2,4-Dichlorophenoxyacetic Acid (2,4-D)

Chemical Summary

U.S. EPA, Toxicity and Exposure Assessment for Children's Health

This TEACH Chemical Summary is a compilation of information derived primarily from U.S. EPA and ATSDR resources, and the TEACH Database. The TEACH Database contains summaries of research studies pertaining to developmental exposure and/or health effects for each chemical or chemical group. TEACH does not perform any evaluation of the validity or quality of these research studies. Research studies that are specific for adults are not included in the TEACH Database, and typically are not described in the TEACH Chemical Summary.

I. INTRODUCTION

2,4-Dichlorophenoxyacetic acid (2,4-D) is a white to yellow crystalline powder, which is commonly used as a broadleaf herbicide (weed killer) in commercially-available products, often in liquid formulations (1-3). 2,4-D is usually found in mixtures of residential, agricultural, and commercial herbicides and pesticides that are applied to broadleaf weeds, wheat, corn, pastureland, lawn, turf, and roadsides (2, 3). 2,4-D is also applied to some recreational-use lakes to control weed growth, predominantly in Minnesota, Washington, and the New England region (1). There are over 1,500 pesticide and herbicide products that contain 2,4-D as the main ingredient (2, 3). The U.S. EPA Office of Pesticide Programs estimated that total domestic U.S. annual usage of 2,4-D is approximately 46 million pounds with 66% of use in agricultural applications (1). 2,4-D is used predominantly in states in the Midwest, Great Plains, and Northwest regions of the U.S. (1).

Reports of health effects following 2,4-D exposure have focused primarily on adult occupational exposures, and experimental animal studies (1, 2). Exposure to 2,4-D has been reported to result in blood, liver, and kidney toxicity (1, 2, 4). Chronic oral exposure in experimental animals have resulted in adverse effects on the eye, thyroid, kidney, adrenals, and ovaries/testes (1). Experimental animal studies have demonstrated delayed neurobehavioral development and changes in neurotransmitter concentrations in offspring exposed during pregnancy or lactation (5-9).

Children are most likely to be exposed following application of 2,4-D as a residential lawn care product (1-3, 10-12). Exposure is most likely to occur via inhalation of indoor air and house dust generally subsequent to lawn care application of 2,4-D (10-12), or via contact with 2,4-D-treated grass or turf (1). Hand-to-mouth activity can also contribute to exposure from 2,4-D-contaminated house dust in younger children (10, 11). The dust on shoes of the person applying the 2,4-D to lawns may be the greatest contributor to indoor 2,4-D contamination (11). Exposure of children may also occur from diet, drinking water, and swimming in lakes treated with 2,4-D (with highest concentrations of 2,4-D occurring within 24 hours of lake treatment) (1).

II. EXPOSURE MEDIA AND POTENTIAL FOR CHILDREN'S EXPOSURE[1]

Exposure Media	Relative Potential for Children's Exposure[2,3]	Basis[4]
Indoor Air	Higher	Inhalation near areas of recent 2,4-D application is the most likely route of exposure for children. Indoor dust may be an important source of exposure if children are near areas of recent lawn or agricultural application, or if parents are occupationally exposed and bring contaminated clothing into the home.
Ambient Air	Medium	Inhalation exposure to 2,4-D via ambient air after outside applications may be a concern, particularly in agricultural areas.
Groundwater	Medium	Low concentrations of 2,4-D have been found in groundwater in some states. Agricultural run-off containing 2,4-D may contaminate groundwater in some areas.
Diet	Lower	2,4-D is applied to food crops as a herbicide, but recent data indicates very low to undetectable concentrations in food supplies.
Drinking Water	Lower	2,4-D has a half-life in water of 4-28 days. Agricultural run-off containing 2,4-D may contaminate groundwater, which may impact drinking water in some areas.
Surface Water	Lower	2,4-D is applied to some lakes to control weed growth, and highest concentrations are present in the water in the first 24 hours after application. Children swimming in treated lakes may be exposed to 2,4-D via dermal and ingestion routes.
Sediment	Lower	2,4-D breaks down readily in sediment and aquatic environments.
Soil	Lower	2,4-D does not persist in soil; its environmental half-life is less than 7 days. Children playing on 2,4-D-treated lawns may be exposed to 2,4-D via the dermal route, or via hand-to-mouth activity.

[1] For more information about child-specific exposure factors, please refer to the Child-Specific Exposure Factors Handbook (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55145).

[2] The Relative Potential for Children's Exposure category reflects a judgment by the TEACH Workgroup, U.S. EPA, that incorporates potential exposure pathways, frequency of exposure, level of exposure, and current state of knowledge. Site-specific conditions may vary and influence the relative potential for exposure. For more information on how these determinations were made, go to http://www.epa.gov/teach/teachprotocols_chemsumm.html.

[3] Childhood represents a lifestage rather than a subpopulation, the distinction being that a subpopulation refers to a portion of the population, whereas a lifestage is inclusive of the entire population.

[4] Information described in this column was derived from several resources (e.g., 1, 2) including studies listed in the TEACH Database (http://www.epa.gov/teach).

III. TOXICITY SUMMARY[5, 6]

Health effects of chronic or acute 2,4-D exposure reported for adults included blood, liver, and kidney toxicity (1, 3, 4). Specific effects included a reduction in hemoglobin and red blood cell numbers, decreased liver enzyme activity, and increased kidney weight (3, 4). Acute exposure can result in skin and eye irritation (1). Acute exposure to very high concentrations of 2,4-D can cause the following clinical symptoms: stupor; coma; coughing; burning sensations in lungs; loss of muscular coordination; nausea; vomiting; or dizziness (3, 4, 13, 14).

Experimental animal studies of chronic oral exposure have reported adverse effects on the eye, thyroid, kidney, adrenals, adrenals, and ovaries/testes (1). In addition, some experimental animal studies have reported teratogenic effects (birth defects) at high doses, including increased fetal death, urinary tract malformation, and extra ribs (15, 16). When adult female experimental animals were exposed to 2,4-D during their pregnancy and lactation periods, their exposed offspring exhibited neurological effects, including delayed neurobehavioral development (5) and changes in several neurotransmitter levels or binding activities (6-9, 17) and ganglioside levels (18, 19) in the brain. Delayed neurobehavioral development was manifested as delays in acquisition of certain motor skills such as the righting reflex (5).

Carcinogenicity weight-of-evidence classification[7]: The U.S. EPA stated, "Based on chronic studies on animals, 2,4-D has been classified as a Group D chemical, one that is not classifiable as to human carcinogenicity. Although 2,4-D continues to be the focus of epidemiological and laboratory studies, both EPA's review and the Scientific Advisory Panel have concluded that the available evidence is insufficient to classify 2,4-D as a human carcinogen" (1) (www.epa.gov/iris/subst/0150.htm). A more recent review by the U.S. EPA in 2005 concluded "there is no additional evidence that would implicate 2,4-D as a cause of cancer" (1). The World Health Organization International Agency for Research on Cancer (IARC) has not evaluated 2,4-D and chlorophenoxy herbicides for carcinogenicity, and these herbicides are not listed as a priority for future evaluation (http://monographs.iarc.fr/ENG/Meetings/prioritylist.pdf).

[5] Please refer to research article summaries listed in the TEACH Database for details about study design considerations (e.g., dose, sample size, exposure measurements).

[6] This toxicity summary is likely to include information from workplace or other studies of mature (adult) humans or experimental animals if child-specific information is lacking for the chemical of interest. Summaries of articles focusing solely on adults are not listed in the TEACH Database because the TEACH Database contains summaries of articles pertaining to developing organisms.

[7] For recent information pertaining to carcinogen risk assessment during development, consult "Guidelines for Carcinogen Risk Assessment and Supplemental Guidance on Risks from Early Life Exposure" at *http://www.epa.gov/cancerguidelines*.

VI. EXPOSURE AND TOXICITY STUDIES FROM THE TEACH DATABASE

This section provides a brief description of human and animal studies listed in the TEACH Database. For more details about study design parameters, e.g., doses and exposure information, please refer to article summaries in the TEACH Database. Any consideration should include an understanding that exposure levels in animal studies, in many cases, are greater than exposure levels normally encountered by humans.

A. *HUMAN EXPOSURE AND EFFECTS*

- Several studies have measured the concentrations of 2,4-D in settings where children might be exposed. 2,4-D was detected in dust on floors and table tops in homes following lawn application (10-12, 20). 2,4-D was also detected in indoor air in homes after application (12). In a survey of some preschools in North Carolina, 2,4-D was detected in dust, indoor air, solid foods, and beverages, and was generally found to be low (20). 2,4-D has been detected in children's urine, providing evidence of children's exposure to 2,4-D (21-24).
- There are few studies of reproductive and developmental effects following 2,4-D exposure of humans. Most information comes from studies of occupational exposures of professional applicators of pesticide and herbicide mixtures that contained 2,4-D. An increase in malformed, immobile, and dead sperm cells was observed in adolescent and adult male 2,4-D applicators, as compared to unexposed controls (25). Also, exposure of adolescent and adult workers to 2,4-D correlated with increases in proliferation responses of lymphocytes (white blood cells) (26) and incidence of anti-nuclear antibodies (proteins produced by lymphocytes that can be associated with autoimmune disease) (27).

B. *EXPERIMENTAL ANIMAL EXPOSURE AND EFFECTS*

2,4-D

- There are few studies on the ability of 2,4-D to cross the placenta and the blood-brain barrier in fetuses. In pregnant rabbits, intravenous injection of 2,4-D resulted in detection of 2,4-D in the placenta (28, 29) and in fetal brain in two studies (28, 30), but not a third (29). In pregnant mice, intravenous injection exposure of 2,4-D resulted in detection of 2,4-D in fetal brain (30).
- Many studies of effects of prenatal exposure to 2,4-D have been performed using an exposure route via the digestive tract by administration through food or by gavage (feeding by a tube into the stomach). Developmental studies described below utilized this route of exposure unless indicated otherwise.
- Several studies have reported teratogenic effects (birth defects) following prenatal 2,4-D exposure. Prenatal exposure to 2,4-D resulted in reduced litter size and increased fetal deaths in rats (15). Reported abnormalities included urinary tract malformations (15) and extra ribs (16). However, in another study of prenatal exposure, developmental toxicity was not observed in exposed rabbits, and was observed in exposed mice only at doses of 2,4-D that caused severe maternal toxicity (31).

- Adverse effects of prenatal exposure to 2,4-D on neurological development have been reported in experimental animal studies. Administration of 2,4-D in these studies occurred via gavage or diet of pregnant females during pregnancy and lactation (5-9, 17), and in some studies continued via diet of offspring into young adulthood at 3 months of age (5-8, 17). Prenatal and lactational exposure to 2,4-D resulted in delays in acquisition of certain motor skills (5), and changes (some increases and some decreases) in neurotransmitter levels in the brains of offspring (6-9). Effects were observed in the serotonergic and dopaminergic responses (5-9, 17). Some effects persisted into adulthood several weeks after exposure of offspring was stopped at weaning in several studies (5-8), but increased D2 receptor binding was reversible after exposure was stopped (17).
- Studies of effects on the immune system are sparse. One study found no effect of prenatal exposure to 2,4-D on inducing errors in normal DNA rearrangements in T cell receptors of thymocytes (developing T lymphocytes, or white blood cells) (32). There were no significant observed effects on tests of B and T lymphocytes responses *in vitro* for offspring exposed to the n-butyl ester form of 2,4-D *in utero* (33).
- Lactational exposure to 2,4-D resulted in reduced growth rate of offspring (34) and significantly decreased numbers of dopaminergic neurons in some regions of the brain (35). Following lactation exposure of pups to 2,4-D, pups whose mothers were malnourished during pregnancy had significantly lower concentrations of iron in their brain than exposed pups born to well-nourished mothers (36).
- Early life exposure by intravenous injection of pups with 2,4-D prior to weaning also resulted in decreased brain weight, neurochemical changes in the brain, and delays in neurobehavioral development (18, 19).

2,4-D in Mixtures

Some animal studies of 2,4-D exposures tested effects of exposures to mixtures of herbicides and pesticides containing 2,4-D. Studies of mixtures were designed to test possible effects of particular mixtures that humans may be exposed to in commercial preparations. A limitation of studies that utilize mixtures is the difficulty in ascertaining whether observed effects were the result of exposure to 2,4-D alone, other chemicals in the mixture, or to the combination of chemicals in the mixture.

Some mixtures are currently in use as commercial products, while others have been used in the past but are no longer used or allowed in the United States. The mixture of 2,4-D and picloran is also know as Tordon, or Australian “Agent White” (37). The mixture of 2,4-D and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) was used in Agent Orange, with other active ingredients, and is no longer used in the United States (38). Mixtures containing amine preparations of 2,4-D, and mixtures containing 2,4-D with mecoprop and dicamba are currently in use in the United States (39).

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- Studies of effects on sperm and offspring of adult male rats and mice exposed to mixtures containing 2,4-D and picloran showed varying results. Exposure of adult male rats to this mixture showed effects on germ cells and subsequent offspring as reported by testicular damage and sperm cell depletion in rats (37, 40). One of these studies also observed reduced growth in fetal offspring of exposed male mice (33), while the other study found no observable change in fetal growth or incidence of malformations (37).
- Prenatal exposure to a commercially-available formulation containing 2,4-D, mecoprop, and dicamba resulted in reduced litter size in mice (39).
- Prenatal exposure to a mixture of 2,4-D and 2,4,5-T resulted in developmental delays in neurobehavioral parameters, and delayed induction of dopamine in the brain of exposed offspring (38, 41, 42).
- Regarding the immune system of exposed offspring, two studies suggested that there was little effect of prenatal exposure to a commercially-available mixture containing an amine preparation of 2,4-D (43, 44). One study detected slightly smaller tumors in adult animals that had been exposed to 2,4-D *in utero* and challenged with tumor cells as adults; the authors postulated that this effect may be a consequence of 2,4-D effect on the immune response (43).

V. CONSIDERATIONS FOR DECISION-MAKERS

- Detailed compilations and analyses of information pertaining to exposure and health effects for 2,4-D are available from the U.S. Reregistration Eligibility Decision (RED) for 2,4-D document (1). A 2,4-D Fact Sheet (3) and a Hazard Summary for 2,4-D (4) are available from the U.S. EPA. A handbook for health care professionals which provides details on symptoms and treatment of pesticide and herbicide poisonings is also available from the U.S. EPA (14).
- Actions to minimize children's exposure to 2,4-D should focus on keeping children, toys, and pets away from lawns after 2,4-D has been applied. The person who applied the lawn treatment should avoid tracking 2,4-D into the home by keeping shoes worn during treatment outside of the home, and washing hands and clothes thoroughly before contact with children (http://www.epa.gov/pesticides/health/children.htm) (45).
- Lawn care products that contain 2,4-D should be stored safely in the home. The U.S. EPA provides practical information on storage of products containing herbicides, pesticides, and other potential hazards (45). Recommendations include storing products in a locked cabinet, never transferring products to another unlabeled container, and washing toys and home surfaces often.

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- Alternatives to regular full-lawn treatment with 2,4-D could be considered. Spot treatment of lawns with 2,4-D can be effective; and other lawn care and feeding practices may reduce or eliminate weeds in lawns without use of 2,4-D. The U.S. EPA provides information on a program that offers alternatives to the use of pesticides, called Integrated Pest Management (46). Also consult local lawn care specialists for more information.
- The U.S. EPA recently reported that, when 2,4-D exposure assessments considered residential exposure to 2,4-D following lawn applications combined with exposure from diet and drinking water, total 2,4-D exposure exceeded the EPA level of concern. As a result, the EPA asked registered users of 2,4-D to lower the maximum concentrations for applications to a maximum application rate of 1.5 pounds acid equivalent per acre (1).
- Concentrations of 2,4-D in urine of children six years of age and older are regularly measured as part of the National Health and Nutrition Examination Survey (NHANES) (21, 22). This comprehensive survey, administered by the U.S. Centers for Disease Control and Prevention (CDC), provides data for a statistically representative national sample. Over 1,300 urine samples for children 6-19 years of age collected in 2001-2002 were tested for 2,4-D. 2,4-D was detected in better than 25 percent of these samples. The 95th percentile concentration of 2,4-D for children ages 6-11 years was 1.55 µg/L, and for children ages 12-19 years was 1.24 µg/L. Median or mean values could not be calculated due to the prevalence of results below the limit of detection (22).
- Consult "Child-Specific Exposure Factors Handbook," EPA-600-P-00-002B, for factors to assess children's dermal absorption and inhalation rates (46). An updated External Draft of the 2006 version of this handbook is available (47).

VI. TOXICITY REFERENCE VALUES

A. Oral/Ingestion

U.S. EPA Reference Dose (RfD) for Chronic Oral Exposure: 1E-2 (or 0.01) mg/kg/day; based on hematologic, hepatic, and renal toxicity in adult rats (www.epa.gov/iris/subst/0150.htm, I.A.1) (48). Last Agency Workgroup Review Date 2/5/86.

U.S. EPA Chronic Dietary (Chronic RfD) Exposure: 0.005 mg/kg/day (new RED, p.21). The U.S. EPA issued 11 reference values for chronic and acute exposures via dietary, oral, dermal, and inhalation routes of exposure, and in some cases, for different age ranges. (For a complete listing of the reference values, go to http://www.epa.gov/oppsrrd1/REDs/24d_red.pdf, p. 21) (1). Last revised June 2005.

U.S. EPA Drinking Water Advisories (10-kg or 22 lb. child): 1 day = 1 mg/L, 10 day = 0.3 mg/L (http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf) (49). Last revised 2006.

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U.S. EPA Maximum Contaminant Level (MCL) for Drinking Water: 0.07 mg/L, with potential health effects of kidney, liver, or adrenal gland toxicity (www.epa.gov/safewater/mcl.html#mcls) (50). Last revised 7/02.

U.S. EPA Maximum Contaminant Level Goal (MCLG): 0.07 mg/L, with potential health effects of kidney, liver, or adrenal gland toxicity (www.epa.gov/safewater/mcl.html#mcls) (50). Last revised 7/02.

B. Inhalation

None available.

VII. U.S. FEDERAL REGULATORY INFORMATION

- The U.S. EPA recently released a Reregistration Eligibility Decision (RED) in June, 2005 (1). This document provides detailed information about potential exposures and health effects, and registered uses of 2,4-D.
- 2,4-D is one of 188 compounds listed as a Hazardous Air Pollutant (HAP) under section 112(b) of the 1990 Clean Air Act Amendments (51).
- The U.S. EPA requires reporting of quantities of certain chemicals that exceed a defined reportable quantity, and that quantity varies for different chemicals (52). Under the Emergency Planning and Community Right-to-Know Act (EPCRA) Section 313 "Toxic Chemicals," quantities of 2,4-D greater than 25,000 pounds manufactured or processed, or greater than 10,000 pounds otherwise used, is required; under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), reporting releases of any quantity exceeding 100 pounds is required (52).

VIII. BACKGROUND ON CHEMICAL

A. CAS Number: 94-75-7

B. Physicochemical Properties: 2,4-D is a white or yellow crystalline powder normally found in liquid formulations. For more information, go to the National Library of Medicine ChemID Web site (*http://chem.sis.nlm.nih.gov/chemidplus*) and search for 2,4-D.

C. Production: Recent estimates of production are not publicly available. Total domestic use in 2001 was estimated to be 28-33 million pounds in the U.S. annually (1).

D. Uses: 2,4-D is a selective herbicide used to kill broadleaf weeds in grass and turf, and in recreational lakes (1, 2). Specific examples of uses include application to broadleaf weeds, sugarcane, sorghum, forestry, and turf. 2,4-D is one of the most highly used herbicides in industrial, commercial, and government markets (2, 3, 53). Total amount of reported releases or disposals of 2,4-D in 2005 was 269,156 pounds (54).

E. Environmental Fate: 2,4-D is readily broken down by microbes in soil and aquatic environments; half-life in soil is 7-10 days and the half-life in water is 3-28 days (1). There is little tendency of 2,4-D to bioconcentrate (2). Leaching to groundwater may occur in coarse and sandy soil that has a low organic content or has a very basic pH (2).

F. Synonyms and Trade Names: Aqua-Kleen, Savage, Weedone, Lawn-Keep, Estone, Crotolin, D 50, Ded-Weed LV-69, Farmco, Miracle, Weed-B-Gone, Vergemaster, Salvo, and others (for a complete list, go to *http://www.epa.gov/safewater/contaminants/dw_contamfs/24-d.html*).

Additional information on 2,4-D is available in the TEACH Database for 2,4-D and at the following Web sites:

www.epa.gov/ttn/atw/hlthef/di-oxyac.html
www.epa.gov/iris/subst/0150.htm
http://extoxnet.orst.edu/pips/24-D.htm

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