The Regulatory History of 2,4-D in the United States

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- 2,4-D has been commercially available for 70 years and has an extraordinary amount of data – both legacy and modern – supporting its continued registration.
- That data has been rigorously evaluated and re-evaluated over the past 6 decades.
- Extensive evaluations by the US EPA and other global regulatory agencies on several areas of potential concern – including carcinogenicity, reproductive toxicity, mutagenicity, developmental toxicity, environmental fate, and others – have consistently found the compound to pose no danger to human health when used according to label directions.

Introduction

Chlorophenoxy herbicides have been commercially available for 70 years and represent one of the most widely used families of herbicides worldwide. 2,4-Dichlorophenoxyacetic acid (2,4-D), the most common of the chlorophenoxy herbicides, is one of the best studied agricultural chemicals. Soon after its introduction in 1947, 2,4-D became widely used and has provided economical, selective, postemergence control of broadleaf weeds in a large variety of crops and non-cropland.

2,4-D remains registered globally with registrations in more than 90 countries. After decades of use, 2,4-D is still the third most widely used herbicide in the United States (USEPA 2015). Ongoing data development and a commitment to registration maintenance have contributed to supporting the continued safe use of this valuable herbicide.

2,4-D has been involved with nearly continuous data development and re-evaluation for the past 60 years, with early regulatory reviews being initiated in the mid-1950s. The most intense re-registrations and re-evaluations occurred in the past 30 years, both in North America and globally. This chapter outlines the regulatory conclusions of United States Environmental Protection Agency…
Regulatory authorities periodically reevaluate pesticides to ensure that products in the marketplace fulfill current requirements and can continue to be used safely. During this process, label revisions, mitigation measures, and refinements in use patterns are applied to all registrations and registrants. The continued data call-ins as listed below assure that 2,4-D maintains those modern standards. 2,4-D meets the EPA’s statutory standard of no unreasonable adverse effects (FIFRA 1996).

**Data Call-ins (DCI) and Data Development**

The US Department of Agriculture (USDA) and US Food and Drug Administration (FDA) were the regulatory agencies for pesticide registration from the mid-1940s to 1970. The US Environmental Protection Agency (USEPA) was established December 2, 1970. The following timeline illustrates USEPA data call-ins for on-going evaluation and assessment of 2,4-D for the past 50 years.

**Timeline for data call-ins and data development**

- 1946 - 2,4-D first national registration established in Canada
- 1947 - 2,4-D first US registration, received in December, from US Department of Agriculture (USDA)
- 1966 - Crop and animal residue Data Call-in (DCI)
- 1980 - Toxicology DCI - USEPA
- 1980 - Toxicology DCI Health Canada Pest Management Regulatory Agency (PMRA)
- 1987 - Dioxin DCI
- 1988 - Registration Standard DCI
- 1989 - Special Review - subchronic & chronic toxicology DCI
- 1996 - FQPA (Food Quality Protection Act)
- 2005 - RED (Reregistration Eligibility Decision) DCI for additional reregistration studies
- 2005 - Dioxin DCI - PMRA
- 2009 - EDSP (Endocrine Disruptor Screening Program)
- 2012 - Registration Review DCI

**Toxicology**

The USEPA has determined that the toxicology database for 2,4-D is complete and robust. 2,4-D is readily absorbed into the blood stream, is removed from the blood plasma by the kidneys unchanged (it is not metabolized), and is rapidly excreted via the urine ($t_{1/2} \sim 5$ to 13 hours) (WHO/FAO 1996, USEPA 1993). At high dose levels, renal saturation occurs, which means that the ability of the kidney to excrete 2,4-D is exceeded at approximately 50 mg/kg bw/day. When this occurs, toxic effects are observed. However, toxic effects are not observed at doses below those causing renal saturation (USEPA 2013a, USEPA 2014, Health Canada 2008).
Developmental (teratology) Effects: Potential effects on the developing animal have been extensively studied. Developmental toxicity was not observed in the rat and rabbit developmental toxicological studies at maternal dose levels below levels of renal saturation (i.e., doses that do not exceed the maternal animal’s ability to excrete 2,4-D). There are clear no-observed-adverse-effect levels (NOAELs) in the developmental studies (USEPA 2013a).

Reproductive: For 2,4-D, there are two studies that specifically assess reproductive toxicity. These are the 2-generation reproduction toxicity study, 1986, and the F1 Extended one-generation reproductive toxicity study, 2010. Multiple reproductive parameters were assessed. A NOAEL was identified (21 mg/kg bw/day) and selected as the point of departure for risk assessment. Because of this, USEPA revised the reference dose (RfD) from 0.05 to 0.21 mg/kg. Since there were no adverse effects observed at this dose, quantifying risks using this dose is protective for any effects occurring at higher dose levels (Marty et al. 2013).

Mutagenicity: USEPA’s current testing requirements focus on tests for mutagenic effects, i.e., heritable changes in DNA that could potentially lead to disease. Based on a full battery of mutagenicity testing, 2,4-D is not considered to be a mutagen (USEPA 2005).

Carcinogenicity: Studies in rats and mice showed no statistically significant tumor response in either species. Furthermore, 2,4-D is not mutagenic, a common flag for potential carcinogenicity. In addition, 2,4-D body residence half-life is short (5 to 13 hours) with no metabolism. USEPA’s Carcinogenicity Peer Committee review in 1997 concluded that 2,4-D be classified as Category D, that is, “not classifiable as to human carcinogenicity,” noting that new 2,4-D oncogenicity studies in rats and mice confirm 2,4-D is not a carcinogen. Global regulatory authorities have finalized their assessments for 2,4-D include the World Health Organization (WHO/FAO 1996), the European Commission (EC 2001), USEPA 2,4-D Reregistration Eligibility Decision (USEPA 2005), Health Canada PMRA (PACR 2006, PACR 2007 and RVD 2008), and the New Zealand Pesticides Board Expert Panel on 2,4-D (NZ 2000). All are in agreement that there is “No evidence of carcinogenicity” in the animal toxicity studies.

The USEPA determined, based on several reviews of epidemiological studies, in addition to the animal studies, that the existing data did not support a conclusion that links human cancer to 2,4-D exposure. The 1994 Science Advisory Panel (SAP) review of epidemiological studies and publications concluded:

“[d]ata are not sufficient to conclude that there is a cause and effect relationship between exposure to 2,4-D and non-Hodgkin’s lymphoma,” and “[s]ome case-control studies have shown a risk of non-Hodgkin’s lymphoma (NHL) in association with farming but many of these studies did not control for other agents in addition to 2,4-D (USEPA 1994).”
Most importantly, USEPA announced in August 2007 that it will not initiate a Special Review of 2,4-D, noting that, “The weight of the evidence does not support a conclusion that 2,4-D, 2,4-DB and 2,4-DP are likely human carcinogens. The Agency has determined that the existing data do not support a conclusion that links human cancer to 2,4-D exposure (FR Notice 2007).”

Neurotoxicity: A complete set of neurotoxicity screening battery (rat) studies have been conducted; acute, 90-day, chronic one-year and developmental neurotoxicity. No treatment-related Functional Observational Battery (FOB) observations are noted at any of the evaluation periods. There is no treatment-related effect on motor activity. In agreement with the chronic toxicity portion of the study, an increased incidence of bilateral retinal degeneration is 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 lowest-observable-adverse-effects level (LOAEL) of 150 mg/kg/day. Developmental Neurotoxicity was not observed in studies on rats. Neuropathological effects were not observed in any study (USEPA 2013).

Endocrine: Regulators have comprehensively evaluated the endocrine effects of 2,4-D. USEPA and PMRA concluded in their review that the rat two-generation reproduction study is valid for the identification and characterization of reproductive and developmental effects, including effects potentially due to endocrine disruption. The extended one-generation reproductive toxicity study on 2,4-D examined endocrine related parameters. For all of the parameters assessed, a clear NOAEL of 21 mg/kg/day was identified, which is used as the point of departure for risk quantification.

USEPA has received all required final study reports and data from the 2009 Endocrine Disruptor Screening Program (EDSP) test. This includes the eleven in-vitro and in-vivo assays from the Tier 1 EDSP battery for 2,4-D. The Tier 1 studies will not affect USEPA’s conclusions on the quantitative endocrine risks posed by 2,4-D for humans given the availability of the extended one-generation reproduction study that comprehensively examined the risks to human health from 2,4-D’s interaction with endocrine system endpoints (Coady 2014, USEPA 2014).

Immunotoxicity: The standard suite of immunotoxicity effects was measured in the extended one-generation reproduction toxicity study. No evidence of a functional deficit in the immune system was observed in the Sheep Red Blood Cell Antibody Forming Cell response and the Natural Killer Cell Activity assays at dose levels approaching or exceeding renal saturation (Marty et al. 2013).

Thyroid: Potential for thyroid toxicity was assessed in the extended one-generation reproduction study. Hormone findings in adult females at the highest dose tested were considered treatment-
related but adaptive and not adverse. The thyroid findings in the other age groups were not treatment-related because there was no dose-response in the changes, and/or the predicted pattern of thyroid hormone changes was not evident. The USEPA has quantified risk of 2,4-D to assure exposures are at least 100-fold lower than levels where renal saturation occurs (USEPA 2013).

Dermal absorption is determined to be 5.8% of the dose (Feldmann and Maibach 1974; USEPA 1996). Nearly 100% is excreted in the urine, with a half-life for excretion of 5 to 13 hours. However, for the final USEPA RED (USEPA 2005) and PMRA RVD (Health Canada 2008) the Agencies harmonized to account for absorption variability and established a dermal absorption factor of 10%.

ENVIRONMENTAL

Degradation: The major route of degradation is aerobic microbial metabolism, 2,4-D is non-persistent (t½ = 6.2 days) in terrestrial (aerobic) environments; moderately persistent (t½ = 45 days) in aerobic aquatic environments; and highly persistent (t½ = 231 days) in anaerobic terrestrial and aquatic environments. Because 2,4-D will be anionic under most environmental conditions, it is expected to be mobile in soil environments; however because of its rapid degradation, downward movement is minimal. The major degrade identified in environmental fate studies for 2,4-D is 2,4-dichlorophenol (2,4-DCP). Toxicity data indicate that 2,4-DCP is less toxic than 2,4-D. USEPA has also determined that residues other than 2,4-D are not of risk concern due to low occurrence under environmental conditions and comparatively low toxicity. Therefore, 2,4-DCP’s estimated drinking water concentrations for human health are based on 2,4-D acid (USEPA 1997).

Water Quality: Monitoring data provided by United States Geological Survey’s (USGS) National Water Quality Assessment Program (NAWQA), indicate an infrequent slight 2,4-D presence in groundwater, concentrations up to 1.4 μg ae/l (ppb), and surface water concentrations up to 8.7 μg ae/l. NAWQA’s evaluation was determined from 6804 groundwater monitoring sites and 4101 surface water monitoring sites. It is important to note that the monitoring data shows that 2,4-D is far below the USEPA Health Advisory (HA) drinking water level and the Maximum Contaminant Level Goal (MCLG) for 2,4-D both set at 70 μg ae/l, while the One-Day HA is 1000 μg ae/l and the Ten-Day HA is 300 μg ae/l. To determine possible exposure USEPA used the protective modeling value, 58 μg ae/l, for PRZM/EXAMS model versus the monitoring value, 8.7 μg ae/l. No direct risk concerns are identified for aquatic taxa (USEPA 2003, USEPA 2013b).

Ecotoxicological

Birds: Based on Mallard duck and Bobwhite quail existing literature and new studies for dietary LC50, bird susceptibility to 2,4-D is low and dietary feeding show lower toxicity than gavage. The
bird reproduction study showed low toxicity for all reproduction parameters with a systemic NOAEL of greater than 1,000 ppm. USEPA finds that acute and chronic risks to birds from 2,4-D exposure are not of concern (USEPA 2013a).

Fish and Invertebrates: The species tested were Bluegill, Rainbow trout, minnow, shrimp, oyster, Daphnia magna, freshwater clams and crayfish. 2,4-D acid and DMA are practically non-toxic to most aquatic fish and invertebrates. While USEPA’s risk assessment projects potential acute and chronic risks to aquatic organisms and plants from 2,4-D in an aquatic environment, the USEPA also concludes, in preparation for the Reregistration Eligibility Document (USEPA 2012), that sufficient risk mitigation efforts have been put in place.

Honeybee: The importance of pollinators and pesticide exposure is recognized. Honeybee data for acute contact exposures (LD_{50} > 88 \, \mu g \, \text{ae/bee}) and acute oral exposure (LD_{50} > 62.6 \, \mu g \, \text{ae/bee}) indicated that 2,4-D is “practically non-toxic” to honeybees on an acute contact or acute oral basis. Considering the results of the acute contact and oral analyses conducted in accordance with the 2014 Pollinator Risk Assessment Framework, acute risk to adult honeybees is not of concern (USEPA 2005).

Risk Assessment

The USEPA and PMRA’s risk assessment is conducted around 2,4-D in its acid form, both free and conjugated.

Exposure risk assessment: The aggregate exposure assessment included contributions from food, drinking water, and non-occupational exposure, and was done for both adults and children. The USEPA’s human health screening risk assessment considered both inhalation and aggregate exposures and concluded that there were no risks of concern.

In assessing residential exposure risks (non-occupational) from spray drift, the USEPA assumes that spray drifts onto a lawn adjacent to an agricultural field being treated, and children immediately play on that lawn. 2,4-D, as being assessed, also has a lawn use. That use has higher lawn turf residues than those estimated from spray drift, and the lawn use shows no human risk concern. Therefore, spray drift will have no risk concern.

In assessing bystander exposure risk, the current USEPA 2,4-D assessment assumes that bystanders are exposed to air concentrations at the edge of a field treated using the use pattern likely to result in the highest volatile residues possible. Based on these assumptions, airborne concentrations of 2,4-D at the edge of the treated field are not of concern.

In assessing pesticide applicators exposure (occupational), there are distinct job functions or tasks
related to applications. Based on the use patterns, current labeling, types of equipment and techniques that can potentially be used, occupational exposure can be expected, e.g., for mixing, loading, and application. However, even with minimal personal protective equipment (PPE) (i.e., no respirator), the occupational handler risk estimates are not of concern (USEPA 2014).

**USEPA Response to NRDC Petition**

In November 2008, the Natural Resources Defense Council (NRDC) submitted a petition requesting that USEPA revoke all tolerances, and cancel all registrations for 2,4-D. USEPA has previously evaluated the issues raised in the petition, including the studies the petition cites, as well as other studies, and concluded that when used according to label directions 2,4-D does not pose an unreasonable risk to human health or the environment. Even if a risk of concern were to be identified, the grounds for registration cancellation or revocation would require that the risk outweigh the benefits. Based on USEPA’s previous conclusions, the NRDC petition would fail that test.

USEPA’s rejection of the NRDC petition in April 2012 was unambiguous, stating that:

“After considering public comments received on the petition and all the available studies, including a state-of-the-science one-generation reproduction study, EPA is denying the request to revoke all 2,4-D tolerances and the request to cancel all 2,4-D registrations (FR Notice 2012).”

Grounds cited by USEPA for its denial are that NRDC’s claims are either without scientific merit, based on misrepresentations, or fail to state sufficient grounds for revocation.

**GLOBAL REVIEWS**

**Europe:** The European Food Safety Authority (EFSA) completed Renewal Assessment Report 2014 (EFSA 2014) as a follow up to the European Commission Health and Safety final review of 2001 (EC 2001). EFSA risk assessment has confirmed: 2,4-D as currently manufactured is unlikely to have genotoxic potential or pose a carcinogenic risk to humans. No developmental findings are noted, and there is no indication of potential androgenic, anti-androgenic, oestrogenic or correlated endocrine adverse effects on the reproduction and reproductive organs in an extended one-generation study. Based on the first-tier assessment, acute and long-term risk to birds is concluded as low. Also, a low acute risk to mammals is concluded for representative uses of 2,4-D on cereals.

**Health Canada PMRA:** Re-evaluation Decision (RVD): Human exposure to 2,4-D is of low concern (Health Canada 2008). The aggregate exposure (i.e., 2,4-D from food and drinking water) represents less than 16.3% of the acute reference dose for the most vulnerable population group (females of childbearing age) and less than 9.9% of the acute reference dose for all other
population groups. For chronic risk, the aggregated exposure represents less than 24% of the chronic reference dose for all population subgroups. The estimated residues from treated crops and drinking water include the most highly vulnerable subpopulation, e.g., children 1 to 6 years old. There is no evidence of carcinogenicity in the animal toxicity studies and Health Canada concludes the epidemiology studies show no clear association between exposure to phenoxy herbicides and human cancers.

Health Canada Re-evaluation Update 2,4-D 2013: PMRA concludes that the data and information submitted under the Pest Control Products Act support the regulatory decisions for 2,4-D (REV 2013).

WHO/FAO: The 1996 JMPR 2,4-D toxicology review gave special attention to animal metabolism. Greater than 94% of the administered 2,4-D dose was recovered within 48 h after treatment with an approximate half-life of 5 hours. The primary route of excretion was the urine (85-94%) with the feces being a minor excretory pathway (2-11%). There was no sex-related difference and rapid excretion in the urine indicate that it has little potential to accumulate in tissues. The joint WHO/FAO meeting concluded there is no evidence of carcinogenicity in either of rat or mouse 2-year chronic toxicity oncogenicity studies.

In June 2015, WHO IARC spent a week conducting a hazard review, assigning 2,4-D a score of 2b - a possible human carcinogen. The IARC’s conclusion that there was “inadequate evidence” in humans aligns with repeated findings of agencies including USEPA, PMRA, EFSA, and WHO bodies. Similarly, the IARC’s evaluation concluded, “epidemiological studies did not find strong or consistent increases in risk of [non-Hodgkin’s lymphoma] NHL or cancers in relation to 2,4-D exposure” (IARC 2015). The IARC describes their methodology, stating “…the Monographs Programme identifies cancer hazards even when risks are very low at current exposure levels.” Cohort epidemiology studies of exposed workers have not confirmed the hypothesis that 2,4-D causes either non-Hodgkin’s lymphoma or soft-tissue sarcomas (WHO/FAO 1996).

New Zealand: The NZ Environmental Risk Management Authority (ERMA) expert group concluded there is inadequate evidence of a causal relationship between exposure to chlorophenoxy herbicides and the development of Non Hodgkin’s Lymphoma (NHL) and other cancers in humans at this time, and the available data could not be interpreted as showing the presence or absence of a carcinogenic effect (NZ 2004). The proposed carcinogenicity classification is consistent with the classifications of the European Commission, Health Canada PMRA and the USEPA.

The extensive database of metabolic, toxicological, ecotoxicological, environmental fate and crop residue studies on 2,4-D has provided no evidence that 2,4-D poses a health risk to humans or the environment when used according to label directions.
Summary

2,4-D is one of the most studied agricultural chemicals. The most recent 30 years of research provide a sound and rich Good Laboratory Practice (GLP) database for continued evaluation and registration of 2,4-D. The extensive database of metabolic, toxicological, ecotoxicological, environmental fate and crop residue studies on 2,4-D has provided no evidence that 2,4-D poses a health risk to humans or the environment when used according to label directions.

The scientific data base on carcinogenicity is comprehensive for animal and epidemiology studies. Several world authoritative bodies, USEPA, WHO/FAO, Health Canada PMRA, New Zealand Pesticides Board Expert Panel and EU Commission, show consistency. Each of these agencies has reviewed the current 2,4-D body of scientific data and have concluded either “no evidence of carcinogenicity” or “inadequate evidence of carcinogenicity” for 2,4-dichlorophenoxyacetic acid.

2,4-D registrants have responded diligently to federal reregistration requirements, state pesticide issues, endangered species concerns, as well as other challenges requiring sustained dedicated attention to product defense and stewardship.

Discovered more than 70 years ago, 2,4-D continues to provide significant benefits to farmers, ranchers, homeowners, and many others who work to protect crops, protected species and valued landscapes.
LITERATURE CITED


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About the author:

Larry Hammond as Chairman of the Technical Committee for the Industry Task Force II on 2,4-D Research Data for 23 years has been instrumental in this role for the reregistration and maintenance of 2,4-D. He retired after 30 years of service to the crop protection industry through several positions with the Dow Chemical Company and Dow AgroSciences. While at Dow Chemical, Hammond helped to establish two world-class field stations for scientific crop protection product research, one in Illinois and another in Brazil. As chairman of the Technical Committee, Hammond helped direct the Task Force data development of more than 300 2,4-D field and laboratory studies and was frequently asked to interpret, defend and communicate about various aspects of this research with regulatory authorities including the US Environmental Protection Agency, Health Canada Pest Management Regulatory Agency and global regulatory support.