

Paraquat Hazards to Fish, Wildlife, and Invertebrates: A Synoptic Review

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Abstract

Paraquat (1,1'-dimethyl-4,4'-bipyridinium) and its dichloride salt (1,1', dimethyl-4, 4'-bipyridinium dichloride) are broad-spectrum contact plant killers and herbage desiccants that were introduced commercially during the past 25 years. Today, they rank among the most widely used herbicides globally and are frequently used in combination with other herbicides. The recommended paraquat field application rates for terrestrial weed control usually range between 0.28 and 1.12 kg/ha (0.25 and 1.0 lb/acre), and for aquatic weed control the range is 0.1 - 2.0 mg/L. Target plant species are unable to metabolize paraquat and tend to contain elevated residues; paraquat-resistant strains of terrestrial flora, whose numbers are increasing, require greater concentrations for control and may contain proportionately greater residues. Paraquat from decayed flora is usually adsorbed to soils and sediments. Paraquat in surface soils generally photodecomposes in several weeks, but paraquat in subsurface soils and sediments may remain bound--and biologically unavailable--for many years without significant degradation.

Paraquat is not significantly accumulated by earthworms and other species of soil invertebrates and is usually excreted rapidly by higher animals; however, delayed toxic effects--including death of birds and mammals--are common. At concentrations below the recommended application rate, paraquat is embryotoxic to developing eggs of migratory waterfowl (0.056 kg/ha) and adversely affects sensitive species of freshwater algae and macrophytes (250 µg/L), larvae of crustaceans (0.9-5.0 µg/L), and frog tadpoles and carp (500 µg/L). Sensitive species of birds are negatively affected at daily dose rates of 10 mg/kg body weight or when fed diets containing 20 mg/kg ration or drinking water containing 40 mg/L. Adverse effects in sensitive mammals were observed at dietary levels of 85 - 100 mg/kg ration and higher or 100 mg/L in drinking water. Acute oral LD50 values for sensitive species of birds were near 200 mg/kg body weight and, for mammals, 22 - 35 mg/kg body weight. Humans are among the more sensitive species, and numerous human poisonings have resulted from accidental or intentional ingestion of a concentrated paraquat formulation.

The biochemical mechanism of paraquat toxicity is due to the cyclic oxidation and reduction in tissues, leading to production of superoxide anion and other free radicals and eventually the highly destructive hydrogen peroxide. The lung is the organ most severely affected in paraquat poisoning, due largely to the preferential accumulation of paraquat in lung alveolar cells. Although many organs are affected by paraquat, death is usually due to progressive pulmonary fibrosis. At present, there is no completely successful treatment for paraquat-induced lung toxicity.

More information is needed in several areas in order to establish effective criteria for the protection of sensitive species of fish and wildlife against paraquat. These include: flux rates of paraquat from soil into terrestrial food chains; biomagnification potential of paraquat in aquatic food chains, with special reference to plants, plant detritus, amphibians, and reptiles, toxicokinetics of mixtures of paraquat and other herbicides applied concomitantly; and the implications of the high sensitivities of crustacean larvae and waterfowl embryos to paraquat. (Eisler, R. 1990. Paraquat hazards to fish, wildlife, and invertebrates: a synoptic review. U.S. Fish and Wildlife Service Biological Report 85 (1.22). 28 pp.

Paraquat (1,1'-dimethyl-4,4'-bipyridinium) is one of the most widely used herbicidal chemicals in the world and is now available in more than 130 countries (Kimbrough 1974; Calderbank 1975; Dasta 1978; Haley 1979; Hughes 1988; L. Smith 1988). Its chemical structure was first described in 1882, its oxidizing and reducing properties in 1933, and its herbicidal properties in 1955. Paraquat was marketed commercially in the United Kingdom in 1962 and registered for use in the United States in 1964. As the dichloride salt, it has found wide use as a nonselective contact herbicide at application rates of 1.12 kg/ha (1 lb/acre) and lower. Useful reviews on ecological and toxicological aspects of paraquat include those by Kimbrough (1974), Smith and Heath (1976), Autor (1977), Dasta (1978), Haley (1979), Summers (1980), Bauer (1983), Onyema and Oehme (1984), L. Smith (1985, 1988), and J. Smith (1988).

Paraquat kills plants by affecting the green parts, not the woody stems, and is usually completely and rapidly inactivated by contact with clay in the soil. In its bound form, paraquat is biologically inert and innocuous to plants and animals (Fletcher 1974).

Numerous human injuries and deaths have resulted from intentional ingestion of the concentrated commercial product (Fletcher 1974; Dasta 1978; Haley 1979; Crome 1986; J. Smith 1988; L. Smith 1988). For example, in the first 10 years following paraquat commercial use, 232 human deaths from paraquat poisoning were reported (about half were suicides), and almost all were due to the drinking of concentrated material. Most poisonings resulted from the ingestion of the 21 % cation concentrate, which had been decanted and stored in empty beer, soft drink, or lemonade bottles; paraquat is a reddish-brown liquid that resembles root beer or cola drinks. One individual sprinkled paraquat on French fried potatoes, thinking it was vinegar. He died 25 days later. Another died after applying the concentrated solution to his beard and scalp to treat a lice infestation. In Japan, more than 1,000 persons each year are reportedly poisoned by paraquat. Initially, paraquat may produce multiorgan toxicity of kidneys, liver, heart, central nervous system adrenal glands, skeletal muscle, and spleen, but the ultimate target organ is the lung, in which progressive irreversible pulmonary fibrosis develops. This effect has been described in humans, rats, mice, guinea pigs, and dogs (Kimbrough 1974; Giri et al. 1979; Hampson and Pond 1988; O'Sullivan 1989). There is no known specific antidote for paraquat poisoning.

In 1977, the discovery by narcotics authorities that some marijuana imported from Mexico had been treated with paraquat as a control agent generated much interest in the media (Dasta 1978; Haley 1979). Up to 70% of the paraquat in paraquat-treated marijuana is converted, on smoking, to bipyridine, a respiratory irritant. Frequent consumption of heavily contaminated marijuana may result in cyanosis and possibly death. The use of paraquat for this purpose has been largely discontinued.

In normal use as a spray, minor reversible injuries are reported to abraded skin, eyes, nose, and fingernails; it is not absorbed through intact skin (Kimbrough 1974; J. Smith 1988). Paraquat is fetotoxic, as judged by deliberate ingestion of concentrated solutions by nine pregnant Taiwanese women. Paraquat crosses the placenta and concentrates there to levels 4 - 6 times that of maternal blood. All fetuses died whether or not an emergency cesarean section was performed (Talbot and Fu 1988). Recent research has focused on the tendency of paraquat to accumulate in neuromelanin of mammals and amphibians and to cause lesions in the pigmented nerve cells, leading to effects very similar those of Parkinson's disease (De Gori et al. 1988; Lindquist et al. 1988).

This report is part of a series of brief reviews on hazards of selected chemicals to fishery and wildlife resources. It was prepared in response to requests for information on paraquat from environmental specialists of the U.S. Fish and Wildlife Service.

Uses

Paraquat is a broad-spectrum contact weed killer and herbage desiccant that is used widely in agriculture and horticulture. Paraquat was formulated in 1882, but its herbicidal properties were not discovered until 1955. Since its introduction in the early 1960's, paraquat has been used extensively in about 130 countries--including Canada, the United Kingdom, and the United States--on a wide variety of agricultural crops (Fletcher 1974; Haley 1979; Kelly et al. 1979; Anonymous 1988).

Primary uses of paraquat include weed control in orchards, plantation crops, and forests; weed control before sowing or before crop emergence; pasture renovation; preharvest desiccation; and aquatic weed control, although use as an aquatic herbicide in the United States is not permitted (Anonymous 1963, 1974; Summers

1980; Dial and Bauer 1984). Paraquat is registered for preplant or preemergence use for cotton, barley, corn, lettuce, melons, peppers, potatoes, sallower, soybeans, sorghum, sugar beets, tomatoes, and wheat. It is also registered for use on noncrop areas, such as roadsides, highway margins, rights-of-way, and around commercial buildings, power plants, storage yards, fence lines, and parkways (Anonymous 1963, 1974). In Switzerland, it is used to control voles (*Arvicola terrestris*) in fruit orchards (Summers 1980).

Paraquat is available as the dichloride or dimethylsulfate salt; both compounds are extremely soluble in water (Kimbrough 1974). In the United States, paraquat dichloride is available as a 29% liquid concentrate containing 240 g/L (2 lb/gal) of paraquat cation, or as a 42 % liquid concentrate. Elsewhere, it is sold as Gramoxone liquid, containing 20-24% of paraquat dichloride (Fletcher 1974; Bauer 1983; Dial and Dial 1987a). Paraquat dichloride concentrates usually contain various wetting agents (condensation products of ethylene oxide and alkyl phenols), spreaders, humectants to promote moisture retention (calcium chloride, glycerol, polyethylene glycol), plant adhesion materials (carboxymethylcellulose, polymethacrylates), and antifoaming agents (Summers 1980).

The recommended field application rates for terrestrial weed control usually range between 0.28 and 1.12 kg paraquat cation per hectare (0.25 and 1.0 lb/acre), or 0.56 and 2.24 kg paraquat dichloride per hectare (0.5 and 2.0 lb/acre)--both applied as an aerosol--and 0.1 and 2.0 mg/L for aquatic weed control, although sensitive aquatic plants may be affected between 0.019 and 0.372 mg/L (Ross et al. 1979; Summers 1980; Bauer 1983; Dial and Bauer 1984).

Paraquat is frequently used in combination with other herbicides (Fletcher 1974; Summers 1980). Water solutions of the dichloride salt, which usually contain 240 g/L, have been successfully mixed with 2,4-D, substituted ureas, dalapon, amitol, and various triazines (Anonymous 1963, 1974).

Background Concentrations

Data are scarce on ecosystems treated with paraquat. It is clear, however, that both terrestrial and aquatic plants accumulate paraquat, and that the compound disappears rapidly from the water column and tends to concentrate in surface muds (Table 1).

Table 1. Paraquat concentrations in field collections of selected organisms and nonbiological materials.

Sample, and other variables	Concentration (mg/kg dry weight)	Reference ^a
Treated fields		
Alfalfa, <i>Medicago sativa</i>	Up to 30	1
Grasses, various species	Up to 60	1
Mud, surface; from British lake treated with 0.5 mg/L		
Days after treatment		
1	1.2	2
2	2.4	2
8	6.7	2
32	11.2	2
197	17.7	2
364	8.0	2
Colorado farm pond treated with 1.0 mg/L		
3 h after treatment		
Water	0.6	3
Mud	1.1	3
Submerged plant, <i>Chara</i> sp.	320	3
Algae, <i>Spirogyra</i> sp.	320	3
4 days after treatment		
Water	0.2	3

Mud	0.8	3
<i>Chara</i> sp.	840	3
<i>Spirogyra</i> sp.	1,300	3
16 days after treatment		
Water	<0.1	3
Mud	16	3
<i>Chara</i> sp.	540	3
<i>Spirogyra</i> sp.	13	3

^a1, Bauer 1983; 2, Way et al. 1971; 3, Earnest 1971.

Environmental Chemistry

General

Paraquat is a nonvolatile, ionic compound that is almost completely insoluble in organic solvents, which is typical of the bipyridyl group of chemicals. As discussed later, the biochemical mechanism of paraquat toxicity is due to the cyclic oxidation and reduction that occurs in various tissues, especially lung, leading to production of superoxide anion and other free radicals; these chemical species react with polyunsaturated free radicals, eventually forming the highly destructive hydrogen peroxide. Excretion of paraquat is rapid in living organisms, but delayed toxic effects, including death, are not unusual. No treatment or chemical has proven completely successful in protecting against paraquat-induced lung toxicity.

Paraquat is strongly adsorbed to soils and sediments and is biologically unavailable in that form; however, it is not degraded significantly for many years, except in surface soils. In surface soils, paraquat loss through photodecomposition approaches 50% in 3 weeks. In freshwater ecosystems, loss from the water column is rapid: about 50% in 36 h and 100% in 4 weeks. In marine ecosystems, 50-70% loss of paraquat from seawater was usually recorded within 24 h.

Chemical Properties

Paraquat is a nonvolatile, ionic compound that is almost completely insoluble in fat, and therefore not likely to be accumulated in food chains (Calderbank 1975). The compound belongs to the bipyridyl group of chemicals and is typical of the many hundreds that have been synthesized, variation usually being the result of introducing different quaternizing groups on the nitrogen atoms, which also shift (Fletcher 1974; Table 2). Paraquat dichloride is produced from pyridine in the presence of sodium in anhydrous ammonia by quaternizing the 4,4'-dipyridyl with methyl chloride (Haley 1979). The common paraquat salts are all fully ionized, and experiments have shown that the anions (e.g., chloride, sulfate, methyl sulfate) do not affect the toxicity of paraquat (Fletcher 1974). Chemical and other properties of paraquat are briefly summarized in Fig. 1 and Table 2.

Mode of Action

Paraquat is absorbed systematically in mammals, following different routes of exposure; absorption is greatest for the pulmonary route, followed by intragastric and dermal routes (Chui et al. 1988). Administration of paraquat by every route of entry tested frequently results in irreversible changes in the lung (Boudreau and Nadeau 1987). In the intestinal tract, where some microbial degradation occurs, most paraquat (95 - 100%) is usually excreted unchanged in feces and urine within 2 days (Summers 1980). Absorption in the gastrointestinal tract ranges from 0.26% in cows to 5% in humans, 8% in guinea pigs, 16% in cats, and up to 20% in rats; the half-time persistence ($T_{1/2}$) of paraquat in certain tissues is 20 - 30 min, but up to 4 days in muscle and 2 days in plasma (Bauer 1983). Delayed toxic effects of paraquat occurring after the excretion of virtually all of the material have caused it to be classified as a 'hit and run' compound--that is, a compound causing immediate damage, the consequences of which are not readily apparent (Conning et al. 1969).

Table 2. Chemical and other properties of paraquat (Anonymous 1963, 1974, 1988; Haley 1979; Kelly et al. 1979; Johnson and Finley 1980; Hudson et al. 1984; Hill and Camardese 1986; Mayer 1987).

Variable	Datum
Chemical name	1,1'-dimethyl-4,4'-bipyridinium
Paraquat (cation)	1,1'-diemthyl-4,4'-bipyridinium dichloride
Paraquat dichloride (salt)	186.2 (cation); 257.2 (salt)
Molecular weight	4685-14-17 (cation); C ₁₂ H ₄ Cl ₂ N ₂ (salt)
CAS number	4685-14-17 (cation); C ₁₂ H ₄ Cl ₂ N ₂ (salt)
Alternate names	Cekuquat, Crisquat, Dextrone, Dextrone X, Dexuron, Dual Paraquat, Esgram, Gramonol, Gramoxone, Gramuron, Herbaxon, Herboxone, Methyl Viologen, Ortho Paraquat, Orvar, Paracol, Paraquat CL, Pathclear, Pillarquat, Pillarxone, Preeglone, PP 148, PP 910, Sweep, Tenaklene Totacol, Toxer Total, Weedol
Solubility at 20° C	
Water	561 g/L
Methanol	144 g/L
Ethanol	1.7 g/L
Acetone	200 mg/L
Most organic solvents	Insoluble or sparingly soluble
Physical state	Solid; white (pure), yellow (technical)
Main uses	Herbicide, desiccant
Specific gravity	1.24–1.26
Melting point	175 °C to 180 °C, decomposes at 345° C
Stability	Stable on exposure to hot acids; unstable in alkalis at pH >10
Flash point	Nonexplosive, nonflammable
Volatility	Nonvolatile

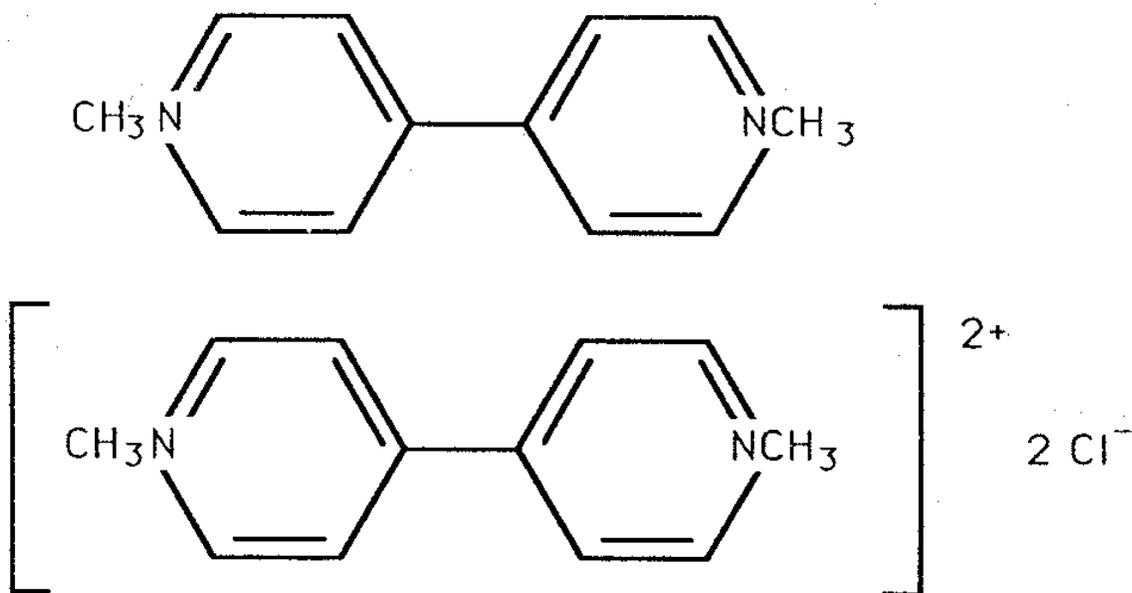


Fig. 1. Structural formula of paraquat cation (*upper*) and of paraquat dichloride salt (*lower*).

Most authorities agree that free radical pathology is the most likely mechanism by which paraquat is cytotoxic (Bus et al. 1976; Frank et al. 1982; Patterson and Rhodes 1982; Combs and Peterson 1983; Onyeama and Oehme 1984; Gabryelak and Klekot 1985; Smith 1985; Wong and Stevens 1986; Seto and Shinohara 1987; Suleiman and Stevens 1987; Darr et al. 1988; Dunbar et al. 1988a; Wegener et al. 1988; Wenning et al. 1988). The biochemical mechanism of paraquat toxicity is related to the cyclic oxidation and reduction of paraquat that occurs in lung cells, which leads to continued production of high levels of superoxide anion (O_2^-) and other cytotoxic oxygen free radicals. Superoxide anion and other oxygen free radicals initiate the peroxidation of membrane lipids, causing tissue damage and death. Paraquat oxidation is coupled with the reduction of molecular oxygen, forming superoxide anion, singlet oxygen, and hydroxyl radicals. These molecular species react with polyunsaturated fatty acid free radicals and, on further oxidation, with lipid hydroperoxide radicals. The hydroperoxide radicals then maintain the formation of new fatty acid radicals while being converted to lipid peroxides in a chain reaction. Various enzymes in the cells catabolize the superoxide radical and reduce the lipid hydroperoxides to less-toxic lipid alcohols. The superoxide anions are converted to hydrogen peroxide and oxygen; hydrogen peroxide is further inactivated to water and oxygen by catalases and peroxidases. In the presence of reduced nicotinamide adenine dinucleotide phosphate (NADPH), paraquat is reduced by microsomal NADPH-cytochrome reductase. The reduction of lipid peroxides by glutathione peroxidase requires reduced glutathione. Because the reduction of oxidized glutathione is coupled with NADPH oxidation by way of glutathione reductase, it seems that the availability of NADPH is essential for paraquat detoxification, and that the critical depletion of NADPH may render the cell more susceptible to lipid peroxidation.

The lung is the organ most severely affected in paraquat poisoning (Campbell 1968; Conning et al. 1969; Haley 1979; Aldrich et al. 1983; Bauer 1983; Combs and Peterson 1983; Christian et al. 1985; Smith 1985; Wong and Stevens 1986; Boudreau and Nadeau 1987; Baud et al. 1988; Dunbar et al. 1988a; Wegener et al. 1988). Pulmonary injury is due largely to the preferential accumulation of paraquat in the lung--mediated by an energy dependent system for uptake of endogenous polyamines--and to the continuous exposure of the lung to atmospheric oxygen. Characteristic signs of poisoning include severe anoxia, marked and widespread fibroblastic proliferation in the alveolar walls around the terminal bronchi and blood vessels, and frequently death. The specific toxicity to the lung can be explained by the accumulation of paraquat in the alveolar Type H cells. These cells are responsible for the synthesis of pulmonary surfactant, the surface-active material lining the alveolar epithelium. The pulmonary surfactant is secreted after storage in cytoplasmic organelles known as lamellar bodies. Therefore, any damage to the alveolar epithelium could alter synthesis and secretion of the pulmonary surfactant. The pulmonary effects of paraquat are probably related to the conversion of paraquat to a free radical followed by conversion to a long-lived dihydroderivative, which causes transformation of normal alveolar epithelial cells to fibroblasts. The increase in toxicity of paraquat by oxygen supports the hydroperoxide theory, in which the reversible action of the free radical's oxidation-reduction gives rise to hydrogen peroxide. Paraquat also depletes NADPH in the isolated lung to the extent of mixed function oxidation impairment. Depletion of NADPH would impair fatty acid and lipoprotein synthesis and inhibit various detoxification and biosynthetic functions.

Other organs and systems affected by paraquat include the kidney (pathology of proximal tubules), liver (hepatocellular necrosis), spleen and thymus (pathology), circulatory system (irregular and feeble heart beat, myocardial congestion, increase in erythrocytes and leucocytes, external pericarditis, myocardium edema), brain (neuronal depletion, myelin destruction), gastrointestinal tract (esophagitis; ulceration of buccal cavity, pharynx, gastric mucosa; mucosal erosion), skin (erythema, hyperkeratosis), reproductive system (degeneration), nervous system (hyperexcitability, irritability, incoordination, convulsions), various enzyme systems, and the eye (Giri et al. 1979, 1982, 1983; Summers 1980; Bauer 1983; Seto and Shinohara 1987, 1988; Hughes 1988; Takegoshi et al. 1988).

Several early indicators of paraquat-induced stress have been proposed, including alkaline phosphatase activity, fibronectin levels, and intracellular calcium uptake. Alkaline phosphatase activity is associated with the lamellar body, and changes in this variable are suggested as indicative of toxicity to Type II alveolar epithelium cells (Boudreau and Nadeau 1987). Levels of fibronectin, an extracellular matrix glycoprotein, were elevated in patients with fibrotic lung diseases and in monkeys given multiple injections of paraquat (Dubaybo et al. 1987). Lung intracellular calcium uptake was significantly disrupted, even at doses that normally produce significant increases in lung water content (Agarwal and Coleman 1988). These subjects seem to merit additional research, as does the role of polyamines in mediating fibrotic changes in the lung (Dunbar et al. 1988b);

paraquat-altered synthesis of proteins, DNA, collagen, and pentose phosphate metabolism (Simon et al. 1983); and hyperoxia--that is, increased oxygen-free radical generation (Frank et al. 1982).

Certain treatments or chemicals provide varying degrees of protection against paraquat-induced lung toxicity and lethality, although no treatment or chemical has proven completely successful. Present treatment of paraquat-poisoned animals and humans is directed to elimination of the material from the body using repeated doses of adsorbents such as Fuller's earth or bentonite; cathartics to reduce paraquat absorption; and hemodialysis, forced diuresis, and hemofiltration to enhance excretion (Fletcher 1974; Autor 1977; Haley 1979; Pond et al. 1987; Kitakouji et al. 1989). The use of 100% oxygen is contraindicated, as mortality is greatly increased (Fletcher 1974; Autor 1977; Wong and Stevens 1986). Toxicity mediated by free radicals can be moderated by several cellular defense mechanisms, including superoxide dismutase, catalase, glutathione peroxidase, vitamin E, and reduced glutathione (Gabryelak and Klekot 1985; Wenning et al. 1988). Recently, a low molecular weight superoxide dismutase mimic, based on manganese, was found to protect mammalian cells against the cytotoxic effects of the superoxide radical produced by paraquat (Darr et al. 1988). Under carefully controlled conditions of administration, certain chemicals reportedly provide limited protection to small laboratory animals: nicotinic acid (Shibata and Iwai 1988); niacin (Heitkamp and Brown 1982); cysteine (Szabo et al. 1986); N-acetylcysteine (Wegener et al. 1988); metallothionein--a metal-binding low molecular weight protein rich in cysteine (Sato et al. 1989); d-penicillamine (Szabo et al. 1986); clofibrate (Frank et al. 1982); lipid-soluble antioxidants (Kohen and Chevion 1988; Wegener et al. 1988); various amino acids (Heitkamp and Brown 1982); phenobarbital (Bus et al. 1976; Summers 1980); methyl prednisolone (Kitazawa et al. 1988); and certain anti-inflammatory drugs (Autor 1977). In plants, the pea (*Pisum sativum*) is protected by cerium chloride--in part, through counteracting peroxide formation (Vaughn and Duke 1983).

Paraquat toxicity is increased and its effects otherwise exacerbated in organisms fed diets deficient in selenium or vitamin E, although high levels of these substances in diets did not provide protection (Autor 1977; Haley 1979; Summers 1980); by methyl prostaglandins (Williams et al. 1988) or diethyl maleate (Summers 1980); and by increased iron and copper (Kohen and Chevion 1988; Ogino and Awai 1988). Dietary changes that do not result in nutrient deficiency or toxicity may affect the biocidal properties of paraquat and other compounds. In studies with rodents subjected to paraquat insult, survival was higher in those fed cereal-based diets versus purified diets, and higher in egg-white (protein) purified diet versus a casein diet (Tanaka et al. 1981; Evers et al. 1982), suggesting a need to use strictly defined diets in the study of paraquat toxicity to control for any paraquat-diet interactions.

Paraquat adhering to the plant surface is usually degraded photochemically (Haley 1979; Summers 1980). Paraquat is phytotoxic through inhibition of processes involving photosynthesis and respiration (Haley 1979; Christian et al. 1985; Anonymous 1988). Its mode of action in plants is similar to that in animals--that is, lipid peroxidation of membranes due to formation of the superoxide radical and related species (Summers 1980). Photosynthetic tissues reduce paraquat to stable free radicals that, on reoxidation, produce hydrogen peroxide. Unsaturated lipids in the cells are oxidized by the peroxide, and damage is dependent largely on production of hydrogen peroxide (Haley 1979; Vaughn and Duke 1983). The reaction is light- and oxygen-dependent (Conning et al. 1969; Kelly et al. 1979).

In bacteria (*Escherichia coli*), paraquat is concentrated, reduced to the monocation radical, and combined with molecular oxygen to produce the superoxide radical within the cell. Copper and iron are essential mediators in bacteriocidal effects; the cytoplasmic membrane is the target organelle in paraquat toxicity to *E. coli*, and extent of damage correlates positively with levels of these metals (Kohen and Chevion 1988).

Fate in Soils and Water

In contact with soil, paraquat is rapidly adsorbed usually in the clay mineral lattice sheets--and inactivated by base exchange; the process is facilitated by the flat and highly polarizable nature of the paraquat ion (Anonymous 1963; Conning et al. 1969; Calderbank 1975; Summers 1980; Kearney et al. 1985). The strong binding of paraquat to soil constituents reduces the mobility of the herbicide due to leaching, although paraquat is displaced from binding sites by low concentrations of ions of ammonium, potassium sodium, and calcium (Smith and Mayfield 1978). Paraquat adsorption is not significantly affected by soil pH, but is modified by soil porosity, moisture content, residence time, and adsorption capacity (Smith and Mayfield 1978; Summers 1980). Paraquat applied to a sandy loam soil at field application rates between 0.56 and 2.24 kg/ha was adsorbed by organic matter and clays, usually in the top centimeter of soil (Smith and Mayfield 1978). Typical soils contain

paraquat at about 300 mg/kg after treatment at recommended applications; however, adsorption capacity varies among soils. Clay minerals, such as kaolinite, can adsorb 2,500 - 3,500 mg/kg, whereas others, such as montmorillonite, adsorb up to 85,000 mg/kg after paraquat treatment (Summers 1980).

Paraquat is not degraded significantly in soil by chemical or microbiological vectors during incubation periods up to 16 months at 250 °C (Smith and Mayfield 1978). For example, paraquat dichloride, applied once annually at 4.48 kg/ha or 4 times annually at 1.12 kg/ha, remained essentially undegraded in the soil for 6 years (Fryer et al. 1975; Moyer and Lindwall 1985). Massive applications to soils of 3,000 kg/ha can persist for at least 6 months without significant degradation (Moyer and Lindwall 1985). Bacterial degradation--which occurs only slowly in soils--consists of demethylation, followed by ring cleavage to eventually form the carboxylated 1-methylpyridinium ion (Fig. 2). Photochemical decomposition of paraquat is the predominant mechanism of paraquat degradation in soils (Smith and Mayfield 1978). In surface soils, paraquat loss through photodecomposition was 20-50% in 3 weeks (Christian et al. 1985). Photochemical degradation products of paraquat include 4-carboxy-1-methylpyridium ion and methylamine hydrochloride (Fig. 2). Laboratory studies have demonstrated that paraquat in soils slated for disposal can be degraded by ultraviolet (UV) irradiation in the presence of oxygen or ozone. Reaction products identified were 4-carboxy-1-methylpyridium ion, 4-picolinic acid, hydroxy-4-picolinic acid, succinic acid, N-formylglycine, malic acid and oxalic acid (as trimethylsilicon derivatives), and 4,4'-bipyridyl (Kearney et al. 1985).

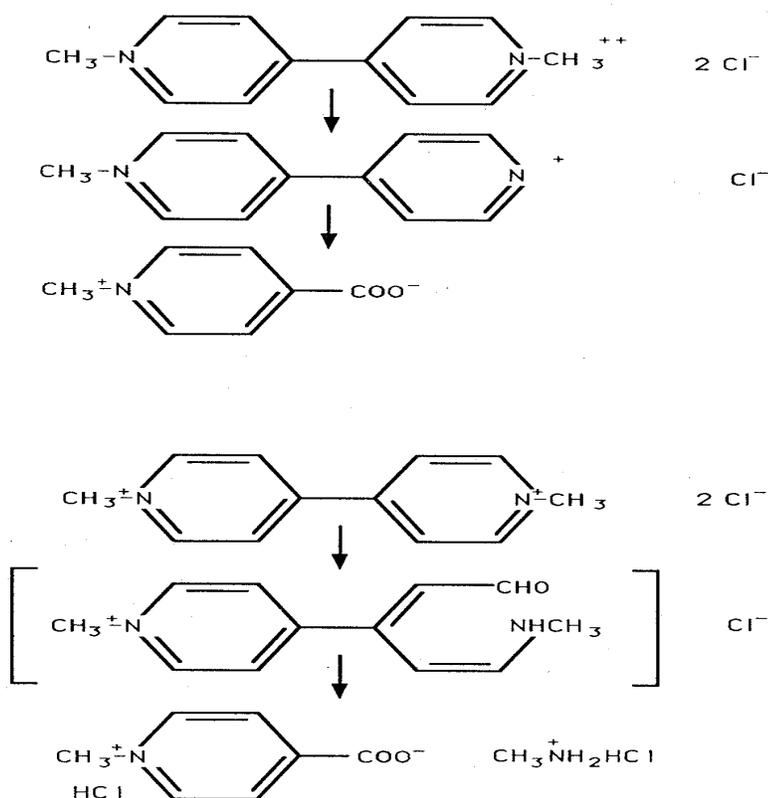


Fig. 2. Proposed pathway of paraquat degradation by a bacterial isolate (*upper*) and by ultraviolet irradiation (*lower*). Modified from Funderburk and Bozarth (1967).

Paraquat is used to control aquatic weeds. It also passes into aquatic environments through rain, where it is rapidly accumulated by aquatic organisms, especially fish (Gabryelak and Klekot 1985). Paraquat applied to control aquatic weeds is accumulated by aquatic macrophytes and algae, and it is adsorbed to sediments and suspended materials. Initial applications of 1 - 5 mg/L in the water column are usually not detectable under field conditions after 8 to 27 days (Summers 1980). The half-time persistence of paraquat in the water column at normal doses for weed control (i.e., 0.5 - 1.0 mg/L) was 36 h; less than 0.01 mg/L was detectable in 2 weeks (Calderbank 1975). In solution, paraquat was subject to photodecomposition and microbial metabolism,

degrading to methylamine and 4-carboxy-1-methylpyridium ion (Kearney et al. 1985). In fresh water, without sediment or plants, 100% of the initial paraquat concentration of 0.5 mg/L was degraded in 35 weeks. When sediments were present, 100% loss from the water column occurred in 6-8 weeks, and when both sediment and aquatic plants were present, paraquat was not detectable in the water column in 3 - 4 weeks (Summers 1980). Mud cores taken from a paraquat-treated lake had elevated paraquat residues but showed no phytotoxic effects on barley seedlings germinated on them (Calderbank 1975).

Paraquat loss from seawater in 24 h was 70% at an initial concentration of 1 mg/L, 68% at 5 mg/L, and 76% at 10 mg/L; most of the loss occurred within the first 60 min (Fytizas 1980).

Lethal and Sublethal Effects

General

Adverse effects of paraquat (death, inhibited germination of seeds, reduced growth) in sensitive species of terrestrial plants and soil microflora have been documented at application rates of 0.28 - 0.6 kg/ha, at soil concentrations of 10 - 25 mg/kg (growth inhibition), and at soil-water concentrations as low as 1.6 mg/L (reduced growth, inhibited synthesis of protein and RNA). Among terrestrial invertebrates, certain species of mites were sensitive to paraquat at recommended rates of application, and the sensitive honeybee (*Apis mellifera*) died when its diet contained 100 mg/kg. However, paraquat in soils was not accumulated by earthworms (*Lumbricus terrestris*) and other species of soil invertebrates after applications up to 112 kg/ha. These points, and others listed in this section, are discussed in greater detail later.

Freshwater algae and macrophytes usually die at paraquat concentrations between 0.25 and 0.5 mg/L; marine algae, however, are relatively resistant and usually require 5 mg/L or higher for significant inhibition in growth to occur in 10 days. Aquatic invertebrates, especially crustaceans, seem to be the most sensitive group, with effects most pronounced at elevated temperatures in early developmental stages. Adverse effects were noted in crab larvae at nominal water concentrations between 0.9 and 5.0 µg/L, although 1,000 µg/L and higher were needed to produce similar effects in other species of aquatic invertebrates. Amphibians and fishes were usually unaffected at concentrations below 3,000 µg/L, although sensitive species such as frog tadpoles and common carp (*Cyprinus carpio*) were affected at 500 µg/L. There was little accumulation of paraquat from the medium by aquatic fauna.

Paraquat is embryotoxic to sensitive species of birds. Concentrations equivalent to 0.056 kg/ha applied in oil solution to the surface of mallard (*Anas platyrhynchos*) eggs inhibited development; when applied in aqueous solution, paraquat was toxic at a dose equivalent to 0.56 kg/ha. In each case, adverse effects occurred below the recommended field application rate of about 1.0 kg/ha. The lowest doses of paraquat that produced harmful effects in sensitive birds were 10 mg/kg body weight (BW) in nestlings of the American kestrel (*Falco sparverius*), 20 mg/kg in the diet of northern bobwhite (*Colinus virginianus*), 40 mg/L in the drinking water of domestic chickens (*Gallus* sp.), and 199 mg/kg BW in mallard (acute oral LD50).

Sensitivity of mammals to paraquat was variable, due to inherent differences in interspecies resistance. Representative mammals were measurably affected at aerosol concentrations of 0.4 - 6.0 µg/L, acute oral doses of 22-35 mg/kg BW, dietary concentrations of 85 - 100 mg/kg and drinking water levels of 100 mg/L.

Terrestrial Plants and Invertebrates

In terrestrial plants, paraquat's action is at the point of local absorption (Anonymous 1963). Characteristic damage signs to susceptible species include wilting and general collapse in herbaceous plants. Regrowth may occur in some perennial plants, but in resistant species temporary scorch may be the most marked effect (Anonymous 1963). In sugarcane (*Saccharum officinarum*), paraquat application severely desiccated the plant within 72 h and disrupted activity of leaf amylase and sucrose (Haley 1979). Paraquat, once absorbed in plants, is likely to persist (Bauer 1983). The addition of cationic or nonionic surface active agents increases the phytocidal effectiveness of paraquat (Anonymous 1963), but in combination with various herbicides, paraquat was markedly less phytotoxic to certain cereal grains (O'Donovan and O'Sullivan 1986).

Paraquat adsorbed to soils is usually unavailable to crops. In wheat (*Triticum aestivum*), effects from

contaminated soils were negligible until soil residues surpassed 600- 1,000 kg/ha, causing growth reduction of 10%, or 1,650 kg/ha, causing elevated residues in leaves but not in grain (Moyer and Lindwall 1985).

Three species of grains (barley, *Hordeum vulgare*; wheat; oat, *Avena sativa*) died (>95% kill) following paraquat application of 0.28 kg/ha (O'Donovan and O'Sullivan 1986). At 0.6 kg/ha, paraquat inhibited germination and growth in seeds of six species of grasses (Kentucky bluegrass, *Poa pratensis*; perennial ryegrass, *Lolium perenne*; bentgrass, *Agrostis tenuis*; tall fescue, *Festuca arundinacea*; red fescue, *Festuca rubra*; orchard grass, *Dactylus glomerata*), but two species of legumes (alfalfa, *Medicago sativa*; red clover, *Trifolium pratense*) were comparatively resistant (Salazar and Appleby 1982). Paraquat was phytotoxic to several species of terrestrial plants (rape, *Brassica napus*; ryegrass; white clover, *Trifolium repens*) for several days following application of 1.1 - 2.2 kg/ha (Summers 1980). Transpiration rate of soybean (*Glycine max*) was lowered at 1 mg/kg (Haley 1979). Paraquat is not considered to be carcinogenic or teratogenic, but is weakly mutagenic to some plants (e.g., 4.1 % chromosomal aberrations in seeds of wheat at 9.3 mg/kg; Haley 1979). Spray solutions containing 0.6 g paraquat per liter applied to crowns of eastern redcedar (*Juniperus virginiana*) killed up to 90% of small trees and up to 30% of large trees; at 0.3 g/L, up to 60% of small trees were affected (Engle et al. 1988). Seedlings of corn (*Zea mays*) sprayed with 0.2% paraquat ion solution for 6 h had decreased rates of total protein synthesis and some polysome dissociation (Wu et al. 1988), suggesting that additional research is needed on mutagenicity of paraquat in plants.

Paraquat resistance has been documented in several genera of weeds. For example, paraquat-resistant strains of barley grass (*Hordeum glaucum*) were first noted in 1982 in Australia; resistant strains (based on chromosome counts and resistance to paraquat) were confined to a small number of alfalfa fields where paraquat had been used consistently for at least 10 years. However, the potential exists for this biotype to be transferred and established in other areas by the movement of livestock, machinery, hay, and seeds (Islam and Powles 1988; Tucker and Powles 1988). Paraquat-resistant strains of weeds have been reported in Australia, Egypt, England, and Japan (Polos et al. 1988). Paraquat-resistant strains of bacteria, ferns, and other species of flora have been documented (Carroll et al. 1988). Paraquat-tolerant ferns (*Ceratopteris richardii*) were 10 to 20 times more resistant than sensitive wild-type strains (Carroll et al. 1988). Paraquat-resistant strains of perennial rye were up to 10 times more resistant than normal susceptible strains (Faulkner and Harvey 1981). In the case of barley grass, survival was reduced 50% at 0.025 kg/ha in normal susceptible biotypes, but in resistant biotypes, 3.2 kg/ha was required (Islam and Powles 1988; Tucker and Powles 1988). Paraquat-tolerant plants may enjoy certain advantages over nonresistant plants, including resistance to various air pollutants. For example, paraquat-tolerant tobacco plants (*Nicotiana tabacum*), which had higher superoxide dismutase activity than controls, were tolerant to aerosol sprays of 2 mg SO₂/L, while controls experienced severe damage (Tanaka et al. 1988).

In every case of resistance, paraquat had been applied 2 or 3 times annually during the preceding 5 - 11 years; in some cases, a cross-resistance to atrazine was also reported (Polos et al. 1988). Paraquat-resistance mechanisms in plants include increased epicuticular wax (preventing penetration), binding of paraquat to cell walls, restricted movement into chloroplasts, and altered redox potential (Polos et al. 1988). For example, sequestration of paraquat within the apoplast of the leaf seems to be inheritable and controlled by a single nuclear gene with incomplete dominance (Islam and Powles 1988). Studies with paraquat-tolerant strains of various plants, including perennial rye and tobacco, suggest that tolerance is related to their general ability to rapidly detoxify the generated oxygen species through increased levels of superoxide dismutase, glutathione reductase, and other antioxidants (Shaaltiel et al. 1988).

At recommended field concentrations paraquat had negligible effect on soil microflora or soil fertility, although it did cause a temporary suspension of soil nitrification (Haley 1979). A concentration as low as 1.0 mg/L completely inhibited ammonium and nitrite oxidation for 40 days in a mixed culture of nitrifying bacteria isolated from soil (Gadkari 1988). Paraquat at 1.6 mg/L adversely affected *Escherichia coli* in 6 h as judged by diminished growth rate and inhibited synthesis of RNA and protein; at a higher concentration of 18.6 mg/L, interference with metabolism of glucose and DNA synthesis was observed (Davison and Papirmeister 1971). Four species of soil bacteria had 50% growth inhibition at paraquat concentrations between 93 and 18,600 mg/kg soil; moreover, the mode of action in some species of microorganisms may differ from the generally accepted mechanisms for paraquat toxicity in mammals (Carr et al. 1986). Sensitive species of soil fungi experienced marked growth inhibition between 10 and 25 mg paraquat per kilogram of soil. (Summers 1980). In

various genera of soil fungi (*Rhizopus*, *Ophiobolus*, *Helminthosporium*, *Fusarium*, *Eurotium*), paraquat concentrations up to 100 mg/L could be tolerated; at higher concentrations, spore germination was suppressed, mycelial growth was inhibited, and spore development was abnormal (Haley 1979).

Terrestrial invertebrates show varying degrees of sensitivity to paraquat. In honeybees, paraquat concentrations of 100 mg/kg syrup (diet) produced toxic signs, 4.4 kg/ha applied as a spray killed 90% in 3 days, and 1,000 mg/L in drinking water killed most in a few days and 100% within 5 weeks (Summers 1980). In soils, adsorbed paraquat may be ingested by soil invertebrates, such as earthworms, but it was not absorbed from the gut into tissues and was rapidly lost when the earthworms were transferred to clean soil (Calderbank 1975). For example, earthworms fed soil treated with 112 kg/ha had 111 mg/kg in gut contents, but <0.3 mg/kg in the carcass without gut (Summers 1980). Two species of springtails (*Collembola*; *Folsomia candida*, *Tullbergia granulata*) were fed diets containing 600 mg/kg for 22 weeks; they survived without measurable adverse effects. However, higher dietary levels of 1,000 and 5,000 mg/kg were associated with decreased survival, lengthier instar development, decreased egg production, and decreased egg viability (*Folsomia candida* and *Tullbergia granulata*) (Subagja and Snider 1981). Adults and larvae of the German cockroach (*Blattella germanica*) died after consuming diets containing 1,000 mg/kg (Summers 1980). Also, paraquat was lethal to two species of mites (*Tetranychus urticae*, *Typhlodromus* sp.) at concentrations below recommended field application rates (Summers 1980).

Aquatic Organisms

In general, paraquat is more toxic to aquatic fauna in soft water than in hard water, more toxic to early developmental stages than to juveniles or adults, and more toxic in formulations containing wetting agents than in formulations without them (Summers 1980). In water, paraquat is taken up rapidly by plants or adsorbed to particulate matter in the water column; however, paraquat is not bioconcentrated by aquatic fauna (Calderbank 1975; Summers 1980). Paraquat effects on aquatic biota are summarized in Table 3, and these data suggest several trends. Early developmental stages of certain species of crustaceans are extremely sensitive, and significant adverse effects occur in the range of 0.9-100 µg/L, although most species of crustaceans and all other species of invertebrates tested were relatively unaffected at concentrations below 1,000 µg/L. Freshwater algae and macrophytes are eliminated after treatment with 250 - 500 µg/L, but marine algae are relatively resistant and require 5,000 µg/L or higher to produce significant growth inhibition. Usually, aquatic vertebrates are not adversely affected and show little accumulation at 1,000 µg/L or lower, but at 500 µg/L, frog tadpoles have low survival and a high frequency of developmental abnormalities, and carp experience biochemical upset.

Paraquat controlled *Typha* and *Phragmites* in Egyptian irrigation canals, drains, and marshes without apparent harm to fishes (Haley 1979). Paraquat residues in decomposed plants become available for adsorption to sediments and bottom muds and are not readily available for microbial degradation (Summers 1980). Indirect fish kills may occur from anoxia due, in part, to consumption of dissolved oxygen by decaying weeds (Bauer 1983). Paradoxically, it has been suggested that paraquat may be helpful in improving the oxygen status of aquatic environments at a concentration of 1 mg/L by restricting nitrate production due to inhibition of bacterial nitrification (Chan and Leung 1986; Gadkari 1988). At effective herbicidal concentrations, paraquat was also toxic to eggs-but not adults-of three species of snail vectors of bilharzias (*Bulinus truncatus*, *Biomphalaria alexandrina*, *Lymnaea calliaudi*); newly hatched snails were the most sensitive (Haley 1979).

Changes in fauna of a reservoir following use of paraquat for weed control are likely to be indirect effects caused by decomposition of angiosperms (Brooker and Edwards 1974). Planktonic invertebrates closely associated with aquatic macrophytes were either eliminated by paraquat or survived at lower densities for at least a year following treatment; analysis of content of fish stomachs showed dietary changes following weed control and reflected availability of many invertebrate species associated with aquatic plants (Brooker and Edwards 1974).

Paraquat can induce activities of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase in many species of plants, invertebrates, and vertebrates. Results of studies with ribbed mussels (*Geukensia demissa*) support the hypothesis that these bivalve mollusks can activate redox cycling compounds and demonstrate responses typical of oxidative stress observed in other species (Wenning et al. 1988). Paraquat also disrupts glucose metabolism and acetylcholinesterase activity and accumulates in melanin. Disrupted glucose metabolism in paraquat-stressed carp was attributed to a high level of circulating epinephrine (Simon et al. 1983). Paraquat-induced acetylcholinesterase inhibition in erythrocytes and electric

organs of the electric eel (*Electrophorus electricus*) was reversible (Seto and Shinohara 1987, 1988). Paraquat tended to concentrate in melanin, as judged by accumulation in neuromelanin of frogs (*Rana temporaria*) after intraperitoneal injection (Lindquist et al. 1988), with important implications for research on Parkinson's disease. It seems that paraquat has a structural similarity to a metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which may induce a Parkinson-like condition; like paraquat, MPTP and its metabolites have melanin affinity (Lindquist et al. 1988).

Birds

Signs of oral paraquat intoxication in birds include excessive drinking and regurgitation, usually within 10 min of exposure. Other signs appeared after 3 h: diarrhea, ruffled feathers, muscular incoordination, imbalance, wing drop, hyporeactivity, slowness, weakness, running and falling, constriction of the pupil, and terminal convulsions. Additional signs reported after dermal exposure include blistering and cracking of skin, lacrimation, wing spread, and wing shivers. Death usually occurred between 3 and 20 h postexposure; remission took up to 12 days (Smalley 1973; Haley 1979; Summers 1980; Hudson et al. 1984). The blood chemistry pattern of paraquat-intoxicated Japanese quail (*Coturnix japonica*) suggested adrenal gland impairment, although recovery from hematologic effects was rapid (Clark et al. 1988). Paraquat causes pseudofeminization of male chicken and quail embryos; testes showed intersexual phenomena and Mullerian duct abnormalities; both sexes had a reduction in gonocyte number (Haley 1979; Bauer 1983).

Table 3. Effect of paraquat on selected species of aquatic plants and animals. Concentrations are milligrams of paraquat cation per liter of medium.

Taxonomic group, organism, and other variables	Concentration (ppm)	Effects	Reference ^a
Algae and macrophytes			
Lesser duckweed, <i>Lemna minor</i>	0.00074	Herbicidal	1
Submerged weeds			
4 species	0.25–0.5	Herbicidal	2
3 species	0.5–2.5	Herbicidal	2
<i>Chara</i> sp., <i>Polygonum</i> sp.	0.5	No adverse effects in 32 days	3
Freshwater algae			
3 species	0.25–1.0	Herbicidal	2
2 species	>5.0	Herbicidal	2
Rooted emergents			
2 species	0.25–0.5	Herbicidal	2
2 species	2.0–3.0	Herbicidal	2
1 species	>5.0	Herbicidal	2
Floating weeds			
Water weed, <i>Elodea canadensis</i>	0.5	Eradicated from British lakes in 32 days for at least 2 years	3
4 species	0.5	Herbicidal	2
Pondweed, <i>Potamogeton pusillus</i>	0.5	Residues of 36 mg/kg dry weight (DW) in 14 days	4, 5
Eurasian watermilfoil, <i>Myriophyllum spicatum</i>	1.0	Residues up to 112 mg/kg DW in 14 days	4, 5
Cattail, <i>Typha latifolia</i>	0.5	Shoreline colonies severely affected after 32-day exposure	3
Duckweed, <i>Spirodella oligorrhiza</i>	0.5	Inhibits chlorosis in 48 h	3
Marine algae			
<i>Isochrysis galbana</i>	5	50% growth inhibition in 10 days	6
<i>Phaeodactylum tricornutum</i>	10	50% growth inhibition in 10 days	6
<i>Dunaliella tertiolecta</i>	20	50% growth inhibition in 10 days	6
<i>Chlorococcum</i> sp.	50	50% growth inhibition in 10 days	6
4 species	2,500–>5,000	Respiration reduced 50% in 2 h	6
Invertebrates			
Mud crab, <i>Rithropanopeus harrisi</i> , larvae	0.00086	LC50 (19 days)	4
<i>Rithropanopeus harrisi</i> , larvae	0.001–0.005	50% mortality before zoeal stage	4
Isopod, <i>Asellus meridianus</i>			
15 C	0.1	LC50 (14 days)	7
15 C	0.58	LC50 (8 days)	7
5 C	0.62	LC50 (14 days)	7
5 C	6.3	LC50 (8 days)	7
Freshwater invertebrates, 3 species (<i>Asellus</i> , <i>Lymnaea</i> , <i>Sialis</i>)	0.5	No deaths in 4 days following spray application to British lake	3
Gastropod, <i>Murex brandaris</i>	1	LC50 (18 days)	8
<i>Murex brandaris</i>	10	LC50 (24 h)	8
<i>Murex brandaris</i>	1–10	Residues (in mg/kg fresh weight [FW] soft parts), after 3-day exposure ranged between 1.5 and 2.8; were dose dependent	8

Hermit crab, <i>Pagurus</i> sp.	1	LC50 (10 days)	8
<i>Pagurus</i> sp.	10	LC50 (36 h)	8
<i>Pagurus</i> sp.	1–5	Residues, in mg/kg whole body FW, after 3-day exposure ranged between 3.2 and 15; were dose dependent	8
Brown shrimp, <i>Penaeus aztecus</i>	>1	50% immobilization in 48 h	6
American oyster, <i>Crassostrea virginica</i>	>1	50% growth reduction in 96 h	6
Louisiana red crayfish, <i>Procambarus clarkii</i>			
Juvenile	1.4	LC50 (96 h)	9
Juvenile	2.4	LC50 (72 h)	9
Adult	17	LC50 (72 h)	9
All stages	Sublethal	Dose-dependent increase in hyperactivity and oxygen consumption	9
Daphnid, <i>Daphnia hyalina</i>	2.5	LC50 (14 days)	7
Daphnid, <i>Daphnia pulex</i>	2.7	50% immobilization in 48 h	10
<i>Daphnia pulex</i>	4	LC50 (48 h)	11
Cladoceran, <i>Simocephalus serrulatus</i>	2.8	50% immobilization in 48 h	10
<i>Simocephalus serrulatus</i>	3.7	LC50 (48 h)	11
Liver fluke, <i>Fasciola hepatica</i>			
Egg through miracidium	5	LC50 (20 days); effects counteracted by dinoseb	12
Egg	6	Delayed embryonic development; delayed hatch of miracidia	12
Egg	8	26% hatch	12
Egg	10	9% hatch	12
Egg	15	No hatch	12
Freshwater copepods, 2 species (<i>Eucyclops</i> , <i>Diaptomus</i>)	5	LC50 (48 h)	13
Freshwater copepods, 2 species	10	LC50 (24 h); effects counteracted by metribuzin, another herbicide	13
Aquatic insects, nymphs			
Corixid, <i>Sigara</i> sp.	5	LC50 (14 days)	7
Baetid, <i>Cloeon dipterum</i>	29	LC50 (14 days)	7
Daphnid, <i>Daphnia magna</i>	6	24% immobilized in 26 h; all mobile daphnids transferred to paraquat-free medium died within 24 h	14
Amphipod, <i>Gammarus fasciatus</i>	11	LC50 (96 h)	10, 11
Ribbed mussel, <i>Geukensia demissa</i>	93	Elevated catalase activity, lipid peroxidation rate, and total superoxide dismutase levels in 12–36 h	15
<i>Geukensia demissa</i>	744	No deaths in 7 days	15
<i>Geukensia demissa</i>	1,190	LC100 (7 days)	15
Chironomid, <i>Psectrocladius</i> sp., 4th instar larvae	>100	LC50 (14 days)	7
Stonefly, <i>Pteronarcys californica</i>	>100	LC50 (96 h)	10, 11
Mosquito larvae, 2 species	275→1,000	LC50	4
Fish			
Common carp, <i>Cyprinus carpio</i>	0.5	After 6 days, 300% increase in phosphorylase and 200% increase in glucose-6-phosphatase activities in liver; increase in sugar level and serum lactic dehydrogenase activity	18
<i>Cyprinus carpio</i>	5	Increase in activities of various liver enzymes, and in blood sugar levels	19

		during 6-day exposure; effects enhanced by the herbicide methidathion	
<i>Cyprinus carpio</i>	10	During 96-h exposure, significant alterations were recorded in lipid peroxidation rate, hemoglobin concentration, and erythrocyte antioxidant enzymes--that is, catalase, superoxide dismutase, and glutathione peroxidase activities	20
<i>Cyprinus carpio</i>	13–214	Acetylcholinesterase activity reduced 50% after 2-h exposure in serum (13 mg/L), heart (39 mg/L), muscle (102 mg/L), and brain (214 mg/L)	21
Freshwater fish 4 species	1	Maximum residues, in mg/kg whole body FW, during 16-day exposure, ranged between 0.6 in green sunfish (<i>Lepomis cyanellus</i>) and 1.6 in bluegill (<i>Lepomis macrochirus</i>); intermediate values recorded for rainbow trout (<i>Oncorhynchus mykiss</i>) and channel catfish (<i>Ictalurus punctatus</i>)	22
3 species	10	In 96-h exposures, paraquat caused exposure-dependent increase in lipid peroxidation rate and in activity enhancement of peroxide metabolism enzymes in erythrocytes	23
Smallmouth bass, <i>Micropterus dolomieu</i>	1	Adverse sublethal effects	22
Striped mullet, <i>Mugil cephalus</i>	1	LC50 (16 days); survivors had pronounced gill histopathology and residues (in mg/kg FW) of 0.2 in muscle, 0.2 in ovary, 4.7 in skin, and 6.1 in digestive tract	8
<i>Mugil cephalus</i>	10	LC50 (60 min)	8
Thai silverbarb, <i>Puntius gonionotus</i>	1	No tissue histopathology after 12-day exposure	24
<i>Puntius gonionotus</i>	1	No tissue histopathology after 12-day exposure; gills normal during 5-day exposure	24
Longnose killifish, <i>Fundulus similis</i>	>1	LC50 (48 h)	6
Mosquitofish, <i>Gambusia affinis</i>	3	Adverse effects	22
<i>Gambusia affinis</i>	604	LC50 (96 h)	5
Zebra danio, <i>Brachydanio rerio</i>	7.5–48.5	LC50 (96 h)	4
Shortfin molly, <i>Poecilia mexicana</i>	12	LC50 (24 h)	5
Medaka, <i>Oryzias latipes</i>			
Egg	12	Normal development	5
Egg	23	Abnormal development	5
Embryo	>50	100% lethal	5
Bluegill, <i>Lepomis macrochirus</i>	13	LC50 (96 h)	10, 11
Guppy, <i>Poecilia reticulata</i>	15–22	LC50 (96 h)	4
Rainbow trout, <i>Oncorhynchus mykiss</i>	15–32	LC50 (96 h)	5, 10, 11
<i>Oncorhynchus mykiss</i>	>100	LC50 (24 h)	10

Brown trout, <i>Salmo trutta</i>	25	LC50 (96 h)	5
Channel catfish, <i>Ictalurus punctatus</i>	>100	LC50 (96 h)	5, 10, 11
Amphibians			
Northern leopard frog, <i>Rana pipiens</i>			
Early gastrula stage	0.1	Normal growth, survival, development, and swimming behavior after 7-day exposure	16
Early gastrula stage	0.5	High mortality, high number of tail abnormalities, reduced growth rate in survivors, abnormal swimming behavior after 7-day (3 days posthatch) exposure to 0.5 mg/L and higher	16
15-day-old tadpoles	0.5	33% dead after exposure for 16 days	17
15-day-old tadpoles	2	95% dead after exposure for 16 days; growth retardation and increase in developmental abnormalities such as tail malformations and cranial defects	17
Fowler's toad, <i>Bufo woodhousei</i>			
<i>fowleri</i> , tadpole	15	LC50 (96 h)	10
<i>Bufo woodhousei fowleri</i>	56	LC50 (24 h)	10
Western chorus frog,			
<i>Pseudacris triseriata</i> , tadpole	28	LC50 (96 h)	10
<i>Pseudacris triseriata</i>	43	LC50 (24 h)	10
Frog, <i>Limodynastes peronii</i> , adult	100	LC50 (96 h)	5
Frog, <i>Adelotus brevis</i> , adult	262	LC50 (96 h)	5

^a1, Ross et al. 1979; 2, Anonymous 1963; 3, Way et al. 1971; 4, Summers 1980; 5, Bauer 1983; 6, Mayer 1987; 7, Brooker and Edwards 1974; 8, Fytizas 1980; 9, Leung et al. 1980; 10, Mayer and Ellersieck 1986; 11, Johnson and Finley 1980; 12, Christian et al. 1985; 13, Naqvi et al. 1981; 14, Crosby and Tucker 1966; 15, Wenning et al. 1988; 16, Dial and Bauer 1984; 17, Dial and Dial 1987b; 18, Simon et al. 1983; 19, Asztalos et al. 1988; 20, Matkovics et al. 1987; 21, Nemcsok et al. 1984; 22, Earnest 1971; 23, Gabryelak and Klekot 1985; 24, Sinhaseni and Tesprateep 1987.

The lowest doses of paraquat causing measurable adverse effects in sensitive species of birds (Table 4) were 0.2 mg/kg BW administered by single intravenous injection to Japanese quail, causing anemia; 0.25 mg/kg applied in oil solution to the surface of mallard eggs, producing reduced survival, reduced growth, and increased frequency of developmental abnormalities; 10 mg/kg BW administered orally for 10 days to nestlings of the American kestrel, causing reduced growth; 20 mg/kg in diet of the northern bobwhite, producing a reduction in egg deposition; 40 mg/L in drinking water of the domestic chicken, causing elevated tissue residues and an increase in the number of abnormal eggs produced; and 199 mg/kg BW in mallards, producing an acute oral LD50.

Paraquat is highly toxic to avian embryos but less toxic to adult birds (Bunck et al. 1986). It is toxic by several routes of administration, including injection and topical application (Hoffman et al. 1985). Of 42 herbicides and insecticides tested, paraquat was the most toxic to mallard eggs. Paraquat applied to eggshell surfaces in nontoxic oil vehicles was significantly more embryotoxic than were aqueous paraquat solutions, presumably due to greater penetration of oil past the shell and membranes (Hoffman and Eastin 1982; Hoffman and Albers 1984; Table 4). The LC50 values for paraquat and mallard eggs were 1.68 kg/ha (1.5 lb/acre) in aqueous emulsion and 0.11 kg/ha (0.1 lb/acre) in an oil vehicle (Hoffman and Eastin 1982). The computed LC50 aqueous value was about 1.5 times that of the recommended field application rate of about 1.0 kg/ha; however, Paraquat in aqueous solution caused some deaths at only half the field level of application, and survivors showed impaired growth and some developmental abnormalities (Hoffman and Eastin 1982; Table 4).

Table 4. Effects of paraquat on selected species of birds.

Species, dose, and other variables	Effects	Reference
Mallard, <i>Anas platyrhynchos</i>		
Fertilized eggs exposed on day 3 of incubation for 0.5 min at room temperature		
Oil solutions		
0.25 mg/kg/egg, equivalent to 0.56 kg/ha or 0.05 lb/acre	17% dead, reduced growth, 16% abnormal development	Hoffman and Eastin 1982
0.5 mg/kg/egg	50% dead, some abnormal survivors	Hoffman and Albers 1984
2.5 mg/kg/egg	83% dead, 60% abnormal	Hoffman and Eastin 1982
Aqueous solutions		
2.5 mg/kg/egg, equivalent to 0.56 kg/ha or 0.5 lb/acre	23% dead, survivors stunted, 9% abnormal	Hoffman and Eastin 1982
8.3 mg/kg/egg	50% dead; computed LC50 concentration about 1.5 times the recommended field application rate; at 1.5–3.0 times the field level, paraquat produced abnormal development, including edema, stunting, and brain malformations	Hoffman and Eastin 1982
27.7 mg/kg/egg	73% dead, 63% of survivors abnormal	Hoffman and Eastin 1982
Adults and juveniles		
199 mg/kg body weight (BW)	Acute oral LD50; deaths usually occurred 3–20 h after treatment; remission took up to 12 days	Hudson et al. 1984
600 mg/kg BW	Percutaneous LD50 for 10- to 11-month-old drakes after a 24-h dermal foot exposure; deaths occurred 6–22 h after treatment; remission took up to 5 days	Hudson et al. 1984
4,048 mg/kg diet	Fatal to 50% after 5 days on treated diet plus 3 days on untreated ration	Heath et al. 1972
Northern bobwhite, <i>Colinus virginianus</i>		
Parent generation (P ₁) fed diets containing 20, 60, 180, or 360 mg/kg ration for 6 weeks; in next generation (F ₁), none was administered	360 mg/kg P ₁ group had reduced fertility and hatchability, significant body weight loss, reduction in ovary and oviduct weight; no histopathology or increase in chick abnormalities; the 180 mg/kg P ₁ group laid significantly fewer eggs during treatment; all F ₁ hens from the 20, 60, and 180 mg/kg groups started laying 1 week later than controls and produced fewer eggs; F ₁ males experienced delay in maturation; F ₁ chicks from the	Bauer 1983, 1985

	20 mg/kg group were significantly heavier than all other groups	
Fed diets containing 25 or 100 mg/kg food for 60 days	No signs of toxicity or impaired learning	Bunck et al. 1986
981 mg/kg diet, 2- to 3-week-old birds	Fatal to 50% after 5 days on treated diet plus 3 days on untreated diet	Heath et al. 1972; Anonymous
Japanese quail, <i>Coturnix japonica</i>		
Juveniles received a single intravenous injection of 0.2, 2, or 20 mg/kg BW	Some deaths in 20 mg/kg group; all survivors from all groups showed hemolytic anemia within 24 h postinjection, recovery beginning within 72 h; the 0.2 mg/kg birds also showed reductions in erythrocyte number, hematocrit, and hemoglobin within 24 h	Clark et al. 1988
14-day-old chicks fed treated diets for 5 days followed by 3 days of untreated food		
500 mg/kg diet	Fatal to 20%	Hill and Camardese 1986
948–970 mg/kg diet	Dietary LD50	Heath et al. 1972; Hill and Camardese 1986
1,516 mg/kg diet	Fatal to 90%	Hill and Camardese 1986
Eggs dusted with 0.4–0.8% paraquat powder	58–79% hatching rate	Bauer 1983
100 mg/L in drinking water	Lethal within 7 days	Summers 1980
American kestrel, <i>Falco sparverius</i>		
Nestlings		
Daily oral doses, for 10 days, of 10, 25, or 60 mg/kg BW	Compared to controls, all groups exhibited reduced growth rate and elevated total sulfhydryl and protein-bound sulfhydryl levels in lung; the 25 mg/kg group had reduced skeletal growth of humerus and femur; in the 60 mg/kg group, 44% died in 4 days, survivors showed abnormal blood chemistry, liver histopathology, kidney damage, reduced skeletal growth of humerus, femur, radius-ulna and tibiotarsus	Hoffman et al. 1985, 1987
Domestic chicken, <i>Gallus sp.</i>		
Egg		
>0.1 mg/kg	Hatching rate reduced after injection	Fletcher 1967; Bauer 1983
0.5 mg	Injected eggs did not hatch	Haley 1979
0.4–0.8% paraquat powder	46–77% hatching rate for eggs dusted with powder	Bauer 1983
Adult		
Single intravenous injection of 25 mg paraquat dichloride/kg BW	60% reduction in urine flow within 50 min	Prashad et al. 1981
40 mg/L drinking water for 14 days, followed by 14 days of paraquat-free water	No effect on egg production or hatchability, but 7% increase in number of abnormal eggs produced; residues in eggs rose to about	Fletcher 1967

	0.1 mg/kg, but declined to below detection limits 6 days after treatment ended; no effect on food and water consumption of hens or on number and type of abnormalities in chicks	
131 mg/kg BW	Acute oral LD50, diet deficient in vitamin E and selenium	Combs and Peterson 1983
148 mg/kg BW	Acute oral LD50, diet deficient in selenium	Combs and Peterson 1983
419 mg/kg BW	Acute oral LD50, diet deficient in vitamin E	Combs and Peterson 1983
Chicks, 8 days old, 200–380 mg/kg BW	Acute oral LD50	Haley 1979; Summers 1980; Bauer 1983
Turkey, <i>Meleagris gallopavo</i>		
20 mg/kg BW	Lethal dose, intravenous injection route	Smalley 1973
100 mg/kg BW	Lethal dose, intraperitoneal injection route	Smalley 1973
290 mg/kg BW	Lethal dose, oral administration route	Smalley 1973
500 mg/kg BW	Lethal dose, dermal route	Smalley 1973
Ring-necked pheasant, <i>Phasianus colchicus</i>		
1,468 mg/kg diet	Fatal to 50% after 5-day treated diet plus 3-day untreated diet	Heath et al. 1972

Nestlings of altricial species, such as the American kestrel, were more sensitive to paraquat exposure than were young or adults of precocial species (Hoffman et al. 1985). Several food items of kestrels (e.g., grasshoppers, small rodents, passerine birds) are readily contaminated by paraquat through direct contact during agricultural spraying or by ingestion of contaminated vegetation (Hoffman et al. 1985). From a comparative viewpoint, however, lungs of nestling kestrels were less sensitive to paraquat than were mammalian lungs (Hoffman et al. 1987).

Northern bobwhite hens immediately exposed to simulated field application rates of paraquat took longer to lay a clutch of eggs once laying had commenced; the completed clutch appeared 10 days later in the season than birds free from paraquat exposure. It is uncertain whether the paraquat-induced delay in sexual maturation produced experimentally will also be reflected in nonlaboratory situations (Bauer 1983, 1985). Turkeys (*Meleagris gallopavo*), for example, held in field plats sprayed 24 h earlier with paraquat at 100 times the recommended agricultural application rate (i.e., up to 14 kg/ha or 200 oz cation per acre) showed no signs of toxicity 30 days after spraying (Smalley 1973).

Acute toxicity of paraquat in the domestic chicken was highly responsive to nutritional selenium status and not to vitamin E status; as little as 0.01 mg Se/kg of ration protected 8-day-old chicks against acute paraquat poisoning (Combs and Peterson 1983). Paraquat administered to chickens by way of diet was less toxic than the same amount administered in drinking water (Fletcher 1967).

Mammals

Resistance to paraquat among mammals varied substantially because of inherent differences in sensitivity between species, route of administration, and reproductive state (Table 5). The lowest recorded doses of paraquat causing measurable adverse effects on growth, survival, or reproduction were aerosol concentrations of 0.4-6.0 µg/L (rat, guinea pig); 0.05 mg administered directly in the lung (rat); intravenous injection of 1-12 mg/kg BW (sheep, dog, rat); subcutaneous injection of 2.4-28 mg/kg BW (rat, mouse, monkey); intraperitoneal injection of 3-10 mg/kg BW (mouse, guinea pig, goat); acute oral dose of 22-35 mg/kg BW (dog, cat, hare, guinea pig); oral application of 70 to 90 mg/kg BW (rat); dietary levels of 85-100 mg/kg of ration (dog, mouse, rat); and drinking water concentration of 100 mg/L (mouse).

In general, intraperitoneal and intravenous injection were the most sensitive administration routes (Bauer 1983). LD50 dermal values, however, are often not true percutaneous values because of oral contamination from normal grooming (Summers 1980). Aerosol exposure to paraquat produced a concentration-dependent rapid, shallow breathing pattern in guinea pigs (*Cavia* sp.) 18 h after exposure (Burleigh-Flayer and Alarie 1988). Aerosol LC50 values in paraquat toxicity tests with mammals were directly related to the duration of exposure, paraquat concentration in spray, and particle size; particles of 3 µm (diameter) seemed most effective (Haley 1979).

Following accidental ingestion, paraquat produces rapidly progressive, fatal, interstitial inflammation and fibrosis of the lung in humans, and this has been produced experimentally in several species of laboratory animals (Butler and Kleinerman 1971; Murray and Gibson 1972). Initial symptoms of paraquat poisoning include burning of the mouth and throat followed by nausea and vomiting. After a latent period of up to several days, increasing respiratory distress develops; death is usually the result of a progressive fibrosis and epithelial proliferation that occurs in the lungs (Kirnbrough 1974). Paraquat poisoning in humans has a mortality of 30-70%, depending largely on the dose ingested. It causes multiorgan failure, including the heart, lungs, kidney, liver, and brain. Although recovery may follow mild involvement of any of these organs, many patients die from progressive untreatable pulmonary fibrosis. This illness usually succeeds renal failure and relates in part to active pulmonary uptake of paraquat (D.W. Webb 1983). In one case, a 15-year-old boy accidentally ingested a mouthful of paraquat and developed severe respiratory distress, necessitating transplantation of one lung; paraquat-induced rejection of the graft resulted in death 2 weeks after the operation (Matthew et al. 1968). Paraquat cannot be absorbed significantly through intact human skin, but in the event of broken or abraded skin brief exposure to a paraquat concentration of 5 g/L may result in death (J. Smith 1988).

Table 5. Effects of paraquat on selected species of mammals.

Species, dose, and other variables	Effect	Reference
Cow, cattle, <i>Bos</i> sp.		
Calves administered 5 mg/kg BW, intravenous injection	No effect on pulmonary function or blood gases after 7 days	Kiorpes et al. 1982
20 mg/L in drinking water for 1 month	No measurable effect	Calderbank 1975
35–75 mg/kg BW	Acute oral LD50	Fletcher 1974; Haley 1979; Summers 1980; Heitkamp and Brown 1982
200–400 mg/kg diet for 30 days	No observable effect; no measurable residues in meat or milk	Calderbank 1975
Dog, <i>Canis familiaris</i>		
25 µg/L air, 60-min exposure	No ill effects	Haley 1979
Fed diets containing 7, 34, 85, or 170 mg/kg ration for 27 months	No significant abnormalities at 7 or 34 mg/kg; toxic effects noted at 85 and 170 mg/kg diet	Anonymous 1974
12 mg/kg BW, single intravenous injection	Extensive lung damage after 7 days	Hampson and Pond 1988
25 mg/kg BW, single intravenous injection	All dead within 36 h; before death, plasma levels of glucose, cortisol, and catecholamines increased and glucose levels decreased; increases in activity of plasma lactic dehydrogenase, creatinine phosphokinase, glutamic oxaloacetic transaminase, creatinine, and rennin; residues in dead dogs (in µg/kg fresh weight [FW]) were highest in bile (41), kidney (8), lung (5), liver (5), spleen (4), heart (3), adrenal (3), pancreas (1), thymus (1), and muscle (1)	Giri et al. 1982, 1983
25–50 mg/kg BW	Acute oral LD50	Heitkamp and Brown 1982; Anonymous 1988

36 mg/kg diet for 2 years	No measurable effect	Haley 1979
Goat, <i>Capra sp.</i> 10 mg/kg BW, intraperitoneal injection	Mild paraquat-related lung tissue changes, but toxicosis was not clinically significant after 10 days	Kiorpes et al. 1982
Guinea pig, <i>Cavia sp.</i> Aerosol exposure (in mg/m ³) 0.1, 0.4, or 0.8, 6 h daily, 5 days weekly, 3-week exposure	Rapid shallow dose-dependent breathing pattern, with return to control values during first 7 days' exposure, suggesting adaptation	Burleigh-Flayer and Alarie 1988
0.7, 4-h exposure, 2-week observation	Decrease in lung volume and increase in respiratory frequency; maximum effects measured several days postexposure with return to control values	Burleigh-Flayer
0.83–2.07, 4-h exposure, flow rate 21 L/min, particles usually <0.65 µ diameter	Concentration-related decrease in lung volume and twofold increase in respiratory frequency 18 days postexposure	Burleigh-Flayer and Alarie 1987
3 mg/kg BW	Acute intraperitoneal LD50	Haley 1979;
22–80 mg/kg BW	Acute oral LD50 in 7 days	Manzo et al. 1979 Murray and Gibson 1972; Haley 1979; Summers 1980; Heitkamp and Brown 1982; Bauer 1983
Chinese hamster, <i>Cricetus spp.</i> Cultured cells subjected to 0.8 mg/L for 3 h, recovery for 21 days	50% frequency of chromosomal aberrations; higher frequency by pretreatment with diethyldithiocarbamate (an inhibitor of superoxide dismutase), or dimethyl maleate (a glutathion scavenger), or at high oxygen concentrations	Sofuni and Ishidate
Cat, <i>Felis domesticus</i> 26–50 mg/kg BW	Acute oral LD50	Fletcher 1974; Haley 1979; Summers 1980; Heitkamp and Brown 1982; Bauer 1983
26–50 mg/kg BW	Peak concentration in blood of 13 mg/L	Conning et al. 1969
Human, <i>Homo sapiens</i> 26–50 mg/kg BW Child, 6-year-old, accidentally swallowed unknown amount of Gramoxone W	Residue in urine 6 days after exposure was 3.6 mg/L; death 7 days after onset of symptoms; autopsy showed ulceration of buccal mucosa, emphysema, severe lung damage, jaundice, renal failure	Campbell 1968
Adult male, died 30 h after swallowing paraquat solution	Histopathology of lung and adrenal gland; residues (in mg/kg FW), highest in kidney (17), followed by lung (6), muscle (4.4), liver (3.8), blood (1.4), skin (0.9), and brain (0.4)	Spector et al. 1978
Ingestion--but not necessarily swallowing--of about 15 mL ("mouthful") of a 20% solution	Fatal dose	Kimbrough 1974; Spector et al. 1978
4→40 mg/kg BW	Acute oral LD50	Manzo et al. 1979; Summers 1980
Ingestion of 30 mg/kg BW	Associated with hepatic, cardiac, or renal failure sometimes death	Dasta 1978
Total ingested dose of 3–6 g	Fatal dose	Haley 1979

Hare, <i>Lepus</i> sp. 35 mg/kg BW	Acute oral LD50	Fletcher 1974
Japanese monkey, <i>Macaca fuscata</i> Adults <3.5 years old, 2 mg/kg BW every 2 days for 8 to 10 days, subcutaneous injection	After 4 injections (8 days), 63% died; after 5 injections, 75% died; all deaths occurred between days 11 and 35; at day 66, survivors had elevated lung collagen and increased ceruloplasmin	Masaoka et al. 1987
Monkey, <i>Macaca</i> sp. 50–75 mg/kg BW	Acute oral LD50 in 7 days	Fletcher 1974; Smith and Heath 1976; Heitkamp and Brown 1982; Bauer 1983
>63 mg/kg BW, oral route	All dead within 2 days; death preceded by convulsions	Murray and Gibson 1972
Mouse, <i>Mus musculus</i> Fed diets containing 45, 90, or 125 mg/kg ration for two generations	At 45 mg/kg and 90 mg/kg, no significant difference from controls in reproductive organ development, fertility, mating behavior, embryotoxicity, or developmental abnormalities; at 125 mg/kg diet, survival was significantly lower, fewer pairs reproduced, females mature later; second-generation mice were more resistant than first generation	Dial and Dial 1987a
Domestic mouse, <i>Mus</i> spp. 1.65 or 3.35 mg/kg BW intraperitoneal injection, or 20 mg/kg BW orally, daily on days 8–16 of gestation	No significant teratogenic effects; low accumulations in embryos	Bus et al. 1975
Fed diets containing 2, 10, 30, or 100 mg/kg ration for 2 years	Maximum no-effect level was 30 mg/kg diet, equivalent to 3.92 mg/kg BW daily for males and 3.82 mg/kg BW daily for females	Anonymous 1988
Single intraperitoneal injection of 8 mg/kg BW on day 9 of pregnancy, or 2 mg/kg BW on day 9, 10, 11, and 12 of pregnancy	No measurable effect on survival, reproduction, birth weight, or chromosomal aberrations; no evidence of mutagenicity to mice liver cells	Selypes et al. 1980
16–30 mg ion/kg BW	LD50, intraperitoneal injection	Manzo et al. 1979; Selypes et al. 1980;
28 mg ion/kg BW 38–120 mg/kg BW	LD50, subcutaneous injection Acute oral LD50	Anonymous 1988 Anonymous 1988 Fletcher 1974; Haley 1979
50 or 100 mg/L in drinking water	Low dose had no effect on growth or survival; high dose group showed increased postnatal mortality after 2 generations	Bauer 1983
Rabbit, <i>Oryctolagus</i> sp. Single intravenous injection of 0.05 mg/kg BW	Plasma concentrations (in mg/L), 0.6 within 2 h, 0.01 at 8 h, and <0.002 at 24 h; estimated half-life (T _b 1/2) of 24.5 h	Yonemitsu 1986
Single intravenous injection of 5 mg/kg BW	Plasma concentrations (in mg/L), about 30 in 2 h, 1 in 8 h, 0.1 in 24 h, and <0.01 in 48 h; estimated T _b 1/2 of 12.8 h; kidney histopathology evident 7 days after injection but lung damage negligible	Yonemitsu 1986
Daily oral administration of 11 mg/kg BW for 30 days	No significant toxic signs	Dikshith et al. 1979

5 intraperitoneal injected doses totaling 2–100 mg/kg BW	At doses of 25 mg/kg BW and higher, rabbits usually died within 4 days posttreatment; no delayed pulmonary changes in rabbits typical of those induced in man and other animals observed in survivors up to 1 month after treatment	Butler and Kleinerman 1971
20 mg/kg BW, intravenous injection	Tended to concentrate in lung; lung histopathology and biochemical upset	Ilett et al. 1974
24 mg/kg BW, 20 dermal applications 49–150 mg/kg BW	No effect Acute oral LD50	Anonymous 1974 Fletcher 1974; Haley 1979
Total 60-min aerosol dose of 250 mg	Significantly increased levels in serum of phospholipids, cholesterol, and triglycerides; reduced growth rate; no evidence of liver or lung damage	Seidenfeld et al. 1984
346–480 mg/kg BW	Acute dermal LD50	Anonymous 1974; Haley 1979
Sheep, <i>Ovis aries</i> Single intravenous injection of 1, 2, 4, or 8 mg/kg BW	Nephrotoxic, producing glomerular and tubular defects in a dose-dependent manner, including inhibited glomerular filtration rates and inhibited paraquat secretion; LD50 (6 weeks), about 1 mg/kg BW; serum levels 60 min postexposure (in mg/L), 0.07 for the 1 mg/kg group, 0.25 for the 2 mg/kg group, 1.23 for the 4 mg/kg group, 2.05 for the 8 mg/kg group	D. B. Webb 1983; D. W. Wegg 1983
50–75 mg/kg BW	Acute oral LD50	Fletcher 1974; Summers 1980; Heitkamp and Brown 1982
Rat, <i>Rattus sp.</i> 0.000116 or 0.000232 ug/kg BW hourly for 7 days, intravenous infusion, equivalent of total dose of 0.0465 mg (low dose) or 0.093 mg (high dose)	No adverse effects evident at low dose; at high dose, survivors showed weight loss, histopathology, increased lung glutathione and glucose-6-phosphate dehydrogenase activity--reflecting paraquat-induced oxidant stress and increased demand on lung NADPH	Dunbar et al. 1988a
0.0001 or 0.0004 mg/L air, daily 6-h exposure for 3 weeks	No effect at 0.0001 mg/L; pulmonary irritation at 0.0004 mg/L	Haley 1979
0.001–1.0 mg/kg BW, entire dose in right lung	Dose-dependent lung injury and fibrosis; tissue fibronectin levels remained elevated 14 days after administration	Dubaybo et al. 1987
0.006 mg/L air, 60-min exposure	LC50; 3 um-size particle most effective	Haley 1979
0.01 or 0.05 mg, injected into brain	Intense pattern of behavioral stimulation, including increased locomotor activity, especially circling, and convulsions; abnormal brain wave patterns	De Gori et al. 1988
0.0116 mg/kg BW, single dose, various routes	Dose administered by intravenous and intragastric routes cleared rapidly; urine and feces major excretion routes; Tb 1/2 in blood	Chui et al. 1988

	about 68 min; dermal- and pulmonary-route doses tended to remain at site of injection	
0.05 mg/kg BW, entire dose in lung	Pulmonary lesions, lung congestion and collapse, edema, hemorrhage, degenerate changes, proliferative fibrosis in lung tissue	Kimbrough and Gaines 1970; Summers 1980
0.09–9.00 mg/kg BW, single subcutaneous injection	Dose-dependent avoidance of foods at >0.5 mg/kg BW; the ED50 for conditioned taste aversion was 2.4 mg/kg BW (minimum effective dose was 0.78 mg/kg BW); none of these doses produce overt clinical or histological signs of toxicity	Dey et al. 1987
0.125 or 0.25 mg/kg BW hourly, continuous intravenous infusion	After 7 days, lungs of high-dose group had elevated putrescine, spermidine, and ornithine decarboxylase activity, reflecting changes in polyamine metabolism; no measurable effects in low-dose group	Dunbar et al. 1988b
Pregnant dams given 1.5, 4.5, or 13.5 mg/kg BW daily from day 7 to day 17 of gestation	No fetal toxicity or teratogenicity in any group, although maternal survival was low in the 13.5 mg/kg group	Anonymous 1988
6 mg/kg BW, intravenous injection Fed diets containing 10, 30, 100, or 300 mg/kg for 2 years	Lung fibrosis No adverse effects in males at 30 mg/kg diet (1.06 mg/kg BW daily) and lower, or in females at 100 mg/kg diet (4.3 mg/kg BW daily) and lower; lung histopathology observed in males at 100 mg/kg diet and both sexes at 300 mg/kg; at growth, reduced food and water intake, abnormal blood chemistry, and increased frequency of cataracts; no conclusive evidence of carcinogenicity	Summers 1980 Anonymous 1988
10 or 30 mg/kg BW, intraperitoneal injection	At both doses there was a decrease in calcium uptake by lung microsomes for 3–4 days postinjection, followed by recovery during next 4 days	Agarwal and Coleman 1988
14–34 mg/kg BW, intraperitoneal injection	LD50	Haley 1979; Manzo et al. 1979; Anonymous 1988
16–18 mg/kg BW, intravenous injection	LD50	Sharp et al. 1972
18 mg/kg BW, single intraperitoneal injection	Significant increases in enzymes and compounds responsible for protecting against lipid peroxidation, including catalase, glucose-6 phosphate dehydrogenase, and nonprotein sulfhydryl	Omaye and Reddy 1980
19–26 mg/kg BW, subcutaneous injection	LD50	Haley 1979; Lock 1979; Anonymous 1988
20 mg/kg BW, intravenous injection Postinjection time 5 min	Residues (in mg/kg), 90 in kidney, 30 in plasma 10–20 in lung, liver, and muscle	Summers 1980
4 h	Residues (in mg/kg), 8 in lung, 6 in kidney, 2 in liver, 0.8 in muscle, 0.3 in plasma	Summers 1980

3 days	Lung contained 3 mg/kg, kidney 0.7, muscle 0.5, liver 0.3, plasma 0.04	Summers 1980
10 days	In survivors, muscle contained 0.25 mg/kg, lung 0.1, kidney 0.06, liver 0.03, plasma 0.01	Summers 1980
Fed diets containing 20, 100, or 200 mg/kg ration for two generations	Maternal and fetal toxicity in 200 mg/kg diet	Anonymous 1988
21 mg/kg BW	90-dose oral LD50 in females	Kimbrough and Gaines 1970
27 mg/kg BW, single intravenous injection	Lung surfactant decreased 32% within 24 h, suggesting loss in alveolar stability	Haley 1979
Adult males, 30 mg/kg BW, intraperitoneal injection	No deaths 72 h after single injection; marked reduction of acid alkaline phosphatase activity in alveolar epithelium of lung	Boudreau and Nadeau 1987
45 mg/kg BW, intraperitoneal injection	After 48 h, marked increase in blood glucose, depressed plasma insulin level, marked depletion of liver glycogen, significant increase in plasma creatinine phosphokinase and glutamic oxaloacetic transaminase activity	Giri et al. 1979
Fed 8-week diets containing 50, 120, or 250 mg/kg ration	No progressive accumulations in tissues; no pulmonary lesions at 50 or 120 mg/kg diet--however, 100% of 250 mg/kg group had pulmonary lesions	Summers 1980
Fed 2-year diet containing 70 mg/kg ration 70–90 mg/kg BW, dermal exposure	No significant toxicity LD50	Anonymous 1974 Kimbrough and Gaines 1970; Kimbrough 1974; Haley 1979; Anonymous 1988
95–174 mg/kg BW	Acute oral LD50	Kimbrough and Gaines 1970; Murray and Gibson 1972; Anonymous 1974, 1988; Kimbrough 1974; Manzo et al. 1979; Heitkamp and Brown 1982; Bauer 1983 Lock 1979
125 mg/kg BW, oral dose	Survivors had decreased kidney glomerular filtration rate within 24 h	Lock 1979
170 mg/kg diet for 2 years	No measurable effect	Haley 1979

Paraquat tends to rapidly localize in selected tissues of injected mice, including melanin, alveolar-type cells of the lung, choroid plexus, muscle, liver, gallbladder, intestinal contents, and proximal tubules of the kidney (Waddell and Marlowe 1980). Half-time persistence of paraquat in rat tissues ranged from 20 - 30 min in plasma to about 5 days in muscle (Sharp et al. 1972).

Acute effects of paraquat poisoning in livestock and small laboratory animals are similar to those in humans (Conning et al. 1969; Murray and Gibson 1972; Rose et al. 1976; Smith and Heath 1976; Haley 1979; Kelly et al. 1979; Manzo et al. 1979; Summers 1980; Table 5). Signs of acute paraquat toxicosis included hyperexcitability leading to convulsions or incoordination, inflammation of the mouth and throat, vomiting, reluctance to eat or drink, diarrhea, tachycardia, eye irritation of the conjunctiva, corneal lesions, skin reddening, skin ulceration, skin necrosis, histopathology of liver and kidney, and respiratory failure. Paraquat was selectively accumulated in lungs of canines, primates, and rodents, regardless of route of administration. Lung pathology included congestion, hemorrhage, edema, and collapse; this was associated with degeneration of alveolar and bronchial cells. Death may occur within 10 days of acute exposure.

Chronic administration of small doses or repeated injections usually produces no clinical signs for several weeks. Generally, signs develop suddenly and include weight loss, anorexia, and death--usually within 10 days of onset of signs (Smith and Heath 1976). Decreased food consumption and consequent loss of body weight are common in paraquat-poisoned rats and dogs. The *area postrema* of the hindbrain is an important neural site for detection of blood-borne chemicals and is speculated to control paraquat-induced taste aversion formation and weight loss (Dey et al. 1987).

Rabbits are comparatively resistant to paraquat-induced lung damage, regardless of the route of administration (Dikshith et al. 1979; Summers 1980; Bauer 1983). However, the closely related hare (*Lepus europaeus*) is comparatively sensitive to paraquat. Hares--placed on alfalfa plots within a few hours after the fields were treated with paraquat at 0.6 kg/ha--experienced 50% mortality in 120 h; survivors that were killed 2 weeks later showed lung damage and ulceration of the lingual mucous membrane. Plant residues were about 30 mg/kg fresh weight for alfalfa and 60 mg/kg for weeds; residues were negligible in tissues of the hare (Lavour et al. 1973). In a similar incident in Italy, Stracciari et al. (1980) found that only 1 of 56 hares found dead had lung damage, although all had elevated urine paraquat levels of 0.5 mg/L. It was concluded that paraquat alone was not the causative agent of death, and that paraquat interactions with other chemicals applied at the same time on other crops in the same area may have been responsible.

Paraquat applications to spruce plantations for grass control had no effect on the movement or density of field mice (*Microtus arvalis*) and voles (*Microtus agrestis*), but shrews (*Sorex* sp.) migrated from treated areas to untreated ones (Summers 1980).

Paraquat is poorly absorbed from the gut and readily excreted. Typical gut absorption rates (%) and peak concentrations in blood (mg/L) were 15-20% and 3- 4 mg/L in rats, 5- 10% and 1 mg/L in guinea pigs, 16% and 13 mg/L in cats, 0.26% in cows, and 1-5% in humans (Conning et al. 1969). Paraquat is actively secreted by a renal mechanism that is vulnerable to paraquat toxicity; poisoning of the secretory component removed a large part of the excretory capacity for paraquat (D. W. Webb 1983). In rats, a single oral LD50 dose produced a reduction in renal function within 24 h. This effect is probably secondary to a decrease in plasma volume with a consequent reduction in renal blood flow (Lock 1979). Paraquat caused mild renal tubular damage in rats; within 24 h of injection of 20 mg/kg BW, there was marked diuresis, sugar and albumin in the urine, and increased plasma urea concentrations (Lock and Ishmael 1979). Paraquat-poisoned mice showed a decreased ability to excrete organic acids and bases, probably reflecting interference with proximal tubule function because no change in glomerular filtration rate was observed (Ecker et al. 1975).

Paraquat was not mutagenic, as judged by noninterference with DNA metabolism, and had no reverse mutation-inducing capability (Anonymous 1988). Paraquat had little or no teratogenicity to mammals (Bus et al. 1975). No teratogenic effects were observed in rats fed diets containing paraquat concentrations of 400 mg/kg for 3 generations (Anonymous 1988). The most common malformations in paraquat-stressed rats were those involving costal cartilage (Bauer 1983). Recent studies demonstrated transplacental transfer of paraquat in pregnant rats and guinea pigs. High concentrations of radiolabeled paraquat were found in the placenta and throughout the fetuses within 30 min of intravenous administration; concentrations in placenta, maternal blood, and fetal blood were in the ratio of 16:4:1 (Ingebrigtsen et al. 1984), suggesting that additional research is needed on paraquat embryotoxicity.

Recommendations

Criteria have not yet been promulgated by regulatory agencies for the protection of sensitive species of fish and wildlife against paraquat.

Degradation rate of paraquat in certain soils can be slow, and the compound can persist for years-- reportedly in a form that is biologically unavailable. However, data are missing or incomplete on flux rates of paraquat from soil into food webs and on interaction dynamics of paraquat with other herbicides frequently applied at the same time. It seems prudent to keep close watch on the residues of paraquat in soils in situations where repeated applications have been made over long periods (Summers 1980).

Aquatic invertebrates, especially early developmental stages of crustaceans, are unusually sensitive to paraquat; adverse effects are documented in the range of 1.0- 100 µg/L (Table 6). For this reason, paraquat should be used with caution in estuarine and marshy areas (Summers 1980). Fish seem to be "safe" against aquatic weed control concentrations of < 1.0 mg paraquat per liter (Summers 1980), but aquatic plants tend to accumulate paraquat from the medium; accordingly, more research is needed on the effects of ingestion of contaminated plants and plant detritus by amphibians, reptiles, and other aquatic fauna (Dial and Dial 1987b).

Eggs of migratory waterfowl seem to be especially sensitive to paraquat at recommended application rates in an oil vehicle, but they were significantly more resistant to the same dose applied in water (Table 6). Application of paraquat in oil solution seems contraindicated in areas containing nesting waterfowl.

Among mammals, humans are among the most sensitive to paraquat, and permissible residues in our diet are low when compared to no-observed-effect levels in other warm-blooded species (Table 6). An air concentration of 0.4 mg/m³ may exceed a safe level for certain mammals, particularly if the size of the aerosol particle is submicroscopic and capable of penetrating the lung (Burleigh-Flayer and Alarie 1988). Accordingly, the present paraquat aerosol standard--set at 0.5 mg/m³--may have to be lowered. Misuse of paraquat has raised the question of cancellation of its registration, cancellation of its use in homes and recreational areas, or changing its packaging to prevent people from drinking it (Haley 1979). In almost all cases of fatal human poisonings, death was due to the ingestion of a concentrated (20%) solution. More dilute formulations (5 % paraquat) are usually not fatal if swallowed accidentally, suggesting that a dilute form of paraquat should be the only formulation permitted commercially (Kimbrough 1974).

Table 6. Proposed paraquat criteria for the protection of natural resources and human health.

Resource, proposed criterion, and other variables	Concentration	Reference ^a
Aquatic organisms		
Adverse effects level, in mg/L		
Algae and macrophytes		
Freshwater	0.25	1
Marine	5.0	2
Invertebrates		
Most species	0.1	3
Sensitive species	0.001	4
Vertebrates		
Most species	1.0	5, 6
Sensitive species	0.5	7, 8, 9
Birds		
Adverse effects level		
Egg surface, in mg/kg egg		
Oil solution	0.25	10
Aqueous solution	2.8	10
Oral administration, in mg/kg		
body weight (BW) daily	10	11, 12
Diet, in mg/kg ration	20	13, 14
Drinking water, in mg/L	40	15
Acute oral dose, in mg/kg BW	199	16
Mammals		

No-observable-effect level		
Livestock		
Forage (alfalfa, clover, pasture, range grasses), in mg/kg	5	17
Laboratory rodents		
Diet, in mg/kg ration		
Male	30	18
Female	100	18
Diet, in mg/kg BW daily		
Male	1.1–6.6	8
Female	4.3–7.1	18
Air, in ug/L		
Adverse effects level		
Blood, in mg/L		
Guinea pig	5	20
Rat	22	20
Cat	70	20
Lung, in ug directly into lung	6	17
Lung, in mg/kg BW	0.05	4, 21
Diet in mg/kg ration	85–100	22
Air, in ug/L, particle size 2.5–5u	0.4–6	17, 23
Drinking water, in mg/L	100	13
Acute oral dose, in mg/kg BW, sensitive species	25–35	4, 13, 15, 17, 18, 24, 25
Human health		
Permissible residues (in food items), in mg/kg fresh weight		
Eggs, milk, meat, meat byproducts of domestic animals	0.01	17
Most fruits and vegetables	0.05	17
Fresh hops	0.1	17
Passion fruit	0.2	17
Almond hulls, cotton seed, beans, hop vines, potatoes, sugar beets, sugarcane	0.5	17
Sunflower seeds	2.0	17
Aerosol standard, in mg/m ³	0.5	26
Acute poisoning level		
Blood, in mg/L	7.4	20

^aReferences: 1, Anonymous 1963; 2, Mayer 1987; 3, Brooker and Edwards 1974; 4, Summers 1980; 5, Earnest 1971; 6, Fytizas 1980; 7, Dial and Bauer 1984; 8, Dial and Dial 1987b; 9, Simon et al. 1983; 10, Hoffman and Eastin 1982; 11, Hoffman et al. 1985; 12, Hoffman et al. 1987; 13, Bauer 1983; 14, Bauer 1985; 15, Fletcher 1967; 16, Hudson et al. 1984; 17, Haley 1979; 18, Anonymous 1988; 19, Kimbrough 1974; 20, Seto and Shinohara 1988; 21, Kimbrough and Gaines 1970; 22, Anonymous 1974; 23, Conning et al. 1969; 24, Murray and Gibson 1972; 25, Heitkamp and Brown 1982; 26, Burleigh-Flayer and Alarie 1988.

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