ChemicalWatch Factsheet

2,4-D

2,4-Dichlorophenoxyacetic acid, commonly known as 2,4-D, is a widely used herbicide in the phenoxy (or phenoxyacetic acid) class of chemicals. It is the most commonly used pesticide in the non-agricultural sector and one of the top ten most commonly used in the agricultural sector, with 25-29 million pounds being used in the U.S. annually.[1] Currently, the technical registrants for 2,4-D are Dow AgroSciences, NuFarm, AGRO GOR, and PBI Gordon, and it is frequently formulated with other herbicides such as dicamba, mecoprop, mecoprop-p, MCPA, and clopyralid, among others.[2]

2,4-D was first registered in the U.S. in the late 1940s, and is infamously known as one of the two ingredients in Agent Orange (the other being 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) –a dangerous mixture used by the military to defoliate Vietnam's forests during the Vietnam War. The toxic legacy of Agent Orange is still felt today by Vietnam War veterans and the people of Vietnam, due to the lasting effects of dioxin contamination.

2,4-D is a general use pesticide. It can be used on a variety of food/feed sites including field, fruit, and vegetable crops. Most of its use occurs on turf and lawns, with products marketed as "weed and feed" –a combination of herbicide and fertilizer. Other use sites include rights-of-way, aquatic environments, and forestry applications. Popular products include Ortho Weed B Gon, Spectracide, and Weedone. The products can come in emulsifiable concentrates, granules, soluble concentrates/solids, water dispersible granules, and wettable powders.[3] 2,4-D is produced in several forms, including acids, salts, amines and esters, and its toxicity varies between the different forms. Currently, the registered forms of 2,4-D are: 2,4-D acid; 2,4-D sodium salt; 2,4-D diethylamine; 2,4-D dimethylamine salt; 2,4-D isopropyl acid; 2,4-D triisopropyl acid; 2,4-D butoxyethyl ester; 2,4-D ethylhexyl ester; 2,4-D isopropyl ester. The dimethylamine salt (DMA) and ethylhexyl ester (EHE) forms account for approximately 90-95% of the total global use.[4]

ChemicalWATCH Stats:

CAS Registry Number: 94-75-7
Trade Name: Crossbow GlyMIX MT, Grazon P+D, Pathway, Aqua-Kleen, Barrage, Malerbane Weedone, Ortho Weed B Gon, Spectracide, Weedtrine- II
Use: Fruit and vegetable crops, turf, lawns, rights-of-way, aquatic sites, forestry applications, post-emergence broadleaf weeds, plant growth regulator in citrus.
Toxicity rating: Toxic.
Signal Words: CAUTION, WARNING, DANGER.
Health Effects: Sensitizer/Irritant, Carcinogenicity, Endocrine Disruption, Developmental and Reproduction, Neurotoxicity.
Environmental Effects: Long Rang Drift, Weed Resistance, Water Contaminant, Toxic to Birds, Toxic to Fish/Aquatic Organisms, Toxic to Bees, Harmful to Pets.

Health effects of 2,4-D are of particular concern due to its widespread distribution and ability to drift off-site. Levels of 2,4-D have been detected in indoor air and surfaces (floors, tables, windowsills) following lawn application of the herbicide. In these instances, exposure levels for children are significantly higher than pre-application, resulting in continuous, long-term elevated exposures. Even though many believed the use of 2,4-D would gradually be reduced and replaced by newer generations of pesticides, 2,4-D use is now expected to grow substantially in the coming years. This is because Dow AgroSciences has begun marketing corn and soybean genetically engineered to be resistant to 2,4-D, allowing farmers to spray more of the herbicide across agricultural regions.

Mode of Action

2,4-D is a selective herbicide used to kill broadleaf weeds for post-emergent control. It is a plant growth regulator, and mimics the natural plant growth hormone, auxin. 2,4-D remains at high levels within plant tissues and causes rapid cell growth. Plants die when their vascular transport systems become blocked and destroyed by abnormally fast growth. While 2,4-D is normally applied to a plant's leaves, it can be absorbed through the roots and stems.

Acute Toxicity

The EPA toxicity class ranges from I-III (on a I-IV scale with I being the most toxic) depending on the form and method of exposure. The acid and salt forms of 2,4-D are considered to be severe eye irritants (Toxicity Category I). Acute symptoms of exposure include coughing, burning, dizziness, loss of muscle coordination, nausea, diarrhea, and vomiting. Blood, liver, and kidney toxicity have all been observed with 2,4-D exposures.[5] Additionally, 2,4-D is one of the few herbicides to cause nervous system damage.[6,7] Effects to the nervous system include inflamed nerve endings, lack of coordination, stiffness in the arms and legs, inability to walk, fatigue, stupor, coma, and death. In persons with impaired

cardiovascular function, inhalation of 2,4-D may exacerbate preexisting conditions.[8] Researchers from a 2004 study also found that dermal exposure to 2,4-D can lead occasionally to mild gastrointestinal irritation and progressive nerve damage.[9] These researchers also found that some of the neuromuscular effects such as muscle twitching, weakness, and loss of tendon reflexes were permanent in patients.

Chronic Toxicity

Laboratory studies with rats show that 2,4-D exposure can lead to tissue injuries indicative of primary hepatic and muscle tissue damage.[10] A Canadian study looking at human hepatoma HepG2 cells exposed to 2,4-D reported that these cells respond to low-level exposure producing a cellular response associated with alterations in the expression of many genes. The affected genes were identified as stress response, cell cycle control, immunological and DNA repair genes.[11] One study looking at possible immune effects found that treated mice produced less bone marrow cells that are responsible for eliciting an antibody response[12] –which could result in fewer antibodies to ward off infection.

Poor semen quality has also been associated with 2,4-D exposure. A study of men living in the agricultural Midwest reported that men with poor semen quality also had 5 times more 2,4-D levels in their urine compared to men with normal semen samples.[13] Occupational exposure to 2,4-D is also associated with an increased risk of Parkinson's disease. 2,4-D has effects on dopaminergic neurons in experimental settings and is associated with more than a 3-fold increased risk of the disease.[14]

Carcinogenicity

In 1987, the International Agency of Research on Cancer (IARC) categorized chlorophenoxy herbicides as '*possibly carcinogenic to humans,*'[15] and although a mounting body of evidence links 2,4-D to various cancers, particularly non-Hodgkin's lymphoma (NHL), EPA has not classified it as a carcinogen. EPA lists the herbicide in Group D for carcinogenicity –*Not classifiable as to human carcinogenicity.* However, a link between 2,4-D and NHL has been demonstrated in the United States, Italy, Canada, Denmark, and Sweden.[16] In general, among herbicides, the phenoxyacetic acids have been significantly associated with NHL.[17] In a study examining Canadian men the risk of NHL was statistically significantly increased by exposure to 2,4-D.[18] A population-based, case-control study by researchers at the National Cancer Institute (NCI) found that among those who mixed or applied 2,4-D, the risk for NHL increased with frequency of use to over threefold for those exposed 20 or more days per year.[19] Farmers using 2,4-D were also associated with an increased risk of NHL in a case-control study embedded in a cohort of 139,000 members of United Farm Workers of America (UFW) diagnosed in California between 1988 and 2001.[20] Despite these studies, the carcinogenic potential of 2,4-D remains controversial. The pesticide industry has criticized some of the studies mentioned here and cites other studies, which support its claim that 2,4-D does not cause cancer. Despite independent data, EPA concluded in its 2005 registration decision that "the data are not sufficient to conclude that there is a cause and effect relationship between exposure to 2,4-D and non- Hodgkin's lymphoma."[21]

Endocrine Disruption

2,4-D has the ability to interfere with the hormonal system. A direct correlation of urinary levels of 2,4-D with elevated levels of the luteinizing hormone (LH) –responsible for stimulating the production of testosterone in males and regulating the menstrual cycle and ovulation in females– suggests a direct effect on hormonal levels by the chlorophenoxy herbicide.[22] Others found that abnormal sperm[23] and higher rates of birth defects[24] were observed in farmers with long-time exposure to 2,4-D. Other studies have found that 2,4-D promotes the proliferation of androgen-sensitive cells by acting synergistically with its main metabolite, 2,4-dichlorophenol (DCP), also known for its endocrine disrupting effects.[25,26]

2,4-D is also known to interfere with the thyroid hormone. According to EPA, data "demonstrate effects on the thyroid and gonads following exposure to 2,4-D, [and] there is concern regarding its endocrine disruption potential."[27] EPA researchers found that persons with urinary 2,4-D presence have low levels of thyroid hormone. Their results also indicate that exposure to 2,4-D was associated with changes in biomarkers that have been linked to risk factors for acute myocardial infarction and type-2 diabetes.[28]

Animal studies have also observed the hormone effects of 2,4-D exposure. One 2005 study observed estrogenic activity in rainbow trout[29] exposed to 2,4-D, while another study found the thyroid glands of laboratory rats were sensitive to 2,4-D as decreases in the thyroid gland transport and production functions, and the impairment of hormone iodination in the thyroid were observed after acute exposure.[30]

Genetic mutation

Several older studies have described 2,4-D as acting as a mutagen and inducing chromosomal aberrations. But newer studies have not been able to confirm these earlier observations.[31,32] However, one study reports that a significant increase in the percentage of chromosome aberrations in bone-marrow and spermatocyte cells was observed after oral administration of 2,4-D in mice. Here, 2,4-D also induced a dose-dependent increase in the percentage of sperm head abnormalities.[33] Additionally, another study looking at herbicide applicators observed that those with high urinary levels of 2,4-D also exhibited altered genomic stability as measured by V(D)J genetic rearrangement frequency. However, this appeared to be reversible months after peak exposure.[34]

Developmental and Reproductive Toxicity

Developmental toxicity has been observed in laboratory rats following exposure to 2,4-D, including increased incidence of skeletal abnormalities.[35] Significantly increased fetal variations were seen in rats at maternally toxic dose levels in excess of 90 mg/kg/day acid equivalent, while reduced fetal viability was observed in hamsters.[36] One study reports fetotoxicity, observed by a decrease in weight and crown-rump length of the newborn pups or embryo resorption in mice, but the results were not significant.[37]

In a two-generation reproduction study in rats, evidence of reproductive and developmental toxicity was shown as increased duration of gestation of dams producing litters which had skeletal abnormalities.[38] There was also reduced gestational and neonatal survival. Exposure to 2,4-D caused delays in brain development and abnormal behavior patterns, including repetitive movements, tremor, decreased social interactions, apathy, and immobility. The intensity of the response is sex-dependent; females appear to be more severely affected than males.[39]

Neurotoxicity

According to EPA documents, neurotoxicity has been observed following exposure to high dose levels of 2,4-D. Clinical signs of neurotoxicity (ataxia, decreased motor activity, myotonia, prostration, lateral recumbency, impaired/loss of the righting reflex, and skin cold to the touch) were observed in pregnant rabbits following exposure to 2,4-D and its amine salts and esters. Neuropathology (retinal degeneration) was observed following 2,4-D exposure in several studies in female rats.[40]

EPA's report has been supported by other research that demonstrates that 2,4-D exposure causes neurotoxic effects, including disruption of cell membrane transportation,[41] and alterations to the blood-brain barrier mechanism.[42] It also causes oxidative stress in specific areas of the brain, including the midbrain (associated with vision, hearing and motor control), the striatum (associated with problem solving, attention, and memory), and the prefrontal cortex (controlling personality, decision-making, and social behavior).[43]

In human observations, many exposed to 2,4-D have exhibited degeneration of the central nervous system, decreased nerve conduction, delayed muscle contraction, as well as suicidal thoughts, depression, anxiety, aggression and post-traumatic stress syndrome.[44]

Risks to Pets

Studies from the National Cancer Institute and other sources have reported an association between exposure to lawn chemi-

Weed Resistance and 2,4-D Resistant Crops

The U.S. Department of Agriculture (USDA) has begun deregulating genetically engineered (GE) corn and soybeans developed to be resistant to 2,4-D. In 2013, the agency released its draft Environmental Impact Statement (DEIS), announcing its plan to deregulate these crops. Despite industry claims that GE crops would reduce the use of toxic herbicides, 2,4-D is now expected to enter the environment at elevated rates, given the widespread use of GE corn and soybean. According to USDA, 2,4-D use on GE corn and soybean crops is estimated to increase 1.75 -3 times current use,[45] with independent estimates much higher. The main reason for the push for 2,4-D tolerant corn and soybean is the failure of glyphosate-tolerant, Roundup Ready (RR) crops. Use of Roundup herbicide on RR crops spawned a new generation of resistant "superweeds" no longer controlled by Roundup. In theory 2,4-D, having a different mode of action, would be able to control these resistant weeds. Not surprisingly, these new GE crops are being marketed as a solution to combat the surge in Roundup-resistant weeds.

USDA notes in its DEIS that given the prevalence of Roundup-resistant weeds, it is "very likely" that 2,4-D resistant weeds will occur, and that the adoption of 2,4-D corn and soybean can have a "potentially significant environmental impact," on the proliferation of resistant weeds, due to an increased reliance on 2,4-D for weed control. The agency also acknowledges that possible onset of 2,4-D resistant weeds will mean that farmers relying on 2,4-D will likely experience "increased socioeconomic impacts from more costly and restrictive weed control alternatives" to combat these weeds. Already, 28 species across 16 plant families have already evolved resistance to the synthetic auxin herbicides, the mode of action to which 2,4-D belongs, with 16 known to be resistant specifically to 2,4-D.[46] As 2,4-D resistance grows, farmers will be forced to switch to even more toxic chemicals to control these weeds, at great economic and environmental costs.

Additionally, a new 2,4-D choline salt formulation (Enlist™), expected to be exclusively used with the new 2,4-D resistant corn and soybeans, is anticipated to have lower volatility (50 times lower) and thus, decreased drift compared to other forms of 2,4-D.[47] However, the technical information supporting this has not been made available for public or peer review.

Overuse of the herbicide glyphosate (Roundup) have created "superweeds," which include varieties of Palmer amaranth (pictured) that are now widespread in the southeastern U.S.

cals and adverse impacts in dogs.[48,49] One study finds that dogs living in and around residences with 2,4-D treated lawns absorb measurable amounts of the herbicide for several days after application. Urine concentrations observed in the study were higher and persisted longer than previous reports.[50] Another study reports that exposure to lawns or gardens treated with phenoxy herbicides was associated with an increased risk of transitional cell carcinoma of the urinary bladder in Scottish Terriers, compared with exposure to untreated lawns or gardens.[51] Several studies have found an association with 2,4-D exposure and canine malignant lymphoma.[52,53]

Environmental Fate and Effects

Under most environmental conditions various forms of 2,4-D will degrade rapidly to form 2,4-D acid. 2,4-D degrades fairly quickly in soils (half-life about 10 days for acid, salt and ester forms),[54] with microbial degradation considered to be the major route in the breakdown of the chemical in soil. It is however, relatively persistent in anaerobic (low oxygen) aquatic environments (half-life ranges from 41 to 333 days).[55] This has implications for fragile wetland areas, especially those under conservation.[56] 2,4-D is toxic to aquatic plants and is more toxic to vascular plants than to non-vascular plants. The amine salts and esters forms are not persistent under most environmental conditions.

Due to its relatively short half-life, 2,4-D is said to have low persistence in both soil and water. 2,4-D is highly mobile as it does not bind with minerals in soils,[57] and has a high potential to leach from soils, but less likely to contaminate groundwater due to its rapid degradation. 2,4-D when applied to surface water is quickly distributed throughout the water body, with a half-life of approximately 1-3 weeks. Its residues may be detected in sediment after six months.[58] According to the U.S. Geological Survey (USGS), 2,4-D is one of the 25 most frequently detected pesticides in U.S. waters.[59] It has already been detected in low concentrations in streams, shallow groundwater, and drinking water in both rural and urban areas in the US.[60] In water, 2,4-D will biodegrade with the rate dependent upon the level of nutrients present, temperature, availability of oxygen, and whether there has been preexposure of the water to 2,4-D contamination.[61]

2,4-D has been shown to have negative impacts on a number of animals. For birds, according to EPA, 2,4-D is classified as moderately toxic to practically non-toxic on an acute oral basis. However, toxicity ranges and does not show distinct differences between the acid, salts, amine salts, and esters.

Generally, the acid and amine salts are practically non-toxic to freshwater and marine fish, but the butoxyethanol ester is highly toxic. When applied as the acid, 2,4-D shows little tendency to bioconcentrate in fish, while if applied as the isooctyl ester, it is expected to bioconcentrate in the absence of metabolization.[62] Similarly, 2,4-D acid and amine salts are slightly toxic to practically nontoxic to aquatic invertebrates, but ester forms have been found to be very highly toxic to slightly toxic to freshwater and marine invertebrates. It is toxic to aquatic plants, being more toxic to vascular plants than to non-vascular plants.[63] 2,4-D can also impact species listed under the jurisdiction of the *Endangered Species Act* (ESA). In 2011, the National Marine Fisheries Service (NMFS) identified 2,4-D as likely to jeopardize all listed salmonid, based on current registration and label directions.[64]

2,4-D and its salts and esters are predicted to pose minimal risk to pollinators, like the honey bee, and other beneficial insects.

2,4-D Drift

2,4-D drift has long been a known problem to off-site locations, endangered species, and non-target crops, as well as to people who live near application sites. For instance, a 2013 report by the Oregon Health Authority found that the urine of residents who lived near forestry applications of 2,4-D had "levels of 2,4-D higher than the general U.S. population."[65] Typically, spraying during windy conditions and using nozzles that create fine spray particles/droplets increase the risk of spray drift. High temperatures and low volatility also increase the risk of drift. Many forms of 2,4-D volatilize above 85°F,[66] and drift has been known to damage specialty crops like tomatoes and grapes half a mile or more from the application site, even at concentrations 100 times below the recommended label rate.[67] The ester form of 2,4-D is considered the most volatile and can be suspended in the air for longer periods of time.[68] In 2,4-D's 2005 registration document, EPA noted that its risk assessment suggests that risks from drift onto non-target plants exceed levels of concern, and proposed spray drift mitigation controls that attempted to decrease the risk that 2,4-D will drift onto non-target plants.[69] Apply-

Altitude and wind affect dispersion. Crop dusting near Calipatria in the Imperial Valley. Photo by Charles O'Rear, 1972

ing 2,4-D during lower temperatures and wind speed, along with selecting nozzles with larger droplet sizes have been recommended on product labels to reduce drift, but a high level of non-compliance with product labels continue to make 2,4-D drift a major concern.

Dioxin Contamination

2,4-D's contamination with dioxins has long been a part of 2,4-D's history, especially as it relates to its makeup of Agent Orange. Much of Agent Orange (2,4-D and 2,4,5-T) was heavily contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) –the most potent dioxin and known carcinogen, even up to 40ppm.[70] 2,4-D becomes contaminated with dioxins during the manufacturing process, but recent technological advancements have strived to reduce dioxin levels. However, according to EPA, little to no information is available on the levels of dioxin contamination present in 2,4-D after synthesis.[71] Thus, the threat of dioxin contamination remains a consequence of 2,4-D use. On average, there may be between 0.06-0.78 ppb dioxin-related forms contaminating 2,4-D, including TCDD.[72] Dioxins have notoriously long half-lives, are bioaccumulative, and present broadly significant health risks developmentally and postnatally, including increased risk of birth defects, cancer, heart disease and diabetes.[73,74]

Regulatory Status and History

2,4-D was one of the first herbicides to be commercially marketed. It was introduced to the U.S. in the late 1940s, first used as one half of Agent Orange, and was subsequently regulated by EPA under the *Federal Insecticide, Fungicide and Rodenticide Act* (FIFRA). The other ingredient, 2,4,5-T has since been banned.

According to EPA, 2,4-D was in pre-Special Review status since 1986, because of concerns regarding the epidemiological links of 2,4-D to non-Hodgkin's lymphoma from both occupational and residential exposure. However, EPA found that a link could not be established and did not move forward with the Special Review, preferring to defer a decision until the registration review. In the interim, the 2,4-D Task Force –a coalition of chemical manufacturers formed to develop data relevant to 2,4-D– agreed to risk reduction measures and a user education program in 1992. According to the agency, it has twice reviewed epidemiological studies regarding 2,4-D and the risk of cancer. In both reviews, completed in 2004, EPA concluded there was no additional evidence that would implicate 2,4-D as a cause of cancer.

In 2005, EPA released its Reregistration Eligibility Decision (RED) which summarizes current data on the human health and environmental effects of 2,4-D; in 2009 an endangered species assessment for the California red-legged frog and Alameda whipsnake was also completed. In spite of reports of water contamination, no total maximum daily loads (TMDL) have been developed for 2,4-D, and currently it is not identified as a cause of impairment for any water bodies listed as impaired as defined under Section 303(d) of the *Clean Water Act.*

In 2008, the National Resources Defense Council (NRDC) filed a petition requesting the cancellation of all registrations of 2,4-D and the revocation of its tolerances. NRDC contended there were various adverse health and environmental impacts related to the chemical's use and charged that the agency's assessment process was flawed, citing a disregard of neurotoxicological data and overlooking exposure of infants to 2,4-D in breast milk.[75] In 2012, EPA responded by rejecting the petition, stating that NRDC's claims do not allege sufficient grounds for cancellation of the 2,4-D registrations, based on the agency's statutory standard for cancellation under FIFRA.[76]

In 2011, the Center for Biological Diversity and the Pesticide Action Network North America filed a lawsuit against EPA for failing to undergo consultation with the U.S. Fish and Wildlife Service and the National Marine Fisheries Service (NMFS) regarding the effects of over 350 pesticides, including 2,4-D, on over 200 endangered and threatened species throughout the United States. NMFS has identified 2,4-D as likely to jeopardize all listed salmonid, based on current 2,4-D use. In November 2013, EPA, U.S. Department of Agriculture, U.S. Fish and Wildlife Service, and NMFS held a stakeholder workshop to discuss scientific approaches to address recommendations for assessing risks from pesticides to endangered and threatened species.

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