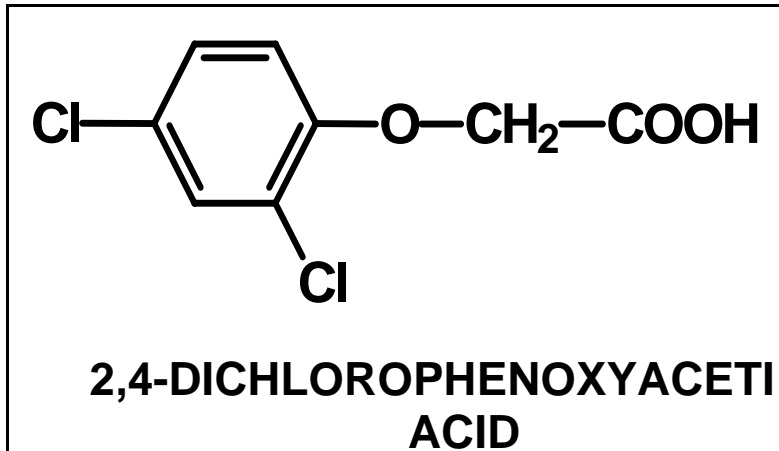


III.3 2,4-DSUMMARY

2,4-D (2,4-dichlorophenoxyacetic acid) is a somewhat selective, systemic broadleaf herbicide that is used to control a variety of submersed, emersed and floating aquatic plants. 2,4-D exists in the acid form as well as in a variety of chemical forms. There are about 66 different formulations of 2,4-D, most of which are registered for terrestrial use. The 2,4-D acid form of this compound is not generally used for aquatic weed control (Reinert and Rodgers, 1987). The two categories of formulations which have been used most commonly for aquatic weed control include the butoxyethanol esters (2,4-D BEE) and the dimethylamine salts (2,4-D DMA) of 2,4-D. There are also a number of formulations being used for aquatic control containing the 2-ethylhexyl esters (2EHE), also known as 2-isooctyl esters (IOE), of 2,4-D (Reinert and Rodgers, 1987). 2,4-D formulations can exist as either emulsifiable concentrates, granulars, soluble concentrates, ready-to-use or pressurized liquids (DFA, 1988). The physical and chemical properties of 2,4-D are dependent on the chemical form of the active ingredient and vary dramatically.

In general, ester formulations of 2,4-D are more toxic to plants and fish than are amine salts. 2,4-D BEE formulations are generally not very soluble in water whereas 2,4-D DMA formulations have relatively high water solubility. Neither type of formulation is very volatile. Hydrolysis of 2,4-D BEE is a major fate process for this compound whereas it is not expected to be a significant fate process for 2,4-D DMA. Biotransformation and biodegradation are the major aquatic fate processes for both types of formulations. 2,4-D BEE tends to bioconcentrate to some degree in various organisms whereas 2,4-D DMA has a very low potential to bioconcentrate.

2,4-D was first introduced as an herbicide by AMCHEM Products, Inc. in 1942 (DFA, 1988). Currently, the parent acid is manufactured by Rhone-Poulenc Agricultural. The various esters and salts are manufactured by a variety of companies. BEE granular formulations are also manufactured by Rhone-Poulenc. The DMA salts are manufactured by Dow-Elanco (Hammond, 1995)..

Many studies have been conducted with various formulations of 2,4-D addressing both toxicity and environmental fate and persistence. The U.S. Environmental Protection Agency (EPA) issued a registration standard for 2,4-D acid and all its chemical forms in September, 1988 (USEPA, 1992). Since that time, the agency has been working with the industry to collect additional information under the mandate of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) amendments of 1988. EPA has not made any final decisions regarding reregistration of 2,4-D (Miller, 1995). The 2,4-D industry as a whole is currently only pursuing reregistration of its 2,4-D DMA formulations for aquatic use. Registration of its 2,4-D 2EHE formulations will only be pursued for non-aquatic uses by the industry. In addition, Rhone-Poulenc is individually pursuing registration of its BEE granular formulation (Hammond, 1995). EPA has not projected a date as to when it will issue a Registration Eligibility Decision (RED) for 2,4-D (Miller, 1995). The industry believes that issuance of an RED will occur sometime in 1997 or 1998 (Hammond, 1995).

REGISTERED PRODUCTS IN MASSACHUSETTS

There are currently eight commercial products, registered for aquatic use in Massachusetts, containing various chemical forms of 2,4-D as the active ingredient. These include Riverdale 2,4-D Granules (containing 28.9% 2,4-D(2-EHE)), Riverdale 2,4-D L.V.4 Ester (containing 67.2% 2,4-D(2-EHE)), Riverdale Weeddestroy AM-40 Amine Salt (containing 47.3% 2,4-D(DMA)), Weedar IVM 44 Broadleaf Herbicide (containing 46.8% 2,4-D(DMA)), Weed-Rhap A-4D (containing 46.7% 2,4-D(DMA)), SEE 2,4-D LV4 (containing 61.74% 2,4-D(2EHE)) (Corte-Real, pers. comm.), Weedar 64 (containing 46.8% 2,4-D(DMA)) and Aqua-Kleen (containing 27.6% 2,4-D(BEE)) (Corte-Real, pers. comm.).

2,4-D USES AND APPLICATION

2,4-D can be used to control submersed, emersed and floating weeds. Liquid formulations of 2,4-D are only registered for the control of floating (e.g., waterhyacinth) and emergent vegetation. Surface applications can be made from a boat or from shore with dilute or concentrated product. Aerial applications can be made by spraying a dilute form of the product. Subsurface applications can be made with weighted trailing hoses from the boat (WSSA, 1983; Aquatic Plant Identification and Herbicide Use Guide, 1988).

Granular 2,4-D formulations can be distributed as either a surface application or as an aerial application using conventional mechanical spreaders or comparable equipment for large areas or a portable spreader for spot treatments (WSSA, 1983).

Ester formulations are volatile. Because of this characteristic, the particular location and use of an ester formulation should be considered carefully, particularly with aerial applications (Aquatic Plant Identification and Herbicide Use Guide.) Longer-chain ester formulations are of lower volatility. Salt formulations have the lowest volatility (WSSA, 1983).

Application rates of specific products vary due to the variation in the amount of active ingredient. The application rate for control of waterhyacinth and emersed vegetation control is 2-4 kg ae (i.e., 2,4-D acid-equivalent) per hectare. For control of canal bank vegetation, 1-2 kg ae per hectare is recommended. For control of watermilfoil, 9.5-38 kg ae per hectare is recommended. Granular formulations should be applied at a rate of 20-40 kg ae per hectare. Maximum water concentrations of 2,4-D should not exceed 0.1 mg/l. Treated water should not be used for irrigation, for agricultural sprays, for livestock watering or as a domestic water supply unless an approved assay indicates that the 2,4-D level does not exceed 0.1 mg/l 2,4-D acid-equivalent (Aquatic Plant Identification and Herbicide Use Guide, 1988).

The best time to apply 2,4-D is in spring or early summer when young vegetation is actively growing. Application should be made in long strips separated by buffer zones. Application of liquid formulations should not be made during high wind or high water flow conditions. Aerial spraying should not be conducted if wind speed exceeds 8 km/hour. Drift control agents should be used when aerial spraying is conducted (Aquatic Plant Identification and Herbicide Use Guide, 1988).

For application of liquid formulations, especially when used on emerged or floating vegetation, use of invert emulsions or polymeric thickeners is recommended. For application of oil-soluble amine formulations, mixture with kerosene or other oil soluble solvent is recommended (Aquatic Plant Identification and Herbicide Use Guide, 1988).

The various formulations of 2,4-D used for aquatic weed control are effective against a variety of plants. Some of these plants are listed in Table III.3-1.

Table III.3-1. List of Aquatic Weeds Controlled by 2,4-D

Arrowhead	<i>Sagittaria</i> spp.
Bladderwort	<i>Utricularia</i> spp.
Bulrush	<i>Scirpus</i> spp.
Coontail or Hornwort	<i>Ceratophyllum demersum</i>
Creeping Waterprimrose	<i>Jussiaea repens</i>
Pickerelweed	<i>Pontederia</i> spp.
Spatterdock, Cow Lily, Yellow Water Lily	<i>Nuphar</i> spp.
Burreed	<i>Sparganium</i> spp.
Waterweed	<i>Elodea</i> or <i>Anacharis</i>
Waterchestnut	<i>Trapa natans</i>
Watermilfoil	<i>Myriophyllum</i> spp.
Water Smartweed	<i>Polygonum</i> spp.
White Waterlily	<i>Nymphaeae</i> spp.
Naiad	<i>Najas flexilis</i>
Pondweed	<i>Potamogeton</i> spp.
Watershield	<i>Brasenia</i> spp.

(Riverdale Chemical Co.)

MECHANISM OF ACTION

2,4-D is readily translocated throughout the plant phloem, especially from foliage to roots, probably along with the products of photosynthesis (Aquatic Plant Identification and Herbicide Use Guide, 1988; Joyce and Ramey, 1986). It is a somewhat selective, systemic growth regulator with hormone-like activity. 2,4-D inhibits cell division of new tissue and stimulates cell division of some mature plant tissue, resulting in inhibition of growth, necrosis of apical growth and eventual total cell disruption and plant death. Low concentrations of 2,4-D may stimulate plant growth (Aquatic Plant Identification and Herbicide Use Guide, 1988). Introduction of saturation levels of artificial auxins (including 2,4-D) into growing plants disrupted the plants' delicate hormonal balance, causing reductions in root uptake of salts and water, phloem transport and photosynthesis, contributing to the death of the plant (White-Stevens, 1971 as cited in HSDB, 1995). 2,4-D also affects plant respiration and food reserves

(Joyce and Ramey, 1986). Since 2,4-D produces many toxic responses, the primary mode of action has not been clearly established (Joyce and Ramey, 1986).

ENVIRONMENTAL FATE AND TRANSPORT

The environmental fate and transport of 2,4-D in aquatic environments is determined by the chemical formulation of the 2,4-D. Although microbial biodegradation is the predominant degradation pathway for 2,4-D and its derivatives, the various chemical formulations of 2,4-D are also subject, to varying degrees, to breakdown via hydrolysis and photolysis.

Estimates of the typical overall half-life of 2,4-D in water range from 10 to greater than 50 days. The primary fate process of 2,4-D in water is microbial biodegradation. There are a variety of organisms in both fresh and marine waters which are capable of degrading 2,4-D. The rate of biodegradation is dependent on a number of factors including the level of nutrients present, temperature, availability of oxygen and whether/not the water has had a prior history of contamination with 2,4-D or other phenoxyacetic acid. 2,4-D is generally more persistent in oligotrophic waters and in waters with high 2,4-D concentrations. Biodegradation half-lives in clear waters have been estimated to be from 18 to greater than 50 days. In muddy waters, biodegradation half-lives have ranged from 10-25 days (HSDB, 1995).

Degradation of 2,4-D in aquatic sediments is generally rapid (less than one day) and occurs mostly through microbial biodegradation (HSDB, 1995). The products of 2,4-D biodegradation include 2,4-dichlorophenol, other hydroxylic aromatics and polymeric acids (HSDB, 1995).

2,4-D butoxyethyl ethers (BEE) have low water solubility (estimated at approximately 12 mg/l) whereas 2,4-D diethylamines (DMA) have relatively high water solubility (about 3.0×10^6 mg/l). The water solubility of the 2,4-D acid ranges from about 600-900 mg/l (Reinert and Rodgers, 1987; Aquatic Plant Identification and Herbicide Use Guide, 1988).

The 2,4-D acid has a Henry's Law (H) value of 6.2×10^{-3} indicating that it is somewhat volatile. The relative rate of volatilization is dependent on the formulation. In general, the acid, inorganic salts and amines are less volatile than the esters, which vary from high to low. The oil soluble amines are considered the least volatile (WSSA, 1983). Both 2,4-D BEE and 2,4-D DMA have relatively low volatility (Reinert and Rodgers, 1987; Aquatic Plant Identification and Herbicide use Guide, 1988). A volatilization half-life of 895 days was calculated for 2,4-D BEE (Reinert and Rodgers, 1987).

The significance of hydrolysis as a 2,4-D fate process varies with the chemical formulation. The 2,4-D acid is somewhat subject to hydrolysis. Hydrolysis is a significant fate process for 2,4-D BEE formulations but is not expected to be an important fate process for the 2,4-D DMA formulations (Reinert and Rodgers, 1987; Aquatic Plant Identification and Herbicide Use Guide, 1988).

There are conflicting reports as to the photolysis of 2,4-D and its derivatives in water. The relative significance of this fate pathway is dependent on the chemical formulation of the 2,4-D

derivative. There are no available data which show direct photolysis of 2,4-D in the atmosphere upon exposure to natural sunlight. Most photolysis studies of 2,4-D have used high-intensity mercury lamps which emit large amounts of ultraviolet (UV) radiation (DFA, 1988). It has been shown, however, that 2,4-D exhibits an absorption maximum at 288 nm extending to greater than 290 nm. Sunlight reaching the earth is composed of wavelengths greater than 280 nm. These facts suggest that 2,4-D may be susceptible to direct photolysis (HSDB, 1995). Whereas some researchers do not believe that photolysis is a significant fate pathway for 2,4-D BEE (Aly and Faust, 1964 as cited in Reinert and Rodgers, 1987) others have calculated a photolysis half-life for these formulations (see Table III.3-4) (Zepp *et al.*, 1975 as cited in Aquatic Plant Identification and Herbicide Use Guide, 1995). Photolysis is generally not expected to be a significant fate pathway for 2,4-D DMA formulations (Reinert and Rodgers, 1987; Aquatic Plant Identification and Herbicide Use Guide, 1988).

The ability of 2,4-D and its derivatives to bioconcentrate in aquatic organisms is again determined by its chemical formulation. One source indicates that there is little evidence that bioconcentration of 2,4-D acid occurs through the food chain. This conclusion was reached after a large-scale monitoring for 2,4-D residues in the many routes of metabolism and degradation that exist in ecosystems (Gray *et al.*, 1983 as cited in HSDB, 1995). Whole body 2,4-D BEE nonequilibrium BCF values were found to be very low, ranging from 2-14 in channel catfish (*Ictalurus punctatus*) and 6-12 in bluegill sunfish in aquaria. The ester was quickly hydrolyzed to the acid form and then rapidly excreted (Rodgers and Stalling, 1972 as cited in Reinert and Rodgers, 1987). Nevertheless, several estimates of the bioconcentration factor (BCF) for 2,4-D BEE formulations were made, varying by study and organism, ranging from 162-408 (Reinert and Rodgers, 1987). The bioconcentration potential for 2,4-D DMA formulations has consistently been shown to be low (Reinert and Rodgers, 1987).

Table III.3-4 and III.3-5 at the end of this 2,4-D summary contain lists of chemical and physical properties for various forms of 2,4-D.

PHARMACOKINETICS

Research conducted with animals and humans indicates that 2,4-D is rapidly absorbed into the body (USEPA, 1988). The amine and ester formulations are rapidly converted to the 2,4-D acid upon absorption (DowElanco, 1995). The 2,4-D butyl ester form is less completely absorbed than other forms and appears to be hydrolyzed to the free acid before absorption (USEPA, 1988).

2,4-D acid has been shown to be almost completely absorbed from the gut in rats. Within 24-48 hours after oral administration, 90-95% of intact 2,4-D was recovered in the urine of rats fed 2,4-D (USEPA, 1988). Ingestion studies with limited numbers of human volunteers indicate that 2,4-D is absorbed rapidly. Significant levels of 2,4-D were detected in the plasma in as early as one hour and peak levels were detected as early as 4-7 hours after ingestion. Humans can also absorb 2,4-D through the skin and/or respiratory tract (USEPA, 1988).

In both lab animals and humans, 2,4-D has been shown to be distributed quickly throughout the body as early as 6-8 hours after oral exposure. 2,4-D distributes to the liver, kidney, spleen, heart and lung at high levels and the muscle, brain and fat at low levels (USEPA, 1988). 2,4-D has also been shown to cross the placenta in mice, rats and sows (USEPA, 1988). In a variety of species given an oral dose of 100 mg/kg 2,4-D plasma half-lives ranged from 3.5-12 hours. In rats given high doses of 2,4-D (i.e., 240 mg/kg), both plasma and tissue half-lives were in the range of 3.0-3.5 whereas in rats given lower doses of 2,4-D, plasma and tissue half-lives were 0.5-0.8 hours (Khanna and Fang, 1966 as cited in Diener, 1992).

Regardless of the exposure route, species or dose, 2,4-D seems to be excreted virtually unchanged. Although there is limited animal and/or human evidence that some 2,4-D is metabolized to 2,4-dichlorophenol or conjugated with amino acids, 2,4-D is largely not subject to biotransformation. In animals, low levels of 2,4-D are excreted in the urine usually within 24-72 hours. In humans ingesting 5 mg/kg 2,4-D, a plasma half-life of 33 hours, a urinary half-life of about 17.7 hours and an overall elimination half-life of 35-48 hours were determined in a study of agricultural spray applicators (USEPA, 1988). Other estimates of overall 2,4-D half-life in the body range from 10-36 hours (DowElanco, 1995). The pharmacokinetics following oral exposure differ somewhat from the pharmacokinetics following dermal exposure (Pelletier *et al.*, 1989 as cited in Diener, 1992). In the absence of continued exposure, essentially all of the absorbed 2,4-D is eliminated within 2-4 days (DowElanco, 1995).

Information on the absorption, distribution and excretion of 2,4-D and its salts and esters is consistent across species in terms of its rapid absorption, its virtually complete elimination via urine and its lack of accumulation potential (Diener, 1992).

Based on evidence from metabolism and pharmacokinetic studies indicating that all forms of 2,4-D are rapidly converted to the acid form upon absorption and that only the acid is detectable in blood and urine soon after dosing, no difference in toxicity among the various forms of 2,4-D is expected (Diener, 1992).

HEALTH EFFECTS

2,4-D Impurities of Toxicological Concern

There is concern regarding the possible contamination of 2,4-D with substances which may magnify adverse health effects. The most noted and controversial of these are the polychlorinated dibenzo-p-dioxins (PCDD), especially 2,3,7,8-tetrachlorodibenzo-p-dioxin, the most toxic of the PCDD congeners. The toxicity of the other PCDD congeners is considered minor in comparison (Diener, 1992). There is much controversy on the interpretation of epidemiological studies conducted of applicators, farmers and others who were exposed to earlier formulations of 2,4-D, in particular Vietnam war veterans who were exposed to the 2,4-D/2,4,5-T mixtures during spraying as a defoliant (Diener, 1992). The formulations of 2,4-D manufactured and sold in the United States today contain very few PCDD contaminants. 2,3,7,8-TCDD and the hexa isomer have not been detected in 2,4-D while several of the less toxic isomers have been detected in amounts of 5-900 ppb. 2,3,7,8-TCDD was detected in earlier

mixtures of 2,4-D/2,4,5-T (USEPA, 1988). Most 2,3,7,8-TCDD contamination of early mixtures occurred during production of 2,4,5-T, not so much during 2,4-D production. It was during use of the two products together that the confounding effect of TCDD became especially prevalent. However, 2,3,7,8-TCDD was not detected in any 2,4-D formulation that did not also contain 2,4,5-T (Diener, 1992).

Earlier formulations of 2,4-D were also studied as to possible contamination with nitrosamine, particularly N-nitrosodimethylamine (NDMA). Most samples tested contained less than 1 ppm of NDMA. Nitrosamines in earlier 2,4-D formulations were formed from nitrates used in preserving metal storage containers. Today, 2,4-D is stored in plastic or epoxy-lined containers (Diener, 1988).

Mammalian Health Effects

Acute:

Much information is available on the acute health effects of 2,4-D to humans from the medical literature reports on attempted suicides via ingestion of very high doses of 2,4-D (doses significantly greater than those potentially associated with exposures to lake water containing the same chemicals applied according to label instructions for aquatic weed control). Early symptoms of exposure include gastritis, vomiting and loss of consciousness. General types of effects noted upon acute ingestion of 2,4-D include irritation of the mouth, throat and gastrointestinal tract, chest pain (from esophagitis), abdominal pain, diarrhea, fibrillary muscle twitching, skeletal muscle tenderness, myotonia, metabolic acidosis, fever, tachycardia, hyperventilation, vasodilation and sweating; some cases have been characterized by coma and convulsions (USEPA, 1988; HSDB, 1995). Death is usually preceded by muscular paralysis (USEPA, 1988). Several cases were also reported in which an unspecified amount of 2,4-D ester was absorbed through the skin, producing polyneuritis but not affecting the eyes or vision (HSDB, 1995). In addition, acute symptoms reported among workers using various esters and salts of 2,4-D include rapid fatigue, headache, loss of appetite, pain in the region of the liver and stomach and reduced sensitivity to taste and smell (HSDB, 1995).

Observations in laboratory animals indicate that acute oral or injection exposure to 2,4-D by various routes of exposure has resulted in vomiting, diarrhea, anorexia, weight loss, ulcers in the mouth, as well as liver and kidney effects, progressive symptoms of muscular incoordination, hindquarter paralysis, stupor and coma in various laboratory animals. Death has been ascribed to ventricular fibrillation and cardiac arrest. The dominant effect consistently noted in a variety of species, regardless of the route of exposure, is myotonia. Acute exposure to high 2,4-D levels has resulted in kidney and skeletal muscle damage in rodents but liver effects were only described in dogs. Significant differences in toxicity are not apparent between 2,4-D and its salts and esters (USEPA, 1988; HSDB, 1995). Table III.3-2 below presents a summary of selected results of acute toxicity tests conducted in laboratory animals with the various forms of 2,4-D addressed in this document.

Table III.3-2. Results of Acute Toxicity Tests Conducted in Experimental Animals

Route	Species	chemical formulation	LD50 (mg/kg/day)	Reference
Oral	rat (males)	acid	980±83	Ylitalo <i>et al.</i> , 1990
	rat	acid (95%)	639 (ae 607)	ITF, 1992
	rat	acid (95%)	764 (ae 726)	ITF, 1992
	rat	acid	699	ITF, 1992
	rat (females)	acid	920	Kitchen and Brown, 1988
	rat (males)	BEE	887 (ae 564)	Gorzinski <i>et al.</i> , 1987
	rat (females)	BEE	831 (ae 565)	Gorzinski <i>et al.</i> , 1987
	rat	BEE	850	ITF, 1992
	rat (males)	IOE	896	ITF, 1992
	rat (females)	IOE	982 (ae 612)	USEPA, 1989
	rat (males)	IOE	>720 but <864	USEPA, 1989
	rat (males)	DMA	1,090 (ae 619)	Gorzinski <i>et al.</i> , 1987
	rat (females)	DMA	863 (ae 490)	Gorzinski <i>et al.</i> , 1987
	rat	DMA	949	ITF, 1992
	mouse	acid	368 (312-434)	Rowe and Hymas, 1954
	dog	acid	100 (25-250)	Rowe and Hymas, 1954
	guinea pig	acid	469 (397-553)	Rowe and Hymas, 1954

dermal	rabbit	2,4-D	1,400	Lehman, 1952
	rat	BEE	>2,000	ITF, 1992
	rabbit	IOE	>2,000	ITF, 1992
	rabbit	DMA	2,244	ITF, 1992
inhal.	rat	acid	1.79 mg/l	EPA, 1989

BEE - Butoxyethanol ester
 DMA - Dimethylamine salt
 IOE - Isooctyl ester
 ae - active ingredient

Diener, 1992

Subchronic:

General subchronic effects observed in animal studies include ataxia, anorexia, retarded growth, increase in muscle tone and changes in blood chemistry (IARC, 1977). Target organs reported affected by 2,4-D in animal studies include the gastrointestinal tract, liver, kidney, brain, pituitary gland, adrenal gland, lungs, thyroid and nervous system.

In rats dosed orally with 2,4-D for 5 days/week for 4 weeks, doses of 5.0 mg/kg/day or higher resulted in significant changes in blood chemistry (Rowe and Hymas, 1954 as cited in USEPA, 1988). At 300 mg/kg/day, effects included gastrointestinal irritation and mild liver effects (i.e., cloudy swelling and increased weights) as well as overt signs of toxicity and mortality (HSDB, 1995; USEPA, 1988).

Subchronic exposure of mice and rats to 2,4-D concentrations of about 15 mg/kg/day resulted in changes in blood and liver enzyme chemistry and changes in kidney, brain, pituitary and adrenal weights (USEPA, 1988).

2,4-D levels of 45 mg/kg/day or higher produced a series of health effects ranging from irritation of the gastrointestinal tract to mild liver effects (Hazelton Laboratories, 1983 as cited in USEPA, 1988).

In contradiction to earlier studies, in a series of 13-week studies in which groups of ten female and male rats were treated with 2,4-D via the diet, 15 mg/kg/day was identified as the NOEL for a number of chemical forms of 2,4-D including the 2,4-D IOE and 2,4-D DMA forms. At higher doses, the two principle target organs are the kidney and thyroid (Diener, 1992).

In another study in which rats were orally dosed with either 1, 5, 15 or 45 mg/kg/day, thyroid effects were noted at 15 mg/kg/day and increased absolute and relative thyroid weights were noted at all levels (Diener, 1992). In mice exposed to doses of 5 to 90 mg/kg/day 2,4-D, histopathological kidney changes were noted at all doses (Diener, 1992).

In groups of beagle dogs exposed orally to 0.0, 0.3, 1, 3 or 10 mg/kg/day 2,4-D in gelatin capsules, subtle histological changes were observed at 3 mg/kg/day in males and females and at 10 mg/kg/day in females only. A NOEL of 1 mg/kg/day was identified (Diener, 1988).

Repeated subcutaneous or intraperitoneal exposures of rats and mice with 100-200 mg/kg/day 2,4-D produced pathological and functional effects in the liver, kidney, lungs, thyroid and nervous systems (Bucher, 1946, Florsheim and Velcoff, 1962, Florsheim *et al.*, 1963 and Desi *et al.*, 1962 as cited in USEPA, 1988).

In rabbits exposed to 2,4-D dermally for three weeks, systemic toxicity was noted at doses of 1,000 mg/kg/day and above. At lower doses, only localized skin irritation was noted (ITF, 1992 as cited in Diener, 1992).

In a series of studies in which rats were subcutaneously injected with 2,4-D ester at doses ranging from 1-250 mg/kg/day, the neurobehavioral toxicity produced by the 2,4-D ester was evaluated by monitoring performance in a battery of diagnostic tests. Results indicated that the 2,4-D ester, when administered to rats repeatedly, impairs neurological function; however considerable tolerance develops after continued exposure (Schulze *et al.*, 1988 as cited in Diener, 1992).

Chronic:

No significant treatment-related gross, histopathological or hematological effects were found in rats that received dietary 2,4-D levels ranging from 5-1250 ppm in the diet for 2 years (Hansen *et al.*, 1971 as cited in USEPA, 1988).

In a two-generation study in which rats were administered 1,000 ppm 2,4-D in drinking water for up to 2 years, no changes in clinical chemistry or tissue histology were noted in maternal rats or in the first or second generation offspring (Bjorklund and Erne, 1966 as cited in USEPA, 1988).

In a two-year rat study in which rats received oral doses ranging from 10-500 ppm 2,4-D, lesions were observed in the kidney, testes and adrenal glands. There was no dose-response relationship observed and the authors concluded that the lesions were not 2,4-D-related (Hansen *et al.*, 1971).

Electroencephalogram changes were noted in monkeys exposed orally to 0.2 mg/kg/day 2,4-D for 3 years, but the toxicological significance of the changes is unknown (Santolucito, 1975 as cited in USEPA, 1988).

In another bioassay, 2,4-D was administered orally to rats and mice at doses ranging from 1-45 mg/kg/day. At the rat interim sacrifice, there was a dose-related increase in kidney effects in the 5, 15, and 45 mg/kg/day groups. These effects were also observed in the terminal sacrifice (104 weeks). A LOEL of 5 mg/kg and a NOEL of 1 mg/kg were determined for the rat (ITF, 1986). At the interim sacrifice in mice, kidney effects were observed in males in the 15 and 45 mg/kg groups. This effect was also seen in the terminal sacrifice at both doses. A similar effect was not observed in the female mice. A LOEL of 15 mg/kg and a NOEL of 1 mg/kg were determined for the mice (ITF, 1987).

Developmental/Reproductive:

A number of epidemiological studies have suggested a possible link between 2,4-D exposure and human reproductive or developmental effects; however, these studies generally were characterized by inadequate exposure information (Diener, 1992).

A number of teratogenicity studies have been conducted in mice, rats and hamsters with various forms of 2,4-D including, among others, the acid, its isooctyl and butoxyethanol esters and its dimethylamine salt (Courtney, 1977, Khera and McKinley, 1972, Schwetz *et al.*, 1971,

Unger *et al.*, 1981, Konstantinova *et al.*, 1976, Collins and Williams, 1971 as cited in USEPA, 1988). Overall, the results of these studies indicate that 2,4-D and its derivatives are embryotoxic or fetotoxic but are only weakly teratogenic or nonteratogenic (USEPA, 1988; Diener, 1992). Available studies indicate that exposures high enough to be toxic to the mother may also be toxic to the fetus (DowElanco, 1995). Sporadic evidence of fetotoxicity was found in rats administered oral 2,4-D levels as low as 12.5-25 mg/kg/day for both 2,4-D and 2,4-D ester (USEPA, 1988). The No Observed Effect Levels (NOEL) for developmental and/or reproductive toxicity varies with the species. Generally, NOELs are about 5, 40 and less than 90 mg/kg/day in rats, hamsters and rabbits, respectively (Diener, 1992). Multigenerational studies indicate that 2,4-D caused increased mortality in preweanling rats but produced no adverse effects on litter size or fertility (USEPA, 1988).

Mice administered 2,4-D or several of its derivatives either orally or subcutaneously during days 6-14 of pregnancy had an increased incidence of fetal anomalies (IARC, 1977). The maximally tolerated dose (i.e., (MTD), the largest daily exposure that causes evidence of toxicity to animals but does not cause excessive deaths over the animals' lifespans) of 2,4-D or equimolar doses of several of its derivatives administered to pregnant Sprague-Dawley mice during days 6-15 of gestation, produced embryo-lethal and growth retarding effects but no teratogenicity. Signs of fetotoxicity included subcutaneous edema, delayed ossification and wavy ribs in rats given oral doses of 100-150 mg/kg/day on days 6-15 of pregnancy (IARC, 1977 as cited in HSDB, 1988). In utero 2,4-D ester exposure to mice produced no changes in humoral immunity and only subtle effects on lymphocytes, blastogenesis of offspring; exposure is unlikely to be of any immunotoxicological or immunoteratological significance (Blakley, 1986 as cited in HSDB, 1995).

Mutagenicity:

2,4-D and its derivatives have been tested in a variety of mutagenicity assays in plants, bacteria, yeast, fruit flies and both *in vitro* and *in vivo* mammalian systems. The majority of the results were either negative or inconsistent. It appears that the mutagenic potential of 2,4-D is linked to differences in pH. At physiological pH, 2,4-D exists in an ionized state which less readily crosses the cell membrane than the nonionized state (USEPA, 1988). Positive mutagenic results were reported for DNA repair-deficient strains of *E. coli* and *B. subtilis* bacteria. Positive results in the gene conversion/complementation tests were obtained with the yeast, *S. cerevisiae* only when the pH of the system was lowered into the acid range where 2,4-D would not ionize. Weakly positive mutagenic results were produced in recessive lethal and somatic mutation assays in *Drosophila*. Positive results were also produced in Chinese hamster lung cells, unscheduled DNA synthesis in cultured human fibroblasts and chromosome aberrations and sister chromosome exchange in cultured human lymphocytes but negative results were produced in a number of other *in vitro* mammalian assays (USEPA, 1988).

Positive mutagenicity results were also obtained in two *in vitro* mouse assays including intraperitoneal injections of 2,4-D induced bone marrow chromosome aberrations and oral

administration of 2,4-D inhibited thymidine incorporated into testicular DNA in mice, but other *in vivo* mammalian assays with mice were negative (USEPA, 1988).

An EPA convened expert panel of toxicologists and epidemiologists concluded that 2,4-D is nonmutagenic based on 26 studies of seven derivatives of 2,4-D conducted under currently accepted testing protocols. The panel concluded that although a number of older studies had produced positive mutagenic results, these studies were characterized by significant experimental deficiencies and that current information suggests that 2,4-D is nongenotoxic (USEPA, 1994).

Carcinogenicity:

A series of five epidemiologic studies provide some evidence of cancer induction from the chlorophenoxy class of herbicides (of which 2,4-D is one). However, both EPA and IARC have concluded that the cancer weight of evidence is limited (USEPA, 1988). The epidemiology studies generally support the concept that broadly defined occupational groups (e.g., farmers, forestry workers) may be at increased risk of certain types of cancer, particularly lymphopietic cancer. Additional studies in which exposures were more closely monitored yielded mostly negative, but also some inconsistent findings on the relationship of 2,4-D exposure and cancer induction. A joint EPA Science Advisory Board/Scientific Advisory Panel (SAB/SAP) concluded that human epidemiologic cohort studies which have tried to identify a link between Non-Hodgkins Lymphoma (NHL) and 2,4-D have generally shown no increased risk of cancer. However, these studies were characterized by a range of inadequacies including small study populations, short followup periods and other (confounding) exposures to agents other than 2,4-D that were not controlled for (USEPA, 1994). A canine epidemiologic study suggests that pet dogs may be at risk from exposure to 2,4-D or to areas treated by a lawn care service. However, there are questions regarding the accuracy of reported exposures as well as the applicability of cancer results in dogs to humans (USEPA, 1994).

Results in toxicology studies are also limited. A study in which rats were administered 2,4-D or the isopropyl, butyl or isooctyl esters by intubation before weaning at 46-100 mg/kg/day and subsequently in the diet at about 14-42 mg/kg/day for 73-90 weeks did not indicate that 2,4-D was tumorigenic. Results in rats administered dietary levels of 0.25-62.5 mg/kg/day for two years were conflicting and unresolved. Rats and mice fed 2,4-D amine salt at 0.1% of the LD50 level for a lifetime did not develop a significant increase in tumors. Mice injected with a single subcutaneous dose of 2,4-D isooctyl ester were associated with reticular cell carcinomas in mice after 78 weeks of latency but similar results were not found in mice injected with subcutaneous doses of 2,4-D acid, isopropyl or isobutyl esters. Skin papillomas were produced in mice only when pretreated with the initiator 3-methylcholanthrene (USEPA, 1988).

A series of lifetime studies conducted by the 2,4-D Industry Task Force in laboratory animals found no evidence of cancer in female rats or in male and female mice fed high doses of 2,4-D (USEPA, 1988). The only finding of concern was an increased incidence of brain astrocytomas in male rats treated at the highest 2,4-D dose of 45 mg/kg/day. There are a number of shortcomings in these studies. These include a reported lack of preneoplastic or target organ

effects, the restriction of tumor development to male rats only, intergroup variability seen among historical controls, the lack of a plausible mechanism of tumorigenesis, the low exposure of the brain to 2,4-D as compared to other organs and the fact that 2,4-D is not strictly related to other known brain carcinogens (Diener, 1992). The joint SAB/SAP concluded that rats (but not other animal species tested) may develop astrocytomas from exposure to 2,4-D, but this outcome has not been reported in the human studies. They expect that an ongoing rat study at higher doses will clarify whether this finding is treatment-related or not (USEPA, 1994).

The SAB/SAP Committee concluded that, at this time, the data are not sufficient to find that there is a cause and effect relationship between exposure to 2,4-D and NHL, but additional studies should be conducted to further evaluate the possibility of such a link (USEPA, 1994).

Recently, the EPA Office of Pesticide Programs (OPP) received the results of two rodent studies in mice and rats. The results of the studies are currently under review to establish a final cancer classification for 2,4-D and to determine whether 2,4-D needs to undergo an EPA Special Review. The EPA initiates a Special Review of a pesticide when there are indications that exposure to the compound is associated with unacceptable adverse effects. For 2,4-D, the necessity of a Special Review will be contingent on the results of a peer review to determine cancer classification and to make final conclusions regarding the available epidemiological, toxicological and other data. A Special Review involves an

intensive review of the risks and benefits associated with the compound. If the risks exceed the benefits, then EPA will take action to better balance risks and benefits. The action can include a range of options from mandating changes in the rate and method of application of the pesticide to canceling the pesticide's registration. The OPP hopes that the decision regarding the necessity of a Special Review will be made some time in 1996 (Bloom, pers. comm.).

Available Toxicity Criteria:

The EPA RfD/RfC Workgroup has developed an oral Reference Dose (RfD) of 0.01 mg/kg/day for 2,4-D based upon a 90-day rat oral bioassay and a 1-year interim report from a 2-year rat bioassay. The RfD is an estimate, with uncertainty spanning perhaps an order of magnitude, of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime (USEPA, 1992).

The EPA Office of Pesticide Programs (OPP) has developed an RfD of 0.003 mg/kg/day based on a two-year feeding study in rats (USEPA, 1995).

The EPA has developed a Maximum Contaminant Level (MCL) for drinking water for 2,4-D of 0.07 mg/l (USEPA, 1988). This drinking water level has been adopted by Massachusetts as a Massachusetts Maximum Contaminant Level (MMCL).

The EPA has also developed an Ambient Water Quality Criterion (AWQC) for 2,4-D of 0.001 µg/l. This concentration represents an acceptable level of 2,4-D in ambient water for a human who drinks the water and eats fish who inhabit the water (USEPA, 1988).

ECOLOGICAL TOXICITY

Avian:

A number of toxicity tests conducted in birds indicate that 2,4-D is only slightly toxic or practically nontoxic to most test birds. LC50 values (i.e., concentrations lethal to 50% of the test population) for ring-necked pheasant, Japanese quail, Bobwhite quail and mallard ducks to be greater than 5,000 ppm for 2,4-D, the butoxyethanol ester of 2,4-D and the dimethylamine salt of 2,4-D (USDA, 1984). Reported LD50 values for 2,4-D acid include an oral dose of 668 mg/kg for rock doves, an oral dose greater than 2,000 mg/kg for 4 month old mallards and an oral dose of 668 mg/kg for 2 month old mallards (HSDB, 1995). 2,4-D was found to be moderately toxic to 4 month old chukar (partridge) with a reported LD50 value of 200-400 mg/kg (HSDB, 1995).

In terms of reproductive or developmental effects, spraying chicken eggs with 2,4-D amine 29 hours before incubation at rates of 1, 10 and 20 times the recommended rates had no adverse effect on any parameter used to evaluate either incubation or subsequent live performance (USDA, 1984). Two studies indicated that spraying eggs of quail, pheasants and chickens with 2,4-D in concentrations up to 10 times the recommended doses, produced no effect on the hatching rate, body weight, sexual differentiation or reproductive performance (as adults) of number of malformed chicks (GEIR, 1985). In another study in which 2,4-D amine was sprayed at a concentration of 1.1 kg active ingredient per hectare on fertile eggs, 77% of ring-necked pheasant embryos, 43% of red partridge embryos and 77% of grey partridge embryos were dead on the nineteenth day of incubation. Surviving embryos were malformed or partially or completely deformed (GEIR, 1985).

Aquatic Organisms:

The toxicity of 2,4-D has been shown to vary with the formulation, the species of fish, the water quality and the environmental conditions (season and temperature). According to several sources, many of the formulations, especially the esters, are toxic to fish (GEIR, 1985). The ester formulations are generally many times more toxic than the corresponding acids or amine salts. Numerous studies show that the 96-hour LC50s for cutthroat trout fingerlings ranged from greater than 50 ppm for the isooctyl ester down to 0.78 ppm for the butyl ester (USDA, 1984). 96-hour LC50s for the dimethylamine salt were reported as 64 ppm for cutthroat trout, 100 ppm for chinook salmon and 236 ppm for smallmouth bass. A 96-hour LC50 of 1313 ppm for grass carp was also reported for the amine salt (GEIR, 1985).

96-hour fish LC50s for the 2,4-D acid are generally higher, ranging from a slightly toxic 26.7 ppm in banded killifish to a practically nontoxic 358 ppm in rainbow trout. Table III.3-3 lists the results of a number of 96-hour acute toxicity assays using 2,4-D acid.

Many studies conducted to assess the effects of 2,4-D on lower aquatic organisms suggest that toxicity varies with the different formulations of 2,4-D (GEIR, 1985). Again, it appears that some ester formulations are the most toxic. A 96-hour LC50 was reported as 6.1 ppm for scud

and 2.6 ppm for sowbug exposed to the butoxyethanol ester of 2,4-D. Results of other lower aquatic organisms exposed to various 2,4-D esters were similar (USDA, 1984). 2,4-D was only slightly toxic to *Daphnia*, with a 48-hour acute LC50 of 25 ppm (DowElanco, 1995). 48-hour TL50s (concentrations at which there is some toxic effect to half the population) of 100 ppm were reported for many crustaceans exposed to the dimethylamine salt (USDA, 1984). A TL50 greater than 100 ppm was reported in crayfish (USDA, 1984).

Bioconcentration factors for zooplankton after field exposure to either the butoxyethanol ester or the dimethylamine of 2,4-D ranged from 1 to 603 (Reinert and Rodgers, 1987).

Plants:

Treatment of a water body with 2,4-D may cause depletion of dissolved oxygen from decomposition of dead weeds as well as habitat loss (Riverdale Chemical Co.)

Table III.3-3. Results of 96-Hour Acute Toxicity Tests Using 2,4-D Acid

Species	Conc. (ppm)	Reference
rainbow trout	358	DowElanco, 1995
fathead minnow	320	DowElanco
american eel	300.6	HSDB, 1995
bluegill	263	Dow Elanco, 1995
carp	96.5	HSDB, 1995
pumpkinseed fish	94.6	HSDB, 1995
guppy	70.7	HSDB, 1995
striped bass	70.1	HSDB. 1995
cutthroat trout	64	USDA, 1995
white perch	40	HSDB, 1995
banded killifish	26.7	HSDB, 1995

Table III.3-4. Properties of 2,4-D BEE

CAS #:	1929-73-3
Molecular formula	C ₁₄ H ₁₈ O ₄ Cl ₂
Molecular weight	321.2
Physical properties	colorless to amber oily liquid
Melting point	NA
Density	NA
Vapor pressure	1.7 x 10 ⁻⁵ - 4.5 x 10 ⁻⁶
Volatility [Henry's Law constant (atm m ³ /mol)]	10 ⁻⁷ -10 ⁻⁵
Photolysis half-life (days)	10-20
Hydrolysis half-life (days)	0.02-26
Biodegradation half-life	0.11-2.3
K _{ow}	3400
K _{oc}	6607-6900
BCF	162-408
Water solubility (mg/l)	12

(Reinert and Rodgers, 1987; Aquatic Plant Identification and Herbicide Use Guide, 1988; USEPA, 1988)

Table III.3-5. Properties of 2,4-D DMA

CAS #:	2008-39-1
Molecular formula	C ₁₀ H ₁₃ O ³ Cl ₂ N
Molecular weight	266.12
Physical properties	white crystalline solid
Melting point	85-87
Density	NA
Vapor pressure	10 ⁻⁶ at 28°C
Volatility [Henry's Law constant (atm m ³ /mol)]	insignificant
Photolysis half-life (days)	insignificant
Hydrolysis half-life (days)	insignificant
Biodegradation half-life	3.9-11 (based on overall half-life)
K _{ow}	low
K _p	0.13-0.25
BCF	1-7
Water solubility (mg/l)	3.0 x 10 ⁶

(Reinert and Rodgers, 1987; Aquatic Plant Identification and Herbicide Use Guide, 1988; USEPA, 1988)

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