Number Applications per Season	Max. Seasonal Application Rate	PHI (days)	REI (hours)
Citrus - Lemons	Acid, IPE	Postharvest packing house to retain buttons	Broadcast	Dip or Spray	Liquid	0.04 lb ae/10 gal (500 ppm)	1	0.04 lb ae/10 gal	NA	None
Citrus (Growth Regulator)	Acid, IPE	Apply in fall oil, water or whitewash sprays to prevent pre-harvest drop of mature fruit and leaves the following spring	Broadcast or directed spray	Aerial, Airblast, Handheld (backpack, manually-pressurized handwand)	Liquid	lemons, oranges, tangelos - 24 ppm; 0.02 lb ae/100 gallons; oranges and grapefruit - 200 ppm (0.17 lb ae/100 gal)	1	lemons, oranges, tangelos - 24 ppm; 0.02 lb ae/100 gallons; oranges and grapefruit - 200 ppm (0.17 lb ae/100 gal)	7	12
		Apply when fruit diameter is less than 0.75 for oranges and 1 inch for grapefruit to increase fruit size				to increase fruit size: 0.1 lb ae/A		0.1 lb ae/A		
Cereal Grains (Wheat, Barley, Millet, Oats, Rye and Teff)	Acid, DMA, 2-EHE, BEE, TIPA, IPA, DEA, Na, Choline	Postemergence; Apply after grain is fully tillered (usually 4 to 8 inches high) but not forming joints in the stem.	Broadcast	Aerial, Groundboom	WP/WSP, Liquid	1.25 lb ae/A	1	1.75 lb ae/A	14	12 - 48 (depending on label)
		Preharvest; Apply when grain is in the dough stage.				0.5 lb ae/A	1			
Field Corn and Popcorn	Acid, DMA, 2-EHE, BEE,	Preharvest; Apply after hard dough (or at denting) stage.	Broadcast; Directed band	Aerial, Groundboom, Tractor-drawn spreader	WP/WSP, Liquid, G	1.5 lb ae	1	1.5 lb ae	7	12-48 (depending on label)

Summary of Directions for Use of 2,4-D										
Use Site	Chemical	Application Timing	Application Type	Application Equipment	Formulation	Maximum Application Rate	Max Number Applications per Season	Max. Seasonal Application Rate	PHI (days)	REI (hours)
	TIPA, IPA, DEA, Choline	Postemergence; Apply when weeds are small and corn is less than 8 inches tall (to top of canopy). When corn is over 8 inches tall, use drop nozzles and keep spray off foliage.	Broadcast; Directed band	Aerial, Groundboom, Tractor-drawn spreader		0.5 lb ae	1	0.5 lb ae		
		Preplant or Preemergence; To control emerged broadleaf weed seedlings or existing cover crops, apply before corn emerges.	Broadcast; Directed band	Aerial, Groundboom, Tractor-drawn spreader		1.0 lb ae	1	1.0 lb ae		
Sweet Corn	Acid, DMA, 2-EHE, BEE, TIPA, IPA, DEA, Choline	Postemergence; Apply when weeds are small and corn is less than 8 inches tall (to top of canopy). When corn is over 8 inches tall, use drop nozzles and keep spray off foliage. Do not make a postemergence application any less than 21 days following prior application.	Aerial and Ground Broadcast; Directed band	Aerial, Groundboom, Tractor-drawn spreader	WP/WSP, G, Liquid	0.5 lb ae	1	0.5 lb ae	45 days	12-48 (depending on label)
		Preplant or Preemergence; To control emerged broadleaf weed seedlings or existing				1.0 lb ae	1	1.0 lb ae		

Summary of Directions for Use of 2,4-D										
Use Site	Chemical	Application Timing	Application Type	Application Equipment	Formulation	Maximum Application Rate	Max Number Applications per Season	Max. Seasonal Application Rate	PHI (days)	REI (hours)
		cover crops, apply before corn emerges.								
Enlist Corn	Choline	Preplant or Preemergence; Apply any time before or after planting, but before corn emerges.	Broadcast	Groundboom	Liquid	1.0 lb ae	1	1.0 lb ae	30	48
		Postemergence; Apply any time up to the V8 growth stage or 30 inches tall, whichever occurs first. For corn heights 30-48 inches, apply using drop nozzles.					2	2.0 lb ae		
Cranberries	Acid, DMA, 2-EHE, BEE, TIPA, IPA, DEA	During dormant season	Broadcast	Aerial, Groundboom, Tractor-drawn spreader	Liquid, G	4.0 lb ae/A	1	4.0 lb ae	30	12 - 48 (depending on label)
		Postemergence; Make directed wipe or spot applications when weed tops are above crop.	Ground wipe or spot	Wick or hand-held nozzle sprayer (backpack, mechanically-pressurized handgun)	WP/WSP, Liquid	1.2 lb ae/A (assuming 10 gal/A = 0.12 lb ai/gal)	2	2.4 lb ae		

Summary of Directions for Use of 2,4-D										
Use Site	Chemical	Application Timing	Application Type	Application Equipment	Formulation	Maximum Application Rate	Max Number Applications per Season	Max. Seasonal Application Rate	PHI (days)	REI (hours)
Fallowland and Crop Stubble	Acid, DMA, 2-EHE, BEE, TIPA, IPA, DEA, Choline	Crop stubble on idle land, or postharvest to crops, or between crops	Broadcast	Aerial, Groundboom, Tractor-drawn spreader	WP/WSP, Liquid, G	2.0 lb ae	2	4.0 lb ae	7	12-48 (depending on label)
Filberts	Acid, DMA	For sucker control; spray to wet leaves and stems of suckers that are 6 to 8 inches in height during April through August	Broadcast	Aerial, Groundboom; Handheld (backpack, manually-pressurized handwand)	Liquid	1 lb ae/A; 1 lb ae/100 gal	4	assumed 1 lb ae/A; 1 lb ae/100 gal	45	48
Grain or Forage Sorghum	Acid, DMA, 2-EHE, BEE, TIPA, IPA, DEA, Na, Choline	Postemergence; Apply when sorghum is 6 to 15 inches tall. If sorghum is taller than 8 inches to top of the canopy, use drop nozzles and keep spray off the foliage.	Broadcast; Directed band	Aerial, Groundboom, Tractor-drawn spreader	WP/WSP, Liquid, G	1.0 lb ae	1	1.0 lb ae	30 days	12-48 (depending on label)
Grapes	Acid, DMA, TIPA, IPA, DEA	Apply after shatter following bloom and before grape shoots reach the ground, or during dormant season.	Ground directed	Groundboom	WP/WSP, Liquid	1.36 lb ae	1	1.36 lb ae	100 days	48 hr.

Summary of Directions for Use of 2,4-D										
Use Site	Chemical	Application Timing	Application Type	Application Equipment	Formulation	Maximum Application Rate	Max Number Applications per Season	Max. Seasonal Application Rate	PHI (days)	REI (hours)
Hops	Acid, DMA, TIPA, IPA, DEA	Postemergence; Make application as a directed treatment to the row middles (directed to ground).	Aerial or ground	Aerial or Groundboom	WP/WSP and Liquid	0.5 lb ae	3	1.5 lb ae	28 days	48 hr.
Orchard Floors (pome fruit, stone fruit and nut /pistachios)	Acid, DMA, TIPA, IPA, DEA, Choline	Postemergence; For control of weeds on the orchard floor. For best results, apply when weeds are small and actively growing.	Ground Broadcast or Spot Treatment	Groundboom or Handheld (backpack, mechnically-pressurized handgun)	WP/WSP, Liquid	2.0 lb ae (liquid: 1.5 lb ai/gal spot)	2	4.0 lb ae	pome fruit: 14 days; stone fruit: 40 days; nut orchards and pistachios: 60 days	48 hr.
Potatoes (Fresh Market Only)	Acid, DMA, 2-EHE, BEE, TIPA, IPA, DEA	Postemergence; Make first application when potatoes are in the pre-bud state (about 7 to 10 inches high). Make second application about 10 to 14 days later.	Aerial or Ground Broadcast Spray	Aerial or Groundboom	WP/WSP or Liquid	0.07 lb ae	2	0.14 lb ae	45 days	12-48 (depending on label)
Rice	Acid, DMA, TIPA, IPA, DEA, Choline	Preplant; Apply 2 to 4 weeks prior to planting rice.	Aerial and Ground Broadcast; Band; Spot Treatment	Aerial, Groundboom	WP/WSP, Liquid	1.0 lb ae	1	1.5 lb ae	60 days	48 hr.
		Postemergence; Apply when rice is in the late tillering stage of development at the time of first joint development, usually 6 to 9 weeks after emergence. Do not				1.5 lb ae	1			

Summary of Directions for Use of 2,4-D										
Use Site	Chemical	Application Timing	Application Type	Application Equipment	Formulation	Maximum Application Rate	Max Number Applications per Season	Max. Seasonal Application Rate	PHI (days)	REI (hours)
		apply after panicle initiation.								
Soybeans	Acid, DMA, 2-EHE, BEE, TIPA, IPA, DEA, Choline	Preplant/Burndown; To control emerged broadleaf weed seedlings or existing cover crops. Apply not less than 15 days prior to planting soybeans.	Aerial and Ground Broadcast; Directed band	Aerial or Groundboom	WP/WSP, Liquid	0.5 lb ae	1	1.0 lb ae	NA	12-48 (depending on label)
		Preplant/Burndown; To control emerged broadleaf weed seedlings or existing cover crops. Apply not less than 30 days prior to planting soybeans.				1.0 lb ae				
		Preplant/Burndown; To control emerged broadleaf weed seedlings or existing cover crops. Apply not less than 7 days prior to planting soybeans.			Liquid	0.5 lb ae	2			
Enlist Soybeans	Choline	Preplant or Preemergence; Apply any time before or after planting, but before soybean emerges.	Broadcast	Groundboom	Liquid	1.0 lb ae	1	1.0 lb ae	30	48

Summary of Directions for Use of 2,4-D										
Use Site	Chemical	Application Timing	Application Type	Application Equipment	Formulation	Maximum Application Rate	Max Number Applications per Season	Max. Seasonal Application Rate	PHI (days)	REI (hours)
		Postemergence; Apply any time after soybean emergence but no later than R2 (full flowering) stage.					2	2.0 lb ae		
Strawberries	Acid, DMA, TIPA, IPA, DEA	Dormant or after last picking; Apply to established plantings whenstrawberries have gone into dormancy or soon after the last picking.	Aerial or Ground Broadcast Spray	Aerial or Groundboom	WP/WSP, Liquid	1.5 lb ae	1	1.5 lb ae	NA	48 hr.
Sugarcane	Acid, DMA, TIPA, IPA, DEA, Choline	Preemergence: Apply before cane emerges to actively growing weeds Postemergence; Apply after cane emerges and through canopy closure; Apply before canes appear for control of emerged broadleaf weeds.	Aerial or Ground Broadcast Spray	Aerial or Groundboom	WP/WSP, Liquid	2.0 lb ae	1	4.0 lb ae/A	Do not harvest prior to crop maturity	48 hr.
Wild Rice	Acid, DMA, TIPA, IPA, DEA	Postemergence; For use only on wild rice grown in commercial paddies. Apply to rice in the 1 to 2 aerial leaves through early tillering stage. Do not spray after wild rice has reached the boot stage.	Aerial and Ground Broadcast; Spot Treatment	Aerial, Groundboom	WP/WSP, Liquid	0.25 lb ae	1	0.25 lb ae	60 days	48 hr.
Aquatic Areas, Forestry, Non-Crop Areas and Turf										

Summary of Directions for Use of 2,4-D										
Use Site	Chemical	Application Timing	Application Type	Application Equipment	Formulation	Maximum Application Rate	Max Number Applications per Season	Max. Seasonal Application Rate	PHI (days)	REI (hours)
Aquatic weeds in ponds, lakes, reservoirs, marshes, bayous, drainage ditches, canals, rivers and streams that are quiescent or slow moving.	Acid, DMA, BEE, TIPA, IPA, DEA, Choline	Postemergence; Apply in spring or early summer (no later than September)	Broadcast or Spot	Aerial, Ground/Boat-boom, Handheld (backpack, mechnically-pressurized handgun)	WP/WSP, Liquid, G	4 ppm; 10.8 lb ae per acre foot; 4 lb ae/A	2	4 ppm; 4 lb ae/A	NA	NA
Irrigation and Ditchbank Applications	Acid, DMA, BEE, TIPA, IPA, DEA, Choline	Postemergence; For best results, treat when weeds are young and actively growing.	Boat or Aerial Spray; Broadcast or Spot	Aerial, Groundboom, Tractor-drawn spreader; Handheld (backpack, mechnically-pressurized handgun)	WP/WSP, G, Liquid	2.0 lb ae; 8 lb ae/100 gal	2	4.0 lb ae	NA	NA
Established Grass Pastures, Rangeland, and Perennial Grasslands not in Agricultural Production (such as Conservation Reserve Program)	Acid, DMA, 2-EHE, BEE, TIPA, IPA, DEA, Choline	Postemergence - biennial and perennial broadleaf weeds (moderately susceptible)	Broadcast and Spot	Aerial, Groundboom, Handheld	Liquid, WP/WSP	2.0 lb ae; 8 lb ae/100 gal	2	4.0 lb ae	7	12-48 (depending on label)

Summary of Directions for Use of 2,4-D										
Use Site	Chemical	Application Timing	Application Type	Application Equipment	Formulation	Maximum Application Rate	Max Number Applications per Season	Max. Seasonal Application Rate	PHI (days)	REI (hours)
Turfgrass: Golf courses, cemeteries, parks, sports fields, lawns	Acid, DMA, 2-EHE, BEE, TIPA, IPA, DEA, Na, Choline	Postemergence	Broadcast or spot	Groundboom, Tractor-drawn spreader, Handheld (Trigger-spray bottle, backpack, manually-pressurized handwand, mechnically-pressurized handgun, belly grinder, rotary spreader)	WP/WSP, Liquid, G, RTU	1.5 lb ae; 1 lb ae/gallon; 0.012 lb ae/gal (homeowner label); 0.028 lb ai/1000 ft^2; 0.012 lb ai/bottle (assume 10 bottles/day)	2	3.0 lb ae	NA	NS
Grass Grown for Seed and Sod Farms	Acid, DMA, 2-EHE, BEE, TIPA, IPA, DEA, Choline	Postemergence	Broadcast or spot	Groundboom, Handheld (backpack, mechnically-pressurized handgun)	WP/WSP, Liquid, G	2.0 lb ae; assumed 2.0 lb ae/100 gal	2	4.0 lb ae	7 days	12-48 (depending on label)
Non-Cropland (Such as fencerows, hedgerows, roadsides, ditches, rights-of-way, utility power lines, railroads, airports, industrial sites, and	Acid, DMA, 2-EHE, BEE, TIPA, IPA, DEA, Choline	Postemergence - Apply to emerged weeds. For best results, treat when weeds are young and actively growing.	Aerial and Ground Broadcast; Spot Treatment	Aerial, Groundboom, Tractor-drawn spreader, Handheld (aerosol can)	WP/WSP, Liquid, G, RTU (PL)	4.0 lb ae (woody plants); 2 lb ae (annual and perennial weeds); 4.0 lb ae/10 gal; 0.014 lb ai/can	annual and perennial weeds: 2; woody plants: 1	4.0 lb ae	NA	NA

Summary of Directions for Use of 2,4-D										
Use Site	Chemical	Application Timing	Application Type	Application Equipment	Formulation	Maximum Application Rate	Max Number Applications per Season	Max. Seasonal Application Rate	PHI (days)	REI (hours)
other non-crop areas.)										
Forest Site Preparation, Forest Roadsides, Brush Control Established Conifer Release (including Christmas Trees)	Acid, DMA, 2-EHE, BEE, TIPA, IPA, DEA, Choline	Postemergence	Broadcast or spot	Aerial, Groundboom, Handheld (backpack)	WP/WSP, Liquid	4.0 lb ae, 4.0 lb ae/100 gal	1	4.0 lb ae	NA	12-48 (depending on label)
		Postemergence - Basal Spray	Basal (spot)	Handheld (backpack)	WP/WSP, Liquid	8.0 lb ae/100 gallons				48 hr.
		Cut Stump; Apply as soon as possible after cutting trees. Thoroughly soak the entire stump with 2,4-D mixture. Also treat exposed roots and bark.	Cut stump	Handheld (trigger spray bottle -- assume 10 32-oz bottles used per day)	Liquid, WP/WSP	8.0 lb ae per 100 gallons of diluent	1	4.0 lb ae	NA	12-48 (depending on label)
		Frill; Make frills with an axe or other tool that can cut overlapping v-shaped notches through the bark in a continuous ring around the base	Frill			8.0 lb ae per 100 gallons of diluent	1	4.0 lb ae	NA	12-48 (depending on label)

Summary of Directions for Use of 2,4-D										
Use Site	Chemical	Application Timing	Application Type	Application Equipment	Formulation	Maximum Application Rate	Max Number Applications per Season	Max. Seasonal Application Rate	PHI (days)	REI (hours)
		of the tree. Treat freshly cut frills with as much 2,4-D mixture as they will hold.								
		Injection; Make injections as near to the root collar as possible, using 1 injection per inch of trunk DBH (4 1/2 feet). For resistant species such as hickory, injections should overlap. For best results, injections should be made during the growing season, May 15 - October 15 in many areas. The injection bit must penetrate the inner bark.	Injection	Injector		1 to 2 ml of 4 lb ae form per injection site (1.27 lb ai/gal and 0.75 mL per injection = 0.00025 lb ai/tree)	1	1 to 2 ml of 4 lb ae formulation per injection site	NA	12-48 (depending on label)

Appendix C. Toxicology Profile and Executive Summaries

C.1 Toxicology Data Requirements

The toxicology data requirements (40 CFR 158.340) for the food uses of 2,4-D are presented below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Study	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	no
870.3465 90-Day Inhalation	yes	yes
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Oncogenicity (rat)	yes	yes
870.4200b Oncogenicity (mouse)	yes	yes
870.4300 Chronic/Oncogenicity	yes	yes
870.5100 Mutagenicity—Gene Mutation – bacterial	yes	yes
870.5375 Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5550 Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotoxicity (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b 90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300 Developmental Neurotoxicity	yes	yes
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	yes
870.7800 Immunotoxicity	yes	yes
Special Studies Comparative thyroid	yes	yes

C.2 Toxicity Profiles

Table C.2.1. Acute Toxicity Categories for 2,4-D[1]	
Study Type	Toxicity Category
Acute Oral (870.1100)	III (all forms)
Acute Dermal (870.1200)	III (all forms)
Acute Inhalation (870.1300)	III (acid, TIPA) IV (all other forms)
Primary Eye Irritation (870.2400)	I (acid, DEA, DMA, IPA, TIPA) III (BEE and 2-EHE) IV (IPE)
Primary Skin Irritation (870.2500)	III (DEA) IV (all other forms)
Dermal Sensitization (870.2600)	Not a dermal sensitizer (all forms with an acceptable study)

1. 2,4-D. HED's Revised Human Health Risk Assessment for the Reregistration Eligibility Decision (RED) Revised to Reflect Public Comments. (Memo, T. Dole, 5/12/05, D316597).

Table C.2.2. Subchronic, Chronic and Other Toxicity Profile – 2,4-D			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral toxicity (Fischer 344 rats)	MRID 41991501 (1991) Acceptable/Guideline 0, 1, 15, 100, 300 mg/kg/day	NOAEL = 15 mg/kg/day LOAEL = 100 mg/kg/day, based on decreases body weight/gain, alterations in hematology and clinical chemistry parameters, and cataract formation in females. At HDT, effects listed above occurred more frequently and/or to a greater extent, as well as histopathological lesions in eyes, liver, testes, adrenals, kidneys, thymus, bone marrow, spleen, thyroids, lungs.
870.3150	Subchronic oral (capsule) toxicity - dogs	MRID 41737301 (1990) Acceptable/Guideline 0, 0.3, 1.0, 3.0, and 10 mg/kg/day]	NOAEL = 1 mg/kg/day LOAEL = 3 mg/kg/day, based on decreased body weight/body-weight gain and food consumption (males), alterations in clinical chemistry parameters [increased BUN (both sexes), creatinine (males)], and decreased testis weight in males. At the highest dose tested, mortality (2 males, 1 female sacrificed moribund), hematology alterations, and microscopic lesions of the kidneys and testes [hypospermatogenesis] were observed.
870.3150	Subchronic oral (diet) toxicity (dog)	MRID 42780001 (1993) Acceptable/Guideline 0, 0.5, 1.0, 3.75, and 7.5 mg/kg/day	NOAEL = 1 mg/kg/day LOAEL = 3.75 mg/kg/day, based on decreased body-weight gain (both sexes) and food consumption (males), as well as alterations in clinical chemistry parameters [increased BUN, creatinine, and alanine aminotransferase] in both sexes, and decreased testes weight and slightly higher incidence of hypospermatogenesis/juvenile testis and inactive/juvenile prostate were observed.

Table C.2.2. Subchronic, Chronic and Other Toxicity Profile – 2,4-D			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3200	21-Day dermal toxicity (rabbit)	MRID 41735301, 41735304 (1990) Acceptable/Guideline 0, 10, 100, 1000 mg/kg/day	NOAEL = 1000 mg/kg/day LOAEL > 1000 mg/kg/day, no adverse effects observed at the limit dose
870.3465	90-Day inhalation toxicity (Sprague Dawley CD®) 6 hr/day, 5 days/week for 28 days	MRID 47398701 (2008) Acceptable/Guideline 0, 0.05, 0.1, 0.3, 1.0 mg/L	Systemic NOAEL = 0.30 mg/L/day Systemic LOAEL = 1.0 mg/L/day based on increased alkaline phosphatase and aspartate aminotransferase levels in females and decreased spleen weights in females. NOAEL (portal-of-entry effects) = not determined. LOAEL (portal-of-entry effects) = 0.05 mg/L/day, based on squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx; not totally resolved following a 4-week recovery period.
870.3700a	Developmental toxicity Fischer 344 rats (GD 6-15)	MRID 00130407, 00130408 (1983) Acceptable/Guideline 0, 8, 25, and 75 mg/kg/day	Maternal NOAEL = 25 mg/kg/day Maternal LOAEL = 75 mg/kg/day, based on decreased body weight gains. Survival was not affected by treatment. Developmental NOAEL = 25 mg/kg/day Developmental LOAEL = 75 mg/kg/day, based on skeletal abnormalities/ malformations.
870.3700b	Prenatal developmental in (New Zealand white rabbit) GD 6-18	MRID 41747601 [1990] Acceptable/Guideline 0, 10, 30, and 90 mg/kg/day	Maternal NOAEL = 30 mg/kg/day Maternal LOAEL = 90 mg/kg/day, based on clinical signs [ataxia, decreased motor activity, loss of righting reflex, cold extremities], abortion (2), decreased body-weight gains. Survival was not affected by treatment. Developmental NOAEL = 30 mg/kg/day Developmental LOAEL = 90 mg/kg/day, based on abortions.

Table C.2.2. Subchronic, Chronic and Other Toxicity Profile – 2,4-D			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3800	Reproduction and fertility effects (Fischer 344 rat)	MRID 00150557 and 00163996 (1985) acceptable/guideline* *new 870.3800 required (see MRID 47972101 below)	Parental NOAEL = 5 mg/kg/day. Parental LOAEL = 20 mg/kg/day, based on decreased female body weight/body weight gain (F1) and male renal tubule alteration (F0 and F1). At HDT, excess toxicity and too few pups for second litter (dose group terminated). Reproductive NOAEL = 20 mg/kg/day. Reproductive LOAEL = 80 mg/kg/day, based on increased gestation length. However, since an increase of less than a day is not considered adverse, reproductive toxicity was not observed in this study. The dose of 80 mg/kg/day was not assessed in the second generation due to the lack of sufficient F1 offspring to mate (excessive pup mortality). Dose is above the threshold of saturation of renal clearance. Offspring NOAEL = 5 mg/kg/day Offspring LOAEL = 20 mg/kg/day based on pup deaths.

870.3800 OECD 443 and 416	Reproduction and fertility effects (Crl:CD(SD) rat) Extended One Generation Reproductive Toxicity (EOGRT) study	47972101 (2010) acceptable/non-guideline* (satisfies OECD guideline) *satisfies the requirement for reproduction/ fertility effects and DNT studies	**Parental (male) systemic NOAEL** = 300 ppm (16.6 mg/kg/day). **Parental (male) systemic LOAEL** = 800 ppm (45.3 mg/kg/day), based on nephrotoxicity manifested as increased kidney weights, and degenerative lesions in the proximal convoluted tubules in the main study P1 rats. **Parental (female) systemic NOAEL** = 600 ppm (40.2 mg/kg/day). No toxicologically relevant effects were identified in P1 females or in the GD 17 satellite female groups at the highest dose tested. **Thyroid toxicity NOAEL** = 800/600 ppm (45.3 mg/kg/day in males and /40.2 mg/kg/day in females), the highest dose tested. The thyroid effects noted in the database were considered to be adaptive. **Offspring (F1 adults) NOAEL** = 300 ppm (20.9/ mg/kg/day in males and 23.3 mg/kg/day in females). **Offspring (F1 adults) LOAEL** = 800/600 ppm (55.6 mg/kg/day in males and 46.7 mg/kg/day in females), based on kidney toxicity manifested as increased kidney weights and increased incidence of degeneration of the proximal convoluted tubules. **F1 offspring NOAEL** = 300 ppm. The dose on a mg/kg/day basis for the PND 22 F1 offspring was not calculated. **F1 offspring (PND 22) LOAEL** = 800/600 ppm, based on decreased body weight observed throughout lactation. **DNT offspring NOAEL** = 800 ppm/600 ppm (81.7 mg/kg/day in males, 59.2 mg/kg/day in females), the highest dose tested [lack of evidence of DNT (FOB parameters, motor activity, and acoustic startle response)]. **DIT offspring NOAEL** = 800/600 ppm (71.8 mg/kg/day in males and 55.3 mg/kg/day in females), the highest dose tested [lack of evidence of DIT [SRBC antibody-forming cell assay (PND 66-70) and Natural Killer Cell assay (PND 87-93)]. **Reproductive NOAEL** = 800/600 ppm (45.3 mg/kg/day in males, 40.2 mg/kg/day in females), the highest dose tested [lack of effect on estrous cyclicity, (P1 females, satellite GD 17 dams, Set 3 F1 offspring) or reproductive indices (mating, fertility, time to mating, gestation length, pre-and post-implantation loss, number of corpora lutea (satellite GD 17 dams), sperm parameters, ovarian follicle counts, and reproductive organ histopathology).
870.4100a	Chronic toxicity (Fischer 344 rat)	MRID 43293901 (1993) MRID 43612001 (1995) MRID 44284501 (1997)	NOAEL = 5 mg/kg/day. LOAEL = 75 mg/kg/day, based on decreased body-weight gain (females) and food

Table C.2.2. Subchronic, Chronic and Other Toxicity Profile – 2,4-D			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
		0, 5, 75, or 150 mg/kg/day Acceptable/Guideline	consumption (females), alterations in hematology [decreased RBC (females), HGB (females), platelets (both sexes)] and clinical chemistry parameters [increased creatinine (both sexes), alanine and aspartate aminotransferase (males), alkaline phosphatase (both sexes), decreased T4 (both sexes), glucose (females), cholesterol (both sexes), and triglycerides (females)], increased thyroid weights (both sexes at study termination), decreased testes and ovarian weights, and microscopic lesions in the lungs (females). At the high-dose level, there were microscopic lesions in the eyes, liver, adipose tissue, and lungs. There was no treatment-related increase in the incidence of any tumor.
870.4100b	Chronic toxicity (Beagle dog)	MRID 43049001 (1993) Acceptable/Guideline 0, 1, 5, or 7.5/10 mg/kg/day	NOAEL = 1 mg/kg/day LOAEL = 5 mg/kg/day, based on decreased body-weight gain (both sexes) and food consumption (females), as well as alterations in clinical chemistry parameters [increased BUN, creatinine, and alanine aminotransferase, decreased glucose] in both sexes, decreased brain weight in females, and histopathological lesions in the liver and kidneys. At the highest dose tested, aspermatogenesis and degeneration of the testes was observed in one male and decreased brain weight was observed in both sexes.
870.4200	Carcinogenicity (Fischer 344 rat)	MRID 43612001 (1995) MRID 44284501 (1997) 0, 5, 75, or 150 mg/kg/day Acceptable/Guideline	See under 870.4100a above
870.4300	Carcinogenicity ($B_6C_3F_1$ CRL BR mouse)	MRID 40061801 (1993) Acceptable/Non-guideline 0, 1, 15, or 45 mg/kg/day	NOAEL = 1 mg/kg/day LOAEL = 15 mg/kg/day, based on treatment-related increase in kidney weights in both sexes and microscopic renal lesions in males. There was no treatment-related increase in the incidence of any tumor type. Doses not adequate to assess carcinogenic potential.
870.4300	Carcinogenicity ($B_6C_3F_1$ CRL BR mouse)	MRID 43879801 (1995) MRID 43597201(1995) Acceptable/Guideline 0, 5, 62/150, or 120/300 mg/kg/day (male/female)	NOAEL = 5 mg/kg/day LOAEL =62/150 mg/kg/day, based on based on an increased absolute and/or relative kidney weights and an increased incidence of renal microscopic lesions. There was no treatment-related increase in the incidence of any tumor type.

Table C.2.2. Subchronic, Chronic and Other Toxicity Profile – 2,4-D			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5100	Salmonella typhimurium TA98, TA100, TA1535, Ta1537, Ta1538	MRID 41409801(1990) Acceptable/guideline 100-1000 µg/plate w/ S9; 66.7-6670 µg/plate w/out S9	No evidence of bacterial mutation w/ and w/out S9
870.5395	*in vivo* mouse micronucleus assay ICR mouse (bone marrow)	MRID 41409804, 41870101 (1990) Acceptable/guideline 40-400 µg/kg	Negative.
870.5450	Unscheduled DNA synthesis assay	MRID 41409807 (1990) Acceptable/guideline	No evidence of induction of unscheduled DNA synthesis
Literature studies cited by NRDC	Mutagenicity/ Genotoxicity (*in vivo* and *in vitro*)	Office of Pesticide Programs, EPA, Reevaluation of the Genetic Toxicology Profile of 2, 4-D. (December 12, 2011).	FRN April 18, 2012 denial of NRDC petition (mutagenicity summary).
870.6200a	Acute neurotoxicity screening battery (Fischer 344 rat)	MRID 43115201 (1994) Acceptable/guideline 0, 15, 75, or 250 mg/kg/day Achieved: 0, 13, 67, or 227 mg/kg/day	NOAEL = 67 mg/kg. LOAEL = 227 mg/kg/day, based on an increased incidence of incoordination and slight gait abnormalities (described as forepaw flexing or knuckling) and decreased total motor activity.
870.6200b	Subchronic neurotoxicity screening battery (Fischer 344 rat)	MRID 43293901 (1994) Acceptable/guideline 0, 5, 75, or 150 mg/kg/day Males 0, 4.6, 71.2, or 141.1 mg/kg/day Females 0, 4.6, 68, 138.9 mg/kg/day	NOAEL = 71/68 mg/kg/day. LOAEL = 141/139 mg/kg/day, based on increased relative forelimb grip strength and increased incidence of bilateral retinal degeneration.
870.6300	Developmental neurotoxicity (Crl:CD(SD) rat)	MRID 47972101 (2010) See under EOGRT	**DNT offspring NOAEL** = 800 ppm/600 ppm (81.7 mg/kg/day in males, 59.2 mg/kg/day in females), the highest dose tested [lack of evidence of DNT (FOB parameters, motor activity, and acoustic startle response)].
870.7485	Metabolism and pharmacokinetics (Fischer 344 rat)	MRID 41737302 (1990)	2,4-D (sodium salt) is well absorbed orally, undergoes limited metabolism, and is eliminated quickly from the body primarily unchanged in the urine; was nearly completely eliminated *via* the urine following single low (>95%; ≈1 mkd) and repeat low (>90%; 100 mkd) doses; majority eliminated within 12 hours; highest levels found in kidneys; following single high dose (≈100 mkd), ≈90% was eliminated in the urine, with 40%-46% being eliminated within the first 12 hours; highest levels in perirenal fat.
870.7485	Metabolism and pharmacokinetics (Crl:CD(SD) rat)	MRID 47417902 (2008)	Compared to the lowest dose (100 ppm), there was an 11-fold, 31-fold, and 60-fold difference in the AUC_{24h} at 400 ppm, 600 ppm and 800 ppm, demonstrating nonlinear kinetics.

Table C.2.2. Subchronic, Chronic and Other Toxicity Profile – 2,4-D			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485	Metabolism and pharmacokinetics (Crl:CD(SD) rat)	MRID 47417901 (2008)	Study provides plasma levels of 2,4-D for both maternal rats and pups of both sexes, as well as levels of 2,4-D in maternal milk, demonstrating that the pups would be exposed to 2,4-D during lactation. Kidney findings confirm the gender-based difference in renal clearance of 2,4-D in adult rats.
870.7600	Dermal penetration (human, male)	Feldman. R. J. and Maibach, H. I. (1974). Percutaneous Penetration of Some Pesticides and Herbicides in Man. Toxicology and Applied Pharmacology. 28: 126-132]. Ross, R.H.; Driver, J.H.; Harris, S.A.; Maibach, H.I. (2005). Dermal absorption of 2,4-D: a review of species differences. *Regulatory Toxicology and Pharmacology* 41: 82-91. Moody, R.P.; Wester, R.C.; Melendres, J.L.; Maibach, H.I. . *Journal of Toxicology and Environmental Health* 36(3):241-50.,1992. MRID 48772102. Harris, S.A.; Solomon, K.R. 1992. *Journal of Toxicology and Environmental Health* 36, 233-240. MRID 48772104. Maibach, H.I.; Feldmann, R.J., 1974. MRID 46859102. Wester, R.C.; Melendres, J.; Sedik, L.; Maibach, H.; Riviere, J.E., 1998. *Toxicology and Applied Pharmacology* 151, 159-165. MRID 48772101	dermal application was 5.8% ± 2.4%; 10% DAF used in previous risk assessments

Table C.2.2. Subchronic, Chronic and Other Toxicity Profile – 2,4-D			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.7800	Immunotoxicity SRBC antibody-forming cell assay and Natural Killer Cell assay (Crl:CD(SD) rat)	MRID 47972101 (2010) See under EOGRT	**DIT offspring NOAEL** = 800/600 ppm (71.8 mg/kg/day in males and 55.3 mg/kg/day in females), the highest dose tested [lack of evidence of DIT [SRBC antibody-forming cell assay (PND 66-70) and Natural Killer Cell assay (PND 87-93)].

C.3 Hazard Identification and Endpoint Selection

C.3.1 Acute Reference Dose (aRfD) - Females age 13-49

Study Selected: Developmental Toxicity Study - rat
MRID No.: 00130407/00130408
Executive Summary: See Appendix A, Guideline § 870.3700a
Dose and Endpoint for Risk Assessment: NOAEL = 25 mg/kg/day based on fetal skeletal malformations (14th rudimentary ribs) at LOAEL = 75 mg/kg/day, which exceeds the threshold of saturation of renal clearance.
Comments about Study/Endpoint/Uncertainty Factors: This endpoint is appropriate for the population of concern (females of child bearing age) and is considered to be a single dose effect. It was concluded that the skeletal findings are real and treatment-related. Although the findings occur only at a dose level that exceeds the renal clearance mechanism (75 mg/kg/day), regulating below the level where this occurs is protective. There are clearly established NOAELs and LOAELs for the population of concern, there are no data gaps in the toxicology database, and the point of departure (POD) is protective of susceptibility.
Uncertainty Factor (UF): 100X [10X interspecies extrapolation (UF_A), 10X intraspecies variability (UF_H), FQPA SF 1X].

C.3.2 Acute Reference Dose (aRfD) - General Population

Study Selected: Acute Neurotoxicity Study - rat

MRID No.: 43115201
Executive Summary: See Appendix A, Guideline § 870.6200
Dose and Endpoint for Risk Assessment: NOAEL = 67 mg/kg/day, based on an increased incidence of incoordination and slight gait abnormalities(forepaw flexing or knuckling) and decreased total motor activity at the LOAEL = 227 mg/kg/day.
Comments about Study/Endpoint/Uncertainty Factors: The endpoint is appropriate for the population of concern (general population) and is considered to be a single dose effect.
Uncertainty Factor (UF): 100X [10X interspecies extrapolation (UF_A), 10X intraspecies variability (UF_H), FQPA SF 1X].

C.3.3 Chronic Reference Dose (cRfD) `

Study Selected: Extended 1-Generation Reproduction Toxicity Study - rat

MRID No.: 47972101
Executive Summary: See Appendix A, Guideline [§ 870.3800; OECD 443 and 416]
Dose and Endpoint for Risk Assessment: parental NOAEL = 21 mg/kg/day (300 ppm), based on kidney toxicity manifested as increased kidney weights and increased incidence of degeneration of the proximal convoluted tubules at LOAEL = 800/600 ppm (males 55.6 mg/kg/day; females 46.7 mg/kg/day).
Comments about Study/Endpoint/Uncertainty Factors: The EOGRT study is considered appropriate for dose and endpoint selection for the chronic dietary exposure assessment. This is a very robust long-term study with a decent dose spread, which evaluates a whole host of endpoints, including the target organ (kidney). The chronic rat study, which was selected previously for the chronic dietary endpoint, was not selected since it has a very large dose spread and the high dose (75 mg/kg/day) exceeds the level of renal clearance in the rat (≈50 mg/kg/day). Other studies in the database with lower NOAELs; *e.g.,* two mouse carcinogenicity studies, also have similar dose-spacing issues and were not selected for the same reason. The NOAEL of the EOGRT study is protective of the LOAELs from the other chronic studies.
Uncertainty Factor (UF): 100X [10X interspecies extrapolation (UF_A), 10X intraspecies variability (UF_H), FQPA SF 1X].

C.3.4 Incidental Oral Exposure (Short- and Intermediate-Term)

Study Selected: Extended 1-Generation Reproduction Toxicity Study - rat
MRID No.: 47972101
Executive Summary: See Appendix A, Guideline [§ 870.3800; OECD 443/416]
Dose and Endpoint for Risk Assessment: parental NOAEL = 21 mg/kg/day, based on decreased body weight observed throughout lactation in F1 offspring (PND 22) at LOAEL = 47 mg/kg/day (800/600 ppm).
Comments about Study/Endpoint/Uncertainty Factors: The EOGRT study is considered appropriate for dose and endpoint selection for the incidental oral exposure assessments. This study was selected instead of the rat developmental toxicity and rat subchronic oral toxicity studies used previously since there is more confidence in the recent EOGRT study, which is a more robust study evaluating multiple parameters. Doses for the EOGRT study were selected based on pharmacokinetics (PK) data from adult rats and offspring. This study is appropriate for both short- and intermediate-term since the study assessed several durations of exposure and life stages [postnatal day (PND) 4, PND 22, and PND 60).
Uncertainty Factor (UF): 100X [10X interspecies extrapolation (UF_A), 10X intraspecies variability (UF_H), FQPA SF 1X].

C.3.5 Dermal Exposure (Short- and Intermediate-Term)

A quantitative dermal assessment is not required for the short-term and intermediate-term dermal scenarios. Since the dermal toxicity study did not evaluate developmental endpoints, and to ensure that developmental effects would not be expected in the dermal toxicity study, the following hazard and exposure characteristics were considered: 1) There was no quantitative susceptibility observed in the developmental or reproductive toxicity studies; developmental toxicity was observed at the same dose as maternal toxicity; 2) there was no dermal or systemic toxicity observed following repeated dermal applications to rabbits at the Limit Dose (1000

mg/kg/day) in a 21-day dermal toxicity study; 3) the use of a 10% human dermal absorption factor (DAF) with the oral developmental LOAEL of 90 mg/kg/day established in the rabbit developmental toxicity study yields a dermal equivalent dose (DED) of 900 mg/kg/day, which is numerically similar to the high-end dermal NOAEL (1000 mg/kg/day) in the dermal rabbit study; 4) similarly, use of the 10% human DAF with the oral developmental LOAEL of 75 mg/kg/day established in the rat developmental study yields a DED of 750 mg/kg/day; 5) the developmental findings in the rat and rabbit occurred at oral dose levels exceeding renal clearance, and clear NOAELs were obtained (dermal equivalent doses of 250 and 300 mg/kg/day); and 6) the use pattern indicates that dose levels required to exceed the renal clearance mechanism would not be attained following human dermal exposure.

Additionally, although there was no thyroid hormone assessment and the thyroid was not weighed in the dermal study, the rat extended 1-generation reproduction toxicity (oral) study performed an assessment of the thyroid for several age groups (F1 offspring on PND 4, PND 22, and PND 62-64, and the P1 gestation day 17 females at dose levels up to/approaching renal saturation (males 45/females 40 mg/kg/day). The changes in thyroid hormones (↓ T_3 and T_4 with ↑TSH levels) observed, along with thyroid histopathological findings, were considered treatment-related, although not adverse (NOAEL for thyroid effects is ≈40 mg/kg/day; dermal equivalent dose of 400 mg/kg/day).

C.3.6 Inhalation Exposure (All Durations)

Study Selected: 28-Day Inhalation Toxicity Study - rat
MRID No.: 47398701
Executive Summary: See Appendix A, Guideline [§ 870.3465]
Dose and Endpoint for Risk Assessment: No NOAEL for portal of entry effects was determined, and the LOAEL was used as the point of departure. The LOAEL for portal of entry effects is 0.05 mg/L (lowest dose tested), based on squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx, which was not totally resolved following a 4-week recovery period. Excessive salivation, labored breathing, and chromodacryorrhea were observed at the high-dose level following the 12th exposure and continued during the remainder of the exposures.

Comments about Study/Endpoint/Uncertainty Factor: This route specific study is appropriate for the short-term and intermediate-term inhalation assessments. The portal of entry effects were squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx. These effects occurred at all dose levels (NOAEL was not identified). The incidence and severity of these effects were increased in a dose-related manner, and the effects persisted following the 4-week recovery period, although the incidence and severity were reduced. A human-equivalent concentration (HEC) was derived from this study based upon the portal of entry effects (residential: 0.013 mg/L; occupational: 0.056 mg/L). A human-equivalent dose (HED) was also calculated (residential: 2.133 mg/kg/day; occupational: 3.18, 6.4, or 11.11 mg/kg/day depending on breathing rate scenario). For details regarding the calculation of the HEC and HED, see Appendix D. Although there was no thyroid hormone assessment and the thyroid was not weighed in the inhalation study, the Crl:CD(SD) rat extended 1-generation reproduction toxicity (oral) study (EOGRT) performed an assessment of the thyroid for several

age groups (F1 offspring on PND 4, PND 22, and PND 62-64, and the P1 gestation day 17 (GD 17) females at dose levels up to/approaching renal saturation (males 45/females 40 mg/kg/day). The changes in thyroid hormones (↓ T_3 and T_4 with ↑TSH levels) observed, along with thyroid histopathological findings, were considered treatment-related, although not adverse (NOAEL for thyroid effects is ≈40 mg/kg/day). The lack of an assessment of the thyroid in the inhalation study is considered inconsequential because the portal of entry endpoint is protective of potential thyroid effects expected to occur at higher concentrations; *i.e.,* at doses that exceed the level of renal clearance. Portal-of-entry effects were observed at all dose levels, and an additional 10X uncertainty factor is applied to the LOAEL to obtain an extrapolated NOAEL used for the inhalation risk assessments.

Uncertainty Factor (UF): LOC=300 (UF_A = 3X, UF_H = 10X, $UF_{LOAEL \rightarrow NOAEL}$= 10X). For the inhalation exposure assessments for short- and intermediate-term durations, a total uncertainty factor of 300X is appropriate [3X for interspecies extrapolation (reduced from 10X because RfC methodology was used, which takes into consideration the pharmacokinetic differences between animals and humans), 10X for intraspecies variation, and a 10X FQPA database uncertainty factor (for extrapolation from a LOAEL to a NOAEL)].

C.4 Executive Summaries

C.4.1 Subchronic Toxicity

870.3100 90-Day Oral Toxicity - Rat

In a subchronic oral toxicity study [MRID 41991501], 10 Fischer 344 rats/sex/group were administered 2,4-dichlorophenoxyacetic acid [96.1% a.i.] *via* the diet for 13 weeks at concentrations of 0, 1 mg/kg/day, 15 mg/kg/day, 100 mg/kg/day, and 300 mg/kg/day.

There were no treatment-related deaths. Clinical signs of toxicity occurred mainly in the high-dose females and included hunched posture [1 high-dose female during weeks 13-14], depressed activity [all high-dose females during first week], and few/no feces [4 high-dose males and all high-dose females during week 1; 5 high-dose females during week 12; 1 high-dose female during week 13]. There was a dose-related increase in the incidence of pale/opaque eyes in both sexes [1/10 controls, 2/10 at 1, 15, and 100 mg/kg/day and 4/10 at 300 mg/kg/day in males; 1/10 controls, 2/10 at 1 mg/kg/day, 1/10 at 15 mg/kg/day, 4/10 at 100 mg/kg/day, and 8/10 at 300 mg/kg/day in females].

Decreased body weights were observed throughout the study at the high-dose level [both sexes], with the magnitude of the deficit increasing with time [males 85%/77% and females 79%/72% of control at weeks 6/13, respectively], and decreased body-weight gains [weeks 0-6: males 72%/females 50% of control; overall: males 63%/females 43% of control] were observed in both sexes at the highest dose level throughout the study. At the next highest dose level, decreased body weight [93% of control at 13 weeks; both sexes] and body-weight gain [overall males 91%/females 89% of control] were observed. A corresponding decrease in food consumption was observed in both sexes at the two highest dose levels.

Complete cataract formation was observed in 7 high-dose [300 mg/kg/day] females and in one female at the next highest [100 mg/kg/day] dose, and posterior subcapsular cataract was observed in 5 high-dose females. Treatment-related alterations in hematology [statistically significant decreases in RBC, HGB, HCT, platelet count, absolute and corrected leukocyte counts, and lymphocyte counts] were observed at the 6- and/or 13-week intervals at the high-dose level [both sexes], and decreased platelet counts were observed in both sexes at the next highest dose level at week 13. Alterations in clinical chemistry [decreased thyroxine and triiodothyronine levels] were observed at 100 and 300 mg/kg/day at both intervals in one or both sexes.

Changes in absolute and/or relative organ weights [adrenals, brain, thymus, heart, kidneys, testes with epididymides (males), ovaries (females), pituitary, liver (increased), thyroids/parathyroids (increased) were observed primarily at the high-dose level [both sexes], and many of these changes may be attributable to decreased body weight. Gross findings, mainly in the high-dose group, included small testes and epididymis and opaque eyes [females]. Treatment-related histopathological changes were observed primarily in the high-dose group and included centrilobular hepatocellular hypertrophy [liver], bilateral retinal degeneration and cataract formation [females], atrophy of the testes [males], hypertrophy of the zona glomerulosa [adrenal cortex, both sexes] and follicular cells [thyroid, females], atrophy of the thymus [both sexes] and spleen [both sexes], congestion and edema of the bone marrow [both sexes], brush border loss in proximal tubular cells [kidney, both sexes]. Many of the lesions correlated well with the alterations observed in hematology and clinical chemistry parameters and/or organ-weight data of the high-dose groups.

The NOAEL is 15 mg/kg/day, based on decreased body weight/body-weight gain, alterations in some hematology [decreased platelets (both sexes)] and clinical chemistry [decreased T_3 (females) and T_4 (both sexes)] parameters, and cataract formation in females at the LOAEL of 100 mg/kg/day.

This subchronic oral toxicity study is classified **Acceptable/Guideline**, and the study satisfies the guideline requirement [OPPTS 870.3100; §82-1] for a subchronic oral toxicity study in the rodent.

870.3150 90-Day Oral Toxicity - Dog

(1) In a subchronic oral toxicity study [MRID 41737301], 5 beagle dogs/sex/group were administered 2,4-dichlorophenoxyacetic acid [96.1%] *via* capsules for 13 weeks at concentrations of 0, 0.3 mg/kg/day, 1.0 mg/kg/day, 3.0 mg/kg/day, and 10 mg/kg/day.

Two males [weeks 4, 13] and one female [week 9] at the high-dose level were sacrificed moribund. Treatment-related clinical signs [thin, languid appearance, anorexia, tremors] were observed at the high-dose level in the three dogs sacrificed *in extremis*. Decreased body weights were observed in males at the two highest dose levels [83% and 80% of control at 3 and 10 mg/kg/day, respectively] and in females at the high-dose level [86% of control] at week 13. Body-weight gains were decreased throughout the study in males

at the two highest dose levels [weeks 0-13: 56% and 44%, respectively]. The mid- and high-dose females displayed decreased body-weight gains also [weeks 0-13: 84% and 52% of control, respectively]. Decreased food consumption was observed in both sexes at the highest dose level and in males at the next highest dose level throughout the study.

Decreased RBC, hemoglobin, hematocrit, and platelet count values were observed in both sexes at the highest dose level, although statistical significance was not always attained [n=4-5]. Treatment-related alterations in clinical chemistry parameters were observed mainly at the two-highest dose levels in both sexes at various times during the dosing period [increased blood urea nitrogen (both sexes), creatinine (both sexes), alanine aminotransferase (high-dose females; males not statistically significant); decreased T4 (both sexes at high-dose; not statistically significant), and glucose (high dose, both sexes]. High-dose females displayed slightly increased kidney and thyroid weights [absolute, relative to body and brain weights] compared to the control group. Decreased testis weight was observed at the two-highest dose levels, and two of the 3 surviving high-dose males and one of the 2 high-dose males sacrificed moribund displayed hypospermatogenesis and giant cell formation. Microscopic lesions [cellular alterations, proximal tubule] were observed in the kidney of both sexes at the high-dose level [3 of 5 males at 3 mg/kg/day, 3/3 surviving males at 10 mg/kg/day, 1 of 4 surviving females at 10 mg/kg/day, and all dogs sacrificed moribund].

The NOAEL is 1.0 mg/kg/day. The LOAEL of 3.0 mg/kg/day is based on decreased body weight/body-weight gain and food consumption (males), alterations in clinical chemistry parameters [increased BUN (both sexes), creatinine (both sexes)], and decreased testis weight (males).

This subchronic oral toxicity study is classified **Acceptable/Guideline**, and it satisfies the guideline requirement [OPPTS 870. 3150; §82-1(b)] for a subchronic non-rodent oral toxicity study.

(2) In a subchronic oral toxicity study [MRID 42780001], 4 beagle dogs/sex/group were administered 2,4-dichlorophenoxyacetic acid [96.7%] *via* the diet for 13 weeks at concentrations of 0, 0.5 mg/kg/day, 1.0 mg/kg/day, 3.75 mg/kg/day, and 7.5 mg/kg/day. The dose levels were selected based on the results of a 4-week range-finding study [MRID 42780004]in which decreased body weight, food consumption, alterations in clinical chemistry parameters, and distended gall bladders were observed at ≥10 mg/kg/day.

There were no deaths, and no treatment-related clinical signs were observed. Decreased body weights were observed in males at the highest dose level [85% of control at week 14] and in females at the lowest and highest dose levels [91% of control] at week 14. Body-weight gains were decreased throughout the study in both sexes at the two highest dose levels but there was no dose-response [overall gain: males 52% and 55% of the control value/females 53% and 58% of the control value at 3.75 and 7.5 mg/kg/day, respectively]. Females at the two lowest dose levels also displayed decreased body-weight gains [overall gain: 74% and 79% of control at 0.5 and 1.0 mg/kg/day,

respectively] compared to the control. Decreased food consumption was observed in males at the two highest dose levels and in all female groups compared to their respective controls, but there was no consistent dose response.

Ophthalmology findings were comparable among the groups for both sexes. There were no apparent treatment-related alterations in hematology among the groups for either sex, with the exception of decreased platelet counts. Decreased platelet counts [73% and 87% of control] were observed in males at the high-dose level at both [week 4 and week 13, respectively] time points. Elevations in blood urea nitrogen [two highest dose levels, both sexes], creatinine [three highest dose levels, both sexes], and alanine aminotransferase [two highest dose levels, both sexes] and decreased glucose levels [two highest dose levels, females] were observed at week 4 and/or week 13; however, a dose response was not always apparent. Although no corroborative histopathological changes were observed in the liver or kidneys, similar changes in several of these clinical chemistry parameters have been observed in other studies on both 2,4-D and the 2,4-D salts and esters in rats and in an earlier subchronic toxicity study in dogs with 2,4-D [MRID 41737301]. In this latter study, microscopic lesions were observed in the kidneys of both sexes at 10 mg/kg/day.

Males at the two highest dose levels displayed a dose-related decrease in testes weight [absolute, relative to body, and relative to brain], although statistical significance was not attained [n=4]. Decreased adrenal weight [absolute and relative to brain] was observed in both sexes at the highest dose level, decreased liver weight [absolute and relative to brain] was observed in both sexes at the highest dose level, and decreased heart weight [absolute and relative to brain] was observed in both sexes at the two highest dose levels, but there was no dose response. Microscopically, hypospermatogenesis/ juvenile testis was observed in 1 control, 1 mid-high [3.75 mg/kg/day], and 2 high-dose [7.5 mg/kg/day] males, and inactive, juvenile prostate was observed in one male in the control, 0.5 mg/kg/day, 1 mg/kg/day, and 3.75 mg/kg/day dose groups and in all 4 high-dose males.

The NOAEL is 1.0 mg/kg/day. The LOAEL of 3.75 mg/kg/day is based on decreased body-weight gain (both sexes) and food consumption (males), as well as alterations in clinical chemistry parameters [increased BUN, creatinine, and alanine aminotransferase] in both sexes, and decreased testes weight.

This subchronic oral toxicity study is classified **Acceptable/Guideline**, and it satisfies the guideline requirement [OPPTS 870. 3150; §82-1(b)] for a subchronic non-rodent oral toxicity study.

870.3200 21-Day Dermal Toxicity – Rabbit

In a 21-day dermal toxicity study [MRID 41735304], 5 Hra: (NZW) SPF rabbits/sex/group were administered the 2,4-dichlorophenoxyacetic acid [96.1%] *via* dermal application [neat material (powder) spread evenly on 4" x 4" gauze pad and moistened with 0.5mL distilled water [6 hours/day, 7 days/week for 21 days at concentrations of 0 [distilled water], 10, 100, and 1000 mg/kg/day.

Treatment had no adverse effect on survival, clinical signs, mean body weight, hematology, clinical chemistry, urinalysis, gross pathology, or histopathology. At the high-dose level, increased kidney weights [absolute and relative] were observed in both sexes, but statistical significance was attained in the females only, and there were no corroborating changes in clinical chemistry parameters or histopathology in the kidneys. 2,4-D was only slightly irritating to the skin of the rabbits, inducing very slight erythema and epidermal scaling, with the females displaying a higher incidence than males.

The NOAEL for dermal and systemic toxicity is 1000 mg/kg/day, the highest dose tested.

This 21-day dermal toxicity study is classified **Acceptable/Guideline** and satisfies the guideline requirement [§82-2; 870.3200] for a 21-day dermal toxicity study.

870.3465 28-Day Inhalation – Rat

In a subchronic inhalation toxicity study (MRID 47398701), 2,4-D *(*99% a.*i., Lot # 2006 24833 8006-USA)* was administered to 10 or 20 Sprague-Dawley CD® rats/sex/concentration by dynamic [nose only] exposure at concentrations of 0, 0.05, 0.10, 0.30 or 1.00 mg/L for 6 hours per day, 5 days/week for 28 days (for a total of at least 20 exposures).

Following nose-only inhalation exposure, 2, 4-D was associated with portal-of-entry effects that consisted of squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx. The incidence and severity of the effects were increased in a dose-related manner, and the effects persisted following the 4-week recovery period, although the incidence and severity were reduced. Clinical signs associated with exposure at the high dose included excessive salivation (day 13 and subsequently), labored breathing (day 13 and subsequently), and chromodacryorrhea (day 12 and intermittently thereafter). A slight decrease in body weight was observed in the high-dose females by day 14 and continued throughout the remainder of the dosing (↓10%) and the recovery periods (↓12%). Body-weight gains were reduced in the high-dose female group throughout the study and recovery period and were accompanied by a reduction in food intake. Although a treatment-related reduction in reticulocyte counts was observed at the mid-high and high-dose levels in both sexes at terminal sacrifice, the toxicological significance is not known. Alkaline phosphatase values were increased in the mid-high and high-dose females and aspartate aminotransferase values were increased slightly in the high-dose females, but no correlating microscopic pathology findings were observed. Lung weights were unaffected by treatment. Females at the high-dose level displayed slight reductions in spleen and thymus weights. Organ weights were comparable among the male groups.

The systemic toxicity LOAEL is 1.0 mg/L/day, based on excessive salivation, labored breathing, and chromodacryorrhea, decreased body weight in females and decreased spleen weights in females. The NOAEL is 0.30 mg/L/day.

A NOAEL for portal-of-entry effects was not determined. The LOAEL for portal-of-entry effects (squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx; not totally resolved following a 4-week recovery period) **is 0.05 mg/L, the lowest dose tested.**

This subchronic inhalation toxicity study in the rat is **Acceptable/guideline**, and it satisfies the guideline requirement for a subchronic inhalation study (OPPTS 870.3465; OECD 413) in the rat.

C.4.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study - Rat

In a developmental toxicity study [MRID 00130407], pregnant Fischer 344 rats [35/group] were administered 2,4-dichlorophenoxyacetic acid [97.5%] *via* gavage at dose levels of 0 [corn oil], 8 mg/kg/day, 25 mg/kg/day, and 75 mg/kg/day from gestation day [GD] 6 through gestation day 15.

There were no treatment-related deaths. Two (one control and one low-dose) dams delivered prematurely on gestation day 19 and, in both instances, the offspring produced were of similar size and development as those from full-term delivery. Clinical signs were comparable among the groups. Body weights were comparable among the groups throughout the study, but dams at the high-dose level displayed a decrease in body-weight gain during the dosing period [79% of control for GD 6-15; 57% of control for GD 6-10], although statistical significance was not attained. The corrected body-weight gain was comparable among the groups. Food consumption data were not reported.

There was a slight decrease in pregnancy rate with increasing dose [85%, 85%, 80% and 77%]. The numbers of corpora lutea, implantations, and live fetuses were comparable among the groups, and there were no dead fetuses. The numbers of resorptions, as well as pre- and post-implantation losses, were not adversely affected by treatment. The number of the dams with 100% resorptions was 2, 0, 1, and 1 [control, low-, mid-, and high-dose groups, respectively]. One control, 2 low-, 4 mid-, and 2 high-dose dams had late resorptions. Fetal body weight and crown-rump length were comparable among the groups, as was the sex ratio.

There were no statistically-significant or treatment-related differences in the incidence of fetal external or visceral malformations. There was an increased incidence of skeletal malformations/variations at the high-dose level that included the presence of 7^{th} cervical ribs [4 fetuses in 3 litters *vs* none in the control], presence of 14^{th} rudimentary ribs [4 fetuses in 3 litters *vs* none in the control]; malaligned sternebrae [15 fetuses in 10 litters *vs* 7 fetuses in 7 litters of the control]; reduced ossification of the vertebral arches [6 fetuses in 5 litters *vs*2 fetuses in 1 litter of the control]; and unossified sternebrae # 5 or #6 [73 fetuses in 22 litters (3.32 fetuses/litter) *vs* 62 fetuses in 24 litters (2.58 fetuses/litter)]. Although none of the increases attained statistical significance, they were

attributed to treatment since some of the findings [maligned sternebrae, 14th rudimentary ribs, and reduced ossification of vertebral arches] were also observed in the F1b pups of dams fed 2,4-D at 80 mg/kg/day [actual dose ≈75 mg/kg/day] in the 2-generation reproduction study in the same strain of rat. Additionally, skeletal findings [2nd wavy ribs, lumbar ribs] and missing sternebrae were observed in another developmental toxicity study using a different strain of rat [Sprague-Dawley] at a comparable dose of 87.5 mg/kg/day [2,4-D].

The maternal toxicity NOAEL is 25 mg/kg/day, and the maternal toxicity LOAEL is 75 mg/kg/day, based on decreased body-weight gain.

The NOAEL for developmental toxicity is 25 mg/kg/day, and the developmental toxicity LOAEL is 75 mg/kg/day, based on increased incidence of skeletal abnormalities.

This developmental toxicity study is classified **Acceptable/guideline**, and it satisfies the guideline requirement [OPPTS 870.3700; §83-3(a)] for a developmental toxicity study in the rodent. NOTE: In 1996, it was determined that the original DER [Document No. 003887] was inadequate, and the study was re-evaluated [Document No. 011934]. The NOEL/LOEL were the same in both reviews. The current EXECUTIVE SUMMARY does not alter the no-effect and effect levels but reflects current terminology for the no-observed-adverse-effect level [NOAEL] and lowest-observed-adverse-effect level [LOAEL]. Additionally, the presence of 7th cervical ribs and 14th rudimentary ribs are considered skeletal malformations; previously listed as skeletal variations.

870.3700b Prenatal Developmental Toxicity Study - Rabbit

In a developmental toxicity study [MRID 41747601], artificially-inseminated female New Zealand White rabbits [20/group] were administered 2,4-Dichlorophenoxyacetic acid [96.1%] at dose levels of 0 [aqueous 0.5% methylcellulose], 10 mg/kg/day, 30 mg/kg/day, and 90 mg/kg/day from gestation day 6 through gestation day 18. NOTE: All dose concentrations were corrected for the 96.1% purity of the test material.

There were no treatment-related deaths. Two does at 90 mg/kg/day aborted [days 21 and 24]. Treatment-related clinical signs of toxicity were observed in the two does that aborted [days 21 and 24, after 13 doses each] and included ataxia in both [days 16-19 and after day 13], and decreased motor activity, loss of righting reflex, extremities that were cold to the touch, and dried feces in doe that aborted on day 21. Body weights were comparable among the groups throughout the study, but body-weight gains were decreased at the high-dose level [↓27%] during the dosing period [days 6-19; statistical significance was not attained]. During days 7-8, the low- and mid-dose groups showed no body-weight gain, and the high-dose group displayed a negative body-weight gain [-0.01 grams] compared to the control [+0.01 gram]. During days 15-19, the high-dose group displayed no body-weight gain, and corrected body-weight gain was decreased at the high-dose level [↓23%; statistical significance was not attained] also. Food consumption was comparable among the groups.

Pregnancy rates were comparable among the groups. Comparable numbers of corpora lutea, implantations, and live fetuses were observed among the groups, and there were no dead fetuses. One control doe had 100% resorptions. The number of resorption, pre- and post-implantation losses, and gravid uterine weights were comparable among the groups.

Mean fetal body weight was comparable among the groups. At the high-dose level, there was a significant increase in the percent of live male fetuses [71.2%] compared to the control [52.8%] and other dose groups [low: 54.4%; mid: 59.4%]. At the high-dose level, the fetal incidence [3 fetuses of one litter; $p<0.01$] of hindlimbs turned inward was increased compared to the control (0) and other treatment groups (0), and the same fetuses displayed domed head [hydrocephaly]. This finding is not considered treatment-related. There were no apparent differences in the incidence of external, visceral, or skeletal variations, anomalies, retardations, or malformations among the groups.

The maternal toxicity NOAEL is 30 mg/kg/day, based on abortions, decreased body-weight gain, and clinical signs of toxicity [decreased motor activity, ataxia, loss of righting reflex, extremities cold to the touch] at the maternal toxicity LOAEL of 90 mg/kg/day.

The developmental toxicity NOAEL is 30 mg/kg/day, based on abortions at the developmental toxicity LOAEL of 90 mg/kg/day.

This developmental toxicity study is classified **Acceptable/Guideline**, and it satisfies the guideline requirement [**§83-3(b)/OPPTS 870.3700**] for a developmental toxicity study in rabbits.

C.4.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects - Rat

(1) In an extended dietary one-generation reproductive toxicity study (MRID 47972101), 2,4-dichloro phenoxyacetic acid (2,4-D; 97.85%-98.6% a.i.; *lot #* 2006 2433 8006-USA) was administered to 27 Crl:CD(SD) young adult rats/sex/dose *via* the diet at dose levels of 0, 100, 300, or 600 (females)/800 (males) ppm [equivalent to 0, ≈5, 15, or 30 (females)/40 (males) mg/kg/day] for approximately four weeks prior to mating and continuing through mating (up to 2 weeks), gestation, and lactation. P1 males were exposed for a minimum of 11 weeks including 7 weeks from the initiation of the mating phase. P1 females were exposed until lactation day 22 (LD22). A satellite group of P1 females (12/dose) were subject to the same exposures as the P1 females on the main study (exposure for 4 weeks during the pre-mating, up to 2 weeks during the mating period and during gestation until termination on gestation day 17 (GD 17). Satellite males were not exposed to dietary 2, 4-D except during co-housing with satellite females during the mating period.

P1 Generation: A comprehensive evaluation of P1 male and P1 female reproductive system was conducted, including an evaluation of gonadal function, the estrous cycle, sperm parameters, mating performance, conception, gestation, parturition and lactation, as well as survival, growth and development of the offspring. Selected systemic toxicity parameters were also evaluated in the P1 males and P1 females.
Satellite GD 17 Females: A satellite group of P1 females (12/dose) was included for assessments of selected systemic toxicity parameters, clinical chemistry/hematology, thyroid hormone levels, thyroid weights, plasma 2, 4-D levels, histopathology, and selected reproductive parameters during gestation (corpora lutea and implantation numbers).
F1 Generation: F1 offspring were evaluated for potential effects on the nervous system, immune system, reproductive and endocrine systems, thyroid function, and other systemic toxicity parameters. 2, 4-D plasma levels were also assessed in the F1 offspring. In-life parameters in all F1 offspring included clinical observations, body weights, feed consumption, anogenital distance, nipple retention and puberty onset. Selected F1 offspring were divided into three different groups (Sets 1, 2, and 3) at weaning (postnatal day 21; PND 21). Each set of F1 offspring was maintained on the test diet until PND 60 (Set 1b F1 offspring), ≈PND 70 (Sets 1a and 2a F1 offspring), or ≈PND 90-139 (Sets 2b and 3 F1 offspring).

Set 1a (10/sex/dose): assessment of general systemic and thyroid toxicity, which included clinical chemistry/hematology parameters, thyroid hormone assessment, and urinalysis (males only). Post-mortem evaluations in Set 1a (PND70) included gross pathology, organ weights and histopathology on a wide range of tissues, including thyroids.
Set 1b (10/sex/dose): developmental neurotoxicity (DNT) assessment, which included functional observational battery (FOB), motor activity and acoustic startle response (ASR). On PND 60, Set 1b animals were perfused for central nervous system (CNS) and peripheral nerve neuropathology evaluation and brain morphometry. A special stain (Luxol Fast Blue) was used to evaluate brain myelination.
Set 2a (10sex/dose): assessment of potential developmental immunotoxicity (DIT): examination of humoral immune function using the sheep red blood cell (SRBC) antibody-forming cell (AFC) assay on PND 70-74.
Set 2b (10/sex/dose): assessment of potential developmental immunotoxicity (DIT): examination of innate cellular immunity using the natural killer cell (NK) assay on PND 87-93.
Set 3 (23-27/sex/dose): assessment of reproductive/endocrine toxicity, which included estrous cycle evaluation and post-mortem evaluations that focused on reproductive organs, sperm assessment, and ovarian follicle counts on PND 139. TK analyses were conducted on Set 3 males and females on PND 63 and 84 to determine plasma 2, 4-D levels.

In addition, selected pups culled on PND 4 were used to assess thyroid hormone levels. Additional data were gathered from F1 offspring not assigned to Sets 1-3. On PND 22, unselected weanlings were either perfused for examination of neuropathology (12/sex/dose) or euthanized for assessment of systemic toxicity, which included thyroid

hormone assessment, organ weights, and post-mortem examinations (gross pathology and histopathology) in 10/sex/dose.

Reproductive and selected data from the F1 generation were used to assess whether a second generation would be produced. None of the criteria were met (Table 1), and a second generation was not assessed in this study.

P1 Adult Rats: There were no treatment-related deaths or clinical signs of toxicity in either sex of P1 adults. Body weights and body-weight gains were comparable among the groups during the pre-mating and mating phases (both sexes) and during gestation and the latter part of lactation (dams). Prior to dietary adjustment of 2, 4-D concentration during the second week of lactation, the 600 ppm dams displayed a decrease in body weight (LD 7; ↓5%) and body-weight gain (LD 1-4; ↓64%), which is consistent with reduced food intake during the first week of lactation. The reduction in food intake can be attributed to the increase in the actual dose (≈65 mg/kg/day) above the targeted level (30 mg/kg/day) during this time. After dietary adjustment, food intake for the 600 ppm dams was above control levels.

There were no apparent treatment-related effects on hematology, differential white blood cell counts, and prothrombin time, and clinical chemistry and urinalysis parameters were comparable among the groups (both sexes). P1 males displayed increased kidney weights (absolute and relative) at 800 ppm, which were accompanied by histopathological findings (degenerative lesion in the proximal convoluted tubules in the outer zone of the medulla) and are consistent with previous findings that the kidney is a target organ. There were no treatment-related findings in the P1 female kidney. Decreased reproductive and accessory sex gland weights were observed at 300 ppm and/or 800 ppm. These changes, however, are related to the concurrent control being outside of the laboratory historical control range. P1 females at 600 ppm displayed increased uterine weights (↑17%, both absolute and relative), although statistical significance was not attained. There were no alterations in estrous cycle pattern in the 600 ppm P1 females compared to the control, and no significant difference in mean estrous cycle length in P1 females at any dose level compared to the control. There were no significant, treatment-related effects on sperm motility or progressive motility, no differences in testicular spermatid and epididymal sperm counts, and no differences in the proportion of abnormal sperm. Male and female mating, conception, fertility, and gestation indices were comparable among the groups, and post-implantation loss was comparable among the groups. Both the time to mating and gestation length were comparable among the groups.

GD 17 Satellite Females: All P1 satellite females survived to scheduled sacrifice, and body weights were comparable among the groups. Hematology and clinical chemistry parameters were comparable among the groups. Reproductive indices and the numbers of corpora lutea and implantations were comparable among the groups. There was a slight increase in resorptions at 600 ppm (0.9 vs 1.5), although there was wide variability (standard deviations exceed the means). There was a slight increase in post-implantation loss at 600 ppm (9.2 vs 5.5). It should be noted that this observation was not corroborated since post-implantation losses in the P1 adults of the definitive study were comparable

amongst all dose groups. Both the 100 ppm and 600 ppm females displayed an increase in thyroid weight (↑9%), but there was no dose-response. There were no statistically significant, treatment-related differences in serum T3, T4, or TSH in the GD 17 satellite females. Although the 600 ppm GD 17satellite females displayed the predicted pattern of thyroid hormone changes (↓ T3 and ↓ T4 with ↑TSH levels) that suggest 2, 4-D exposure may adversely affect thyroid function at doses above the renal saturation clearance, the thyroid effects noted below renal saturation are not considered sufficiently robust to be adverse.

F1 Offspring: There were no treatment-related effects on the numbers of live or dead F1 pups born/litter or on pup survival or sex ratio. Slightly lower body weights were observed in the 600 ppm pups during early lactation, which coincided with the dams decreased food intake LD 1-4 and LD 4-7). Pup body weight (600 ppm) remained lower in the 600 ppm pups (↓6%) during PND 14-21. There was no significant, treatment-related difference in absolute or relative anogenital distance in either sex and no differences in nipple/areolae retention between control and high-dose groups in either sex. F1 males at 800 ppm displayed a 1.6 days delay in preputial separation (well within normal variability), which was accompanied by a very slight reduction in body weight compared to the control (↓2.1 grams; 99% of control). The age at vaginal opening was comparable among the groups of F1 females.

F1 Offspring Thyroid Assessments: PND 4 - There were no statistically-significant differences in serum T3, T4, or TSH in PND 4 culled pups. T4 was reduced to a similar extent in both sexes at the 300 ppm (↓14%-15%) and 600 ppm/800 ppm (↓12%-14%) dose levels, and female PND 4 pups showed an incr ease in TSH (↑19%) at 600 ppm. **F1 PND 22 Weanlings** - F1 PND 22 males displayed a statistically-significant reduction (↓28%) in T4 at 800 ppm, and F1 PND 22 females displayed a non-statistically significant reduction (↓20%) in T4 at 600 ppm. T3 was reduced in the males at 300 ppm (↓19%) and 800 ppm (↓13%), but there was no dose response. **F1 PND 62-64** - Both sexes displayed increased TSH at 300 ppm (↑26%) and at 800 ppm (males ↑23%))/600 ppm (females ↑24%)), although the increase in males was not dose-related and none of the differences in thyroid hormone levels were statistically significant. T4 was decreased at 800 ppm in males (↓13%). Though these findings suggest that 2, 4-D exposure may adversely affect thyroid function at doses above the renal saturation clearance, the thyroid effects noted below renal saturation are not considered sufficiently robust to be adverse.

F1 Unselected Offspring (PND 22 weanlings): There were no effects on survival of the unselected weanlings used for systemic toxicity (non-perfused). All treated males displayed a decrease in body weight (↓9%-10%) compared to the control males. Decreased adrenal weights were observed in males at 800 ppm (absolute ↓37% and relative ↓29%). The decreases in kidney (↓15%), liver (↓18%), testes (↓15%), and thyroid (↓14%) weights observed in males at 800 ppm were slightly greater than the body-weight deficit of 10%. Organ weights were comparable among the groups of females. There were no significant differences in perfused absolute brain weights, cerebral lengths and widths or cerebellar lengths and widths in perfused F1 PND 22 weanlings of either sex. There were no neuropathological observations attributed to treatment in the perfused F1

PND 22 weanlings, and no treatment-related changes in myelin in either males at 800 ppm or females at 600 ppm.

F1 Offspring Set 1a (PND 70): All Set 1a pups survived to scheduled sacrifice. Males at 800 ppm displayed decreased body weight (↓11%-17%) and body-weight gains (↓11%-25%) throughout the study period, with the magnitude of the reduction lessening with time of exposure. Females displayed comparable body weight/gain among the groups. Platelet counts were reduced in the 800 ppm males but not in the females at any dose level. Both sexes displayed a slight increase in ALT (↑18%/25%) and an increase in triglyceride (↑31%/43%) levels. Although some of the decreases in organ weights observed in the 800 ppm males may be attributed to the 10% decrease in body weight at termination, the decreases in liver (↓16%), pituitary (↓14%), and adrenal glands (↓12%) might be related to treatment. Increased uterine weights (↑31% absolute and ↑32% relative) were observed at 600 ppm. Although statistical significance was not attained, the finding is considered treatment-related since a similar increase was observed at 600 ppm in the P1 and Set 3 F1 females. Increased ovarian weight (↑9%) was observed in the 600 ppm F1 Set 1a females, although statistical significance was not attained. Increased kidney weights (↑9% absolute and ↑11% relative) were observed in the females at 300 ppm and 600 ppm, although there was no dose-response and kidney weights were comparable among the male groups. Decreased thymus weights (↓12% absolute and ↓10% relative) were observed in females at 600 ppm and in Set 3 females at 600 ppm (↓14% absolute and ↓13% relative). An increased incidence of degeneration of the proximal convoluted tubule in the kidney was observed in males at 300 ppm and 800 ppm and in females at 600 ppm. Regarding the terminal stage of estrous, 2 of 10 females at 300 ppm and 3 of 10 females at 600 ppm displayed proestrus, whereas none of the 10 females in the control and 100 ppm groups displayed proestrus.

F1 Offspring Set 1b (PND 54-56): There were no significant differences in body weight/gain in either sex. There was an increase in the level of urination in all treated male groups compared to the control group, but there was no dose response. There was a 10% reduction in hind limb grip strength at 800 ppm in males and at 600 ppm in females. Males at 800 ppm displayed a decrease in total motor activity (↓10%), whereas females at 600 ppm showed an increase (↑12%). During the first half of the session, all male groups displayed a similar motor activity level (were within 6%), whereas the 800 ppm males showed a progressive lessening of activity with increased time; *i. e.,* the 800 ppm males displayed decreased activity compared to the control (↓11%, ↓16%, ↓30%, and ↓34% in Epochs 5, 6, 7, and 8, respectively). Males at 800 ppm displayed a different acoustic startle response (ASR) initially compared to the control males. There was no apparent difference in ASR in females. There were no significant differences in perfused absolute brain weights, cerebral lengths and widths, or cerebellar lengths and widths in either sex (PND 60). There were no treatment-related (1) microscopic changes in the central or peripheral nervous system in the perfused offspring; (2) changes in myelin; or (3) changes in microscopic measurements of structures in the cerebral cortex, cerebellum, thalamus, or hippocampus.

F1 Offspring Set 2a (PND 67-73): Developmental Immunotoxicity (Primary Immune Response to Sheep Red Blood Cells): There were no deaths. Slight decreases in body weights and body-weight gains were observed in males at 800 ppm (↓6%-10% and ↓15%) and females at 600 ppm (↓8%-9% and ↓10%). Terminal body weights were comparable among the male and female groups. Both absolute (↓10%) and relative (↓8%) thymus weight decreases were observed in the males at 800 ppm and in the females at 600 ppm [absolute (↓13%) and relative (↓10%)]. Males at 300 ppm showed a 17% decrease in thymus weight but no dose response. Spleen weights were slightly lower in females at 600 ppm [absolute (↓13%) and relative (↓14%)]. There was no significant difference in response for AFC/spleen and AFC/10^6 splenocytes among the male groups. Females at 600 ppm displayed a non-significant decrease of 54% for AFC/spleen and 27% for the AFC/10^6 splenocytes.

F1 Offspring Set 2b (PND 67-73): Developmental Immunotoxicity (Natural Killer Cell Activity): There were no deaths, and body weights/gains showed a similar slight reduction in males at 800 ppm as observed in the other offspring groups. Female body weights/gains were comparable among the groups. Terminal body weights (PND 87-93) were comparable among the groups (both sexes). There were no significant treatment-related effects on absolute or relative spleen or testes weights in males, and no significant treatment-related effects on spleen weights in females (only organs weighed). There were no significant, treatment-related differences in the percent target cell cytotoxicity at any dose level compared to control (both sexes), and 2, 4-D did not alter the cytotoxic ability of splenic NK-cells in male or female rats at any dose level.

F1 Offspring Set 3 (PND 90 or 139): Reproductive Toxicity: There were no treatment-related deaths or clinical signs of toxicity. Terminal body weights were comparable among the groups (both sexes). No significant differences were observed in mean estrous cycle length at any dose level compared to the control. There were no significant, treatment-related effects on the numbers of small follicles, growing follicles, or total follicles. There were no significant, treatment-related effects on sperm motility or progressive motility, no differences in testicular spermatid and epididymal sperm counts, and no differences in the proportion of abnormal sperm between the control and 800 ppm males. Absolute (↓9%) and relative (↓8%) pituitary gland weights were significantly lower in the 800 ppm males and absolute (↓9%) and relative (↓10%) pituitary gland weights were non-significantly lower in the 600 ppm females. There was no associated histopathology in the pituitary glands. Uterine weights were increased at 300 ppm (↑10% absolute and ↑10% relative) and 600 ppm (↑10% absolute and ↑11% relative) compared to the controls. Thymus weights were decreased (↓14% absolute and ↓13% relative) in females at 600 ppm, although statistical significance was not attained. No histopathological changes were observed in the pituitary or thymus in either sex. A degenerative lesion was observed in the kidney (proximal convoluted tubule) in both sexes at 300 ppm and at 600 ppm/800 ppm. Ovarian follicle counts were comparable between the control and 600 ppm females (PND 139).

The parental systemic LOAEL is 800 ppm (45.3 mg/kg/day in males), based on nephrotoxicity manifested as increased kidney weights, and degenerative lesions in

the proximal convoluted tubules in the main study P1 rats. The parental systemic NOAEL is 300 ppm (16.6 mg/kg/day in males). No toxicologically relevant effects were identified in P1 females or in the GD 17 satellite female groups at the highest dose tested (600 ppm; 40.2 mg/kg/day).

The thyroid toxicity NOAEL is established at 800/600 ppm (45.3 mg/kg/day in males and /40.2 mg/kg/day in females), the highest dose tested. The thyroid effects noted in the database were considered to be adaptive.

The offspring (F1 adults) LOAEL is 800/600 ppm (55.6 mg/kg/day in males and 46.7 mg/kg/day in females), based on kidney toxicity manifested as increased kidney weights and increased incidence of degeneration of the proximal convoluted tubules. The offspring NOAEL is 300 ppm (20.9/ mg/kg/day in males and 23.3 mg/kg/day in females).

The F1 offspring (PND 22) LOAEL is 800/600 ppm, based on decreased body weight observed throughout lactation. The offspring NOAEL is 300 ppm. The dose on a mg/kg/day basis for the PND 22 F1 offspring was not calculated.

The DNT offspring (PND 21-60) LOAEL is >800/600 ppm (81.7 mg/kg/day in males, 59.2 mg/kg/day in females), based on the lack of evidence of DNT (FOB parameters, motor activity, and acoustic startle response). The DNT offspring NOAEL is 800 ppm/600 ppm (81.7 mg/kg/day in males, 59.2 mg/kg/day in females).

The DIT offspring (PND 139) LOAEL is >800/600 ppm (71.8 mg/kg/day in males, 55.3 mg/kg/day in females), based on the lack of evidence of DIT [SRBC antibody-forming cell assay (PND 66-70) and Natural Killer Cell assay (PND 87-93)]. The DIT offspring NOAEL is 800/600 ppm (71.8 mg/kg/day in males and 55.3 mg/kg/day in females), the highest dose tested.

The reproductive LOAEL is > 800/600 ppm (45.3 mg/kg bw/day in males, 40.2 mg/kg bw/day in females), based on the lack of effect on estrous cyclicity, (P1 females, satellite GD 17 dams, Set 3 F1 offspring) or reproductive indices (mating, fertility, time to mating, gestation length, pre-and post-implantation loss, number of corpora lutea (satellite GD 17 dams), sperm parameters, ovarian follicle counts, and reproductive organ histopathology). The reproductive NOAEL is 800/600 ppm (45.3 mg/kg bw/day in males, 40.2 mg/kg bw/day in females), the highest dose tested.

This study is classified **Acceptable/non-guideline**. The study does not satisfy a guideline requirement for 2, 4-D. It satisfies the data call-in requirements for 2, 4-D for OCSPP 870.3800 (Reproduction and Fertility Effects), OCSPP 870.6300 (Developmental Neurotoxicity), OCSPP 870.7800 (Immunotoxicity). The study is in accordance with the OECD extended one-generation reproductive toxicity study guideline (OECD 443, 416; November, 2010).

COMMENT: The major change is a change in the offspring (F1 adults) LOAEL from 300 ppm to 600 ppm, making the new NOAEL 300 ppm. Both the PMRA and EPA do not consider the kidney effects occurring at PND 70 and PND 139 to be adverse at the 300 ppm dose level in either sex. Although there was some degeneration in the males at 300 ppm on PND 70, this did not correlate with increased kidney weight and was not really different from controls on PND 139. One would expect the degeneration to be worse after a prolonged exposure. There is clear correlation in both sexes at 800/600 ppm and at both time points.

A few typos were identified subsequent to the finalization of the DER, which include: (1) in the paragraph for P1 adult rats on page 3, it should have indicated that no alterations were observed in estrous cycle pattern in the P1 females rather than F1 females; (2) page 50, first line should read from PND 21-69 (not PND 21-56).

(2) In a 2-generation reproduction study (MRID 00150557 and MRID 00163996), 30 F0 Fischer 344 rats/sex/dose were administered 2,4-D (97.5% a.i.) *via* the diet for 105 days prior to mating and through gestation and lactation of two litters and for 30 days after weaning of the last litter at target dose levels of 0, 5, 20, and 80 mg/kg/day. Rats were mated, one male with one female. The resulting F1a litters were weaned at day 28 *post partum*. After a two-week rest period, the Fo parental rats were re-bred using different male/female combinations to produce the F1b litters, from which 30 males/30 females/group were selected to become the F1 parents. The F1 generation (30 rats/sex/group) was administered the test material at target dose levels of 0, 5, or 20 mg/kg/day [high dose level dropped due to excess toxicity; there were an insufficient number of F1b pups] *in utero* and continuously *via* the milk or feed for 126 days postnatally and prior to mating and through gestation and lactation to two litters (F2a and F2b) and for 30 days after weaning the last litter.

There were no apparent treatment-related deaths, and clinical signs were comparable among the groups throughout the study. During the pre-mating dosing period, body weights of the F0 parental animals were slightly lower (males ↓3%-5% by week 6; females ↓4%-5% by week 13)) at the high-dose levels for both sexes. Body weight gains of the F0 high-dose males were decreased initially (weeks 2-3; ↓14%) and overall (weeks 0-13 and weeks 0-40; ↓7%), as were these of the high-dose females [weeks 0-1 (↓21%); weeks 0-13 (↓8%); weeks 0-40 (↓6%).

The high-dose F0 dams displayed a significantly lower body weight throughout gestation [F1a litter (↓5%-6%)] and by gestation day 20 during F1a pregnancy (↓10%). The high-dose F0 dams displayed a significant reduction in body weight gains during both gestation periods, with the greater deficit being observed during the second gestation period [F1a liters: days 0-7 (↓33%*); days 13-20 ↓5%); days 0-20 (↓13%); F1b litters: days 0-7 (↓30%*); days 13-20 (↓41%**); days 0-20 (↓33%**)]. The high-dose F0 dams displayed decreased body weight on day 7 of lactation (both litters: ↓7%-8%), but body weights were significantly increased compared to the controls at day 28 of lactation (F1a↑8%/F1b ↑11%). Body weight gains were significantly reduced during lactation days 1-7 for both litters (F1a ↓60%; F1b ↓94%). Overall, however, the high-dose dams

displayed positive body weight gains during lactation days 1-28 compared to negative body weight gains in the control and other treatment groups.

Food consumption (g/rat/day) during the pre-mating period was slightly lower (↓5%-6%) in the high-dose females during a few weeks, but on a g/kg/day basis, both sexes at the high dose displayed a slight increase (↑4%) in food consumption compared to the control. During the first week of the 2-week rest period following the weaning of the first letter, the F0 dams displayed a significant decrease in food consumption (↑16%-17%). Food consumption was decreased at the high-dose level during both gestation periods (F1a during first 2 weeks (↑7%-9%); F1b during the third week (↑18%). A significant decrease in food consumption was observed throughout lactation (both litters) at the high dose (F1a litter (↓42%); F1b litter (↓17%-29%). At necropsy, no treatment-related adverse effects were observed at any dose level, although the F0 females displayed increased kidney weights at all dose levels, but there was no dose response.

There were no apparent, treatment-related, adverse effects on body weights or body weight gains of the F1 parental animals during the pre-mating dosing period at the two remaining dose levels, although the mid-dose males (20 mg/kg/day) displayed an initial decrease in body weight gain [weeks 35-36 (↓9%**) and weeks 36-37 (↓11%**)]. At 20 mg/kg/day, there were no significant differences in body weights in the F1 dams during gestation (F2a litters ↓1%-5%; F2b litters ↓4%-5%) or body weight gains [F2a litters ↓15% (days 7-13); F2b litters ↓17% (days 0-7); ↓14% (days 13-20); ↓10% (days 0-20)], and comparable body weights/gains were observed during lactation (both litters). Food consumption was comparable among the groups (both sexes) throughout the study. At necropsy, no treatment-related adverse effects were observed at either dose level, although the F1 males and females displayed slightly increased kidney weights at the 20 mg/kg/day dose level, and the females at this dose displayed a slight increase in liver weight.

F0 Generation: No apparent adverse effect was observed on fertility. Pre-coital intervals were comparable among the groups. The duration of gestation was significantly increased in the high-dose (80 mg/kg/day) F0 females producing the F1b pups (22.5 days *vs* 21.9 days), although the delay was less than a day. The gestation survival index was comparable among the groups for the F1a pups but significantly decreased for the F1b litters (31.7% vs 97.8%). There was a significant decrease in the number of female fetuses at the high dose (39% vs 54%). The number of F1b pups born dead/dying by day 1 (110) was significantly increased at the high-dose level compared to the control (5). F1a litter size was slightly lower at the high-dose level compared to the control (9.0 vs 10.1), but F1b litter size was significantly lower than the control (5.1** vs 9.5). The F1a pup viability was comparable throughout weaning, but F1b pup viability was significantly lower throughout the weaning period. There was a significant decrease in F1b pup survival to lactation day 4 at the high-dose level (86%) compared to the control (100%) and other dose groups (≥98%), as well as survival to lactation day 28 (71% vs 99%-100% in control and other dose groups). Decreased pup body weight (F1a males ↓11%/F1a females ↓10% on day 1; F1a males ↓25%/F1a females ↓19% on day 28/F1b males ↓22%/F1b females ↓15% on day 1; F1b males ↓27%/F1b females ↓24% on day 28)

and decreased body weight gains (F1a males ↓32%/F1a females ↓30% on days 1-4; F1a males ↓25%/F1a females ↓20% on days 4-28/F1b males ↓74%/F1b females ↓57% on days 1-4; F1b males ↓24%/F1b females ↓22% on days 4-28) were observed at the high dose level, with the F1b litters displaying the greater effect. At the mid-dose level, there was a slight decrease in body weight (F1a males ↓7%/females ↓6%); F1b males ↓16%/females ↓13% on day 28) and body weight gains (F1a males ↓8%/females ↓7%; F1b males ↓17%/females ↓15% during days 4-28), with the F1b litters displaying the greater effect.

Skeletal anomalies and reduced ossification were observed in the high-dose F1b pups (80 mg/kg/day) that were dead at birth (only dose level examined).

F1 Generation. No apparent adverse effect was observed on fertility at either dose level. Pre-coital intervals and gestation lengths were comparable among the groups. The gestation survival index and viability index were comparable among the groups for both the F2a and F2b litters. Litter size, pup body weights, and sex ratio were comparable among the groups in both the F2a nad F2b litters.

Degenerative changes in the tubules of the cortical region (high-dose F0 males) and outer medullary regions (mid- and high-dose F0 males, mid-dose F1 males) of the kidneys were found in a subsequent histopathological examination. The original reviewer noted that these effects on the kidney were not found originally but during a subsequent re-examination of the tissues, casting doubt on the quality of the histopathological examination of the reproductive organs. However, the RfD/QA Peer Review Committee determined that, based on the lack of effects on reproductive organs in the subchronic and chronic studies at similar or higher dose levels, reevaluation of these tissues (testes and ovaries) is not necessary (HED Document No. 011908, dated 5/9/96).

The NOAEL for parental toxicity is 5 mg/kg/day (target dose; actual dose range of 3.8-13.5 mg/kg/day) and the parental LOAEL is 20 mg/kg/day (target dose; actual dose range of 14-48 mg/kg/day), based on decreased female body weight/body weight gain (F1) and male renal tubule alteration (F0 and F1).

The NOAEL for reproductive toxicity is 20 mg/kg/day (target dose; actual dose range of 18-35 mg/kg/day). Previously, the LOAEL for reproductive toxicity was set at 80 mg/kg/day (target dose; actual dose range of 69-114 mg/kg/day), based on an increase in gestation length. However, the increase (<1 day) is not considered adverse. The dose of 80 mg/kg/day was not assessed in the second generation due to the lack of sufficient F1 offspring to mate (excessive pup mortality). The dose is above the threshold of saturation of renal clearance. Reproductive toxicity was not observed in this study.

The NOAEL for offspring toxicity is 5 mg/kg/day (target dose; actual dose range of 7.2-13.5 mg/kg/day) and the LOAEL for offspring toxicity is 20 mg/kg/day (target dose; actual dose range of 26-48 mg/kg/day), based on decreased pup body weight (F1b). At 80 mg/kg/day (target dose; actual dose range of 76.1-133 mg/kg/day), there was an increase in pup deaths.

This 2-generation reproduction study is classified **Acceptable/guideline**. This study satisfies the guideline requirement (OCSPP 870.3800) for a 2-generation reproduction study in the rat.

C.4.4 Chronic Toxicity

870.4100a (870.4300) Chronic Toxicity – Rat

In a combined chronic toxicity/carcinogenicity study [MRID 43612001], 50 Fischer 344 rats/sex/group were administered 2,4-dichlorophenoxyacetic acid [96.4%] *via* the diet for up to 24 months at concentrations of 0, 5 mg/kg/day, 75 mg/kg/day, and 150 mg/kg/day. The achieved doses were 4.77, 73.15, and 144.98 mg/kg/day [males] and 4.89, 73.11, and 143.52 mg/kg/day [females], respectively. Additionally, 10 rats/sex/group were sacrificed at 12 months [interim sacrifice]. NOTE: The interim sacrifice data were reported in MRID 43293901, HED Document No. 011614, along with the chronic neurotoxicity screening battery substudy.

There were no treatment-related deaths or clinical signs of toxicity. Decreased body weight was observed throughout the study at the high-dose level in both sexes [males 92%-96%/females 74%-90% of control] and at the mid-dose level in females [86%-90% of control]. At week 13, decreased body weight was very slight in the high-dose males [96% of control] and somewhat greater in the high-dose females [90% of control]. At study termination, both sexes displayed decreased body weight at the high-dose level [males 92%/females 74% of control] with the females displaying a greater effect than males. The mid-dose females also displayed a decrease in body weight at study termination [86% of control]. Body-weight gains were decreased throughout the study in females [3-month interval (86% and 74% of control); 6-month interval (88% and 71% of control), and overall (77% and 52% of control)] at the mid- and high-dose levels, respectively. Similarly, high-dose males displayed decreased body-weight gains throughout the study [83%-87% of control]. Consistent with the decreased body-weight gains was a decrease in food consumption, which was observed at the mid-dose level in females [-3.9%] and in both sexes at the high-dose level [males (-4.7%)/females (-11.6%)].

Ophthalmology findings at study termination consisted of increased incidences of constricted blood vessels, fundus and hyper-reflective, fundus in the high-dose males and an increased incidence of lens opacity in the high-dose females compared to the control and lower dose groups. Decreased RBC, HCT, and HGB values were observed at various time points in the mid- and high-dose females, and platelet counts were decreased at various time points in both sexes at the mid- and high-dose levels. Elevations in creatinine were observed in both sexes at the mid- and high-dose levels throughout the study, except at termination when comparable levels were observed among the male groups. Increased aspartate aminotransferase [mid- and high-dose males], alanine aminotransferase [mid- and high-dose males], and alkaline phosphatase [mid- and high-dose, both sexes], and decreased glucose levels [mid-dose females, high-dose both

sexes], cholesterol [mid- and high-dose, both sexes], and triglycerides [mid-dose females and high-dose both sexes] were observed throughout the study, although a dose response was not always apparent. There was a dose-related decrease in T4 values throughout the study in both sexes at the mid- and high-dose levels, and the females displayed the greater effect except at study termination.

Thyroid weights were increased in the mid-dose females and in both sexes at the high-dose level at the 12-month interim sacrifice. At study termination, thyroid weights were increased in both sexes at the mid- and high-dose levels, although the mid-dose males did not attain statistical significance and the increase at the mid-dose level [both sexes] was greater than at the high-dose level. Decreased testes weights were observed at the high-dose level at both the interim and terminal sacrifices and at the mid-dose level at study termination, although statistical significance was not attained at the mid dose. Decreased ovarian weights were observed at the high-dose level at both sacrifice times and in the mid-dose females at study termination. The decreases in testes and ovarian weights are consistent findings in other studies on 2,4-D and its salts/esters. Kidney weights were increased only at the interim sacrifice in males at the mid- and high-dose levels [dose-related].

Gross pathology findings included decreased fat in high-dose females at both sacrifice times, multifocal pale foci in the lungs [interim: 1 mid-dose, 10 high-dose females; terminal: 4 high-dose males, one control, 4 mid-, 40 high-dose females], and lens opacity in high-dose females at termination. Microscopically, there were increased incidences of lesions in the bone marrow [decreased hematopoiesis in high-dose females at the interim sacrifice], eyes [retina degeneration in 1 male and 9 females at high dose], kidney [proximal tubule degeneration in mid- and high-dose males and females], liver [altered tinctorial properties in mid-dose females and both sexes at high dose], lungs [multifocal alveolar histiocytosis in mid-dose females and both sexes at high dose], adipose tissue [atrophy in mid-dose female, both sexes at high dose], testes [atrophy at high dose], and thyroid [hyperplasia-high-dose males; hypertrophy and epithelial cells-high-dose females] at the interim sacrifice. At study termination, there were increased incidences of cataracts and retina degeneration of the eyes in both sexes at the high-dose level, and the severity of the retina degeneration was increased also. In the liver, there was an increased incidence of increased size of the hepatocytes with altered tinctorial properties in both sexes at the high-dose level. In the lungs, both the incidence and severity of inflammation were increased at the high-dose level in both sexes, and the incidence of atrophy of the adipose tissue was increased at the high-dose level in both sexes at termination. Tumor incidence was not affected by treatment.

The NOAEL is 5 mg/kg/day. The LOAEL of 75 mg/kg/day is based on decreased body-weight gain (females) and food consumption (females), alterations in hematology [decreased RBC (females), HGB (females), platelets (both sexes)] and clinical chemistry parameters [increased creatinine (both sexes), alanine and aspartate aminotransferases (males), alkaline phosphatase (both sexes), decreased T4 (both sexes), glucose (females), cholesterol (both sexes), and triglycerides (females)], increased thyroid weights (both sexes at study termination), decreased

testes and ovarian weights, and microscopic lesions in the lungs (females). At the high-dose level, there were microscopic lesions in the eyes, liver, adipose tissue, and lungs. There was no treatment-related increase in the incidence of any tumor.

This chronic toxicity/carcinogenicity study is classified ACCEPTABLE/Guideline, and it satisfies the guideline requirement [OPPTS 870. 4300; §83-5] for a chronic toxicity/carcinogenicity study in the rat.

NOTE: The current study was performed to address whether the finding of an increased incidence of astrocytomas of the brain found in the 1986 rat study [MRID 00160876; TXR# 0005234] was attributable to 2,4-D. The HED Carcinogenicity Peer Review Committee [CPRC; TXR No. 0050017] concluded that the doses used in the 1986 rat study were not adequate to assess the carcinogenic potential of 2,4-D. In the 1986 study, there was a significant trend for astrocytomas in male rats but no pair-wise significance. The incidence in both the treated and control males exceeded the historical control incidence for this tumor. Additionally, the CPRC concluded that the high-dose level in the 1986 study was not adequate. The current repeat chronic toxicity/carcinogenicity study in rats was performed at higher dose levels. There was one astrocytoma in the brain of males at the high dose *vs* none in the control. There was one tumor each in the control and high-dose female group. However, all of the brains of the rats in the low- and mid-dose groups were not examined. The HED Carcinogenicity Peer Review Committee [CPRC; TXR No. 0050017] requested that the slides of the low- and mid-dose brains of the males be evaluated. These additional data were submitted [MRID 44284501], and no additional tumors were observed. The additional data do not alter the findings of the study.

870.4100b Chronic Toxicity - Dog

In a chronic oral toxicity study [MRID 43049001], 5 beagle dogs/sex/group were administered 2,4-dichlorophenoxyacetic acid [96.7%] *via* the diet for 52 weeks at concentrations of 0, 1 mg/kg/day, 5 mg/kg/day, and 7.5 mg/kg/day. The target high-dose level of 10 mg/kg/day was reduced to 7.5 mg/kg/day during week 8, due to loss of body weight/failure to gain weight early in the study.

There were no treatment-related deaths or clinical signs. One female at 5 mg/kg/day was sacrificed on Day 130 in a moribund condition; however, death was attributed to an abdominal inflammatory condition. Decreased body weight was observed throughout the study at the high-dose level in both sexes, with females displaying the greater effect. By week 3, high-dose females displayed a 13% deficit in body weight compared to the control females. At the high-dose level at 8 weeks when the dose level was lowered, both sexes at the high-dose level displayed decreased body weight compared to the controls [males 90%/females 82% of control]. At week 13, the high-dose males were 94% of control and the high-dose females were 82% of control. At study termination, both sexes displayed decreased body weight at the mid- [males 89%/females 87% of control] and high-[males 87%/females 75% of control] dose levels compared to the controls. The low-dose females also displayed a decrease [87% of control] in body weight at study

termination. Body-weight gain was decreased throughout the study in females at all dose levels [weeks 1-13 (75%, 70%, and 35% of control); 1-52 (73%, 64%, and 36% of control) at the low-, mid-, and high-dose levels, respectively]. Similarly, males displayed decreased body-weight gains throughout the study (except the low-dose group during weeks 1-13) compared to the control, although there was no dose-response [weeks 1-13 (100%, 70%, 74% of control); 1-52 (78%, 63%, 67% of control]. Food consumption was decreased throughout most of the study, mainly at the high-dose level [both sexes], but statistical significance was not attained.

Ophthalmology findings were comparable among the groups for both sexes. There were no apparent treatment-related alterations in hematology or urinalysis among the groups for either sex. Elevations in blood urea nitrogen, creatinine, and alanine aminotransferase, and decreased glucose levels [mid-dose males, high-dose both sexes] were observed throughout the study [mid- and high-dose levels, both sexes], although a dose response was not always apparent, especially in the males. Alkaline phosphatase was decreased in both sexes at the high-dose level at week 4. Similar alterations in these clinical chemistry parameters have been observed in subchronic studies in rats and dogs on 2,4-D, and its amine salts and esters.

There was a dose-related decrease in absolute brain weight in females, with statistical significance being attained at the mid- and high-dose levels. Males at the high dose also displayed decreased brain weight, but statistical significance was not attained. In general, the organ-weight effects observed can be attributed to the lower body weight, although the decreased testes weights at the high-dose level and decreased ovarian weights at the mid- and high-dose levels are consistent findings in other studies on 2,4-D and its salts/esters. Microscopically, liver [perivascular, chronic active inflammation (males 1/5, 1/5, 3/5, 4/5; females 0/5, 0/4, 4/5, 3/5 with increasing dose) and sinusoidal lining cell pigment (females; 1/5, 2/4, 5/5, 4/5 with increasing dose)] and kidney [minimal increase in the frequency and average severity of pigment in the tubular epithelium (males 2/5, 4/5, 5/5, 5/5; females 1/5, 1/4, 5/5, 5/5 with increasing dose)] lesions were observed at the mid- and high-dose levels in both sexes. Aspermatogenesis and degeneration were observed in one male at the high-dose level compared to none in the other groups.

The NOAEL is 1 mg/kg/day. The LOAEL of 5 mg/kg/day is based on decreased body-weight gain (both sexes) and food consumption (females), as well as alterations in clinical chemistry parameters [increased BUN, creatinine, and alanine aminotransferase, decreased glucose] in both sexes, decreased brain weight in females, and histopathological lesions in the liver and kidneys.

This chronic oral toxicity study is classified **Acceptable/Guideline**, and it satisfies the guideline requirement [OPPTS 870. 4100; §83-1] for a chronic, non-rodent, oral toxicity study.

C.4.5 Carcinogenicity

870.4200a Carcinogenicity Study - rat

In a chronic toxicity/carcinogenicity study with **a chronic neurotoxicity screening battery substudy** [MRID 43293901], 50 Fischer 344 rats/sex/group [main study]; 15/sex/group [substudy] were administered 2,4-dichlorophenoxyacetic acid [96.4%] *via* the diet for up to 24 months at concentrations of 0 [basal diet], 5 mg/kg/day, 75 mg/kg/day, and 150 mg/kg/day [achieved doses were 4.6, 71.2, and 141.1 mg/kg/day [males] and 4.6, 68.0, and 138.9 mg/kg/day [females], respectively. Additionally, 10 rats/sex/group were sacrificed at 12 months [interim sacrifice]. *NOTE: This DER presents the results of the interim [one-year] sacrifice and neurotoxicity substudy.*

There were no treatment-related deaths or clinical signs of toxicity. Decreased body weight was observed throughout the first year of the study at the high-dose level in both sexes [males 91%/females 88% of control at the interim sacrifice] and at the mid-dose level in females [94% of control at the interim sacrifice]. At 90 days, the decrease in body weight was very slight in the high-dose males [96% of control] and somewhat greater in the mid- [95% of control] and high-dose [90% of control] females. Body-weight gains were decreased throughout the first year at the mid- and high-dose levels in both sexes, although statistical significance was not always attained in males at the mid-dose level [2-week interval (males: mid-dose 90%/high-dose 84%; females: mid-dose 81%/high-dose 63% of control); 3-month interval (males: mid-dose 98%/high-dose 88%; females: mid-dose 87%/high-dose 75% of control); and 1-year interval (males: mid-dose 95%/high-dose 82%; females: mid-dose 89%/high-dose 73% of control). Consistent with the decreased body-weight gains was a slight decrease in food consumption, which was observed in both sexes at the high-dose level.

Ophthalmology findings were comparable among the groups at the interim sacrifice. Decreased RBC [mid- and high-dose females (6 & 12 months) and high-dose males (12 months)], HCT [mid- and high-dose females and high-dose males (6 & 12 months)], HGB [high-dose females (6 months)], WBC 9high-dose females (6 months)], and platelet counts [mid- and high-dose females and high-dose males (6 & 12 months) were observed. A dose-related increase in aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase was observed in the mid- and high-dose males at 6 months but not at 12 months. The mid- and high-dose females displayed a dose-related increase in alkaline phosphatase values at both the 6 and 12-month intervals. Cholesterol levels were decreased in the mid- (males at 12 months only) and high-dose rats of both sexes at both time intervals. T4 values were decreased at both time points in both sexes at the mid- and high-dose levels, although the mid-dose males at 6 months did not attain statistical significance. The only urinalysis finding was a decrease in specific gravity , which was observed in both sexes and time points at the mid- and high-dose levels.

Thyroid weights [absolute and relative] were statistically-significantly increased in the mid-dose females [≈20% greater than control] and in both sexes at the high-dose level [≈20% greater than control] at the 12-month interim sacrifice. Decreased testes weights [absolute and relative to brain] were observed at the high-dose level at 12 months [≈15% lower than control]. Kidney weights [absolute and relative] were increased at the 12-

months sacrifice in males at the mid- [7%-12% greater than control] and high-dose [8%-16% greater than control] levels [dose-related].

Gross pathology findings included decreased fat in high-dose females [4/10] and multifocal pale foci in the lungs [1/10 mid-dose, 10/10 high-dose females]. Microscopically, there were increased incidences of lesions in the bone marrow [decreased hematopoiesis in high-dose females], eyes [bilateral retina degeneration in 1 male and 10 females at high dose], kidney [proximal tubule degeneration in mid- and high-dose males and females], liver [altered tinctorial properties in mid-dose females and both sexes at high dose], lungs [multifocal , subacute to chronic inflammation (mid-dose females, both sexes at high dose), alveolar histiocytosis in females at high dose], adipose tissue [atrophy in mid- and high-dose females], testes [atrophy at high dose], and thyroid [decreased secretory material, epithelial cells-high-dose females].

The NOAEL is 5 mg/kg/day. The LOAEL of 75 mg/kg/day is based on decreased body weight (females)/body-weight gain (both sexes), alterations in hematology [decreased RBC, HCT, and platelets (females)], clinical chemistry parameters [increased alanine and aspartate aminotransferases (males), alkaline phosphatase (both sexes), decreased cholesterol (both sexes), and decreased T4 (both sexes)], and urinalysis [decreased specific gravity (both sexes)], increased kidney weights (males), increased incidence of degeneration of the descending proximal tubules (both sexes), hepatocellular hypertrophy with altered tinctorial properties (females), lung inflammation (females), adipose tissue atrophy (females). At the high-dose level, there also were microscopic lesions in the eyes (both sexes), liver (males), testes (males), thyroid (females), and lungs (males).

Neurotoxicity Study

No treatment-related, hand-held, FOB observations were noted at any of the evaluation periods. Relative forelimb grip strength was significantly increased in both sexes at the high-dose level, but there was no treatment-related change in absolute grip strength. There was no treatment-related effect on motor activity. In agreement with the chronic toxicity portion of the study, an increased incidence of bilateral retinal degeneration was observed in the high-dose females.

The NOAEL for neurotoxicity is 75 mg/kg/day, based on increased relative forelimb grip strength and increased incidence of bilateral retinal degeneration at the LOAEL of 150 mg/kg/day.

This chronic toxicity/neurotoxicity study in the rat is classified **Acceptable/guideline**, and it satisfies the guideline requirement [OPPTS 870. 6200; §82-7] for a subchronic neurotoxicity study in the rat.

870.4200b Carcinogenicity (feeding) - Mouse

In a carcinogenicity study [MRID 43879801 and 43597201], 50 $B_6C_3F_1$ CRL BR mice/sex/group were administered 2,4-dichlorophenoxyacetic acid [96.4%] *via* the diet for 104 weeks at concentrations of 0, 5 mg/kg/day [both sexes], 62 [males]/150 [females] mg/kg/day, and 120 [males]/300 [females] mg/kg/day. Additionally, 10 mice/sex/group were sacrificed at 52 weeks [interim sacrifice].

There were no treatment-related deaths or clinical signs of toxicity in either sex. Body weight, body-weight gain, and food consumption were comparable among the male groups throughout the study. Females at the high-dose level displayed a slightly lower body weight at the 3- and 6-month intervals [96% of control]. Body-weight gains were decreased significantly at all dose levels in the females at the 3-month interval [93%, 94%, and 86% of control at the low-, mid-, and high-dose, respectively], and the high-dose females continued to display a reduced body-weight gain at the 6-month [91% of control] and 12-month [91% of control] intervals. There were no consistent changes in food consumption in the female groups.

Ophthalmology and hematology parameters [RBC, HGB, HCT, platelets] were comparable among the groups [both sexes]; no thyroid parameters were monitored.

There was a dose-related increase in kidney weights in both sexes. In males, increased kidney weights [absolute and relative] were observed at the mid- and high-dose levels at the terminal sacrifice only. In females, increased kidney weights were observed at the mid- and high-dose levels at both the interim and terminal sacrifices.

Gross pathology findings were comparable among the groups [both sexes]. Microscopically, there was an increased incidence of lesions in the kidneys of both sexes at the mid- and high-dose levels. In males at the interim/terminal sacrifices, renal lesions were characterized as degeneration with regeneration of the descending limb of the proximal tubule in the mid- [20%/50%] and high-dose [100%/96%] males *vs* none in the low dose or control males; decreased vacuolization of the renal proximal tubule in mid- [80%/78%] and high-dose [100%/96%] males *vs* 0% in the low-dose and control males. Additionally at the terminal sacrifice, there was an increased incidence of mineralization of the tubule(s) in the mid- [58%] and high- [72%] dose males compared to the low and control groups [38% and 32%, respectively]. In females, the renal lesions were characterized by hypercellularity in the descending part of the proximal tubule at both the interim and terminal sacrifices at the mid- [80%/64%] and high-dose [100%/50%] levels *vs* 0% in the low- and control females. There was no treatment-related increase in any tumor type in either sex.

The NOAEL is 5 mg/kg/day. The LOAEL of 62 mg/kg/day [males]/150 mg/kg/day [females] is based on an increased absolute and/or relative kidney weights and an increased incidence of renal microscopic lesions. There was no treatment-related increase in the incidence of any tumor type.

This carcinogenicity study is classified ACCEPTABLE/Guideline, and it satisfies the guideline requirement [OPPTS 870. 4200; §83-2] for a carcinogenicity study in the mouse.

NOTE: In the mouse study, there was an increase in hemangiosarcomas of the spleen in male mice at the low and mid doses, which was not sustained at the highest dose; however, the slides from all male mice at the low and mid doses were not evaluated. The HED Carcinogenicity Peer Review Committee [CPRC; TXR No. 0050017] requested that the slides of the low- and mid-dose spleens of the males be evaluated. These additional data were submitted [MRID 44284502]. The spleen of 35 male mice in the low-dose [5 mg/kg/day] group and 33 in the mid-dose [62.5 mg/kg/day] group were examined by light microscopy. No neoplasms were observed. When all of the data on the 50 male mice/group were combined, there was no dose-related increase in hemangiosarcomas or in possible preneoplastic lesions, such as extramedullary hematopoiesis. It was concluded that the additional data do not alter the findings of the study. There was another mouse carcinogenicity study [MRID 40061801] conducted at dosages of 1, 15, and 45 mg/kg/day. No treatment-related increase in tumor incidence was found; however, this latter study was classified unacceptable because the high dose was considered inadequate to assess the carcinogenic potential of 2,4-D.

C.4.6 Mutagenicity

Gene Mutation

870.5100, Bacterial reverse mutation test 41409801 Acceptable/guideline	No evidence of bacterial mutation with or without S9.
870.5450, Unscheduled DNA synthesis assay 41409807 Acceptable/guideline	No evidence of induction of unscheduled DNA synthesis.
870.5395, In vivo mouse micronucleus test 41409804 Acceptable/guideline	No significant increase in frequency of micronucleated polychromatic erythrocytes in bone marrow at any time point.
Literature studies	Office of Pesticide Programs, EPA, Reevaluation of the Genetic Toxicology Profile of 2,4-D (December 12, 2011).

C.4.7 Neurotoxicity

870.6200 Acute Neurotoxicity Screening Battery

In an acute neurotoxicity study (MRID 43115201), Fischer 344 rats (10/sex/dose) were orally administered 2,4-D (96.6% a.i.; Lot# 909) once *via* gavage at doses of 0 (corn oil), 15, 75, or 250 mg/kg (actual dose: 0, 13, 67, or 227). Neurobehavioral evaluations, consisting of Functional Operational Battery (FOB) and motor Activity, were conducted pre-study (-Day 1), on Day 1 (≈5-6 hours post dose, peak-effect time), and on Days 8 and 15 post dose. At terminal sacrifice (Day 15), rats were euthanized and neuropathological examination was performed on control and treated rats (5/sex/dose).

No treatment-related mortalities occurred during the study. No significant differences were noted in the mean body weights or mean body weight gains in either sex. Clinical signs and neurobehavioral evaluation revealed treatment-related changes. During the Day

1 FOB evaluations, increased incidences of incoordination (6/10 males; 4/10 females) and slight gait abnormalities, described as forepaw flexing or knuckling, were observed in high-dose rats (8/10 males; 8/10 females). Slight gait abnormalities, observed in a single mid-dose female, were not judged to be treatment-related since no other signs of toxicity were evident. Minimal gait abnormalities, not judged to be treatment-related, were observed in one low-dose female and one each mid- and high-dose male. On the Day 2 and Day 3 clinical examinations, incoordination was noted in high-dose rats. The incidence of incoordination decreased to control levels by Day 4 in males and Day 5 in females. In high-dose rats, total motor activity was significantly lower at Day 1 only. No treatment-related gross or neuropathological findings were present.

Based on the results of this study, the LOAEL for systemic toxicity was not determined in males and females; the NOEL for systemic toxicity was 227 mg/kg in males and females. The LOEL for neurobehavioral effects was 227 mg/kg in males and females; the NOEL for neurobehavioral effects was 67 mg/kg in males and females.

This study is classified as Acceptable/Guideline, and it satisfies guideline requirements (§81-8) for an acute neurotoxicity screening battery in the rat.

870.6200 Subchronic Neurotoxicity Screening Battery

See under Chronic toxicity/carcinogenicity - rat

870.6300 Developmental Neurotoxicity Study

See under 2-generation reproduction study (EOGRT)

C.4.8 Metabolism

870.7485 Metabolism - Rat

The metabolism of [phenyl-U-C14]-2,4-D was studied in male & female Fischer 344 rats (MRID 47417901). The phenyl ring-labeled compound was administered as a single oral dose of 1.04 - 1.05 or 97.1 - 97.4 mg/kg, or as a single oral dose of 1.06 mg/kg following a 14 day pretreatment with unlabeled 2,4-D at approximately 1 mg/kg/day.

At least 85.5-93.7% of an oral dose was absorbed from the GI tract. Among the orally dose groups, approximately 85.5-93.7% of the dose was eliminated in urine and 3.6-10.5% of the dose was eliminated in feces. In the IV-dose groups approx. 90.94-91.84% of the dose was eliminated in urine and 1.99-2.16% of the dose was eliminated in feces. At sacrifice, total radioactive residue in the carcass was less than 0.52-0.69% of the dose at the low oral dose and 1.17-2.57% at the high oral dose. No differences between the sexes were found as to extent of absorption or excretion at any dose level. At the high dose level, it appears that a non-linear region (of decreased clearance) was reached in the disposition of 2,4-D.

Parent 2,4-D was the major metabolite found in the urine, amounting to 72.9-90.5% of the dose among the orally dosed animals of the main experiment. Small amounts of uncharacterized compounds A and B (0.6-1.3% and 0.0-0.7% of the dose, respectively), were found in the urine. Classified as acceptable.

870.7600 Dermal Absorption - Rat

There is 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 Ross. EPA principally relied on an *in vivo* human study, which showed an average dermal absorption of 5.8% (Feldman). 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 selected a value of 10 percent.

C.4.9 Immunotoxicity

870.7800 Immunotoxicity

In an extended dietary one-generation reproductive toxicity study (MRID 47972101), 2,4-dichloro phenoxyacetic acid (2,4-D; 97.85%-98.6% a.i.; *lot #* 2006 2433 8006-USA) was administered to 27 Crl:CD(SD) young adult rats/sex/dose *via* the diet at dose levels of 0, 100, 300, or 600 (females)/800 (males) ppm [equivalent to 0, ≈5, 15, or 30 (females)/40 (males) mg/kg/day] for approximately four weeks prior to mating and continuing through mating (up to 2 weeks), gestation, and lactation. F1 offspring were evaluated for potential effects on the immune system. F1 offspring were maintained on the test diet until ≈PND 70 (Set 2a F1 offspring) or ≈PND 90-139 (Set 2b F1 offspring).

Set 2a (10sex/dose): assessment of potential developmental immunotoxicity (DIT): examination of humoral immune function using the sheep red blood cell (SRBC) antibody-forming cell (AFC) assay on PND 70-74.
Set 2b (10/sex/dose): assessment of potential developmental immunotoxicity (DIT): examination of innate cellular immunity using the natural killer cell (NK) assay on PND 87-93.

F1 Offspring Set 2a (PND 67-73): Developmental Immunotoxicity (Primary Immune Response to Sheep Red Blood Cells): There were no deaths. Slight decreases in body weights and body-weight gains were observed in males at 800 ppm (↓6%-10% and ↓15%) and females at 600 ppm (↓8%-9% and ↓10%). Terminal body weights were comparable among the male and female groups. Both absolute (↓10%) and relative (↓8%) thymus weight decreases were observed in the males at 800 ppm and in the females at 600 ppm [absolute (↓13%) and relative (↓10%)]. Males at 300 ppm showed a 17% decrease in thymus weight but no dose response. Spleen weights were slightly lower in females at 600 ppm [absolute (↓13%) and relative (↓14%)]. There was no significant

difference in response for AFC/spleen and AFC/10^6 splenocytes among the male groups. Females at 600 ppm displayed a non-significant decrease of 54% for AFC/spleen and 27% for the AFC/10^6 splenocytes.

F1 Offspring Set 2b (PND 67-73): Developmental Immunotoxicity (Natural Killer Cell Activity): There were no deaths, and body weights/gains showed a similar slight reduction in males at 800 ppm as observed in the other offspring groups. Female body weights/gains were comparable among the groups. Terminal body weights (PND 87-93) were comparable among the groups (both sexes). There were no significant treatment-related effects on absolute or relative spleen or testes weights in males, and no significant treatment-related effects on spleen weights in females (only organs weighed). There were no significant, treatment-related differences in the percent target cell cytotoxicity at any dose level compared to control (both sexes), and 2, 4-D did not alter the cytotoxic ability of splenic NK-cells in male or female rats at any dose level.

The DIT offspring (PND 139) LOAEL is >800/600 ppm (71.8 mg/kg/day in males, 55.3 mg/kg/day in females), based on the lack of evidence of DIT [SRBC antibody-forming cell assay (PND 66-70) and Natural Killer Cell assay (PND 87-93)]. The DIT offspring NOAEL is 800/600 ppm (71.8 mg/kg/day in males and 55.3 mg/kg/day in females), the highest dose tested.

This study is classified **Acceptable/guideline,** and it satisfies the guideline requirement (870.7800) for an immunotoxicity study.

C.4.10 Special/Other Studies

(1) In a pharmacokinetic titration study (MRID 47417902), adult, non-pregnant female Sprague-Dawley Crl:CD(SD) rats (4/dose) were administered 2,4-D (99% a.i.; Lot # 2006 2433 8006-USA)) in the diet at 0, 100, 200, 400, 600 or 800 ppm for 29 days. These doses (time-weighted average doses) were equivalent to 0, 7, 15, 30, 45, and 58 mg/kg/day. The test material intake during the last week of dosing averaged 0, 7, 14, 27, 41, and 56 mg/kg/day. The parameters evaluated included daily cage-side observations, weekly clinical examinations, body weights, food consumption, and gross pathological examinations. To calculate systemic exposure, diurnal area under the plasma concentration time curve (AUC_{24h}) was determined by collecting 3 blood samples (6:00 am, 9:00 am, and 5:00 pm) the day after the 4-week exposure period.

All rats survived to scheduled sacrifice, and there were no treatment-related signs of toxicity. Females at the 600 ppm and 800 ppm dose levels displayed reduced body-weight gains (↓29% and ↓58%, respectively) after one week of exposure and overall (↓18% and ↓33%, respectively), compared to control. At termination, body weights were slightly reduced (↓4% and ↓8%, respectively) at the 600 ppm and 800 ppm dose levels. No changes were observed at necropsy.

The difference in the AUC_{24h} between the 100 ppm (21.2 µg h mL^{-1}) and 200 ppm (67.6 µg h mL^{-1}) dose groups was 3-fold, which is greater than the expected 2-fold from the

actual doses ingested. Compared to the lowest dose (100 ppm), there was an 11- (233 µg h mL^{-1}), 31- (650 µg h mL^{-1}), and 60-(1285 µg h mL^{-1}) fold difference in AUC_{24h} at 400 ppm, 600 ppm, and 800 ppm, respectively.

The study report states that in all cases, C_{max} was found to be at the time of the first blood sampling (6:00 am; Figure 1, from page 28 of the report), corresponding to active feeding right before the lights are turned on (Saghir, *et al.*, 2006). However, the individual data show that one 200 ppm female and two 400 ppm females displayed higher levels at 9:00 am than at 6:00 am; one 100 ppm female showed nearly identical levels at 6:00 am and 9:00 am and the highest level was observed at 5:00 pm; one 200 ppm female and one 800 ppm female displayed the highest level at 5:00 pm (Table 4).

2, 4-D was eliminated from the plasma at the same rate constant corresponding to an elimination half-life of 4 to 8 hours.

COMMENT: Although it is acknowledged that the dose groups are small (4 rats/dose), there is considerable variability among the rats, which resulted in the standard deviations being, in several cases, greater than the means.

This pharmacokinetic titration study in female, non-pregnant rats is classified Acceptable/non-guideline. There is no guideline requirement for this type of study. The purpose of the study was to better characterize the pharmacokinetics of 2, 4-D in adult, non-pregnant Sprague-Dawley rats following dietary exposure for use in setting dose levels for the extended 1-generation reproduction study (MRID 47972101). In the initial dietary dose range-finding study (MRID 47417901; separate abbreviated DER), the dose spread at the lower levels (100 ppm and 400 ppm) in the female rats did not allow a clear definition of the dose at which nonlinear kinetics likely began.

(2) In a dose range-finding/pharmacokinetics study (MRID No. 47417901), male and female Sprague-Dawley Crl:CD(SD) rats (10/sex/dose) were administered 2,4-D (99% a.i.; Lot # 2006 2433 8006-USA) in the diet at dose levels of 0, 100, 400, 1000/800, 2000/1200, or 1600 ppm during the premating period (≈4 weeks). Due to marked effects on food consumption and body weights at the highest dose levels, dietary adjustments were made to the 1000 ppm and 2000 ppm dose levels on test day 20 (TD 20). The dietary concentrations provided doses of 6, 23, 50, 86, and 92 mg/kg/day for P1 males and 7, 27, 60, 91, and 103 mg/kg/day for P1 females (average values from pre- and post-mating and postweaning intakes). A few days prior to breeding, 4 P1 adult rats/sex/dose were subjected to timed blood collection (3 samples/rat/day). Rats were mated for a maximum of 2 weeks, and exposure of the P1 males continued for ≈7 weeks after the start of the mating phase, with timed blood collection (3 samples/rat/day from 4 males/dose) prior to termination. P1 females were exposed through gestation and with timed blood collection (same as for P1 males) on lactation days 4 and 14 (LD 4 and LD 14), and post-weaning on TD 95, the day prior to termination. Milk samples were collected on LD 4 and LD 14 (4 females/dose). A satellite group of P1 female rats (6/dose) was included for an assessment of 2, 4-D pharmacokinetics during gestation. Satellite females were subjected to the same exposure schedule as the main study P1

females through mating (≈4 weeks premating, up to 2 weeks during mating phase) and also during gestation until termination on gestation day (GD) 17. Blood was collected from satellite females on GD 17 with timed blood collection (3 samples/rat) from 4 pregnant females/dose. All rats were examined twice daily for clinical signs of toxicity and morbidity. Clinical observations, body weights, and food consumption were monitored weekly (both sexes), and reproductive performance was evaluated. Kidney weights were recorded for all rats, and histopathology of the kidney was evaluated in the control and high-dose rats (both sexes).

Litters were culled on postnatal (PND) 4 to 10 pups (5/sex when possible). Litter parameters (litter size, pup body weight, and sex ratio) were recorded. Pups were weaned on PND 21 and group housed from PND 21-28 to minimize post-weaning stress. Thereafter, pups were housed individually. On PND 4, 14, 21, and 28, terminal blood samples were collected from 1 pup/sex/litter from 4 litters/dose. Timed blood samples (3 samples/rat from 4/sex/dose) were collected from PND 35 rats. During the exposure period, body weight, food consumption, and cageside observations were recorded in the F1 offspring.

There were no treatment-related effects on conception, time to mating, gestation length, or pup sex ratio. At 2000/1200 ppm, the fertility (80%) index was reduced compared to the control (100%). At 1600 ppm, both the mating (80%) and fertility (70%) indices were reduced compared to the control (100%). According to the investigators, the small sample size, omission of uterine staining for implantation sites, and the lack of gross or microscopic examination preclude a determination of whether the findings were treatment-related. P1 males showed comparable body weight/gain among the groups, whereas P1 females at 2000/1200 and 1600 ppm dose levels displayed decreased body weight/gains (overall ↓50% and ↓63%, respectively) and food consumption during the premating and mating periods. Gestation body weight/gain were variable, but mainly lower at the 1600 ppm (GD 17: ↓16%) and 2000/1200 ppm (GD 17: ↓13%) dose levels. Body weights of the dams during lactation were comparable among the groups, although body-weight gains during the first week of lactation were reduced at the 2000/1200 ppm (↓26%) and 1600 ppm (↓22%) levels. Increased kidney weights were observed at 1600 ppm (P1 males) and at ≥ 1000/800 ppm (P1 females), and multifocal, degenerative lesions in the proximal convoluted tubules of the renal medulla were found on microscopic examination in P1 males at ≥400 ppm and in females at ≥800 ppm.

Pup survival was comparable among the groups through LD 7. At 1600 ppm, decreased survival was observed on LD 14, and this group was terminated prior to LD 21. By LD 21, decreased survival was observed at 2000/1200 ppm (↓30%). Decreased pup body weights were observed by LD 4 at 1600 ppm (both sexes ↓15%-17%), by LD 7-LD 21 at 2000/1200 ppm (males ↓21%-41%/females ↓24%-44%), and by LD 14 at 1000/800 ppm (males ↓14%-23%/females ↓13%-20%). At 1000/800 ppm, post-weaning (PND 28-35) body weights (males ↓33%-35%/females ↓30%-32%) and body-weight gains (males ↓37%/females ↓36%) were decreased compared to the control.

This study provides plasma levels of 2, 4-D for both the maternal rats and pups of both sexes, as well as 2, 4-D levels in maternal milk. An estimated dose to the pups was not provided. These data may be useful in future assessments regarding lactational exposure.

Dose levels for the extended one-generation reproduction study were selected based on the results of this study and a pharmacokinetic titration study (MRID 47417902; separate DER). The kidney findings confirm the gender-based difference in the renal clearance of 2,4-D in adult rats. Based on this gender difference, different high-dose levels were selected for males and females for the definitive extended one-generation reproductive toxicity test. The male high dose was ≈40 mg/kg/day (dietary concentration 800 ppm), a dose that was anticipated to be slightly higher than the inflection point for nonlinear TK in male pups from PND 35 to adulthood. The female high dose was ≈ 30 mg/kg/day (600 ppm), which was anticipated to be clearly higher than the inflection point in pups and female adults. The mid- and low-dose levels were the same for male and female rats. The low dose of 5 mg/kg/day (100 ppm) was predicted to identify a clear NOAEL and was consistent with the NOEL dose identified in the previously conducted 2,4-D dietary 2-generation reproduction study (MRID 00150557; Tasker, 1985). If exposure-related effects were seen in the high-dose group, the mid-dose of 15 mg/kg/day (300 ppm) was expected to provide dose-response data relevant to human risk evaluation (unless these effects were limited to doses clearly above linear TK). It was anticipated the 300 ppm mid-dose would be slightly above the inflection point for non-linear TK in female adults and pups and within the range of linear TK for adult males and post-weaning male pups. The dose levels selected for use in the extended one-generation reproduction study on 2, 4-D were 100, 300, or 600 (females)/800 ppm (males). During protocol review, a dose level of 50 mg/kg/day was discussed as an appropriate high dose, which was considered adequate for assessing effects slightly above renal clearance saturation.

This dose range-finding study is classified **Acceptable/non-guideline**. There is no guideline requirement for this type of study. The purpose of the study was to provide information for use in setting dose levels for the extended 1-generation reproduction study (MRID 47972101).

Appendix D. HEC/HED Calculations

HEC Calculations for Occupational/Residential Exposure:

- Assume occupational handler exposure for 8 hrs/day and 5 days/week.
- Assume residential bystander exposure for 24 hrs/day and 7 days/week.
- For residential handler exposure, there is no duration adjustment.

$HEC = NOAEL_{study}$ * (daily duration of $exposure_{animal}$/daily duration of $exposure_{human}$) * (days/week of $exposure_{animal}$/days/week of $exposure_{human}$) * RDDR

Occupational Handler HEC = 0.05 mg/L * (6/8) * (5/5) * 1.49 = 0.056 mg/L.
Residential Bystander HEC = 0.05 mg/L* (6/24)*(5/7)* 1.49 = 0.013 mg/L.
Residential Handler HEC = 0.05 mg/L * 1.49 = 0.075 mg/L.

Route-to-Route Extrapolation

HED's route-to-route extrapolation converts human and animal values from mg/L concentrations to mg/kg oral equivalent doses. The equation uses a single conversion factor to account for default body weights and respiratory volumes.

Using the HEC calculated (based upon squamous metaplasia, epithelial hyperplasia with mixed inflammatory cells within larnyx), a conversion of the inhalation concentration to a dose (mg/L to mg/kg/day) was conducted as follows:

Human-Equivalent Dose (HED, mg/kg/day) = Dose (HEC value, mg/L) x A x CF (L/hr/kg) x D (hours) = mg/kg

Where:

A	=	absorption: ratio of deposition and absorption in respiratory tract compared to absorption by the oral route (1).
CF	=	conversion Factor; a L/hr/kg factor which accounts for respiratory volume and body weight for a given species and strain (11.8).
D	=	duration; duration of daily animal or human exposure (hours).

Therefore, the occupational human equivalent dose for 2,4-D is calculated as follows:

Occupational Handler HED:
(0.05 mg/L) x (6/8) x (5/5) x 1.49 x 1 x (11.8 L/hr/kg) x (8 hrs) = 5.29 mg/kg/day

Residential Handler HED:
(0.05 mg/L) x 1.49 x 1 x (11.8 L/hr/kg) x (2 hrs) = 1.76 mg/kg/day

HEC and HED calculations are summarized in Table D.1. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X due to the calculation of HECs accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. The intraspecies uncertainty factor remains at 10X. Since a NOAEL was not attained in the inhalation study, a 10X uncertainty factor is required for LOAEL to NOAEL extrapolation.

Table D.1: Inhalation HEC and HED Calculation Summary						
Population	Scenario	Tox duration adjustment		HEC		HED
		hr/day	day/wk	mg/L	mg/m3	(mg/kg-day)
Occupational	Handler	8	5	0.056	55.88	5.29
Residential	Handler	NA	NA	0.0745	74.5	1.76
	Bystander	24	7	0.0133	13.3	NA

Summary

The route-specific subchronic inhalation study in rats was selected to evaluate inhalation exposures. The NOAEL was not determined. The LOAEL of 0.05 mg/L is based on histopathological findings in the larynx (squamous metaplasia and epithelial hyperplasia with increased mixed inflammatory cells within the larynx). Human equivalent concentrations (HECs) were derived using the LOAEL and the regional deposited dose ratio (RDDR). The RDDR accounts for the particulate diameter [mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD)] and estimates the different dose fractions deposited along the respiratory tract. The RDDR also accounts for interspecies differences in ventilation and respiratory tract surface areas. For the subchronic inhalation toxicity study with 2,4-D, a RDDR was estimated at 1.49 based on portal of entry effects (histopathological findings in the larynx) seen at the LOAEL of 0.05 mg/L, with a MMAD of 1.7 μm and GSD of 1.98.

Human equivalent doses (HEDs) were subsequently calculated from the HECs for residential and occupational handler scenarios. HEC and HED calculations are summarized in Table D.1. The standard interspecies extrapolation uncertainty factor can be reduced from 10X to 3X due to the calculation of HECs accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. The intraspecies uncertainty factor remains at 10X. Since a NOAEL was not attained in the inhalation toxicity study, a 10X uncertainty factor is required for LOAEL to NOAEL extrapolation.

Appendix E. Review of Human Research

Human Studies Review

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from PHED 1.1; the AHETF database; the Outdoor Residential Exposure Task Force (ORETF) database; and the Residential SOPs, are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[14].

[14] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

Appendix F. Tolerance Summary for 2,4-D.

Tolerance Summary for 2,4-D (40 CFR §180.142).			
Commodity	Established Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments
(a) General			
Almond hulls	0.1	0.10	
Asparagus	5.0	5.0	
Barley, bran	4.0	4.0	
Barley, grain	2.0	2.0	
Barley, hay	-	50	Recommended in Memo T. Goodlow, D340921, 10/18/07
Barley, straw	50	50	
Berry, group 13	0.2	0.10	Harmonize with Codex
Cattle, fat	0.3	0.30	
Cattle, kidney	4.0	4.0	
Cattle, meat	0.3	0.30	
Cattle, meat byproducts, except kidney	0.3	0.30	
Corn, field, forage	6.0	10	Recommended in Memo, A. LaMay, D389455, 8/8/13
Corn, field, grain	0.05	0.05	
Corn, field, stover	50	50	
Corn, pop, grain	0.05	0.05	
Corn, pop, stover	50	50	
Corn, sweet, forage	6.0	6.0	
Corn, sweet, kernel plus cob with husks removed	0.05	0.05	
Corn, sweet, stover	50	50	
Cotton, gin byproducts	-	1.5	Recommended in Memo, A. Lamay, D423374, xx,xx,2015
Cotton, undelinted seed	-	0.08	Recommended in Memo, A. Lamay, D423374, xx,xx,2015
Cranberry	0.5	0.50	
Fish	0.1	0.10	
Fruit, citrus, group 10	3.0	2.0	Harmonize with Canada
Fruit, pome, group 11	0.05	0.10	Recommended in Memo, T. Goodlow, D336596, 4/16/07
Fruit, stone, group 12	0.05	0.10	Recommended in Memo, T. Goodlow, D336596, 4/16/07
Goat, fat	0.3	0.30	
Goat, kidney	4.0	4.0	
Goat, meat	0.3	0.30	
Goat, meat byproducts, except kidney	0.3	0.30	
Grain, aspirated fractions	40	40	
Grape	0.05	0.10	Recommended in Memo, T. Goodlow, D336596, 4/16/07
Grass, forage	360	360	
Grass, hay	300	300	
Hop, dried cones	0.2	0.20	
Horse, fat	0.3	0.30	
Horse, kidney	4.0	4.0	
Horse, meat	0.3	0.30	
Horse, meat byproducts, except kidney	0.3	0.30	
Millet, forage	25	25	
Millet, grain	2.0	2.0	

Tolerance Summary for 2,4-D (40 CFR §180.142).			
Commodity	Established Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments
Millet, hay	-	50	Recommended in Memo T. Goodlow, D340921, 10/18/07
Millet, straw	50	50	
Milk	0.05	0.05	
Nut, tree, group 14	0.2	0.20	
Oat, forage	25	25	
Oat, grain	2.0	2.0	
Oat, hay	-	50	Recommended in Memo T. Goodlow, D340921, 10/18/07
Oat, straw	50	50	
Pistachio	0.05	0.05	
Potato	0.4	0.40	
Rice, grain	0.5	0.50	
Rice, hulls	2.0	2.0	
Rice, straw	10	10	
Rye, bran	4.0	4.0	
Rye, forage	25	25	
Rye, grain	2.0	2.0	
Rye, straw	50	50	
Sheep, fat	0.3	0.30	
Sheep, kidney	4.0	4.0	
Sheep, meat	0.3	0.30	
Sheep, meat byproducts, except kidney	0.3	0.30	
Shellfish	1.0	1.0	
Sorghum, grain, forage	0.2	0.20	
Sorghum, grain, grain	0.2	0.20	
Sorghum, grain, stover	0.2	0.20	
Soybean, forage	0.02	0.02	
Soybean, hay	2.0	2.0	
Soybean, seed	0.02	0.01	Recommended in Memo, A. LaMay, D389455, 8/8/13
Strawberry	0.05	0.10	Recommended in Memo, T. Goodlow, D336596, 4/16/07
Sugarcane, cane	0.05	0.05	
Sugarcane, molasses	0.2	0.20	
Teff, bran	4.0	4.0	
Teff, forage	25.0	25.0	
Teff, grain	2.0	2.0	
Teff, straw	50.0	50.0	
Vegetable, leaves of root and tuber, group 2	0.1	0.10	
Vegetable, root and tuber, except potato, group 1	0.1	0.100	
Wheat, bran	4.0	4.0	
Wheat, forage	25	25	
Wheat, grain	2.0	2.0	
Wheat, straw	50	50	
(c) Tolerances with regional registrations.			
Rice, wild, grain	0.05	0.05	
(d) Indirect or inadvertent residues.			
Animal feed, nongrass, group 18	0.2	0.20	
Avocado	0.05	0.05	
Cotton, undelinted seed	0.05	-	Recommendation to delete and move to general section (a) in Memo, A. Lamay, D423374, xx,xx,2015

Tolerance Summary for 2,4-D (40 CFR §180.142).			
Commodity	Established Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments
Dill, seed	0.05	0.05	
Okra	0.05	0.05	
Vegetable, brassica leafy, group 5	0.4	0.40	
Vegetable, bulb, group 3	0.05	0.05	
Vegetable, cucurbit, group 9	0.05	0.05	
Vegetable, foliage of legume, group 7	0.2	0.20	
Vegetable, fruiting, group 8	0.05	0.05	
Vegetable, leafy, except brassica, group 4	0.4	0.40	
Vegetable, legume, group 6	0.05	0.05	

International Residue Limits

2,4-D (PC Code: 030001; Date of Request: 01/07/2016)

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[1]	Codex[2]
40 CFR 180.142: Plant/Livestock: 2,4-D (2,4-dichlorophenoxyacetic acid), both free and conjugated, determined as the acid		(2,4-dichlorophenoxy)acetic acid		2,4-D
Commodity	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[1]	Codex[2]
Almond hulls	0.1			
Asparagus	5.0	5.0		
Barley, bran	4.0			
Barley, grain	2.0			
Barley, straw	50			
Berry, group 13	0.2	0.01 Bushberry subgroup 13-07B		0.1 berries and other small fruits
Cattle, fat	0.3	0.3		
Cattle, kidney	4.0	3		5 Edible offal (mammalian)
Cattle, meat	0.3	0.3		0.2 meat from mammals other than marine mammals)
Cattle, meat byproducts, except kidney	0.3	0.3		5 Edible offal (mammalian)
Corn, field, forage	6.0			
Corn, field, grain	0.05	0.05		0.05
Corn, field, stover	50			40
Corn, pop, grain	0.05			
Corn, pop, stover	50			
Corn, sweet, forage	6.0			
Corn, sweet, kernel plus cob with husks removed	0.05	0.05		0.05 (*)
Corn, sweet, stover	50			
Cotton, undelinted seed	0.08			
Cotton, gin by-products	1.5			
Cranberry	0.5	0.5		0.1 berries and other small fruits
Fish	0.1			
Fruit, citrus, group 10	3.0	2.0		1 citrus fruits Po
Fruit, pome, group 11	0.05	0.05		0.01 pome fruits (*)

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[1]	Codex[2]
Fruit, stone, group 12	0.05	0.05		0.05 stone fruits (*)
Goat, fat	0.3	0.3		
Goat, kidney	4.0	3		5 Edible offal (mammalian)
Goat, meat	0.3	0.3		0.2 meat from mammals other than marine mammals)
Goat, meat byproducts, except kidney	0.3	0.3		5 Edible offal (mammalian)
Grain, aspirated fractions	40			
Grape	0.05			0.1 berries and other small fruits
Grass, forage	360			
Grass, hay	300			400 hay or fodder (dry) of grasses
Hop, dried cones	0.2			
Horse, fat	0.3	0.3		
Horse, kidney	4.0	3		5 Edible offal (mammalian)
Horse, meat	0.3	0.3		0.2 meat from mammals other than marine mammals)
Horse, meat byproducts, except kidney	0.3	0.3		5 Edible offal (mammalian)
Millet, forage	25			
Millet, grain	2.0			
Millet, straw	50			
Milk	0.05	0.03		0.01 milks
Nut, tree, group 14	0.2			0.2
Oat, forage	25			
Oat, grain	2.0			
Oat, straw	50			
Pistachio	0.05			
Potato	0.4	0.4		0.2
Rice, grain	0.5			0.1
Rice, hulls	2.0			
Rice, straw	10			10
Rye, bran	4.0			
Rye, forage	25			
Rye, grain	2.0			2
Rye, straw	50			
Sheep, fat	0.3	0.3		
Sheep, kidney	4.0	3		5 Edible offal (mammalian)
Sheep, meat	0.3	0.3		0.2 meat from mammals other than marine mammals)
Sheep, meat byproducts, except kidney	0.3	0.3		5 Edible offal (mammalian)
Shellfish	1.0			
Sorghum, grain, forage	0.2			
Sorghum, grain, grain	0.2			0.01 (*)
Sorghum, grain, stover	0.2			
Soybean, forage	0.02			
Soybean, hay	2.0			0.01 soya bean fodder (*)

Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[1]	Codex[2]
Soybean, seed	0.02	0.02		0.01 soya bean (dry) (*)
Strawberry	0.05	0.05		
Sugarcane, cane	0.05			0.05
Sugarcane, molasses	0.2			
Teff, bran	4.0			
Teff, forage	25.0			
Teff, grain	2.0			
Teff, straw	50.0			
Vegetable, leaves of root and tuber, group 2	0.1			
Vegetable, root and tuber, except potato, group 1	0.1			
Wheat, bran	4.0			
Wheat, forage	25			
Wheat, grain	2.0			2
Wheat, straw	50			100
MRLs with No US Equivalent				
Eggs		0.01		0.01 (*)
Fat of hogs		0.05		
Meat of hogs		0.05		
Meat byproducts of hogs		0.05		
Fat of Poultry		0.05		
Poultry meat		0.05		0.05 (*)
Poultry, edible offal of		0.05		0.05 (*)
Completed: M. Negussie; 01/16/2016				

[1] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.
[2] * = absent at the limit of quantitation; Po = postharvest treatment, such as treatment of stored grains. PoP = processed postharvest treated commodity, such as processing of treated stored wheat. (fat) = to be measured on the fat portion of the sample. MRLs indicated as proposed have not been finalized by the CCPR and the CAC.

(c) *Tolerances with regional registrations.* Tolerances with regional registration, as defined in §180.1(l), are established for residues of the herbicide, plant regulator, and fungicide 2,4-D, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels is to be determined by measuring residues of 2,4-D (2,4-dichlorophenoxyacetic acid), both free and conjugated, determined as the acid, in or on the follow commodities:

Commodity	**Parts per million**
Rice, wild, grain	0.05

(d) *Indirect or inadvertent residues.* Tolerances are established for indirect or inadvertent residues of the herbicide, plant regulator, and fungicide 2,4-D, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerances levels is to be determined by measuring residues of 2,4-D (2,4-dichlorophenoxyacetic acid), both free and conjugated, determined as the acid, in or on the following commodities:

Commodity	**Parts per million**
Animal feed, nongrass, group 18	0.2
Avocado	0.05
Cotton, undelinted seed	0.05
Dill, seed	0.05

Okra	0.05
Vegetable, brassica leafy, group 5	0.4
Vegetable, bulb, group 3	0.05
Vegetable, cucurbit, group 9	0.05
Vegetable, foliage of legume, group 7	0.2
Vegetable, fruiting, group 8	0.05
Vegetable, leafy, except brassica, group 4	0.4
Vegetable, legume, group 6	0.05

Appendix G. Physical and Chemical Properties of the Various Forms of 2,4-D

NOTE: Taken from Revised Reregistration Eligibility Decision Memo, T. Dole, 2005, D316597.							
Active ingredient (PC Code)	Color	Physical State	Melting Point/ Boiling Point	Density/ Specific Gravity	Octanol/Water Partition Coeff.	Vapor Pressure	Solubility
2,4-D acid (030001)	white	crystalline solid	m.p. 138-141C	s.g.=1.416 at 25C	Log K_{OW} 0.001 M sol'n pH 5 2.14 pH 7 0.177 pH 9 0.102	1.4 x 10^{-7} mmHg at 25C	water = 569 mg/L at 20C g/100 g at 25 C acetone = 85.0 benzene = 1.07 diethyl ether = 220 ethanol = 130.0 isopropanol = 31.6 toluene = 0.067 xylene = 0.58
2,4-D Na salt (030004)	white	powder	m.p. 200C	bulk = 42.2 lb/ft^3 at 25C	Not available; salt dissociates to Na+ and 2,4-D anion in water		water = 4.5 g/100 mL at 25 C
2,4-D DEA salt (030016)	cream	powder	m.p. 83C	bulk = 0.762 g/cm3 at 25 C	2.24 x 10^{-2} at 25 C	9.98 x 10^{-8} mmHg at 25C	mg/g at 25 C water = 806 acetonitrile = 47 ethanol = 280 n-octanol = 36
2,4-D DMA salt (030019)	amber	aqueous liquid	m.p. 118-120 C (PAI)	s.g. = 1.23 at 20 C	Not available; salt dissociates to DMA+ and 2,4-D anion in water	<1 x 10^{-7} mm Hg at 25 C	g/100 mL at 20 C water = 72.9 (pH 7) acetonitrile = 1.06 hexane = 3.59 methanol = >50 g/100 g n-octanol = 5.41 toluene = 0.165
2,4-D IPA salt (030025)	amber	aqueous liquid	m.p. 121 C (PAI)	s.g. = 1.15 at 20 C	Not available; salt dissociates to IPA+ and 2,4-D anion in water		g/100 mL at 20 C water = 17.4 (pH 5.3) acetonitrile = 2.16 hexane = 0.00436 methanol = >50 g/100 g n-octanol = 3.11 toluene = 0.336

NOTE: Taken from Revised Reregistration Eligibility Decision Memo, T. Dole, 2005, D316597.							
Active ingredient (PC Code)	Color	Physical State	Melting Point/ Boiling Point	Density/ Specific Gravity	Octanol/Water Partition Coeff.	Vapor Pressure	Solubility
2,4-D TIPA salt (030035)	amber	aqueous liquid	m.p. 87-110 C (PAI)	s.g. = 1.21 at 20 C	Not available; salt dissociates to TIPA+ and 2,4-D anion in water		g/100 mL at 20 C water = 46.1 (pH 7) acetonitrile = 12.3 Isopropanol = 14.4 Acetone = 11.7 methanol = >50 g/100 g n-octanol = 7.6 toluene = 0.6
2,4-D BEE (030053)	dark amber	liquid	b.p. 89 C	s.g. = 1.225 at 20 C	log = 4.13-4.17 at 25 C	2.4 x 10^{-6} mm Hg at 25 C	g/100 mL at 20 C water = insoluble acetone = >53.6 acetonitrile = >48.6 hexane = >46.3 methanol = >49.6
2,4-D 2-EHE (030063)	dark amber	liquid	b.p. 300 C	s.g. = 1.152 at 20 C	log = 5.78 (temp not available)	3.6 x 10^{-6} mm Hg at 25 C	water = 86.7 ppb g/100 mL at 20 C acetone = >54.0 acetonitrile = >49.1 hexane = >45.7
2,4-D IPE (030066)	pale amber	liquid	b.p. 240 C	s.g. = 1.252 at 25 C	253.8 ± 44.4 (temp not available)	5.3 x 10^{-6} mbar	water = 0.023 g/100 mL fully miscible in dichloromethane, hexane, isopropanol, and toluene

Appendix H. Summary of Occupational Handler Inhalation Risk Estimates

Exposure Scenario (equipment/use site)		Application Rate	Amount Handled / Area Treated	Inhalation MOE (LOC = 300)			
				No-R	PF5 R	PF10	EC
M/L for Granulars							
Aerial	Non-cropland	4 lb ai/acre	350 acres	**180**	890	1,800	3,600
	Irrigation and Ditchbank Applications; Fallowland and Crop Stubble; Non-cropland	2 lb ai/acre	350 acres	360	1,800	3,600	7,300
	Aquatic areas, non-flowing water (e.g., ponds, lakes, fountains)	10.8 lb ai/acre-foot	210 acre-feet	**110**	550	1,100	2,300
	Field Corn and Popcorn	1.5 lb ai/acre	1200 acres	**140**	690	1,400	2,800
	Field Corn and Popcorn; Sweet Corn; Grain or Forage Sorghum	1 lb ai/acre	1200 acres	**210**	1,000	2,100	4,200
	Field Corn and Popcorn; Sweet Corn	0.5 lb ai/acre	1200 acres	410	2,100	4,100	8,500
Tractor-drawn Spreader or Sold Spreader (for aquatic sites)	Golf course (fairways, tees, greens)	1.5 lb ai/acre	40 acres	4,100	21,000	41,000	85,000
	Golf course (tees and greens only)	1.5 lb ai/acre	5 acres	33,000	170,000	330,000	680,000
	Sod / Grass grown for Seed	2 lb ai/acre	80 acres	1,600	7,800	16,000	32,000
	Irrigation and Ditchbank Applications; Fallowland and Crop Stubble; Non-cropland	2 lb ai/acre	80 acres	1,600	7,800	16,000	32,000
	Cranberries; Non-cropland areas	4 lb ai/acre	80 acres	780	3,900	7,800	16,000
	Aquatic areas, non-flowing water (e.g., ponds, lakes, fountains)	10.8 lb ai/acre-foot	210 acre-feet	**110**	550	1,100	2,300
	Field Corn and Popcorn	1.5 lb ai/acre	200 acres	830	4,100	8,300	17,000
	Field Corn and Popcorn; Sweet Corn; Grain or Forage Sorghum	1 lb ai/acre	200 acres	1,200	6,200	12,000	25,000
	Field Corn and Popcorn; Sweet Corn	0.5 lb ai/acre	200 acres	2,500	12,000	25,000	51,000
M/L for Liquids							
Backpack	Rights-of-way (e.g., utilities, railroad, roadways)	0.4 lb ai/gallon	1000 gallons	4,800	24,000	48,000	13,000
	Irrigation and Ditchbank Applications	0.08 lb ai/gallon	1000 gallons	24,000	120,000	240,000	64,000

Exposure Scenario (equipment/use site)		Application Rate	Amount Handled / Area Treated	Inhalation MOE (LOC = 300)			
				No-R	PF5 R	PF10	EC
Mechanically-pressurized Handgun	Rights-of-way (e.g., utilities, railroad, roadways)	0.4 lb ai/gallon	1000 gallons	4,800	24,000	48,000	13,000
	Irrigation and Ditchbank Applications	0.08 lb ai/gallon	1000 gallons	24,000	120,000	240,000	64,000
Aerial	Cranberries; Non-cropland areas	4 lb ai/acre	350 acres	1,400	6,900	28,000	3,600
	Asparagus; Fallowland and Crop Stubble; Established Grass Pastures, Rangeland, and Perennial Grasslands not in Agricultural Production (such as Conservation Reserve Program); Irrigation and Ditchbank Applications; Non-cropland areas	2 lb ai/acre	350 acres	2,800	14,000	37,000	7,300
	Strawberries	1.5 lb ai/acre	350 acres	3,700	18,000	55,000	9,700
	Filberts	1 lb ai/acre	350 acres	5,500	28,000	110,000	15,000
	Hops	0.5 lb ai/acre	350 acres	11,000	55,000	550,000	29,000
	Citrus	0.1 lb ai/acre	350 acres	55,000	280,000	8,500	150,000
	Aquatic areas, non-flowing water (e.g., ponds, lakes, fountains)	10.8 lb ai/acre-foot	210 acre-feet	850	4,300	8,000	2,300
	Sugarcane	2 lb ai/acre	1200 acres	800	4,000	11,000	2,100
	Field Corn and Popcorn; Rice	1.5 lb ai/acre	1200 acres	1,100	5,400	13,000	2,800
	Cereal Grains (Wheat, Barley, Millet, Oats, Rye and Teff)	1.25 lb ai/acre	1200 acres	1,300	6,400	16,000	3,400
	Field Corn and Popcorn; Sweet Corn; Grain or Forage Sorghum; Rice; Soybean	1 lb ai/acre	1200 acres	1,600	8,000	28,000	4,200
	Cereal Grains (Wheat, Barley, Millet, Oats, Rye and Teff); Field Corn and Popcorn; Sweet Corn; Soybean	0.5 lb ai/acre	1200 acres	3,200	16,000	32,000	8,500
	Wild Rice	0.25 lb ai/acre	1200 acres	6,400	32,000	64,000	17,000
	Potato	0.07 lb ai/acre	1200 acres	23,000	120,000	230,000	61,000
	Forestry	4 lb ai/acre	1200 acres	400	2,000	4,000	1,100

Exposure Scenario (equipment/use site)		Application Rate	Amount Handled / Area Treated	Inhalation MOE (LOC = 300)			
				No-R	PF5 R	PF10	EC
Injector (Tree Injection)	Forestry	0.00025 lb ai/tree	20 trees	380,000,000	1,900,000,000	3,800,000,000	1,000,000,000
Airblast	Citrus	0.1 lb ai/acre	40 acres	480,000	2,400,000	4,800,000	1,300,000
Groundboom	Golf course (tees and greens only)	1.5 lb ai/acre	5 acres	260,000	1,300,000	2,600,000	680,000
	Golf course (fairways, tees, greens)	1.5 lb ai/acre	40 acres	32,000	160,000	320,000	85,000
	Sod / Grass grown for Seed	2 lb ai/acre	80 acres	12,000	60,000	120,000	32,000
	Orchard/Vineyard	2 lb ai/acre	40 acres	24,000	120,000	240,000	64,000
	Low Bush Blueberries	5 lb ai/acre	80 acres	4,800	24,000	48,000	13,000
	Cranberries; Non-cropland areas	4 lb ai/acre	80 acres	6,000	30,000	60,000	16,000
	Low Bush Blueberries	3.75 lb ai/acre	80 acres	6,400	32,000	64,000	17,000
	Asparagus; Fallowland and Crop Stubble; Orchard Floors (pome fruit, stone fruit and nut/pistachios); Established Grass Pastures, Rangeland, and Perennial Grasslands not in Agricultural Production (such as Conservation Reserve Program); Irrigation and Ditchbank Applications; Non-cropland areas	2 lb ai/acre	80 acres	12,000	60,000	120,000	32,000
	Strawberries	1.5 lb ai/acre	80 acres	16,000	80,000	160,000	42,000
	Highbush blueberries	1.4 lb ai/acre	80 acres	17,000	86,000	170,000	46,000
	Grapes	1.36 lb ai/acre	80 acres	18,000	89,000	180,000	47,000
	Filberts	1 lb ai/acre	80 acres	24,000	120,000	240,000	64,000
	Hops	0.5 lb ai/acre	80 acres	48,000	240,000	480,000	130,000
	Aquatic areas, non-flowing water (e.g., ponds, lakes, fountains)	10.8 lb ai/acre-foot	210 acre-feet	850	4,300	8,500	2,300
	Sugarcane	2	200	4,800	24,000	48,000	13,000

Exposure Scenario (equipment/use site)		Application Rate	Amount Handled / Area Treated	Inhalation MOE (LOC = 300)			
				No-R	PF5 R	PF10	EC
		lb ai/acre	acres				
	Field Corn and Popcorn; Rice	1.5 lb ai/acre	200 acres	6,400	32,000	64,000	17,000
	Cereal Grains (Wheat, Barley, Millet, Oats, Rye and Teff)	1.25 lb ai/acre	200 acres	7,700	38,000	77,000	20,000
	Field Corn and Popcorn; Sweet Corn; Enlist Corn; Grain or Forage Sorghum; Rice; Soybean; Enlist Soybean	1 lb ai/acre	200 acres	9,700	48,000	97,000	25,000
	Cereal Grains (Wheat, Barley, Millet, Oats, Rye and Teff); Field Corn and Popcorn; Sweet Corn; Soybean	0.5 lb ai/acre	200 acres	19,000	97,000	190,000	51,000
	Wild Rice	0.25 lb ai/acre	200 acres	38,000	190,000	380,000	100,000
	Potato	0.07 lb ai/acre	200 acres	140,000	690,000	1,400,000	360,000
Post-Harvest Automated System	Citrus	0.004 lb ai/gallon	25,000 gallon solution	19,000	Not calculated		
M/L WSP (engineering control for wettable powders)							
Backpack	Rights-of-way (e.g., utilities, railroad, roadways)	0.4 lb ai/gallon	1000 gallons	No Data			4,400
	Irrigation and Ditchbank Applications	0.08 lb ai/gallon	1000 gallons	No Data			22,000
Mechanically-pressurized Handgun	Rights-of-way (e.g., utilities, railroad, roadways)	0.4 lb ai/gallon	1000 gallons	No Data			4,400
	Irrigation and Ditchbank Applications	0.08 lb ai/gallon	1000 gallons	No Data			22,000
Aerial	Non-cropland	4 lb ai/acre	350 acres	No Data			1,300
	Asparagus; Fallowland and Crop Stubble; Established Grass Pastures, Rangeland, and Perennial Grasslands not in Agricultural Production (such as Conservation Reserve Program); Irrigation and Ditchbank Applications; Non-cropland areas	2 lb ai/acre	350 acres	No Data			2,500
	Strawberries	1.5 lb ai/acre	350 acres	No Data			3,300
	Hops	0.5 lb ai/acre	350 acres	No Data			10,000

Exposure Scenario (equipment/use site)		Application Rate	Amount Handled / Area Treated	Inhalation MOE (LOC = 300)			
				No-R	PF5 R	PF10	EC
	Aquatic areas, non-flowing water (e.g., ponds, lakes, fountains)	10.8 lb ai/acre-foot	210 acre-feet	No Data			780
	Forestry	4 lb ai/acre	1200 acres	No Data			370
	Sugarcane	2 lb ai/acre	1200 acres	No Data			730
	Field Corn and Popcorn; Rice	1.5 lb ai/acre	1200 acres	No Data			980
	Cereal Grains (Wheat, Barley, Millet, Oats, Rye and Teff)	1.25 lb ai/acre	1200 acres	No Data			1,200
	Field Corn and Popcorn; Sweet Corn; Grain or Forage Sorghum; Rice; Soybean	1 lb ai/acre	1200 acres	No Data			1,500
	Cereal Grains (Wheat, Barley, Millet, Oats, Rye and Teff); Field Corn and Popcorn; Sweet Corn; Soybean	0.5 lb ai/acre	1200 acres	No Data			2,900
	Wild Rice	0.25 lb ai/acre	1200 acres	No Data			5,900
	Potato	0.07 lb ai/acre	1200 acres	No Data			21,000
Groundboom	Golf course (tees and greens only)	1.5 lb ai/acre	5 acres	No Data			240,000
	Golf course (fairways, tees, greens)	1.5 lb ai/acre	40 acres	No Data			29,000
	Sod / Grass grown for Seed	2 lb ai/acre	80 acres	No Data			11,000
	Orchard/Vineyard	2 lb ai/acre	40 acres	No Data			22,000
	Non-cropland	4 lb ai/acre	80 acres	No Data			5,500
	Asparagus; Fallowland and Crop Stubble; Orchard Floors (pome fruit, stone fruit and nut/pistachios); Established Grass Pastures, Rangeland, and Perennial Grasslands not in Agricultural Production (such as Conservation Reserve Program); Irrigation and Ditchbank Applications; Non-cropland	2 lb ai/acre	80 acres	No Data			11,000
	Strawberries	1.5 lb ai/acre	80 acres	No Data			15,000
	Highbush blueberries	1.4	80	No Data			16,000

Exposure Scenario (equipment/use site)		Application Rate	Amount Handled / Area Treated	Inhalation MOE (LOC = 300)			
				No-R	PF5 R	PF10	EC
		lb ai/acre	acres				
	Grapes	1.36 lb ai/acre	80 acres	No Data			16,000
	Hops	0.5 lb ai/acre	80 acres	No Data			44,000
	Aquatic areas, non-flowing water (e.g., ponds, lakes, fountains)	10.8 lb ai/acre-foot	210 acre-feet	No Data			780
	Sugarcane	2 lb ai/acre	200 acres	No Data			4,400
	Field Corn and Popcorn; Rice	1.5 lb ai/acre	200 acres	No Data			5,900
	Cereal Grains (Wheat, Barley, Millet, Oats, Rye and Teff)	1.25 lb ai/acre	200 acres	No Data			7,100
	Field Corn and Popcorn; Sweet Corn; Grain or Forage Sorghum; Rice; Soybean	1 lb ai/acre	200 acres	No Data			8,800
	Cereal Grains (Wheat, Barley, Millet, Oats, Rye and Teff); Field Corn and Popcorn; Sweet Corn; Soybean	0.5 lb ai/acre	200 acres	No Data			18,000
	Wild Rice	0.25 lb ai/acre	200 acres	No Data			35,000
	Potato	0.07 lb ai/acre	200 acres	No Data			130,000
Applicator (sprays)							
Aerial	Cranberries; Non-cropland areas	4 lb ai/acre	350 acres	No Data			62,000
	Asparagus; Fallowland and Crop Stubble; Established Grass Pastures, Rangeland, and Perennial Grasslands not in Agricultural Production (such as Conservation Reserve Program); Irrigation and Ditchbank Applications; Non-cropland areas	2 lb ai/acre	350 acres	No Data			120,000
	Strawberries	1.5 lb ai/acre	350 acres	No Data			160,000
	Filberts	1 lb ai/acre	350 acres	No Data			250,000
	Hops	0.5 lb ai/acre	350 acres	No Data			490,000
	Citrus	0.1 lb ai/acre	350 acres	No Data			2,500,000

Exposure Scenario (equipment/use site)		Application Rate	Amount Handled / Area Treated	Inhalation MOE (LOC = 300)			
				No-R	PF5 R	PF10	EC
	Aquatic areas, non-flowing water (e.g., ponds, lakes, fountains)	10.8 lb ai/acre-foot	210 acre-feet	No Data			38,000
	Sugarcane	2 lb ai/acre	1200 acres	No Data			36,000
	Field Corn and Popcorn; Rice	1.5 lb ai/acre	1200 acres	No Data			48,000
	Cereal Grains (Wheat, Barley, Millet, Oats, Rye and Teff)	1.25 lb ai/acre	1200 acres	No Data			58,000
	Field Corn and Popcorn; Sweet Corn; Grain or Forage Sorghum; Rice; Soybean	1 lb ai/acre	1200 acres	No Data			72,000
	Cereal Grains (Wheat, Barley, Millet, Oats, Rye and Teff); Field Corn and Popcorn; Sweet Corn; Soybean	0.5 lb ai/acre	1200 acres	No Data			140,000
	Wild Rice	0.25 lb ai/acre	1200 acres	No Data			290,000
	Potato	0.07 lb ai/acre	1200 acres	No Data			1,000,000
	Forestry	4 lb ai/acre	1200 acres	No Data			18,000
Airblast	Citrus	0.1 lb ai/acre	40 acres	23,000	110,000	230,000	1,600,000
Groundboom	Golf course (tees and greens only)	1.5 lb ai/acre	5 acres	170,000	830,000	1,700,000	1,300,000
	Golf course (fairways, tees, greens)	1.5 lb ai/acre	40 acres	21,000	100,000	210,000	160,000
	Sod / Grass grown for Seed	2 lb ai/acre	80 acres	7,800	39,000	78,000	62,000
	Orchard/Vineyard	2 lb ai/acre	40 acres	16,000	78,000	160,000	120,000
	Cranberries; Non-cropland areas	4 lb ai/acre	80 acres	3,900	19,000	39,000	31,000
	Asparagus; Fallowland and Crop Stubble; Orchard Floors (pome fruit, stone fruit and nut/pistachios); Established Grass Pastures, Rangeland, and Perennial Grasslands not in Agricultural Production (such as Conservation Reserve Program); Irrigation and Ditchbank Applications; Non-cropland	2 lb ai/acre	80 acres	7,800	39,000	78,000	62,000
	Strawberries	1.5	80	10,000	52,000	100,000	82,000

Exposure Scenario (equipment/use site)		Application Rate	Amount Handled / Area Treated	Inhalation MOE (LOC = 300)			
				No-R	PF5 R	PF10	EC
		lb ai/acre	acres				
	Highbush blueberries	1.4 lb ai/acre	80 acres	11,000	56,000	110,000	88,000
	Grapes	1.36 lb ai/acre	80 acres	11,000	57,000	110,000	90,000
	Filberts	1 lb ai/acre	80 acres	16,000	78,000	160,000	120,000
	Hops	0.5 lb ai/acre	80 acres	31,000	160,000	310,000	250,000
	Aquatic areas, non-flowing water (e.g., ponds, lakes, fountains)	10.8 lb ai/acre-foot	210 acre-feet	550	2,700	5,500	4,300
	Sugarcane	2 lb ai/acre	200 acres	3,100	16,000	31,000	25,000
	Field Corn and Popcorn; Rice	1.5 lb ai/acre	200 acres	4,100	21,000	41,000	33,000
	Cereal Grains (Wheat, Barley, Millet, Oats, Rye and Teff)	1.25 lb ai/acre	200 acres	5,000	25,000	50,000	39,000
	Field Corn and Popcorn; Sweet Corn; Enlist Corn; Grain or Forage Sorghum; Rice; Soybean; Enlist Soybean	1 lb ai/acre	200 acres	6,200	31,000	62,000	49,000
	Cereal Grains (Wheat, Barley, Millet, Oats, Rye and Teff); Field Corn and Popcorn; Sweet Corn; Soybean	0.5 lb ai/acre	200 acres	12,000	62,000	120,000	98,000
	Wild Rice	0.25 lb ai/acre	200 acres	25,000	120,000	250,000	200,000
	Potato	0.07 lb ai/acre	200 acres	89,000	440,000	890,000	700,000
Mechanically-pressurized Handgun	Rights-of-way (e.g., utilities, railroad, roadways)	0.4 lb ai/gallon	1000 gallons	**120**	610	1,200	No Data
Applicator (Granulars)							
Aerial	Cranberries; Non-cropland areas	4 lb ai/acre	350 acres	No Data			**230**
	Fallowland and Crop Stubble; Non-cropland	2 lb ai/acre	350 acres	No Data			460
	Irrigation and Ditchbank Applications	2 lb ai/acre	350 acres	No Data			460
	Aquatic areas, non-flowing water (e.g., ponds, lakes, fountains)	10.8 lb ai/acre-foot	210 acre-feet	No Data			**140**
	Field Corn and Popcorn	1.5 lb ai/acre	1200 acres	No Data			**180**

Exposure Scenario (equipment/use site)		Application Rate	Amount Handled / Area Treated	Inhalation MOE (LOC = 300)			
				No-R	PF5 R	PF10	EC
	Field Corn and Popcorn; Sweet Corn; Grain or Forage Sorghum	1 lb ai/acre	1200 acres	No Data			270
	Field Corn and Popcorn; Sweet Corn	0.5 lb ai/acre	1200 acres	No Data			540
Tractor-drawn Spreader	Golf course (fairways, tees, greens)	1.5 lb ai/acre	40 acres	5,900	29,000	59,000	32,000
	Golf course (tees and greens only)	1.5 lb ai/acre	5 acres	47,000	240,000	470,000	260,000
	Sod / Grass grown for Seed	2 lb ai/acre	80 acres	2,200	11,000	22,000	12,000
	Cranberries; Non-cropland areas	4 lb ai/acre	80 acres	1,100	5,500	11,000	6,000
	Fallowland and Crop Stubble; Irrigation and Ditchbank Applications; Non-cropland areas	2 lb ai/acre	80 acres	2,200	11,000	22,000	12,000
	Aquatic areas, non-flowing water (e.g., ponds, lakes, fountains)	10.8 lb ai/acre-foot	210 acre-feet	160	780	1,600	850
	Field Corn and Popcorn	1.5 lb ai/acre	200 acres	1,200	5,900	12,000	6,400
	Field Corn and Popcorn; Sweet Corn; Grain or Forage Sorghum	1 lb ai/acre	200 acres	1,800	8,800	18,000	9,600
	Field Corn and Popcorn; Sweet Corn	0.5 lb ai/acre	200 acres	3,500	18,000	35,000	19,000
Applicator (Liquids)							
Trigger-spray bottle (Spot)	Landscaping, turf (lawns, athletic fields, parks, etc.)	0.012 lb ai/bottle	10 bottles	58,000	290,000	580,000	No Data
Aerosol can	Non-cropland areas	0.014 lb ai/can	10 cans	2,300	12,000	23,000	No Data
Injector (Tree Injection)	Forestry	0.00025 lb ai/tree	Negligible exposure				
Flagger for Aerial Spray Applications							
Citrus		0.1 lb ai/acre	350 acres	34,000	170,000	340,000	No Data
Cranberries; Non-cropland areas		4 lb ai/acre	350 acres	860	4,300	8,600	No Data
Asparagus; Fallowland and Crop Stubble; Established Grass Pastures, Rangeland, and Perennial Grasslands not in Agricultural Production (such as Conservation Reserve		2 lb ai/acre	350 acres	1,700	8,600	17,000	No Data

Exposure Scenario (equipment/use site)		Application Rate	Amount Handled / Area Treated	Inhalation MOE (LOC = 300)			
				No-R	PF5 R	PF10	EC
Program); Irrigation and Ditchbank Applications; Non-cropland areas							
Strawberries		1.5 lb ai/acre	350 acres	2,300	12,000	23,000	No Data
Filberts		1 lb ai/acre	350 acres	3,400	17,000	34,000	No Data
Hops		0.5 lb ai/acre	350 acres	6,900	34,000	69,000	No Data
Sugarcane		2 lb ai/acre	350 acres	1,700	8,600	17,000	No Data
Field Corn and Popcorn; Rice		1.5 lb ai/acre	350 acres	2,300	12,000	23,000	No Data
Cereal Grains (Wheat, Barley, Millet, Oats, Rye and Teff)		1.25 lb ai/acre	350 acres	2,800	14,000	28,000	No Data
Field Corn and Popcorn; Sweet Corn; Grain or Forage Sorghum; Rice; Soybean		1 lb ai/acre	350 acres	3,400	17,000	34,000	No Data
Cereal Grains (Wheat, Barley, Millet, Oats, Rye and Teff); Field Corn and Popcorn; Sweet Corn; Soybean		0.5 lb ai/acre	350 acres	6,900	34,000	69,000	No Data
Wild Rice		0.25 lb ai/acre	350 acres	14,000	69,000	140,000	No Data
Potato		0.07 lb ai/acre	350 acres	49,000	250,000	490,000	No Data
Flagger for Aerial Granular Applications							
Cranberries; Non-cropland areas		4 lb ai/acre	350 acres	2,000	10,000	20,000	No Data
Fallowland and Crop Stubble; Irrigation and Ditchbank Applications; Non-cropland areas		2 lb ai/acre	350 acres	4,000	20,000	40,000	No Data
Field Corn and Popcorn		1.5 lb ai/acre	350 acres	5,400	27,000	54,000	No Data
Field Corn and Popcorn; Sweet Corn; Grain or Forage Sorghum		1 lb ai/acre	350 acres	8,100	40,000	81,000	No Data
Field Corn and Popcorn; Sweet Corn		0.5 lb ai/acre	350 acres	16,000	81,000	160,000	No Data
M/L/A Liquids							
Backpack Ground/soil-directed	Orchard Floors (pome fruit, stone fruit and nut/pistachios)	1.5 lb ai/gallon	40 gallons	2,700	14,000	27,000	No Data

Exposure Scenario (equipment/use site)		Application Rate	Amount Handled / Area Treated	Inhalation MOE (LOC = 300)			
				No-R	PF5 R	PF10	EC
Trigger-spray bottle Frill (hack-and-squirt)	Rights-of-way (e.g., utilities, railroad, roadways)	0.4 lb ai/gallon	2.5 gallons	6,900	35,000	69,000	No Data
	Forestry	0.08 lb ai/gallon	2.5 gallons	35,000	170,000	350,000	No Data
Backpack Broadcast	Rights-of-way (e.g., utilities, railroad, roadways)	0.4 lb ai/gallon	40 gallons	380	1,900	3,800	No Data
	Cranberries	0.012 lb ai/gallon	40 gallons	13,000	64,000	130,000	No Data
	Citrus	0.0002 lb ai/gallon	40 gallons	770,000	3,800,000	7,700,000	No Data
	Citrus	0.0017 lb ai/gallon	40 gallons	90,000	450,000	900,000	No Data
	Filberts	0.001 lb ai/gallon	40 gallons	150,000	770,000	1,500,000	No Data
	Landscaping, turf (lawns, athletic fields, parks, etc.)	1 lb ai/gallon	40 gallons	**150**	770	510,000	No Data
	Irrigation and Ditchbank Applications; Established Grass Pastures, Rangeland, and Perennial Grasslands not in Agricultural Production (such as Conservation Reserve Program); Sod farms; Grass Grown for Seed	2 lbs ai/acre	5 acres	16,000	82,000	510,000	No Data
	Aquatic areas, non-flowing water (e.g., ponds, lakes, fountains)	4 lbs ai/acre	5 acres	8,200	41,000	1,500	No Data
Backpack Ground/soil-directed	Christmas Tree farm	0.08 lb ai/gallon	40 gallons	51,000	260,000	41,000	No Data
	Forestry	0.08 lb ai/gallon	40 gallons	51,000	260,000	160,000	No Data
Backpack Spot	Landscaping, turf (lawns, athletic fields, parks, etc.)	1 lb ai/gallon	40 gallons	4,100	21,000	82,000	No Data
Manually-pressurized Handwand Broadcast (foliar)	Citrus	0.0002 lb ai/gallon	40 gallons	1,800,000	8,800,000	18,000,000	No Data
	Citrus	0.0017 lb ai/gallon	40 gallons	210,000	1,000,000	2,100,000	No Data
	Filberts	0.001 lb ai/gallon	40 gallons	350,000	1,800,000	3,500,000	No Data
	Landscaping, turf (lawns, athletic fields, parks, etc.)	1 lb ai/gallon	40 gallons	350	1,800	3,500	No Data
Mechanically-pressurized Handgun	Low Bush Blueberries	0.1 lb ai/gallon	1000 gallons	490	2,400	4,900	No Data
	Low Bush Blueberries	0.0375	1000	1,300	6,500	13,000	No Data

Exposure Scenario (equipment/use site)		Application Rate	Amount Handled / Area Treated	Inhalation MOE (LOC = 300)			
				No-R	PF5 R	PF10	EC
Drench/Soil-/Ground-directed		lb ai/gallon	gallons				
	Cranberries	0.012 lb ai/gallon	1000 gallons	4,100	20,000	41,000	No Data
	Orchard Floors (pome fruit, stone fruit and nut/pistachios)	1.5 lb ai/gallon	1000 gallons	**32**	**160**	320	No Data
Mechanically-pressurized Handgun Broadcast	Golf course (tees and greens only)	1.5 lb ai/acre	5 acres	30,000	150,000	300,000	No Data
	Golf course (fairways, tees, greens)	1.5 lb ai/acre	5 acres	30,000	150,000	300,000	No Data
	Landscaping, turf (lawns, athletic fields, parks, etc.)	1.5 lb ai/acre	5 acres	30,000	150,000	300,000	No Data
	Irrigation and Ditchbank Applications; Established Grass Pastures, Rangeland, and Perennial Grasslands not in Agricultural Production (such as Conservation Reserve Program); Sod farms; Grass Grown for Seed	2 lbs ai/acre	5 acres	4,900	24,000	49,000	No Data
	Aquatic areas, non-flowing water (e.g., ponds, lakes, fountains)	4 lbs ai/acre	5 acres	2,400	12,000	24,000	No Data
	Post-harvest treatment	0.004 lb ai/gallon	25,000 gallon solution	1,100	Not calculated		
M/L/A WSP							
Backpack Ground/soil-directed	Orchard Floors (pome fruit, stone fruit and nut/pistachios)	1.5 lb ai/gallon	40 gallons	2,700	14,000	27,000	No Data
	Christmas Tree farm	0.08 lb ai/gallon	40 gallons	51,000	260,000	510,000	No Data
	Forestry	0.08 lb ai/gallon	40 gallons	51,000	260,000	510,000	No Data
Backpack Spot	Landscaping, turf (lawns, athletic fields, parks, etc.)	1 lb ai/gallon	40 gallons	4,100	21,000	41,000	No Data
Backpack Broadcast	Rights-of-way (e.g., utilities, railroad, roadways)	0.4 lb ai/gallon	40 gallons	380	1,900	3,800	No Data
	Landscaping, turf (lawns, athletic fields, parks, etc.)	1 lb ai/gallon	40 gallons	**150**	770	1,500	No Data
	Irrigation and Ditchbank Applications; Established Grass Pastures, Rangeland, and Perennial Grasslands not in Agricultural Production (such as Conservation Reserve Program); Sod farms; Grass Grown for Seed	2 lbs ai/acre	5 acres	16,000	82,000	160,000	No Data

Exposure Scenario (equipment/use site)		Application Rate	Amount Handled / Area Treated	Inhalation MOE (LOC = 300)			
				No-R	PF5 R	PF10	EC
	Aquatic areas, non-flowing water (e.g., ponds, lakes, fountains)	4 lbs ai/acre	5 acres	8,200	41,000	82,000	No Data
Manually-pressurized Handwand Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	1 lb ai/gallon	40 gallons	350	1,800	3,500	No Data
Mechanically-pressurized Handgun Broadcast	Irrigation and Ditchbank Applications; Established Grass Pastures, Rangeland, and Perennial Grasslands not in Agricultural Production (such as Conservation Reserve Program); Sod farms; Grass Grown for Seed	2 lbs ai/acre	5 acres	4,900	24,000	49,000	No Data
	Aquatic areas, non-flowing water (e.g., ponds, lakes, fountains)	4 lbs ai/acre	5 acres	2,400	12,000	24,000	No Data
	Golf course (tees and greens only)	1.5 lb ai/acre	5 acres	3,100	16,000	31,000	No Data
	Golf course (fairways, tees, greens)	1.5 lb ai/acre	5 acres	3,100	16,000	31,000	No Data
	Landscaping, turf (lawns, athletic fields, parks, etc.)	1.5 lb ai/acre	5 acres	3,100	16,000	31,000	No Data
Mechanically-pressurized Handgun Drench/Soil-/Ground-directed	Orchard Floors (pome fruit, stone fruit and nut/pistachios)	1.5 lb ai/gallon	1000 gallons	**32**	**160**	320	No Data
	Low Bush Blueberries	0.1 lb ai/gallon	1000 gallons	490	2,400	4,900	No Data
	Low Bush Blueberries	0.0375 lb ai/gallon	1000 gallons	1,300	6,500	13,000	No Data
	Cranberries	0.12 lb ai/gallon	1000 gallons	410	2,000	4,100	No Data
L/A Granulars							
Backpack Ground/soil-directed	Forestry	4 lb ai/acre	1 acres	4,400	22,000	44,000	No Data
Backpack Broadcast	Irrigation and Ditchbank Applications; Established Grass Pastures, Rangeland, and Perennial Grasslands not in Agricultural Production (such as Conservation Reserve Program)	2 lbs ai/acre	5 acres	1,800	8,900	18,000	No Data
	Aquatic areas, non-flowing water (e.g., ponds, lakes, fountains)	4 lbs ai/acre	5 acres	890	4,400	8,900	No Data
Belly grinder Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	1.5 lb ai/acre	1 acres	4,600	23,000	46,000	No Data

Exposure Scenario (equipment/use site)		Application Rate	Amount Handled / Area Treated	Inhalation MOE (LOC = 300)			
				No-R	PF5 R	PF10	EC
Rotary spreader Broadcast	Golf course (tees and greens only)	1.5 lb ai/acre	5 acres	5,600	28,000	56,000	No Data
	Golf course (fairways, tees, greens)						
	Landscaping, turf (lawns, athletic fields, parks, etc.)						