Environmental Health Criteria 39

PARAQUAT AND DIQUAT

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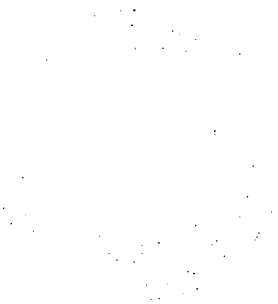

World Health Organization
Geneva, 1984

The **International Programme on Chemical Safety (IPCS)** is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

While every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication, mistakes might have occurred and are likely to occur in the future. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors found to the Manager of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

In addition, experts in any particular field dealt with in the criteria documents are kindly requested to make available to the WHO Secretariat any important published information that may have inadvertently been omitted and which may change the evaluation of health risks from exposure to the environmental agent under examination, so that the information may be considered in the event of updating and re-evaluation of the conclusions contained in the criteria documents.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Palais des Nations, 1211 Geneva 10, Switzerland (Telephone no. 988400 - 985850).

ENVIRONMENTAL HEALTH CRITERIA FOR PARAQUAT AND DIQUAT

Following the recommendations of the United Nations Conference on the Human Environment held in Stockholm in 1972, and in response to a number of World Health Resolutions (WHA23.60, WHA24.47, WHA25.58, WHA26.68), and the recommendation of the Governing Council of the United Nations Environment Programme, (UNEP/GC/10, 3 July 1973), a programme on the integrated assessment of the health effects of environmental pollution was initiated in 1973. The programme, known as the WHO Environmental Health Criteria Programme, has been implemented with the support of the Environment Fund of the United Nations Environment Programme. In 1980, the Environmental Health Criteria Programme was incorporated into the International Programme on Chemical Safety (IPCS). The result of the Environmental Health Criteria Programme is a series of criteria documents.

A WHO Task Group on Environmental Health Criteria for Paraquat and Diquat was held in Geneva from 5 - 10 December 1983. Dr M. Mercier opened the meeting on behalf of the Director-General. The Task Group reviewed and revised the draft criteria document and made an evaluation of the health risks of exposure to paraquat and diquat.

The draft documents were prepared by Dr A. Bainova of Bulgaria.

The efforts of all who helped in the preparation and finalization of the document are gratefully acknowledged.

* * *

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PARAQUAT

1. SUMMARY AND RECOMMENDATIONS

1.1 Summary

1.1.1 General properties

Paraquat (1,1'dimethyl, 4,4' bipyridyl) is a non selective contact herbicide. It is produced in several countries including China, Province of Taiwan, Italy, Japan, the United Kingdom, and the USA, and it is used world-wide in approximately 130 countries. If not manufactured under strictly controlled conditions, it can contain impurities that are more toxic than the parent compound. It is almost exclusively used as a dichloride salt and is usually formulated to contain surfactant wetters.

Both its herbicidal and toxicological properties are dependent on the ability of the parent cation to undergo a single electron addition to form a free radical which reacts with molecular oxygen to reform the cation and concomitantly produce a superoxide anion. This oxygen radical may directly or indirectly cause cell death.

Paraquat can be detected because of its ability to form a radical. Numerous analytical procedures are available.

1.1.2 Environmental distribution and transformation - environmental effects

Paraquat deposits on plant surfaces undergo photochemical degradation to compounds that have a lower order of toxicity than the parent compound.

On reaching the soil, paraquat becomes rapidly and strongly adsorbed to the clay minerals present. This process inactivates the herbicidal activity of the compound. While free paraquat is degraded by a range of soil microorganisms, degradation of strongly-adsorbed paraquat is relatively slow. In long-term field studies, degradation rates were 5 - 10% per year. Strongly-bound paraquat has no adverse effects on soil microfauna or soil microbial processes.

Paraquat residues disappear rapidly from water by adsorption on aquatic weeds and by strong adsorption to the bottom mud. The toxicity of paraquat for fish is low, and the compound is not cumulative. Normal applications of paraquat for aquatic weed control are not harmful to aquatic organisms. However, care should be taken when applying paraquat to water containing heavy weed growth to treat only a

part of the growth, since oxygen consumed by subsequent weed decay may decrease dissolved oxygen levels to an extent that may be dangerous for fish. Treated water should not be used for overhead irrigation for 10 days following treatment.

Paraquat is not volatile and following spraying the concentrations of airborne paraquat have been shown to be very low. Under normal working conditions, the exposure of workers in spraying and harvesting operations remains far below present TLVs and the exposure of passers-by or of persons living downwind of such operations is lower still.

Normal paraquat usage has been shown not to have any harmful effects on birds.

Finite paraquat residues are to be expected only when a crop is sprayed directly. Cattle allowed to graze on pasture 4 h after spraying at normal application rates did not suffer any toxic effects. Consequent residues in products of animal origin are very low.

1.1.3 Kinetics and metabolism

Although toxic amounts of paraquat may be absorbed after oral ingestion, the greater part of the ingested paraquat is eliminated unchanged in the faeces. Paraquat can also be absorbed through the skin, particularly if it is damaged. The mechanisms of the toxic effects of paraquat are largely the result of a metabolically catalyzed single-electron reduction-oxidation reaction, resulting in depletion of cellular NADPH and the generation of potentially toxic forms of oxygen such as the superoxide radical.

Absorbed paraquat is distributed via the bloodstream to practically all organs and tissues of the body, but no prolonged storage takes place in any tissue. The lung selectively accumulates paraquat from the plasma by an energy-dependent process. Consequently, this organ contains higher concentrations than other tissues. Since the removal of absorbed paraquat occurs mainly via the kidneys, an early onset of renal failure following uptake of toxic doses will have a marked effect on paraquat elimination and distribution and on its accumulation in the lung.

1.1.4 Effects on experimental animals

A characteristic dose-related lung injury can be induced in the rat, mouse, dog and monkey, but not in the rabbit, guinea-pig and hamster. The pulmonary toxicity is characterized by initial development of pulmonary oedema and damage to the alveolar epithelium, which may progress to fibrosis. Exposure to high doses of paraquat may also cause less severe toxicity to other organs, primarily the liver and

kidney. Minor toxic effects have been noted only at high doses in the nervous, cardiovascular, blood, adrenal and male reproductive systems.

Paraquat has not been found to be teratogenic or carcinogenic in long-term studies on rats and mice. In vitro mutagenicity studies have been inconclusive although generally suggestive of weak potential activity, while in vivo studies were negative.

1.1.5 Effects on man

Occupational exposure to paraquat does not pose a health risk if the recommendations for use are followed and there is adherence to safe working practices. This has been shown in several studies evaluating the potential risk either short- or long-term. However, nail damage, epistaxis, and delayed skin damage have been described and may generally be taken as an indication that work practices should be reviewed.

In the small number of reported cases of paraquat poisoning allegedly resulting from occupational exposure, the cause can be identified as one or a combination of a number of factors, viz contamination of the skin with concentrated products, use of inadequately diluted solutions, use of faulty equipment, misuse of equipment (e.g., blowing blocked spray jets) or failure to take action in the event of contamination of skin or clothing. Eye and skin damage can follow splashes with the concentrate.

A large number of cases of suicidal or accidental poisoning from paraquat has been reported. With the exception of a few unusual cases in which the liquid concentrate was improperly used to treat body lice, poisoning has followed its ingestion or, in a few cases, ingestion of the granular formulation.

Two types of fatal poisoning can be distinguished: acute fulminant poisoning leading to death within a few days, and a more protracted form that may last for several weeks, resulting in fatal pulmonary fibrosis. Depending on the severity of the poisoning, there may be involvement of kidneys, liver, and other organs. Extensive damage to the oropharynx and the oesophagus are usually seen in cases of ingestion of liquid concentrate.

After ingestion, speed is imperative in commencing emergency treatment and it should be noted that this can take place before arrival of the patient at hospital.

The response to treatment of paraquat poisoning is very disappointing and the mortality rate remains high. In less severe cases, without lung damage, recovery has always been complete.

The possibility of recovery clearly depends on the dose of paraquat taken and the time interval between ingestion and the commencement of emergency treatment.

1.2 Recommendations

1.2.1 General

Where practical and reasonable, the availability and use of the 20% liquid product should be limited to bona fide agriculturalists, horticulturalists, and professional users who work with trained personnel, properly maintained equipment, and adequate supervision.

Every effort should be made to prevent the practice of decanting or rebottling of the product into improperly labelled containers.

Further research should be carried out in order to achieve a safer commercial product and a reduced incidence of fatalities.

National Registers of cases of poisoning should be maintained for all classes of chemicals - including paraquat. The information so obtained should be made available to International bodies such as WHO.

1.2.2 Prevention and treatment

Attention should be drawn to the fact that persons with skin lesions (either pre-existing or following contamination with paraquat) should not be permitted to take any part in spraying procedures until the skin condition has resolved.

It must be stressed that treatment of persons with paraquat poisoning should be instituted as early as possible. The likelihood of recovery from a fatal dose is greatest when therapy begins within 5 - 6 h of poisoning.

1.2.3 Experimental work

Further research should be undertaken on the mechanism of retention of paraquat in, amongst others, the lung and also on the concomitant damage caused at the molecular level.

Information was presented to the Task Group showing that saturation of the cation exchange capacity of soils is not observed under field conditions. This indicates that residual phytotoxicity from directly available paraquat is unlikely. It is recommended that such information be published.

Existing mutagenicity and carcinogenicity studies, although generally suggesting that paraquat is unlikely to produce genotoxic effects in man, require more detailed information.

The group has been informed that new long-term toxicity and carcinogenicity assays have been completed recently and recommends that the results be made available in the public literature.

2. IDENTITY, PROPERTIES AND ANALYTICAL METHODS

2.1 Identity

Paraquat is a non-selective contact bipyridylium herbicide. The term has been applied to 2 technical products: 1,1'-dimethyl-4,4'-bipyridylium dichloride ($C_{12}H_{14}N_2Cl_2$) or 1,1'-dimethyl-4,4'-bipyridylium dimethylsulfate ($C_{12}H_{14}N_2[CH_3SO_4]_2$).

2.2 Physical and Chemical Properties

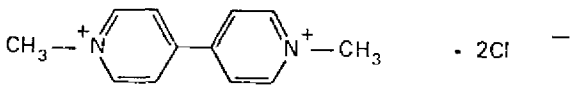
Pure paraquat salts are white and the technical products yellow. They are crystalline, odourless, hygroscopic powders with a relative molecular mass of 257.2 for paraquat dichloride and 408.5 for paraquat dimethylsulfate. The relative molecular mass of the paraquat ion is 186.2 (Summers, 1980). Some of the other physical properties of paraquat dichloride, the salt most used for herbicide formulations, are listed in Table 1.

Table 1. Physical properties of paraquat[a]

Specific gravity at 20 °C	1.240 - 1.260
Melting point	175 - 180 °C
Boiling point	approximately 300 °C with decomposition
Solubility in water at 20 °C	700 g/litre
pH of liquid formulation	6.5 - 7.5
Vapour pressure	not measurable

[a] From: Worthing (1979).

Paraquat is slightly soluble in alcohol and practically insoluble in organic solvents (Haley, 1979). The chemical structure of paraquat (1,1'-dimethyl-4,4'-bipyridylium dichloride) is:



Paraquat is non-explosive and non-flammable in aqueous formulations. It is corrosive to metals and incompatible with alkylarylsulfonate wetting agents. It is stable in acid or neutral solutions but is readily hydrolysed by alkali.

Paraquat readily undergoes a single-electron reduction to the cation radical. The redox potential for this reaction is 446 mv. This chemical property led to its use as a redox indicator dye (methyl viologen) as early as 1933 (Summers, 1980).

2.3 Analytical Methods

The analytical methods for paraquat determination have been reviewed by Haley (1979) and Summers (1980). Current procedures in common use are listed in Table 2. Spectrophotometric determinations involve the reaction of paraquat with 1% aqueous sodium dithionite in 0.1 N sodium hydroxide. The absorbance of the resulting blue cation measured at 600 nm can be used as a measure of the paraquat concentration. Diquat does not interfere because its radical cation is green in colour. For residue level determinations (e.g., sub mg/kg levels) the higher intensity absorption at 396 nm for the paraquat radical and the 379 nm for the diquat radical are more commonly used. Calderbank & Yuen (1965) developed a column chromatographic spectrophotometric method that was successfully applied for soil, biological tissues, and food. The sensitivity was 0.01 mg/kg. Gas chromatographic and high-pressure liquid chromatographic analyses were used satisfactorily. High-pressure liquid chromatography with ultraviolet detection was proposed by Pryde & Darby (1975) for determining the paraquat content of urine with a sensitivity of 100 µg/litre.

A comparison of thin-layer chromatography with the spectrophotometric methods for determining paraquat in human tissues showed that the former method gave less favourable results, because of the presence of large amounts of interfering substances from the tissues (Tsunenari et al., 1975; Haley, 1979). Spectrophotometric determination of paraquat, after alkaline reduction with sodium dithionite, has been published (Leary, 1978) for soil, and plant and biological tissues, the sensitivity limit being 0.01 mg/kg when a 50 g sample was used.

In a comparison of colorimetric, gas-liquid chromatographic techniques and radioimmunoassay (Levitt, 1979; Stewart et al., 1979), it was shown that the latter was a rapid method with satisfactory sensitivity for determining paraquat in serum, urine, and organ tissues from poisoned patients. The variation in detection limits in paraquat determinations in soil, water, and plant and animal material

Table 2. Analytical methods for paraquat

Matrix	Analytical procedure	Detection limits[a]	Reference
Soil	spectrophotometry	0.01 mg/kg	Calderbank & Yuen (1965)
	spectrophotometry	-	Leary (1978)
	spectrophotometry	0.5 mg/kg	Pope & Benner (1974)
	gas chromatography	0.01 mg/kg	Khan (1974)
	gas chromatography	0.01 mg/kg	Payne et al. (1974)
Water	spectrophotometry	0.01 mg/litre	Calderbank & Yuen (1965)
	gas chromatography	0.01 mg/litre	Soderquist & Crosby (1972)
	gas chromatography	0.01 mg/litre	Khan (1974)
	gas chromatography	0.01 mg/litre	Payne et al. (1974)
	gas chromatography	10 mg/litre	Ukai et al. (1977)
	spectrophotometry	-	Pope & Benner (1974)
Air	spectrophotometry	0.01 mg/m^3	Calderbank & Yuen (1965)
	gas chromatography	0.5 ng/m^3	Seiber & Woodrow (1981)
Biological tissues	spectrophotometry	0.01 µg/ml	Calderbank & Yuen (1965)
	spectrophotometry	0.01 µg/ml	Berry & Grove (1971)
	spectrophotometry	0.01 µg/ml	Beyer (1970)
	gas chromatography	0.03 µg/ml	van Dijk et al. (1977)
	gas chromatography/mass spectrophotometry	0.025 µg/ml	Draffon et al. (1977)
	radioimmuno assay	0.12 µg/ml	Levitt (1979)
	radioimmuno assay	0.10 µg/ml	Proudfoot et al. (1979)
Plants	spectrophotometry	0.01 mg/kg	Calderbank & Yuen (1965)
	spectrophotometry	0.01 - 1 mg/kg	Dickes (1979)
	gas chromatography	0.01 - 1 mg/kg	Paschal et al. (1979)
	gas chromatography	-	Harrington (1979)

[a] The figures refer to the detection limits in the assay solutions.

is related to the size of the sample obtained, its purity, and the extraction of the paraquat ion from the material tested.

(a) Soil

Analytical methods include spectrophotometry (Calderbank & Yuen, 1965; Leary, 1978) and gas chromatography (Khan, 1974; Payne et al., 1974).

(b) Water

The concentration of paraquat in water has been determined by treating the lesser duckweed (Lemna minor) with the test sample and comparing the time taken to produce chlorosis with known concentrations. This procedure has been used to determine herbicide residues in ponds and streams with a sensitivity of 0.075 mg/litre. Determination of chlorosis in Phaseolus vulgaris or Lemna polyrhiza was classified as more sensitive than the chemical analyses (Haley, 1979).

A change in cell-membrane permeability, as indicated by the leakage of electrolytes from treated fronds of Lemna minor, was used by O'Brien & Prendeville (1978) to detect paraquat in water. The minimum detectable concentrations ranged from 1.8 - 1.7 µg of paraquat cation/ml, after 3 h of treatment, to 180 and 17 ng/ml after 72 h of exposure to light.

Ukai et al. (1977) found a gas chromatographic method suitable for paraquat determination with a sensitivity of 10 - 90 µg/ml water, using 4-anisidine as the internal standard. Pope & Benner (1974) have also used a spectrophotometric method.

(c) Air-working environment

Sprayed or dusted, paraquat is absorbed on filter/sorbent systems. The absorbed paraquat is dissolved and determined spectrophotometrically using one of the classical methods (Calderbank & Yuen, 1965; Staiff et al., 1975; Anderson et al., 1981). Carlstrom (1971) applied a colorimetric method for analysing paraquat formulations. Seiber & Woodrow (1981) developed a nitrogen-selective gas chromatographic method for paraquat determination in airborne particulate matter.

(d) Plants

The method of Calderbank & Yuen (1965) is considered to be the best procedure for determining paraquat in crops, treated plants, and food. The limit of the spectrophotometric analysis ranged from 0.01 - 0.1 mg/kg, depending on the crop. A gas chromatographic method for paraquat residues in food was

suggested by Dickes (1979). A procedure based on gas-liquid chromatography (Paschal et al., 1979) provided linear working curves over a paraquat concentration range of 0 - 20 µg/g, determined by extraction from 1 g samples of sunflower seeds. The method has been proposed for herbicide analyses in plant materials. A vapour-phase chromatographic technique, used for determining paraquat in wood (Harrington, 1979), is based on the liberation of methyl chloride after pyrolysis.

(e) Biological material

A spectrophotometric method, applied for determining paraquat residues in milk (ICI, 1972), had a detection limit of 0.01 mg/litre sample. Analyses of the plasma (serum) and urine of subjects poisoned by paraquat are important for diagnosis and prognosis. Tompsett (1970) described a method for analysing biological samples from patients suffering from accidental oral intoxication. Paraquat extracted from human blood, urine, and faeces was separated on a strong acid cation-exchange resin (Beyer, 1970), reacted with sodium dithionite, and determined spectrophotometrically at 391 nm. The method had a sensitivity of 0.01 µg ion/ml in a 250 ml aliquot of urine. A similar procedure, published by Pickova (1978), for estimating paraquat levels in the urine of patients had a sensitivity of 30 µg in a sample of 50 - 500 ml. Gas chromatographic methods were successfully used (Dijk, van et al., 1977; Draffon et al., 1977).

A radioimmunoassay using ^{3}H-labelled paraquat was found to be a sensitive method for analysing plasma, urine, and biological tissues (ICI, 1979). Antibodies to paraquat were prepared in rabbits and tested for sensitivity by a charcoal separation technique (Levitt, 1979). The results showed that the antibodies were specific for the herbicide. A comparison of radioimmunoassay and gas liquid chromatographic techniques (Levitt, 1979; Proudfoot et al., 1979) showed the high sensitivity of this method. The total assay time was no more than 30 min. A series of 50 serum specimens from persons poisoned with paraquat were tested by radioimmunoassay and colorimetric analysis (Stewart et al., 1979); the results from both methods corresponded closely.

Tsunenari et al. (1975) used 7 analytical methods for determining paraquat with a view to diagnosing accidental, suicidal, or homicidal poisoning. Colorimetry, with dithionite thin-layer chromatography, was used for the qualitative assay of paraquat in biological tissues, while ion-exchange resin column chromatography, with colorimetry or gas chromatography, was used for the quantitative assay. Tsunenari et al. (1981) also studied the influence of putrefaction on paraquat determinations in autopsy materials.

Detection was possible, even in tissues in advanced stages of decomposition.

3. SOURCES IN THE ENVIRONMENT

3.1 Introduction

3.1.1 Industrial technology

Paraquat does not occur naturally. It was originally synthesized by Weidel & Russo as reported in 1882 (Summers, 1980). Its herbicidal properties were discovered only in 1955. The compound is produced by coupling pyridine in the presence of sodium in anhydrous ammonia and quaternizing the 4,4'-bipyridyl with methyl chloride (Fig. 1).

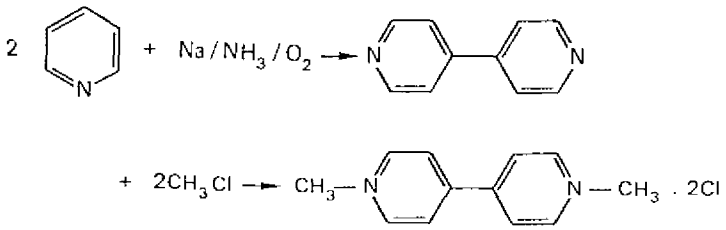


Fig. 1. Synthesis of paraquat (Calderbank & Slade, 1976).

When bipyridyl is refluxed with methyl iodide, the iodide salt is obtained. Haley (1979) and Summers (1980) thoroughly reviewed the published methods for paraquat synthesis, and for the separation and purification of bipyridylium salts. The yields obtainable vary from 20% to 96% of pure product.

The first commercial paraquat formulation approved for agricultural use was Gramoxone®.

3.1.2 Impurities

Aqueous solutions of paraquat used as herbicides must correspond to the FAO Specification Code 56/13/S/6 (FAO, 1973). This requires a description of the active ingredient in the formulation, of the impurities, of the physical and chemical properties, and of the methods for determining the components. The only impurity permitted in paraquat is free 4,4'-bipyridyl at a maximum level of 0.25% of the paraquat content.

3.2 Production and Use

Paraquat is produced in several countries, including China, Province of Taiwan, Italy, the United Kingdom, and the USA. Formulations of the active ingredients (mainly paraquat dichloride) are used in more than 130 countries world-wide. Paraquat dimethylphosphate is used in the USSR. Since its introduction for agricultural use in 1962, paraquat has been widely used for weed control and as a dessicant. In many countries, paraquat is formulated locally, only the technical active ingredient being imported. Records of world production of paraquat are not available.

Technical paraquat dichloride has been formulated in liquid concentrates or granules. Water-soluble granules containing paraquat (25 g/kg) and diquat (25 g/kg) are used for weed control in private gardens. Paraquat is sold under a variety of trade names which are summarized in Table 3.

Gramoxone® is a dark aqueous solution containing a paraquat dichloride concentration of 200 ± 10 g/litre. Its specific gravity at 20 °C is 1.1 and the crystallization point is -5 °C to 10 °C. It is not flammable and, in its original polyethylene containers, is stable for a long time under normal atmospheric conditions. The formulation is incompatible with anionic surface active agents and decomposes in ultraviolet radiation. Gramoxone® rapidly corrodes aluminium; zinc, iron, and tinplate are more resistant.

Paraquat is a total contact herbicide used to control broad-leaved and grassy weeds. It should be sprayed when the weeds are young and less than 30 cm high. It kills all green tissues, but does not harm the mature bark. Paraquat is used for plantation crops (banana, cocoa-palm, coffee, oil-palm, rubber, etc.) and for citrus fruits, apples, plums, vines, and tea. On certain crops (potato, pineapple, sugar-cane, sunflower), it is used as a dessicant; it is also used as a cotton defoliant. It is applied around the trees in orchards and between the rows of crops.

Uncropped land on industrial sites, railways, roadsides, etc. can be cleared of weeds by applying paraquat at higher concentrations.

Gramoxone S® is largely applied for aquatic weed control.

Application rates usually range from 250 g - 1500 g/ha (1.1 - 7.1 litre of Gramoxone®), but, for grass and stubble clearing, up to 2200 g of the herbicide are used per ha. The working dilutions vary from 1 - 5g per litre paraquat in water. It is applied by ground sprayers (not mist-blowers) in 200 - 500 litres solution/ha.

Table 3. Paraquat trade names[a]

Products	Countries	Paraquat content (W/V for liquids, W/W for solids)
Dextrone X	United Kingdom	20%
Dexuron	United Kingdom	10%, also contains diuron
Duanti	Germany, Federal Republic of	2.5%, also contains diquat
Dukatalon	Israel	9%, also contains diquat
Esgram	United Kingdom	20%
Frankol Prompt	Germany, Federal Republic of	10%, also contains diuron
Gramazin	Italy	10%, also contains simazine
Gramixel	Germany, Federal Republic of	10%, also contains diruon
Gramanol	United Kingdom, Ireland, Belgium, Greece, Middle East	14%, also contains monolinuron
Gramoxone	worldwide	20%
Gramoxone S	worldwide	20%
Gramoxone W	discontinued	20%
Gramoxone ZU	The Netherlands, Belgium	20%
Gramuron	Africa, Italy	10%, also contains diuron
Katalon	Israel	20%

Table 3 (contd).

Ortho Paraquat CL	USA	24.6% (2 lb/US gal)
Ortho Spot Weed & Grass Killer	USA	0.2% (Solid Stream Aerosol)
Orvar	United Kingdom	5%
Paracol	Malaysia, Indonesia, Philippines Chile, Peru	10%, also contains diquat
Paradi	Australia	10%, also contains diquat
Pathclear	United Kingdom, New Zealand	2.5%, also contains diquat, 3 aminotriazole and simazine
Preeglone	Denmark, Norway	2.5%, also contains diquat
Preeglone	Belgium, France, Spain	12%, also contains diquat
Preeglone Extra	New Zealand	9%, also contains diquat
Priglone	France, Switzerland	12%, also contains diquat
Seythe	United Kingdom	20%
Spray Seed	Australia	10%, also contains diquat
Terraklene	United Kingdom, Ireland, Denmark, France, Switzerland	10%, also contains simazine
Tota-Col	Wide range of countries	10%, also contains diuron
Tryquat	Australia	10%, also contains diquat
Weedol	The Netherlands, Ireland, United Kingdom	2.5%, also contains diquat
Weedrite	Canada	2.5%
Weedrite Aerosol	Canada	0.44%

[a] From: Fletcher (1975).

3.3 Mechanism of the Herbicidal Effect

The herbicidal activity of paraquat is dependent on the parent molecule undergoing a single-electron redox cycling reaction. Paraquat is reduced to the paraquat radical, which, in the presence of molecular oxygen, is immediately reoxidized forming the parent molecule and superoxide radicals (O_2^-) (Conning et al., 1969). As early as 1960, Mees had shown that oxygen was necessary for the herbicidal activity of paraquat, suggesting the importance of the redox cycling and O_2^- formation in mediating toxicity. Paraquat was not toxic to plant leaves incubated under anaerobic conditions, despite the continuation of photosynthetic reactions capable of forming paraquat radicals. Exposure of the anaerobic incubates to air, however, resulted in immediate onset of toxicity. Dodge (1971) subsequently confirmed that isolated plant chloroplasts could form the paraquat radical under anaerobic conditions. The possibility that O_2^- generation may be an essential component of the herbicidal activity was further supported in a study by Youngman & Dodge (1979). These investigators observed that the phytotoxicity of paraquat in plant cotyledons was decreased by a copper chelate of D-penicillamine. The chelate possessed activity similar to the enzyme superoxide dismutase (EC 1.15.1.1) (Lengfelder & Elstner, 1978), an enzyme that detoxifies O_2^- (McCord & Fridovich, 1969).

The generation of O_2^- may lead to many potentially cytotoxic reactions, including the membrane-damaging process of lipid peroxidation (Bus & Gibson, 1979). When plant leaves were incubated with paraquat, there was rapid stimulation of the formation of malondialdehyde, which is an indicator of lipid peroxidation (Dodge, 1971).

4. ENVIRONMENTAL DISTRIBUTION AND TRANSPORTATION

4.1 Photochemical Degradation

4.1.1 Photochemical degradation on plant surfaces

In agricultural practice, much of the paraquat sprayed is initially deposited on plant surfaces. Slade (1965, 1966) applied paraquat dichloride droplets to maize, tomato, and broad-bean plants. Determinations carried out at intervals of 100 days showed that degradation was caused by photochemical decomposition on the leaf surfaces but not by metabolism. Degradation products isolated from plants sprayed with ^{14}C-paraquat dichloride included 4-carboxyl-1-methyl-^{14}C-pyridylium chloride and methylamine-^{14}C-hydrochloride. No $^{14}CO_2$ was detected as a photochemical decomposition product. The photochemical degradation of paraquat dichloride continued after the plants were dead (Fig. 2). Paraquat photodegradation products were not translocated from the dessicated leaves of the plants, nor were they found in the crops (cereals and fruits), when weeds were treated with paraquat during 3 - 4 successive seasons (Calderbank, 1966).

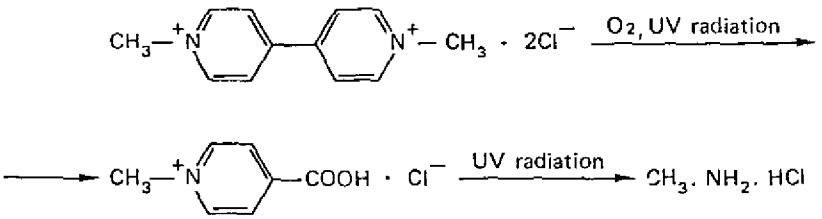


Fig. 2. Photochemical paraquat dichloride degradation (Slade, 1965).

The rate of decomposition was related to the intensity of UV radiation between 285 and 310 mμ present in daylight. In strong sunlight, about 2/3 of the applied herbicide decomposed within a 3-week period. Vegetation directly sprayed with paraquat (1.12 kg/ha) was analysed at intervals up to 4 months. The residues varied from 5 - 200 mg/kg. The 4-carboxyl-1-methylpyridynium chloride ranged from 0.02 - 5 mg/kg (about 7% of the paraquat residues determined on dry leaves). The toxicity of 4-carboxyl-1-methylpyridylium for mammals was low, the acute oral LD_{50} in rats being more than 5000 mg/kg body weight (FAO/WHO, 1971).

The degradation product from the photochemical destruction of paraquat dimethylsulfate was N methyl-isonicotinic acid methylsulfate (Fig. 3).

A 90-day feeding test (Broadhurst et al., 1966) on rats revealed that levels of 20 000 - 5000 mg/kg of the N-methyl-isonicotinic acid methylsulfate were not toxic.

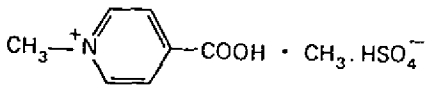


Fig. 3. N-methyl isonicotinic acid methylsulfate (FAO/WHO, 1971).

4.1.2 Photochemical degradation of paraquat on soil and other mineral surfaces

Slade (1966) showed that there was a breakdown, similar to that on plant surfaces, if spots of paraquat on silica gel were exposed to direct sunlight. When ^{14}C-paraquat dichloride was sprayed on the bare soil surface of a field during a hot sunny period, traces of 4-carboxy-1-methylpyridynium chloride were detected in the top inch of soil for the first few weeks afterwards (Calderbank & Slade, 1976). Radioassay showed that the total soil residue did not markedly decrease during a 6 - 18 month period, so that, in agricultural practice, UV degradation of herbicide reaching the soil should be regarded as insignificant.

The principal intermediates of photochemical paraquat degradation on plants or soil surfaces are of low toxicity. They decompose easily and are not expected to produce adverse environmental effects.

4.2 Microbial Degradation

Microbial paraquat degradation has been thoroughly reviewed by Haley (1979). Baldwin et al. (1966) identified many soil microorganisms capable of degrading paraquat. The herbicide was decomposed by Corynebacterium fascians, Clostridium pasteurianum, and Lipomyces starkeyi. Several other microorganisms were found to degrade paraquat (Smith et al., 1976; Tchipilska, 1980) but Lipomyces starkeyi proved to be the most active (Burns & Audus, 1970). Burns & Audus (1970) concluded that microbiological degradation was possible only for a short time following the application of paraquat to soil. Once adsorbed on to clay materials, the paraquat was inaccessible to microorganisms. Microbial degradation of paraquat in the field is therefore relatively slow.

Studies of 4-carboxyl-1-methylpyridilium chloride in soil have demonstrated that the radiolabelled product readily decomposes to form several chemical substances, including carbon dioxide. No significant residues of the compound have been determined in plants as a result of uptake from the soil. Wright & Cain (1970) isolated Achromobacter D from the soil; this utilized the 4-carboxyl-1-methylpyridylium chloride and the methylamine originating from the N-methyl group of the molecule. The NADH and the oxygen requirement indicated the possibility of direct oxidative fission of a partly reduced ring to form dialdehyde, which was then hydrolysed to formate, methylamine, and succinic dialdehyde. The end-products of the microbial ring degradation were formate, succinate, and carbon dioxide.

4.3 Environmental Adsorption and Transformation

4.3.1 Soil

The property of paraquat that is most important in nullifying its impact on the environment is its rapid and complete binding to clay soils. Desorption of the herbicide from soil particles, for the purpose of chemical analysis, requires destruction of the mineral particles by refluxing with strong sulfuric acid. The strong adsorption to clay has been attributed to the flat and highly polarizable nature of the paraquat ion (Coats et al., 1966; Knight & Denny, 1970). Weber et al. (1965) reported that the adsorption appeared to be one of ion exchange and was very rapid, the rate of adsorption depending on the rate at which the paraquat ion contacted the adsorbing particles.

In highly organic soils, the weaker adsorption sites of soil organic matter delay the redistribution of paraquat without inactivating it herbicidally. In this connection, Khan (1980) reported tests showing a remarkable affinity of humic substances in the soil for the paraquat ion. These humic substances enhance the degradation of pesticides via non-biological pathways.

It has been demonstrated that on soil containing 98% organic matter, the herbicidal effects of 1.12 and 2.24 kg of paraquat/ha persisted for 16 - 29 days, but such soils are not widespread naturally. Burns & Audus (1970) studied the migration of paraquat from soil organic matter to clay mineral particles. The transfer of the paraquat from the organic to the inorganic fraction, through a membrane, was 90% complete within 6 h. The remaining 10% took about 2 days to be transferred. No paraquat was detected in the organic fraction after 4 days. At high paraquat concentrations (more than 20 mg/kg in equilibrium solution), the total adsorption

capacity was greater than normal in soils with high organic content, as opposed to those with low organic content.

Mithyanta & Perur (1975) studied samples of 4 different soils treated with paraquat in different experimental schemes. After 24 h, the soils were extracted with a water solution of ammonium chloride. The percentages of paraquat, extractable with water, ranged from 4.8 - 66.9%, depending on the type of soil and the conditions. Data on the persistence of paraquat in the soil have also been compiled by Coats et al. (1966), Knight & Tomlinson (1967), Knight & Denny (1970), and Burns & Audus (1970).

As summarised in section 4.2, free paraquat is degraded by a range of microorganisms, but degradation of strongly adsorbed paraquat is relatively slow. In plot studies, degradation was very slow or non-detectable (Riley et al. 1976). However, in long-term field studies, degradation rates were 5 - 10% per year. This is greater than the rate required to prevent saturation of the deactivation capacity of soils.

In a long-term trial on a loamy soil, plots were treated with 0, 90, 198, and 720 kg paraquat/ha, which was incorporated to a depth of 15 cm. These rates were equivalent to 0, 50, 110, 400% of the soils strong absorption capacity (Gowman et al., 1980; Wilkinson, 1980; Riley, 1981). Over the 7 years, paraquat residues declined by 5% per year (sig $\underline{P}$ = 0.05) on the 90 kg/ha plots and by 7% per year (sig $\underline{P}$ = 0.01 on the 198 and 720 kg/ha plots. The rate of decline on the 198 and 720 kg/ha plots was significantly greater ($\underline{P}$ = 0.01) than on the 90 kg/ha plots.

In another long-term trial on a sandy loam, plots were treated annually with 4.4 kg/ha for 12 years (Hance et al, 1980). The rate of loss of paraquat soil residues was about 10% per year and the soil residues tended to plateau when the rate of application equalled the rate of degradation. Data for the last 4 years (total 16 years) has confirmed the early results (Hance, unpublished data).

Some paraquat could be recovered from its tightly bound form by chemical destruction of the soil from field plots, several years after application. The limit of paraquat adsorption, at which further treatment would result in phytotoxic activity, was considered to be important. Strong adsorption capacity was defined as the measure of paraquat that can be adsorbed by the soil without entailing phytotoxic effects, and this capacity was determined in several kinds of soil with various clay and organic contents (Knight & Tomlinson, 1967). Mechanical analyses, pH, and organic matter content were also determined. Independently of the soils studied, it was found that, by applying 1 kg/ha per year, it would take from 30 - 1440 years to saturate the top 15 cm of soil at strong adsorption sites. The conditions of study

precluded any form of paraquat degradation or metabolism in the soil. Riley et al. (1976) reviewed the hazard of continuous application of 0.1 - 2 kg paraquat ion/ha, assuming soil contamination by 10 - 100% of the amount applied. Bound paraquat soil residues were not adsorbed by living organisms. Paraquat residues did not induce any effects on microarthropods or microorganisms. Continued application of the herbicide in different soils has been investigated by Pestemer et al. (1979). The ED_{50} values[a] for phytotoxic action on lettuce ranged from 0.01 mg/litre paraquat solution in agar-agar to 98 - 1930 mg/litre in different soils, depending on their constituents, and 31 - 57.6 mg paraquat residues/kg have been determined in the soil samples. There is evidence (Hance et al., 1980) that strongly-bound paraquat residues were degraded in soil by microbial activity at a rate of 5 - 10% per annum. A correlation was reported between the paraquat residues, the number of treatments, doses, and depth of soil sampling.

Although, as mentioned, adsorption on clay is important, extremely sandy soils can adsorb and inactivate significant quantities of the herbicide, as illustrated by studies on a South African vineyard soil that contained only 1% clay (Riley et al., 1976). Over an 8-year period, more than 20 applications (total 15.6 kg paraquat/ha) resulted in saturation of about 20% of the soil-paraquat-strong-adsorption capacity in the top 2.5 cm. The paraquat residues were not phytotoxic in the field or in greenhouse tests on different plants. No paraquat residues were detected (<0.05, <0.03, <0.03 mg/kg) in leaves, grapes, and twigs, respectively.

Very low concentrations of free paraquat would be detected easily by their phytotoxicity. Five trials at 4 sites were conducted by Newman & Wilkinson (1971). In 4 of the trials, single applications of paraquat at 112 kg/ha were made at sites subjected to normal agricultural practice. At this unrealistic, extremely high rate, short-duration residual phytotoxicity was observed. On undisturbed plots of mineral soils, seedlings did not appear for several months; on organic soils, the time lag was even longer. After cultivation, there was no further indication of phytotoxicity. In the 5th trial, a total of 565 kg/ha was applied in 5 doses over 4 1/2 years. The plot then remained undisturbed, apart from periodic cultivation of the top 20 mm to prepare a seedbed. It was at this site that phytotoxicity to ryegrass seedlings was detected, and free paraquat was determined in the surface soil using the Lemna minor bioassay. Phytotoxicity was confined to the surface layer of the soil. The free paraquat that had

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[a] ED_{50} = median effective dose.

leached out of the top 2.5 cm had been adsorbed in the deeper soil layers, and this was confirmed by the absence of residual phytotoxicity when the site was more deeply cultivated.

However, the extreme situations seen in high-dosage trials are not encountered in practice and only serve to show the possible consequences for the environment of a gross overdose of the herbicide. Thus, when paraquat is used in normal application doses, no adverse environmental effects can be expected.

Accidental spillage is probably the most likely cause of high levels of residual paraquat. The 200 g of paraquat contained in 1 litre of Gramoxone® would be completely inactivated by the addition of 10 kg of bentonite, for inactivation can be effected either by cultivation and mixing other soil with the contaminated layer or by adding clay minerals. Simulated spills of paraquat have also been treated with sodium borohydride or alkali (Staiff et al., 1981); within 1 day the paraquat in the soil had been effectively degraded.

4.3.2 Water

The ecological effects of paraquat in water have been studied in relation to its use as an aquatic herbicide at a normal concentration of 1 mg/litre (Newman & Way, 1966; Grzenda et al., 1966). Following this use, the concentration present in water decreased to about half of the initial 1 mg/litre level within 36 h, and, in less than 2 weeks, the concentration was below 0.01 mg/litre. Weed-sample analysis, 4 days after paraquat application, showed a residue of approximately 25 mg/kg, suggesting that absorption by the weed was mainly responsible for paraquat removal. Mud-residue analysis 5 1/2 months after treatment showed that 36% of the applied paraquat remained in the mud, and 70% of that was found in the top 2.5 cm. In the mud, paraquat had been adsorbed on to the mineral material. Since bottom mud often has organic components, the residues may be more accessible to bacterial degradation. Compared to other products, paraquat appears to be the herbicide of choice for future use in water supplies because of its rapid disappearance from water (6 - 14 days after treatment) (Grzenda et al., 1966). The residues were not desorbed from the bottom sediments, and mud taken from the bottom of a paraquat-treated lake carrying inactivated residues, showed no toxic effects on barley seedlings that germinated on it (Way et al., 1971).

Wauchope (1979) discussed the fate of pesticides in water draining from fields after rain. For most formulations, a total loss of 1.5%, or less, of the amount applied was the rule, except when severe rainfall occurred within 1 - 2 months

following treatment. Nearly all the pesticides examined were lost by runoff; only those binding strongly to clay particles, such as paraquat, were carried off in the sediment phase of runoff. The lack of paraquat runoff loss has also been discussed by Smith et al. (1978).

Grover et al. (1980) compared the efficiency of various herbicidal treatments for weed control in a series of irrigation ditches. At the relatively low dose of 2.2 kg/ha, paraquat resulted in aquatic weed suppression from 1973 to 1976, and this made for satisfactory water flow without environmental contamination. Water that contains small amounts of paraquat residues loses them rapidly on contact with soil, the adsorption process being irreversible (Knight & Tomlinson, 1967; Calderbank, 1972). Thus treated water may be used quite safely for channel irrigation, if an interval of 10 days is observed between treatment of the water and its use, because the paraquat will be unavailable to the plant roots. Caution should, however, be exercised in prolonged crop irrigation until the residue is well below 0.1 mg/litre, although phytotoxic damage is unlikely at even 0.5 mg paraquat/litre (Calderbank, 1972).

Coats et al. (1966) treated 0.1 ha experimental ponds with paraquat to obtain a concentration of 0.4 mg/litre. The soil in one of the ponds was stirred twice after 24 h. Analysis of the water over several weeks revealed a decrease from 0.4 mg/litre to 0.01 mg/litre after several weeks, but when the soil of the pond was stirred, the paraquat concentration fell from 0.75 mg/litre to <0.01 mg/litre after 8 - 12 days. In static water experiments, the concentration of 0.5 - 1 mg/litre fell rapidly to about 0.1 mg/litre within 4 - 7 days of treatment in 4 trials performed by Calderbank (1972). These reductions in the paraquat concentration were due to its rapid adsorption and concentration in aquatic plants. Decaying weeds transported it to the bottom mud (Table 4) where it was not released back into the water (Way et al., 1971).

Earnest (1971) treated a pond with paraquat at an initial concentration of 1.14 mg/litre. No residues were detected in the water after 16 days (limit of detection 0.01 mg/litre); in the mud the concentration was 1.13 mg/kg after 3 h and 3.25 mg/kg after 99 days. These data were confirmed by Grover et al. (1980).

Grover et al. (1980) studied irrigation water from ditches. Three days after treatment with 2.2 kg paraquat/ha, the concentrations in the water used to flood the treated ditches were less than 0.01 mg/litre, and paraquat residues in the ditch water ranged from 0.002 - 0.034 mg/litre in samples taken 3 - 5 days after foliar applications.

Table 4. Residues of paraquat in water, weed, and bottom mud[a]

		Days after treatment					
		1	4	16	32	175	420
Trial 1	water (mg/litre)	0.31	0.12	ND			
	weed (mg/kg)	13.70	25.80	21.0	0.55		
	mud (mg/kg)	3.70	-	-	-	57.1	20.1
Trial 2	water (mg/litre)	0.37	ND	ND	ND	-	-
	weed (mg/kg)	25.50	40.0	37.8	27.8	-	-
	mud (mg/kg)	ND	0.97	0.23	0.32	6.6	0.96

[a] From: Way et al. (1971).
ND - not detectable.

4.3.3 Air

Paraquat is not volatile. Dry deposits of ^{14}C-paraquat chloride exposed at room temperature showed no measurable loss in 64 days (Coats et al., 1966). Exposure to paraquat in the air is not important in spraying and harvesting operations; the skin is the principal route of occupational exposure (Chester & Woollen, 1982; Staiff et al., 1975).

Air concentrations of paraquat were measured on summer days by Makovskii (1972) using the method of Calderbank & Yuen (1965). About 1 - 1.3 kg paraquat/ha had been applied as a herbicide or desiccant in 0.25 - 0.35% water solutions. The paraquat aerosol concentrations varied according to spraying method and work-place (Table 5). Using the same analytical method, Staiff et al. (1975) examined 35 sites after paraquat application with tractor-mounted field sprayers or hand-pressure garden dispensers. The working solutions contained 0.15% paraquat for field use, and 0.44% for garden use. The respiratory exposure of field and garden operators was below the limit of detection (<0.001 mg paraquat/h).

Mature cotton fields (Seiber & Woodrow, 1981) were sprayed with paraquat, the dose being 0.94 kg/ha. The air paraquat concentrations measured downwind decreased regularly from the extrapolated interval-average values of 4.31 and 10.7 µg/m^3 1 metre downwind of the 2 fields to <50 ng/m^3 at 400 metres away in the same direction. Forty-five percent of the aerosol particles had diameters ranging from 0.01 to 4 µm. The remaining 55% had a median diameter of 12 µm. Downwind samples taken 2 - 4 h after spraying contained 1 - 10% of the amount dispersed, but, after 5 - 7 h, no paraquat was detectable in the air.

Table 5. Paraquat total airborne concentrations (mg/m³) in working areas[a]

Place of sampling		Number of samples	Mean concentrations ± SE
Working area	sprayer loading	28	0.13 ± 0.03
	tractor cabin (in direction of wind)	16	0.37 ± 0.07
	tractor cabin (against the wind)	16	0.55 ± 0.01
	manual spraying	16	0.18 ± 0.04
Treated field	after 5 min	16	0.05 ± 0.01
	after 10 min	32	< 0.01
	after 20 min	16	0
Distance from treated field	200 m	8	0.08 ± 0.01
	400 m	8	0.04 ± 0.01

[a] From: Makovskii (1972).

A study of Malaysian plantation workers, occupationally exposed to paraquat, revealed a mean total airborne exposure of 0.97 µg/m³ for spray operators. This exposure is less than present TLVs (Chester & Woollen, 1982). Wojeck et al. (1983) reported that after spraying paraquat in fields of tomatoes and citrus, the total airborne exposure ranged from 0 - 0.070 mg/h. It was less than 0.1% of the total body exposure (12.16 - 168.59 mg/h) in all trials.

During mechanical harvesting of cotton dessicated by paraquat, the maximum levels in airborne dust were found to be 1245 ng/m³ outside the cabin of the tractor and 516 ng/m³ inside the open cabin. With the cabin door closed, the concentration was only 13.7 ng/m³. The trapped particulate matter consisted of dessicated plant material and soil dust. A cascade impactor analysis established that 57% of the paraquat had a median particle diameter of 4 µm, 23%, 12 µm, and 11%, 3 µm. Cotton harvesting generated particulate concentrations in the field comparable to those immediately downwind of the field during spraying. Bearing in mind the highest paraquat air concentration in the harvest-time air (0.0012 mg/m³), a harvester operator's maximum exposure through inhalation was calculated to be 0.01 mg/8 h/day (Seiber & Woodrow, 1981).

Bulgaria has established a maximum allowable concentration (MAC) of 0.01 mg paraquat/m³ (1972), the Federal Repulic of Germany 0.1 mg/m³ (1982), Hungary 0.02 mg/m³ (1978), and the USA a TLV of 0.1 mg/m³ (1982).

4.3.4 Plants

Paraquat residues on plants have been reviewed several times by the Joint Meeting on Pesticide Residues (JMPR) (FAO/WHO, 1971, 1973, 1983). The residues found after paraquat was used as a desiccant are summarized in Tables 6 and 7 (Calderbank, 1968).

Table 6. Paraquat residues (mg/kg) in cotton 10 days after dessication at 0.55 kg/ha[a]

Fraction analysed	Paraquat found
Cotton as picked, including trash and balls	2.00
Ginned seed	0.18
Mechanically reginned seed	0.08
Acid-delinated seed	0.05
Lint cotton	3.00
Trash	3.70
Hulls	0.13
Crude oil	ND
Meal	0.02

[a] From: Calderbank (1968).

Coats et al. (1966) reported that ^{14}C-paraquat applied to wheat as a 1% solution was translocated in the plants, including the roots. Slade (1966) studied the degradation of ^{14}C-paraquat dichloride and its photochemical degradation products in plants. Maximum loss occurred in tomato, broad-bean, and maize when the paraquat remained on the leaf surfaces during sunny days.

In potatoes treated with paraquat as a desiccant, Makovskii (1972) found a residue of 0.05 mg/kg, and there was no change after the potatoes had been boiled. No residues (limit of detection 0.01 mg/kg) were found in fruits (apples, citrus fruits, plums, pears), tea, and cereals. In tests on sunflower seeds treated with 0.25 or 0.5 kg paraquat/ha, residues of up to 0.9 mg/kg were found in the whole seed, up to 1.2 mg/kg in sunflower meal, and no residue in the oil

Table 7. Paraquat residues (mg/kg) in food crops 3 - 21 days after dessication[a]

Crop	Rate of application (lb/acre)	Paraquat found
Barley	0.50 - 1.00	3 - 10
Wheat	0.50 - 1.00	1 - 2.5
Maize	0.50 - 1.20	ND - 0.2
Rice (with husk)	0.15 - 0.54	0.7 - 22
Rice (de-husked or polished)	0.15 - 0.54	ND - 0.2
Peas, beans, sunflower seed	0.35 - 1.20	ND - 0.2
Sorghum seed	0.25 - 1.00	0.1 - 0.4
Cotton (as picked)	0.50 - 1.00	2 - 3
Potatoes	0.50 - 1.50	0.02 - 0.13
Onions	0.50 - 2.00	ND - 0.05
Sugar cane juice	0.50 - 2.00	ND
Seed oils (sunflower, rape, sesame, cotton)	up to 1.20	ND

[a] From: Calderbank (1968).

(Anonymous, 1979). Therefore, the use of sunflower meal in the diet of hens, dairy cattle, and other livestock would not result in paraquat levels exceeding current standards.

Seiber et al. (1979) determined the paraquat residues in treated cotton (the foliage and bolls of the live plant, the lint and seed of harvested cotton, the gin waste and the lint and non-lint components). Gin waste residues were surveyed during 5 months of open storage. The paraquat dose had been 0.21 and 2.0 kg/ha. The results obtained are summarized in Table 8. The minimal degradation of paraquat in the plants studied was confirmed by Hills et al. (1981).

Significant paraquat residues are to be expected only when a crop is directly sprayed.

After spraying fields of marijuana with paraquat for the purpose of eradication, residues of paraquat were detected in marijuana (Smith, 1978; Patrick, 1980). Of the 54 samples collected in 1976, 7.4% were positive and of 46 samples collected in 1977, 19.6% were positive.

Table 8. Paraquat residues (mg/kg) in cotton plants[a]

Material	Days after treatment	Leaves	Lint	Non-lint	Seeds
Standing cotton plants	2	13.1	22.10		0.06
	6	8.2	3.80		0.06
Harvested seed cotton stored in field	18		7.15		0.25
	49		4.85		0.18
Gin waste	49		2.7	9.3	
	119		5.3	10.1	
	171		5.8	9.7	

[a] From: Seiber et al. (1979).

4.3.5 Animals

The effects and fate of ^{14}C-paraquat orally-administered to cattle at 8 mg/kg body weight were studied by Stevens & Walley (1966). Seven days after this single dose, 0.03 - 0.08 g/litre had been excreted in the milk and 2.4 g/litre in the urine of the cows. The total paraquat excretion in the milk was only 0.01% of the ingested dose. In cows given daily oral doses of 8 mg paraquat/kg for 3 weeks, residues of less than 0.01 mg/litre were detected in the milk (FAO/WHO, 1977). Cattle did not suffer any toxic effects over a 4-week period when turned loose on pasture immediately after it had been sprayed with 1.12 kg paraquat/ha (Calderbank et al. 1968). During the first 2 weeks of grazing on the dried herbage, it was estimated that the cattle ingested approximately half of their acute oral LD_{50} (36 - 54 mg/kg body weight) every day. Paraquat levels in the herbage ranged from about 400 mg/kg 1 day after spraying, to about 200 mg/kg 14 days after treatment; 14 - 35 days after spraying the levels were 135 - 214 mg/kg. The 4-carboxyl-1-methylpyridylium chloride content during the trial period was 5.1 - 3.4 mg/kg. By the 4th week of the study, paraquat levels in the urine were 0.01 - 0.19 mg/litre and in the faeces, 0.9 - 42 mg/kg. Only on the first day after spraying were paraquat residues (0.02 mg/litre) found in the milk of 2 cows; no residues were found (< 0.005 mg/litre) thereafter. The only organs of a slaughtered animal that contained paraquat were the kidney (0.03 mg/kg) and the stomach (0.05 mg/kg).

The fate of paraquat in large animals is addressed far more completely in the Evaluations of the 1976 Joint Meeting on Pesticide Residues (JMPR) (FAO/WHO, 1977).

Rabbits were fed with lucerne treated with normal-use levels of paraquat (Lavaur et al., 1979). Immediately after spraying, the paraquat residues were 272 mg/kg (dry weight of lucerne). After 24 h and 48 h, they were 114 mg/kg and 62 mg/kg, respectively. No systemic toxicity symptoms or gastrointestinal damage were observed in the treated rabbits.

When hens were given paraquat at 40 mg/litre in their drinking-water for 14 days, the amount of paraquat found in the eggs rose to 0.1 mg/kg, but fell to less than 0.005 mg/kg, 6 days after cessation of treatment (Fletcher, 1967). Eggs from hens eating grain containing paraquat at a concentration of 10 mg/kg contained residues below 0.025 mg/kg.

5. BIOLOGICAL ACTIVITY OF RESIDUES

5.1 Soil Organisms

Haley (1979) reviewed the effects of paraquat on soil microorganisms and fungi, while Tu & Bollen (1968), Curry (1970), Radaelli & Martelli (1971), Roslycky (1977), and Smith et al. (1981a) studied the effects of paraquat on the size and composition of the microbial soil populations, total microbial respiration in the soil, the rate of organic matter degradation, and the number of soil microorganisms. None of these authors found any adverse ecological effects from normal and excessive (up to 32 times the normal dose) paraquat treatment, although in some cases nitrification was temporarily suppressed or activated, and some bimodal microbiological effects were observed with intermediate herbicide concentrations (Tu & Bollen, 1968; Tchipilska, 1980).

At normal doses, paraquat had no adverse effect on endomycorrhiza formation and function (Smith et al., 1981a), on total populations of bacteria, actynomyces, fungi (Roslycky, 1977; Haley, 1979; Tchipilska, 1980; Smith et al., 1981a), or on 24 different species of soil fauna taken from 2 plots at a depth of 3.8 cm (Curry, 1970).

Curry (1970), and Riley et al. (1976) made extensive studies of the effects of normal and high doses of paraquat on microarthropod and earthworm populations at sites at different stages of cultivation. The herbicide was neither harmful nor repellant to earthworms, nor was there any evidence of a toxic effect or of paraquat accumulation in any species examined. When the residues in the top 2.5 cm of soil reached 20 mg/kg, the highest concentration determined in Allolbophora caliginosa, living near the surface, was 3.2 mg/kg (live weight). Worms from highly-dosed plots eliminated paraquat residues within 36 h, when placed in clean soil.

5.2 Effects of Residues on Crop Yields

The absence of adverse effects from residual paraquat on the growth and yield of crops grown in paraquat-treated soils has been demonstrated by Knight & Tomlinson (1967), Damanakis et al. (1970), Newman & Wilkinson (1971), and Riley et al. (1976). It is known that the paraquat-inactivation capacity of soils varies widely. Paraquat has been tested on soils of low adsorption capacity, it has been used repeatedly on the same soil (section 4.3.1) and has been tested at extremely high concentrations. The absence of any reports or observations of long-term phytotoxic effects confirms the data obtained in greenhouse and laboratory studies.

5.3 Effects on Fish and Aquatic Organisms

Despite variation in LC_{50}s for fish (67 - 110 mg/litre after 24 h, 38 - 62 mg/litre after 48 h, more than 25 - 32 mg/litre after 96 h), the herbicide has proved to have a wide margin of safety for warm- and cold-water fish species (Calderbank, 1972). The toxicity of paraquat for fish varies with the species, the size of the fish, and the softness or hardness of the water. A large number of aquatic species have shown a 100% survival at 96 mg/litre over 96 h, though the decreased oxygen concentration following decay of weeds, may be dangerous in extreme situations. Rainbow trout tolerated 1 mg paraquat/litre water in prolonged toxicity tests and only a 30% mortality was recorded after 16 days of repeated exposure (Calderbank & Slade, 1976). At the end of the test, 0.54 mg paraquat/kg was found in the rainbow trout. In a 7-day exposure test at 1 mg paraquat/litre, the herbicide was detected in the gut (0.41 mg/kg) and liver (0.35 mg/kg), but not in the meat of the fish (< 0.025 mg/kg). Water snails collected from 2 ditches, 12 weeks after treatment of the waters with 1 mg/litre were found to contain 0.43 mg herbicide/kg. Fish (major carp fingerlings) exposed to paraquat in the presence of weeds were more susceptible than those in weed-free environments (Singh & Yadav, 1978), owing to the changed oxygen content of the water. Where there is heavy weed growth, the oxygen taken up by weed decay may dangerously reduce the oxygen available for aquatic organisms. To avoid this, as far as possible, paraquat should be applied before weed growth becomes dense and only to one part of the water- course or lake at a time (FAO/WHO, 1973).

5.4 Effects on Birds

Paraquat is less toxic for birds than for mammals. The acute oral LD_{50} for the hen is 262 - 380 mg/kg body weight (Table 11). The acute oral and 24-h percutaneous (applied to feet) LD_{50} for mallards are 200 and 600 mg/kg body weight, respectively (Hudson et al., 1979). For duck, pheasants, and quail, LC_{50} values of paraquat when mixed in the diet are 1000 mg/kg of food or more (Summers, 1980); residues on sprayed vegetation would not therefore be expected to present a hazard for birds.

When paraquat was sprayed directly on to pheasants' eggs before incubation, treatment rates up to 2 kg paraquat/ha did not have any effect on egg hatchability or on the birds' reproductive organs (Newman & Edwards, 1980). In a similar study with Japanese quail eggs, sprays containing paraquat levels of up to 3 kg/ha did not have any effect on hatchability or development of reproductive organs (Edwards et

al., 1979). Thus, normal spray rates should not induce any adverse effects, even if paraquat is sprayed directly on eggs.

Bird populations have been monitored in detail, over a 5-year period, on a farm in the United Kingdom where paraquat use was much higher than normal; the average application to the whole arable area was 0.6 kg/ha per year. The paraquat was applied beneath hedgerows and along fence lines. The farm maintained an excellent wild bird population (40 species), including ground-nesting birds (Edwards, 1979). Most species were at a similar or greater density than the national average in the United Kingdom.

The Ministry of Agriculture, Fisheries, and Food in the United Kingdom has carried out detailed investigations on mammalian and avian deaths that could have been caused by pesticides. For the period 1971 - 81, the normal use of pesticide was not found to have caused any significant adverse effects on mammals and birds (MAFF, 1980a, 1981). The Ministry concluded, "It is widely believed that the use and misuse of paraquat is responsible for a considerable number of wildlife casualties. There is no evidence from the investigations to support this allegation...." (MAFF, 1980b).

6. KINETICS AND METABOLISM

6.1 Animal Studies

6.1.1 Absorption

6.1.1.1 Oral absorption

Daniel & Gage (1966) studied the absorption of ^{14}C-paraquat following oral and subcutaneous single-dose administration to rats. About 76 - 90% of the oral doses were found in the faeces, and 11 - 20% in the urine; most of the subcutaneous dose (73 - 88%) was found in the urine and only 2 - 14.2% in the faeces. This, together with the absence of marked biliary excretion, was evidence that paraquat was poorly absorbed from the gut. This low rate of absorption was confirmed by Litchfield et al. (1973) and Conning et al. (1969). Rats, guinea-pigs, and monkeys orally administered LD_{50} doses of ^{14}C-paraquat had low peak serum concentrations (2.1 - 4.8 mg/litre) (Murray & Gibson, 1974). The radioactivity levels reached a maximum 30 - 60 min after administration and then remained relatively constant for 32 h. A dose of 126 mg/kg body weight resulted in a rat serum level of 4.8 - 4.7 mg/litre.

In fasting dogs, low oral doses of paraquat were rapidly but incompletely absorbed, the peak plasma concentration being attained 75 min after dosing (Bennett et al., 1976). After an oral dose of 0.12 mg/kg body weight, 46 - 66% was absorbed in 6 h. For doses of 2 - 5 mg/kg, only 22 - 38% and 25 - 28% of the dose was absorbed, respectively. Dose-dependent data from dogs and whole-body autoradiography suggest that absorption is facilitated in the small intestine. Some non-ionic surfactants (0.001%) increased ^{14}C-paraquat transport through isolated gastric mucosa models, but histological evaluation suggested that this was due to damage of the epithelial cell membranes (Walters et al., 1981).

6.1.1.2 Pulmonary absorption

Absorption of paraquat following instillation and inhalation in the lung has been described in several studies (Gage, 1968a; Kimbrough & Gaines, 1970; Seidenfeld et al., 1978; Popenoe, 1979). The uptake of ^{14}C-paraquat after an intratracheal injection of 1.86 nmol/lung was investigated in the isolated perfused rat lung by Charles et al. (1978). The efflux of ^{14}C-paraquat was diphasic with a rapid phase half-life of 2.65 min and a slow phase half-life of 356 min. It was suggested that the slow phase represented a storage

pool, possibly responsible for the pulmonary toxicity of paraquat. Various doses of ^{3}H-paraquat (10^{-5} - 10^{-12} g) in 0.1 ml saline were introduced directly into the left bronchus of rats (Wyatt et al., 1981). Fifteen min after instilling 10^{-8} of ^{3}H-paraquat, 90% of the ion could be accounted for in the tissues and urine, 50% being present in the lung. With doses at or greater than 10^{-5} g, pathological changes were seen in the lung, similar to those seen after systemic poisoning. Zavala & Rhodes (1978) reported that the lung of the rabbit was highly sensitive to paraquat intrabronchial instillation in doses ranging from 0.1 g - 1 pg; moderately sensitive to intraveneously administered paraquat (25 mg/kg body weight); resistant to the herbicide when given intraperitoneally or subcutaneously (25 mg/kg body weight).

6.1.1.3 Dermal absorption

Paraquat absorption through animal and human skin has been studied using an in vitro technique (Walker et al., 1983). Human skin was shown to be impermeable to paraquat, having a very low permeability constant of 0.73. Furthermore, human skin was found to be at least 40 times less permeable than animal skins tested (including rat, rabbit, and guinea-pig). There are no in vivo studies on the rate of absorption of paraquat through the skin. However, observations of dose-related dermal toxicity in experimental animals and human percutaneous poisoning have provided some qualitative information concerning the dermal absorption of paraquat (further discussed in section 8.2.2.2).

6.1.2 Distribution

Since the most characteristic feature of paraquat toxicity is lung damage, it is important to stress the high concentrations and retention of paraquat in the lung tissues, relative to other tissues, following oral, intravenous, intraperitoneal, subcutaneous, and intrabronchial routes of administration in rats, guinea-pigs, and monkeys (Sharp et al., 1972; Ilett et al., 1974; Murray & Gibson, 1974; Kurisaki & Sato, 1979; Waddell & Marlowe, 1980). An association between paraquat concentrations in the lung and degree of toxicity or lung injury has been reported (Sharp et al., 1972; Ilett et al., 1974; Waddell & Marlowe, 1980; Wyatt et al., 1981). Some of their data are summarized in Tables 9 and 10.

Toxic doses of paraquat were administered orally and iv to rats (Sharp et al., 1972). Paraquat concentrations in the whole blood were the same as those in the plasma. The distribution of the herbicide in various tissues was then

Table 9. Paraquat distribution in tissues

	Route of entry	Dose	Species	Time after treatment	Tissue	Concentration
1.	Intrabronchial	10 ng	rat	60 min	plasma	0.0092 µg/litre
					lung	5.2 ng
					kidney	0.052 ng
					liver	-
					heart	-
					brain	-
2.	Intravenous	20 mg/kg	rat	24 h	plasma	0.7 mg/litre
					lung	8.0 mg/kg
					kidney	1.45 mg/kg
					liver	0.48 µg/g
					heart	0.75 mg/kg
					brain	-
3.	Intravenous	20 mg/kg	rat	24 h	plasma	ND
					lung	11.36 µm/kg
					kidney	1.93 µmol/kg
					liver	0.90 µmol/kg
					heart	1.13 µmol/kg
					brain	0.87 µmol/kg
		20 mg/kg	rabbit	24 h	plasma	0.28 µmol/litre
					lung	7.9 nm/g
					kidney	5.25 µmol/kg
					liver	1.59 µmol/kg
					heart	1.52 µmol/kg
					brain	0.49 µmol/kg

Table 9 (contd).

Route of entry	Dose	Species	Time after treatment	Tissue	Concentration
4. Intraperitoneal	15 mg/kg	rat	24 h	plasma	0.32 µmol/litre
				lung	26.28 µm/kg
				kidney	10.4 µmol/kg
				liver	5.04 µmol/kg
				heart	4.59 nmol/g
				brain	1.22 µmol/kg
5. Oral	126 mg/kg	rat	16 h	plasma	0.90 mg/litre
				lung	5.0 mg/kg
				kidney	7.00 mg/kg
				liver	2.1 mg/kg
				heart	2.7 mg/kg
				brain	-
	22 mg/kg	guinea-pig	16 h	plasma	0.03 mg/litre
				lung	1.29 mg/kg
				kidney	1.99 mg/kg
				liver	0.08 mg/kg
				heart	0.31 mg/kg
				brain	-

1. From: Wyatt et al. (1981).
2. From: Sharp et al. (1972).
3. From: Ilett et al. (1974).
4. From: Maling et al. (1978).
5. From: Murray & Gibson (1974).

Table 10. Paraquat distribution in tissues (in mg/kg (mean) tissue)

Route of Entry	Dose (mg/kg body weight)	Species	Time after dosing	Lung	Kidney	Liver	Heart	Plasma
1. Oral	126	rat	1 h	3.3	27.5	2.0	1.8	4.7
			4 h	3.7	4.5	4.4	0.9	0.8
			32 h	13.6	9.4	5.7	2.8	1.1
			64 h	1.7	1.0	7.7	0.2	0.1
2. Intravenous	20	rat	1 h	9.0	25.0	5.0	-	6.0
			4 h	8.0	6.0	2.0	-	0.3
			24 h	6.0	1.0	0.4	-	0.07
			2 days	4.0	0.8	0.3	-	0.05

1. From: Murray & Gibson (1974).
2. From: Sharp et al. (1972).

followed for 10 - 18 days. The lung had the greatest retention and consequently contained the highest concentration 4 h after dosing. Four to 10 days after dosing, the paraquat concentration in the lung was 30 - 80 times higher than that in the plasma. The high lung-tissue concentrations of paraquat were confirmed by Ilett et al. (1974) for rats and rabbits after iv injection of 20 mg ^{14}C-paraquat/kg body weight. Although the herbicide showed a selective localization in rabbit lung, the concentration decreased far more rapidly in rabbit lung than in rat lung. The rabbit did not show any histological or biochemical signs of lung damage, and no evidence of covalent binding of paraquat in lung tissue was found by Ilett et al. (1974). After thorough washing of tissue precipitate with dilute trichloroacetic acid, only insignificant amounts of ^{14}C-paraquat were detected in protein from the brain, heart, kidney, liver, lung, and plasma.

Autoradiographic studies using ^{14}C-paraquat have been carried out on mice and rats (Litchfield et al., 1973). Paraquat was observed in nearly all organs 10 min after intravenous injection of 20 mg/kg body weight. Waddell & Marlowe (1980) obtained similar autoradiographic results in mice, after intravenous injection of 288 - 338 µg ^{3}H-paraquat dichloride/kg body weight. Cellular resolution autoradiography showed that paraquat was confined almost entirely to cells having the distribution of alveolar Type II cells. These cells are known to be susceptible to the toxicity of paraquat (Kimbrough & Gaines, 1970). Waddell & Marlowe (1980) suggested that it was unlikely that the radioactivity was bound to cellular constituents.

No paraquat was detected in rat kidney, brain, liver, or lung when paraquat was administered in the diet at a concentration of 50 mg/kg for a period of 8 weeks. At 120 mg/kg, it was found in low concentrations in the lung, kidney, gastrointestinal system, and brain (Litchfield et al., 1973). At 250 mg/kg, it was detected in the tissues within 2 weeks. No sex differences or any clear pattern of accumulation were noted throughout the 8-week study. Within 1 week of return to a normal diet, no paraquat was detected in any tissue examined. Histological changes were observed in all lungs of animals fed paraquat at 250 mg/kg diet.

Rose et al. (1974a) demonstrated an energy-dependent accumulation of paraquat in slices of rat lung that obeyed saturation kinetics. The same investigators also examined the ability of paraquat to accumulate in tissue slices from other organs in vitro (Rose & Smith, 1977). The herbicide in brain, adrenal gland, and kidney slices accumulated; however, the uptake was less than 10% of that observed in the lung slices. The authors established the uptake of paraquat by the lung in various species (rat, rabbit, dog, monkey, man). The human

lung accumulated paraquat as strongly as that of the rat and there was a relationship between the concentration of paraquat in the different lung areas and the development of microscopic lung lesions. It has been demonstrated that the rate of paraquat efflux from lung tissue is less than its rate of accumulation in the lung slices (Smith et al., 1981). Efflux from lung slices, prepared from rats dosed iv with the herbicide, was found to be biphasic. There was a fast component (half-life 20 min), followed by a first-order slow component characterized by a half-life of 17 h. The half-life *in vitro* was similar to that seen *in vivo* following iv administration to rats.

6.1.3 Metabolic transformation and excretion

Paraquat participates to a considerable extent in cyclic reduction-oxidation reactions. After undergoing a single electron reduction in tissues, the resultant free radical is readily oxidized by molecular oxygen to the parent compound (section 6.3). This leads to an overall excretion of essentially unchanged paraquat in the urine after oral administration to rats (Murray & Gibson, 1974) .

Daniel & Gage (1966) reported that paraquat was metabolized by gut microflora following oral dosing of rats. This observation was not confirmed in subsequent studies (Murray & Gibson, 1974) and was later attributed to a problem with the method (FAO/WHO, 1977).

Urinary concentrations of paraquat following oral administration are relatively low (Daniel & Gage, 1966: Murray & Gibson, 1974; Sharp et al., 1972; Maling et al., 1978) and are thus used to estimate its elimination from the body.

Sharp et al. (1972) reported a biphasic elimination of paraquat from the plasma of rats after iv injection. The initial rapid phase had a 20 - 30 min half-life, and the slower phase a half-life of 56 h. Murray & Gibson (1974) also showed prolonged paraquat elimination after oral administration to rats, guinea-pigs, and monkeys. The urinary and faecal routes were equally important in all species studied. The faecal content was due mainly to elimination of unabsorbed paraquat. Prolonged elimination of paraquat in all animals tested indicated retention of the herbicide in the body.

Following iv administration to rats, about 75 - 79% of the dose was excreted in the urine within 6 h (Maling et al., 1978). The plasma disappearance of an iv dose of paraquat of 5 mg/kg was fitted to a 3-compartment model. Total body clearance was estimated to be 8.39 ± 0.54 ml/kg per min (Maling et al., 1978). The relatively high concentration of paraquat in the duodenal and jejunal walls suggested biliary

secretion of the herbicide, and the authors' hypothesis was supported by the observation of radioactivity in the intestines of mice in whole-body autoradiographic studies (Waddell & Marlowe, 1980).

Since absorbed paraquat is mainly removed via the kidneys, the early onset of renal failure will have a marked effect on paraquat elimination and distribution, including accumulation in the lung. Hawksworth et al. (1981) used the dog as a model to evaluate the influence of paraquat-induced renal failure on the kinetics of paraquat elimination. After iv injection of a trace dose of ^{14}C-paraquat (30 - 50 µg/kg body weight) in dogs, the kinetics of distribution was described by a 3-compartment model. To obtain a good fit of the curve, it was necessary to sample the central (plasma) compartment for at least 24 h after dosing. Simulation of paraquat levels in the peripheral compartments suggested the existence of a compartment with rapid uptake and removal (kidney) and another with slow uptake (lung). The renal clearance of paraquat approximated total body clearance indicating that paraquat elimination occurs through renal excretion. The urinary excretion rate of an iv dose was rapid, approximately 80 - 90% of the dose being eliminated during the first 6 h. Intravenous injection of a large toxic dose of paraquat (20 mg/kg body weight), however, brought about a marked decrease in renal clearance, from 73 ml/min to 18 ml/min after 2 1/2 h and 2 ml/min after 6 h. This data suggested that damaged renal tubules could contribute to paraquat accumulation in the lung.

6.2 Observations on Human Beings

6.2.1 Observations on paraquat poisoning after ingestion: non-fatal cases

Tompsett (1970) reported a case of ingestion of 45 g of Weedol (2.5% paraquat). On hospital admission, the gastric aspirate contained 0.215 g paraquat/litre and the urine 0.148 g/litre. After 2 - 4 h, paraquat concentrations dropped to 5.1 mg/litre in the urine and 0.4 mg/litre in the serum but, 16 - 24 h after admission, the urinary level was 0.95 mg/litre, while no paraquat was detectable in the serum. Paraquat was also detected in the urine for up to 15 days after poisoning, while at the same time serum concentrations were below the detectable limits in chemical analysis (Fletcher, 1975).

The cumulative elimination of paraquat in the faeces and urine of a patient was followed for 7 days by van Dijk et al. (1975). Faecal elimination increased from 340 mg the first day to 530 mg after 7 days, while cumulative urinary excretion

reached 50 mg the 1st day and increased to 75 mg after 7 days. It was calculated that only 87 mg of paraquat had been absorbed from a total ingestion of about 637 mg, determined in the urine, dialysate, and faeces. In this patient, less than 14% of the ingested paraquat was absorbed through the gastrointestinal system.

6.2.2 Observations on paraquat poisoning after ingestion: fatal cases

It is well established that paraquat lung disease resulting in death is usually preceded or accompanied by renal insufficiency. This contributes to the retention of paraquat in body tissues. Nevertheless, Fairshter et al. (1979) detected only small concentrations (below 0.09 mg/kg) of paraquat in several organs of patients who died 3 weeks after ingestion.

The detection of 27 mg paraquat/litre in the bile of a woman after autopsy suggested that some faecal paraquat might be attributable to biliary excretion (Dijk et al., 1975).

6.2.3 Significance of paraquat concentrations in cases of paraquat poisoning

Not only oral ingestion, but also dermal absorption of paraquat after occupational overexposure, resulted in measurable urinary levels of paraquat. The determination of paraquat in urine and serum is an important biological exposure test for the diagnosis and the prognosis in cases of human poisoning.

Wright et al. (1978) followed the urinary excretion of paraquat in 16 patients (7 of whom died). The total amount of paraquat excreted ranged from 0.6 mg to 386 mg. The excretion rate decreased rapidly during the 48 h following ingestion, though less rapidly in the patients who eventually died. All patients excreting 1 mg of paraquat or more per hour, for 8 h or more after ingestion, died.

Plasma-paraquat concentrations were measured by gas chromatography, radioimmunoassay, and colorimetric methods in 79 patients with paraquat poisoning (Proudfoot & Stewart, 1979). At any given time after ingestion (within a limit of 35 h), plasma concentrations were significantly higher in the patients who died (Fig. 4). Patients whose plasma concentrations were not higher than 2.0, 0.6, 0.3, 0.16, and 0.10 mg paraquat/litre at respectively, 4 h, 6 h, 10 h, 16 h, and 24 h after the poisoning, were likely to survive. When plasma levels exceeded 0.3 mg/litre 15 h after ingestion, a fatal outcome could be expected, despite treatment. These conclusions were supported by the studies performed on 28 patients by Bismuth et al. (1982).

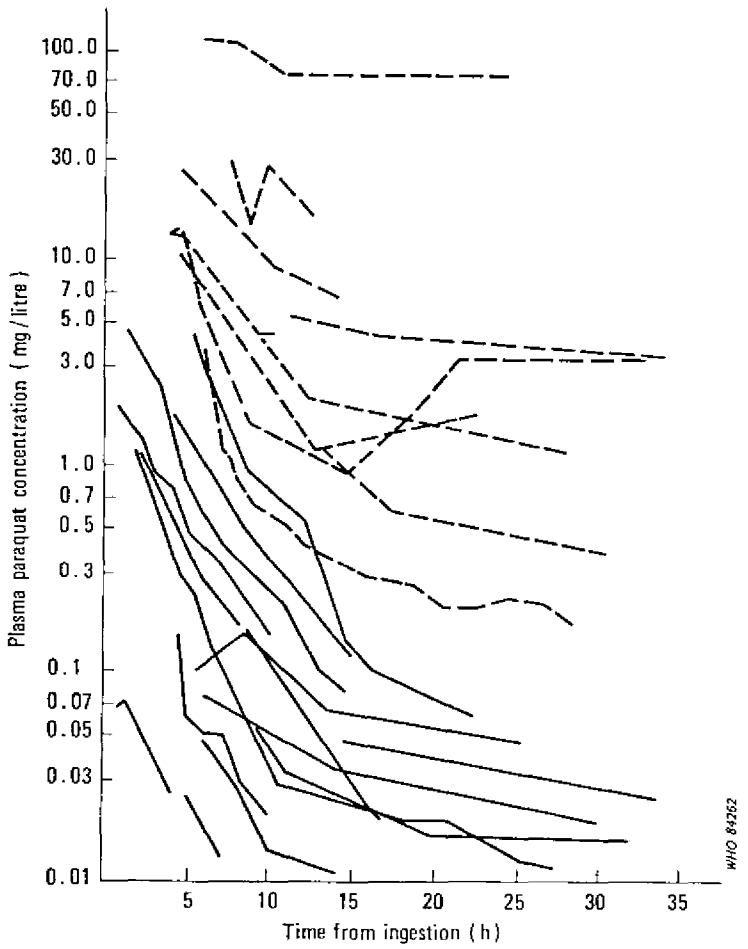

Fig. 4. Serial plasma-paraquat concentrations in 25 patients (Proudfoot, 1979). Fatal cases are indicated by broken lines and survivors by solid lines.

6.3 Biochemical Mechanisms

The mechanism of the toxic action of paraquat has been extensively investigated. Several reviews or monographs have summarized the biochemical mechanism of paraquat toxicity in plants (Calderbank, 1968), bacteria (Fridovich & Hassan, 1979), and animals (Bus et al., 1976; Autor, 1977; Smith et al., 1979; Bus & Gibson, in press).

Paraquat has long been known to participate in cyclic reduction-oxidation reactions in biological systems. The compound readily undergoes a single electron reduction in tissues, forming a free radical. In an aerobic environment, however, a free radical is immediately oxidized by molecular oxygen, generating the superoxide radical ($O_2^{\cdot -}$). The reoxidized paraquat is capable of accepting another electron and continuing the electron transfer reactions in a catalytic manner (Fig. 5). Research into the mechanism of paraquat toxicity has identified at least 2 partially toxic consequences of the redox cycling reaction: a) generation of $O_2^{\cdot -}$, and b) oxidation of cellular NADPH, which is the major source of reducing equivalence for the intracellular reduction of paraquat. Generation of $O_2^{\cdot -}$ can lead to the formation of more toxic forms of reduced oxygen, hydrogen peroxide (H_2O_2,) and hydroxyl radicals ($OH^{\bullet}$). Hydroxyl radicals have been implicated in the initiation of the membrane-damaging by lipid peroxidation, depolymerization of hyaluronic acid, inactivation of proteins and damage to DNA (Hassan & Fridovich, 1980). Depletion of NADPH, on the other hand, may disrupt important NADPH-requiring biochemical processes such as fatty acid synthesis (Smith et al., 1979).

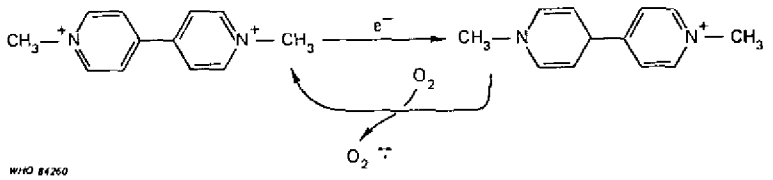

Fig. 5. Paraquat reduction oxidation.

The importance of molecular oxygen and the potential role of $O_2^{\cdot -}$ generation in mediating have been implicated in studies on plants (section 3.3), bacteria, and in in vitro and in vivo mammalian systems. In cultures of Escherichia coli, Hassan & Fridovich (1977, 1978, 1979) demonstrated that paraquat stimulated cyanide-resistant respiration, which could be almost entirely accounted for by an NADPH-dependent formation of $O_2^{\cdot -}$. The possibility that formation of $O_2^{\cdot -}$ might be responsible for the toxicity of paraquat in bacteria was supported by observations that bacteria containing elevated activities of superoxide dismutase, an enzyme that detoxifies $O_2^{\cdot -}$, were resistant to paraquat

toxicity (Hassan & Fridovich, 1977, 1978; Moody & Hassan, 1982).

In vitro studies on preparations of lung and liver from various animal species have supported the hypothesis that paraquat redox cycling and associated $O_2^{\cdot-}$ and H_2O_2 generation also occur in mammalian systems (Gage, 1968b; Ilett et al., 1974; Montgomery, 1976, 1977; Steffen & Netter, 1979; Talcott et al., 1979). Bus et al. (1974) reported that the single electron reduction of paraquat in mammalian systems was catalysed by microsomal cytochrome P-450 reductase and NADPH. The observation that the in vivo toxicity of paraquat in animals is markedly potentiated by exposure to elevated oxygen tensions further supported the potential role for molecular oxygen in mediating toxicity (Fisher et al., 1973b; Autor, 1974; Bus & Gibson, 1975; Witschi et al., 1977; Kehrer et al., 1979; Keeling et al., 1981).

The results of in vivo studies conducted by Bus et al. (1974) suggested that stimulation of lipid peroxidation, which was dependent on paraquat redox cycling and associated $O_2^{\cdot-}$ generation, might be an important toxic mechanism in mammalian systems. Consistent with this hypothesis, animals fed diets deficient in selenium or vitamin E, in order to diminish cellular antioxidant defences, were significantly more sensitive to paraquat toxicity than control animals (Bus et al., 1975; Omaye et al., 1978). In contrast to these studies, a number of studies have shown that paraquat inhibited in vitro microsomal lipid peroxidation (Ilett et al., 1974; Montgomery & Niewoehner, 1979; Steffen & Netter, 1979; Kornburst & Mavis, 1980). Subsequent studies have indicated, however, that paraquat would stimulate microsomal lipid peroxidation when an adequate supply of electrons (NADPH) and in vitro oxygen tensions were maintained (Trush et al., 1981, 1982).

Despite the evidence described above, the hypothesis that lipid peroxidation is the underlying toxic mechanism functioning in vivo has not been conclusively demonstrated. Direct quantification of paraquat-induced lipid peroxidation damage in vivo by analysis of tissue malondialdehyde levels or ethane exhalation, both markers of peroxidation injury, has been largely unsuccessful (Reddy et al., 1977; Shu et al., 1979; Steffen et al., 1980). Furthermore, attempts to counteract paraquat toxicity by administration of various antioxidants have also been unsuccessful (Fairshter, 1981).

Superoxide radicals generated in paraquat redox cycling may induce biochemical changes other than the initiation of peroxidation reactions. Ross et al. (1979) demonstrated that paraquat increased DNA strand breaks in cultured mouse lymphoblasts. Paraquat was also reported to induce a

superoxide-dependent stimulation of guanylate cyclase (EC 4.6.1.2) activity in rat liver (Viseley et al., 1979) and guinea-pig lung (Giri & Krishna, 1980). These investigators postulated that increased cyclic GMP might stimulate the pulmonary fibroproliferative changes characteristic of paraquat toxicity (section 7.1.1.1). In other studies, paraquat has also been found to increase collagen synthesis in rat lung (Hollinger & Chvapel, 1977; Greenberg et al., 1978; Thompson & Patrick, 1978; Hussain & Bhatnagar, 1979).

Redox cycling of paraquat has also been proposed to lead to increased oxidation of cellular NADPH (Brigelius et al., 1981; Keeling et al., 1982). The activity of pentose shunt enzymes in the lung rapidly increased in rats administered paraquat, which suggested an increased demand for NADPH (Fisher et al., 1975; Rose et al., 1976). The observation that paraquat decreased fatty-acid synthesis in lung slices (Smith et al., 1979) further supported this hypothesis, since fatty acid synthesis requires NADPH. Direct analysis of NADPH in the lung has confirmed that paraquat treatment decreased the NADPH content in rat lung (Witschi et al., 1977; Smith et al., 1979). These observations led Smith et al. (1979) to propose that oxidation of NADPH might not only interrupt vital physiological processes, such as fatty-acid synthesis, but also render tissues more susceptible to lipid peroxidation by decreasing the equivalents (NADPH) necessary for the function of the antioxidant enzyme glutathione peroxidase (EC 1.11.1.9) (Fig. 6).

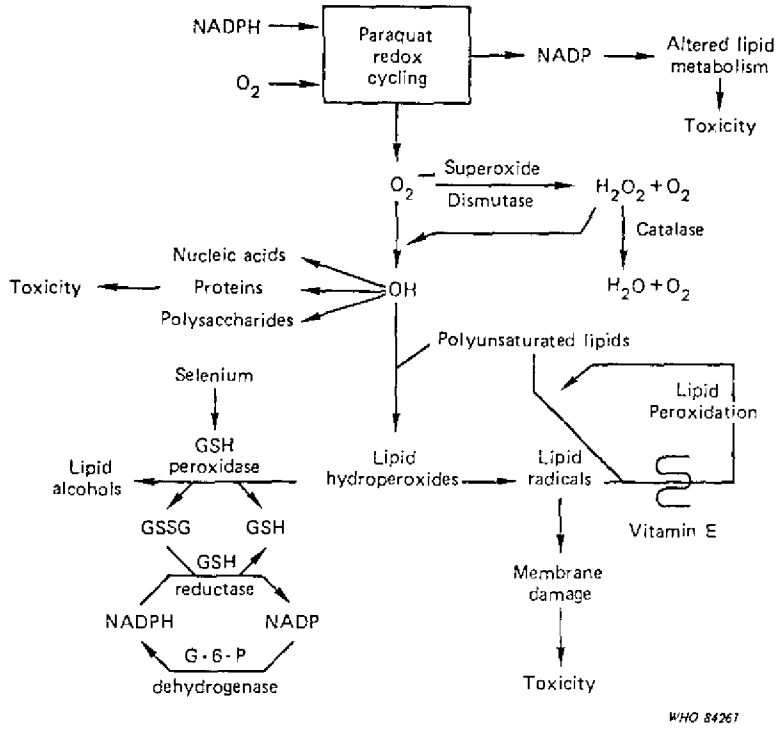

Fig. 6. Proposed biochemical mechanism of paraquat toxicity (Bus & Gibson, 1982).

7. EFFECTS ON ANIMALS

7.1 Effects on Experimental Animals

7.1.1 Respiratory system

Toxicity studies in rats, mice, dogs, and monkeys (Clark et al., 1966; Kimbrough & Gaines, 1970; Murray & Gibson, 1972; Makovskii, 1972; Kelly et al., 1978) demonstrated that paraquat had a specific effect on the lung (Table 11). Administration by every route of entry tested whether parenteral (Fisher et al., 1973a; Robertson, 1973; Hunsdorfer & Rose, 1980), oral (Clark et al., 1966; Bainova, 1969a; Kimbrough, 1974; Tsutsui et al., 1976; Dikshith et al., 1979), dermal (Howe & Wright, 1965; Bainova, 1969b; McElligott, 1972), or inhalatory (Gage, 1968b; Bainova, 1971; Makovskii, 1972; Seidenfeld et al., 1978) resulted in irreversible changes in the lung.

Clark et al. (1966) reported that, in rats, in the earlier stages after a single toxic oral dose of paraquat, breathing was gasping or deep and fast, but some days after a single or repeated toxic doses, the respiration became increasingly laboured, and the hairs around the mouth and nares were soiled with a brownish liquid. The extensive alveolar oedema observed in severe intoxication was responsible for the development of hypoxia, cyanosis, and dyspnoea. The progressive development of pulmonary fibrosis was accompanied by difficulty in breathing, gasping, and hyperpnoea (Smith et al., 1973).

Exposure of rats to high concentrations of respirable paraquat aerosols was accompanied by shallow respiration. Within 2 - 3 h, the test animals became dyspnoeic, cyanotic, and inactive, and there were signs of local eye and nose irritation (Gage, 1968a).

7.1.1.1 Pathomorphological lung studies

Macroscopic examination of the lungs revealed that lesions and their severity were dependent on the dose of paraquat and the time between exposure and sacrifice (or death). The wet weight of the lung increased after a single treatment, owing to oedema and haemorrhage. The pathogenesis of the paraquat lung lesion has been well characterized, and has been reviewed by Smith & Heath (1976). The acute pulmonary toxicity of paraquat in animals has been described as occurring in two phases (Smith & Heath, 1976). In the initial "destructive" phase, alveolar epithelial cells were extensively damaged and their subsequent disintegration often resulted in a completely denuded alveolar basement membrane.

Table 11. Effects on experimental animals of repeated oral, dermal, or inhalation exposure to paraquat

Species	Dosage	Duration	Effects obtained	Reference
Rat	diet - 125 mg/kg	2 years	no toxic effects	Howe & Wright (1965)
Dog	diet - 50 mg/kg		no toxic effects	
Rat	diet - 0.25 mg/kg	27 days	death; histological changes in the lung	Clark et al. (1966)
Rat	diet - 300, 400, 500, 600, 700 mg/kg	90 days	cumulative toxic effects; chronicity factor (Hayes) 5.2; histological changes in the lung	Kimbrough & Gaines (1970)
Rat	oral - 4, 9, 25 mg/kg body weight per day	30 days	inhibition of ChE activity, increasing GPT activity in the serum; biochemical and histological changes in the lung, kidney, liver	Bainova (1969, 1975)
Rat	oral - 1.3, 2.6 mg/kg body weight per day	4 1/2 months	increased GPT and G-6-P-isomease activities in the serum; biochemical and histological changes in lung, kidney, liver	Bainova (1969, 1975)
Rat	oral - 3.3, 1.3, 0.13 mg/kg body weight per day	1 year	the higher doses were toxic for both species tested; no-observed-adverse-effect levels:	Makovskii (1972)
Guinea-pig	oral - 1.0, 0.4, 0.04 mg/kg body weight per day		for rat 0.13, guinea-pig 0.04 mg/kg body weight per day	

Table 11 (contd).

Species	Dosage	Duration	Effects obtained	Reference
Rat	diet - 20 - 30 mg/kg body weight per day	30 days	histological and electron-optical lung changes	Kimbrough (1974)
Mouse	diet - 25, 50, 70 mg/kg	80 weeks	death; dose-dependent clinical and histological changes in the lung, liver, kidney, and other organs tested	FAO/WHO (1973)
Rat	oral - 25, 50, 100 mg/kg body weight per day	1 - 5 days	body weight loss; increased serum LDH, GOT activity; no haematological changes; histological changes in the lung, kidney, liver, myocardium	Tsutsui et al. (1976)
Rat	drinking-water - 1.3, 2.6 mg/litre	2 years	mortality increased; histological changes in the lung, but only minimal at the lowest level	Bainova & Vulcheva (1977)
Rabbit	dermal - 2.8, 4.5, 7, 14 mg/kg body weight per day	20 days	skin irritation; mortality and toxic effects at 7 & 14 mg/kg/day. LD_{50} 4.5 mg/kg/day; no-observed-adverse-effect level 2.8 mg/kg/day	Clark et al. (1966)
Rat	dermal - 2, 5, 15, 30, 45 mg/kg body weight per day	21 days	skin irritation; mortality and toxic effects at 5 - 45 mg/kg/day; histological changes in the lung, kidney, liver, myocardium; LD_{50} 15 mg/kg/day; no-observed-adverse-effect level 2 mg/kg/day	Bainova (1969a)

Table 11 (contd).

Species	Dosage	Duration	Effects obtained	Reference
Rabbit	dermal - from 1.56 - 50 mg/kg per day (with occlusion) from 2.4 - 192 mg/kg body weight per day (without occlusion)	20 days	skin irritation; mortality and toxic effects at 3.13 - 192 mg/kg/day; LD_{50} 4.5 mg/kg/day with occlusion and 24 mg/kg/day without occlusion; No-observed-adverse-effect levels: 1.56 and 2.4 mg/kg/day with and without occlusion	McElligott (1972)
Rat	inhalation[a] - 0.75 mg/m³ 0.4, 0.1, 0.06 mg/m³ 0.003 mg/m³ 6 h daily	4 days 15 days 60 days	at higher concentrations (0.40 & 0.75 mg/m³) histological changes in the lung; no-observed-adverse-effect levels from 0.003 - 0.06 mg/m³ 6 h daily; TLV - 0.1 mg/m³ paraquat aerosol	Gage (1968)
Rat	inhalation[a] - 1.1, 0.05 mg/m³ 6 h daily	4 1/2 months	biochemical, histochemical, and histological changes in the lung at 1.1 mg/m³; no-observed-adverse-effect level below 0.05 mg/m³ paraquat aerosol	Bainova et al. (1972)
Rabbit	inhalation[a] - 10 mg paraquatin 100 ml water for the aerosol 2 h daily	3 months	no clinical, functional and histological changes in the lung; no toxic effects	Seidenfeld et al. (1978)

[a] Respirable paraquat aerosol.

Pulmonary oedema was also a characteristic of the destructive phase, and was frequently of sufficient severity to result in the death of the animals. Animals surviving the initial destructive phase, which occurred in the first 1 - 4 days after acute paraquat overexposure, progressed to what has been termed the "proliferative" phase. In this phase, the lung was infiltrated with profibroblastic cells that rapidly differentiated into fibroblasts which, in some cases, progressed to fibrosis. The histopathological outcome of the second phase may be influenced by the treatment regimen, however. Administration of repeated low doses of paraquat, which less severely damaged the alveolar epithelial cells, could also induce a hyperplasia of the Type II cells. This response may represent an attempt by the lung to repair the damaged epithelium.

Following a single high dose of paraquat to animals, the earliest ultrastructural changes were observed in the Type I alveolar epithelial cells, approximately 4 - 6 h after treatment, and were usually characterized by cellular and mitochondrial swelling, increased numbers of mitochondria, and the appearance of dark granules in the cytoplasm. When a high dose (approximately LD_{50} or greater) was given, the lesions in the Type I cells often progressed to the point of complete cellular disintegration leaving areas of exposed basement membrane (Kimbrough & Gaines, 1970; Smith et al., 1973; Smith & Heath, 1974; Vijeyaratnam & Corrin, 1971; Klika et al., 1980).

In contrast to the effects on Type I pneumocytes, however, the capillary endothelial cells were remarkably resistant to the toxic effects of paraquat (Sykes et al., 1977).

Ultrastructural lesions in the alveolar Type II pneumocytes were also observed shortly after single dose paraquat exposure, although, generally, these lesions were not apparent until after the first lesions were seen in the Type I cells (Kimbrough & Gaines, 1970). Swollen mitochondria and damage to the lamellar bodies usually occurred between 8 and 24 h after a high dose of paraquat (Robertson, 1973; Robertson et al., 1976). Progressive deterioration of the Type II cells continued, resulting in completely denuded alveolar basement membranes and debris-filled alveolar spaces (Vijeyaratnam & Corrin, 1971). Infiltration and proliferation of fibroblasts may produce fibrosis that obliterates the alveolar structure (Smith & Heath 1974).

Vijeyaratnam & Corrin (1971) observed that less severely affected parts of the lung appeared to undergo epithelial regeneration, 7 - 14 days after a single dose of paraquat. Electron microscopic examination revealed the alveoli to be lined with cuboidal epithelial cells that closely resembled Type II pneumocytes except for a general lack of lamellar

bodies. Similar phenomena have also been noted by other investigators who administered paraquat in the diet (Kimbrough & Linder, 1973) or as repetitive intraperitoneal administrations (Smith et al., 1974). Thus, in animals where the paraquat dose was sufficient to kill only the Type I pneumocytes, the surviving Type II cells repaired the damaged epithelium by proliferating and subsequently differentiating into Type I epithelial cells. Inhaled paraquat in aerosol produced initial necrosis and sloughing of the epithelia and type 2 pneumocyte hyperplasia, fibroblast proliferation, and increased synthesis of collagen in mice (Popenoe, 1979).

Histochemical alterations have been noted in rats exposed through inhalation to 1.9 and 1.1 mg/m^3 paraquat respirable aerosol, 6 h/day, 6 days/week, for 4 1/2 months. The histoenzyme activity of NAD lactate dehydrogenase-diaphorase, ß-glucuronidase (EC 3.2.1.31), and acid phosphatase (EC 3.1.3.2) was enhanced in the epithelial cells and in areas of pneumonitis (Bainova et al., 1972). The changes were concentration-related, although the activity of succinate dehydrogenase (EC 1.3.99.1) and aspartate esterase appeared to be less pronounced in comparison with the controls (Bainova et al., 1972).

7.1.1.2 Species differences in lung injury

Butler & Kleinerman (1971) injected rabbits intraperitoneally with total doses of from 2 - 100 mg/kg body weight. Thymus atrophy was observed, but most lungs showed only occasional and small histological deviations that were poorly correlated with the clinical signs of paraquat intoxication. The study confirmed the resistance of the rabbit to paraquat-induced lung lesions (Clark et al., 1966), and no evidence of any kind of pulmonary disease was found; nor could significant lung injury be established in rabbits after 30 days ingestion of 11 mg paraquat/kg in distilled water (Dikshith et al., 1979). However, some animals showed pulmonary fibrosis and emphysema, and a few changes were present in all parenchymatous organs (Mehani, 1972; Zavale & Rhodes, 1978; Dikshith et al., 1979). The rabbit also proved to be less sensitive, than the rat, after inhalation exposure (Gage 1968a; Seidenfeld et al., 1978).

According to Murray & Gibson (1972), and Hundsdorfer & Rose (1980), guinea-pigs treated orally or sc did not develop the same type of progressive pulmonary fibrosis as paraquat-intoxicated rats. In hamsters, a single administration did not induce lung damage, but prolonged exposure resulted in lung fibrosis (Butler, 1975).

In conclusion, for lung toxicity studies, a characteristic dose-related pulmonary fibrosis can be induced in the rat,

mouse, dog, and monkey (Murray & Gibson, 1972) but not in the rabbit, guinea-pig, or hamster.

7.1.1.3 Lung function studies

Rabbits exposed to an aerosol of 200 mg paraquat in 100 ml distilled water (Seidenfeld et al., 1978) survived more than 3 exposures but showed significantly reduced arterial oxygen tension and an increased alveolar arterial O_2 gradient; specific compliance decreased and functional residual capacity and breathing frequency increased. Lam et al. (1980) administered paraquat at 27 mg/kg body weight ip to rats and 0.5 mg/kg body weight intratracheally. After 12 h, decreases were observed in total lung capacity, functional residual capacity, vital capacity, residual volume, and alveolar volume. These deviations persisted for 72 h. Oral administration of paraquat at doses ranging from 1 mg/kg body weight - 13.5 mg/kg body weight to rats resulted in functional lung changes after 24 h.

Thus clinical, functional, and pathomorphological studies after single and repeated exposure demonstrated that the spectrum of paraquat lung disease depended on the magnitude of the dose and the manner of administration (Seidenfeld et al., 1978; Restuccia et al., 1974).

7.1.2 Renal system

In paraquat toxicity, kidney damage often precedes signs of respiratory distress (Clark et al., 1966; Butler & Kleinerman, 1971; Murray & Gibson, 1972) (Table 11). Paraquat is excreted mainly via the urine and the concentrations of the herbicide in the kidneys are relatively high (section 6.1). Gross pathological and histological examinations of paraquat-poisoned rats, guinea-pigs, rabbits, and dogs revealed vacuolation of the convoluted renal tubules and proximal tubular necrosis (Bainova, 1969a; Murray & Gibson, 1972; Tsutsui et al., 1976). The degeneration of the proximal tubular cells has also been confirmed by electron-optical studies (Fowler & Brooks, 1971; Marek et al., 1981).

Paraquat is actively secreted by the kidney base transport system. The nephrotoxicity caused by paraquat is pronounced and appears to be restricted to the proximal nephron (Ecker et al., 1975: Gibson & Cagen, 1977; Lock & Ishmael, 1979; Purser & Rose, 1979).

7.1.3 Gastrointestinal tract and liver

The clinical signs of acute and chronic oral poisoning (Kimbrough & Gaines, 1970; Murray & Gibson, 1972; Bainova,

1969a) or of ip injection (Butler & Kleinerman, 1971) include transient diarrhoea and body weight loss, decreased food intake, and dehydration. Some of the animals vomited soon after paraquat administration. Residual skin contamination after dermal toxicity studies on rabbits (McElligott, 1972) caused severe tongue ulceration and an unwillingness to eat. The adverse irritant effects were minimized by continued restraint after skin decontamination of the treated rabbits.

There have been several reports of liver damage following exposure to high doses of paraquat (Clark et al., 1966; Bainova, 1969a; Murray & Gibson, 1972; Tsutsui et al., 1976; Gibson & Cagen, 1977, Cagen et al., 1976). Centrilobular necrosis of hepatocytes with proliferation of the Kupfer cells and bile canals have been described.

In general, liver damage in experimental animals has not been severe compared with lung and kidney damage. Serum enzyme activities (SGOT, SGPT, LAP) only increased when large amounts of paraquat were given (Giri et al., 1979).

7.1.4 Skin and eyes

The herbicide can provoke local irritation of the skin and eyes. Clark et al. (1966) found skin irritation in rabbits only when paraquat was applied beneath occlusive dressings in aqueous solutions (total dose 1.56, 5.0, and 6.25 mg ion/kg body weight). In mice and rats, the application of 5 - 20 g paraquat/litre solutions in single and 21-day repeated dermal toxicity tests provoked dose-related toxic dermatitis with erythema, oedema, desquamation, and necrosis (Bainova, 1969b). Doses from 1.56 to 50 mg/kg, in repeated 20-day studies using the occlusive technique (McElligott, 1972) resulted in local erythema and scab formation. The histological changes consisted of parakeratosis and occasional intra-epidermal pustules. A delayed skin irritant action of the herbicide was reported by Fodri et al. (1977) in guinea-pig studies.

No skin sensitization was observed in studies on guinea-pigs when paraquat was applied (Bainova, 1969b; Fodri et al., 1977).

The instillation of dilutions of paraquat (up to 500 g/litre) in rabbit eye induced inflammation within 24 h and this continued for 96 h (Clark et al., 1966). Sinow & Wei (1973) introduced 62.5, 125, 250, 500, and 1000 paraquat/litre into the rabbit eye. Concentrations of 62.5 and 125 g/litre caused severe conjunctival reactions; higher levels (250 - 500 g/litre) provoked iritis and pannus, while at the 500 g/litre concentration there was corneal opacification, iritis, and conjunctivitis. All rabbits receiving 0.2 ml of paraquat at 1000 g/litre in 1 eye or 0.2 ml of a concentration of 500

g/litre in both eyes died within 6 days of application (Sinow & Wei, 1973).

Both conjunctival and dermal application of different concentrations induced systemic toxicity (Sinow & Wei, 1973; Clark et al., 1966; Bainova, 1969b; Kimbrough & Gaines, 1970; Makovskii, 1972; McElligott, 1972), lung, kidney, and liver damage, and death.

7.1.5 Other systems

No specific functional, histological, or biochemical effects of paraquat have been reported in other systems that have been examined; this is of prime importance in an evaluation of its toxicity. When lethal doses of paraquat are given to rats, symptoms consistent with neurological disturbances have been observed. These include decreased motor activity, lack of coordination, ataxia and dragging of the hind limbs (Smith et al., 1973). Also associated with near lethal or lethal doses are damage to the myocardium (Tsutsui et al., 1974), haemolytic anaemia (Bainova, 1969a), increased haemosiderin in the spleen (Bainova et al., 1972) and increased concentrations of plasma corticosteroids (Rose et al., 1974b).

7.1.6 Effects on reproduction, embryotoxicity, and teratogenicity

7.1.6.1 Effects on reproduction

Some histological changes in the testes have been reported in a few paraquat toxicity studies. Butler & Kleinerman (1971) found multinuclear giant cells in rabbit testicular tubules. When paraquat was orally administered at 4 mg/kg body weight to male rats for 60 days and the testes were examined, there were no significant deviations in the spermatozoa count or motility, nor were there any biochemical changes in the several enzymes of testes homogenates. The histoenzyme activity of lactate dehydrogenase, succinate dehydrogenase, DPN-diaphorase, alkaline phosphatase, and acid phosphatase in the treated animals did not differ from that of the controls, nor did quantitative and qualitative histological examination of the testicular tubule cells reveal any abnormality.

A 3-generation reproduction study has been carried out on rats treated with paraquat ion at 100 mg/kg diet (FAO/WHO, 1973). There were no significant abnormalities in fertility, fecundity, and neonatal morbidity or mortality, nor were there any signs of gonadotoxicity or structural or functional

lesions. Pulmonary function in the treated offspring was normal.

Clegg (1979) has reviewed animal reproduction and carcinogenicity studies conducted in relation to the safe use of pesticides.

7.1.6.2 Embryotoxicity and teratogenicity

Oral or ip administration of high doses of paraquat to mice and rats on various days of gestation produced significant maternal toxicity, evidenced by increased mortality rates (Bainova & Vulcheva, 1974; Bus et al., 1975). Examination of the fetuses from the higher-dose groups revealed a reduction in fetal body weights, delayed ossification of the sternabrae, and increased resorption rate in mice, as a result of the maternal intoxication. The minimal embryotoxic effect seemed due in part to difficulty in crossing the placenta, reflected by low concentrations of paraquat in the embryo relative to maternal tissues (Bus et al., 1975). The absence of a specific embryotoxic action of paraquat has also been observed and reported in other studies on rats (Khera et al., 1968; Luty et al., 1978), mice (Selypes et al., 1980), and rabbits (FAO/WHO, 1973).

In a perinatal toxicity study, Bus & Gibson (1975) administered paraquat at 50 or 100 mg/litre in the drinking-water to pregnant mice beginning on day 8 of gestation, with continued treatment of the litters up to 42 days after birth. Paraquat treatment did not alter postnatal growth rate, although the mortality rate in the 100 mg/litre-treated mice increased to 33% during the first 7 days after birth. It was also noted that paraquat at 100 mg/litre significantly increased the sensitivity of the pups to oxygen toxicity on days 1, 28, and 42 after birth.

7.1.7 Mutagenicity

Paraquat has been found to have minimal to no genotoxic activity when evaluated in a variety of *in vitro* and *in vivo* test systems. In studies producing weakly positive results (Moody & Hassan, 1982; Parry 1977, 1973; Tweats, 1975; Benigni et al., 1979; Bignami & Grebelli, 1979), which were limited to *in vitro* studies, paraquat genotoxicity was accompanied by high cytotoxicity. These results are best explained by Moody & Hassan (1982), who showed that the mutagenicity of paraquat in bacterial test systems (*Salmonella typhimurium* TA 98 and TA 100) was mediated by the formation of superoxide. However, other investigators (Andersen et al., 1972; Levin et al., 1982) did not find mutagenic activity in bacterial test systems. Furthermore, paraquat was not mutagenic when

evaluated in human leukocytes and in in vivo cytogenetic tests on mouse bone marrow (Selypes & Paldy, 1978) and dominant lethal tests on mice (Pasi et al., 1974; Anderson et al., 1976).

7.1.8 Carcinogenicity

A carcinogenicity study was performed on mice at dietary levels of 25, 50, and 75 mg/kg per day for 80 weeks (FAO/WHO, 1973). There were reduced weight gains among the animals receiving paraquat, but deaths during the study were associated with respiratory disease. Clinical and histopathological examination determined that paraquat was not tumorigenic in mice.

A 2-year exposure of rats to 1.3 and 2.6 mg/litre, daily, in the drinking-water provoked histopathological changes in the lung, liver, kidney, and myocardium. The lung lesions were dose-related; inflammation, atelectasis, reactive proliferation of the epithelium, pulmonary fibrosis, and pulmonary adenomatosis were noted, but no sign of tumour growth or atypism (Bainova & Vulcheva, 1977). Nor was any increased tumour incidence reported in rats in a 2-year study with a maximum dietary level of 250 mg/kg diet (12.5 mg/kg body weight per day) (FAO/WHO, 1971).

Bainova & Vulcheva (1977) did not discover any indication of tumorigenicity in a 2-year study on rats receiving paraquat at 1.3 or 2.6 mg/litre in their drinking-water (Table 11).

While testing the carcinogenicity of urethane in mice, Bojan et al. (1978) also attempted to evaluate the influence of paraquat on urethane-induced lung tumorigenesis. It is felt that the results of this study are not of relevance for the assessment of the carcinogenic potential of paraquat.

7.2 Effects on Farm Animals

The effects of paraquat on farm animals has been discussed in section 4.3.5. The LD_{50} doses have been established for hen, turkey, cow, and sheep (Howe & Wright, 1965; Clark et al., 1966; Smalley, 1973). Massive doses resulted in convulsions, neurological symptoms, and death due to respiratory failure.

Domestic animals may ingest paraquat by feeding on a sprayed area, as a result of spray drifting on to their pasture, by drinking water contaminated with paraquat used as an aquatic herbicide, or by feeding on a crop sprayed with paraquat as a dessicant. Sheep and calves were given paraquat at concentrations of up to 20 mg/litre drinking-water for 1 month without any obvious ill effects (Howe & Wright, 1965; Calderbank, 1972), and a cow dosed with 2/3 of the LD_{50} of

^{14}C-paraquat gave milk containing less than 0.1 mg/litre. Field tests demonstrated that cattle did not suffer any toxic effects when turned loose on pasture after it had been sprayed with paraquat at 0.45 kg/ha. The same trial showed that horses had local lesions of the mouth and increased mucous secretion after grazing on newly-sprayed pasture (Calderbank et al., 1968). The hazard to stock feeding on such pasture depends on the density of the pasture, the dose of the herbicide, and the length of time that has elapsed since its application.

Paraquat was fed to cattle at levels in herbage of 200 - 400 mg/kg for 1 month without any apparent ill effects, and no residues could be detected in the meat and milk (Calderbank et al., 1968).

However, all domestic animals should be kept far from freshly-sprayed areas, and when crops are treated with paraquat, due attention should be paid to the accepted maximum residue limits.

7.3 Dose-Effect of Paraquat

The acute LD_{50} values for paraquat in various species are given in Tables 12 and 13. The acute toxicity studies of paraquat salts (dichloride, dimethylsulfate, dimethylphosphate) have not shown any significant differences in the acute oral and ip LD_{50} in rats (Clark et al., 1966; Makovskii, 1972).

There were no significant differences in the oral LD_{50} values obtained for the same species from different laboratories, but the acute oral LD_{50} values among the species examined varied.

The effects of repeated paraquat exposure are summarized in Table 11. Paraquat was administered, orally and in the diet, to rats, mice, guinea-pigs, and dogs. The guinea-pigs appeared to be very sensitive (Makovskii, 1972). According to Kimbrough & Gaines (1970), Makovskii (1972), and Bainova (1975), the herbicide has a moderate cumulative toxicity. The joint FAO/WHO meeting (1976) decided on a no-observed-adverse-effect level of 1.5 mg/kg body weight per day in the rat and 1.25 mg/kg body weight per day in the dog. As can be seen from Table 11, effects at lower levels have been observed in other studies.

Guinea-pigs, monkeys, cattle, and human subjects are more sensitive, while rats and birds are less sensitive to paraquat through the gastrointestinal route.

Table 12. Paraquat LD_{50} (mg/kg body weight) and LC_{50} (mg/m^3) in various species

Species/Sex	Oral LD_{50}	Dermal LD_{50}	Inhalation LC_{50} respirable paraquat aerosol
Rat	200[a]		1[c]
Rat (F)	100[e]	90[e]	10[f]
Rat (M)	110[e]	80[e]	10[f]
Rat	126[i]	350[g]	6[g]
Mouse		62[d]	
Rabbit		500[a]	
Rabbit		236[b]	
Rabbit		240[h]	
Guinea-pig	40 - 80[a]		
Guinea-pig (M)	30[b]		
Guinea-pig	22[i]		
Guinea-pig	42[g]	319[g]	4[g]
Monkey	50[i]		
Cat	40 - 50[a]		
Cat (F)	35[b]		
Hen	300 - 380[a]		
Hen	262[b]		
Turkey	250 - 280[j]	approximately 375[j]	
Cow	50 - 75[a]		
Sheep	50 - 75[a]		

[a] Howe & Wright (1965).
[b] Clark et al. (1966).
[c] Gage (1968).
[d] Bainova (1971).
[e] Kimbrough & Gaines (1970).
[f] Bainova & Vulcheva (1972).
[g] Makovskii (1972).
[h] McElliot (1972).
[i] Murray & Gibson (1972).
[j] Smalley (1973).

7.4 Methods for Decreasing Paraquat Toxicity

These have been studied in connection with requirements in the case of paraquat poisoning in man. Clark (1971) showed the efficacy of Bentonite and Fuller's earth in binding orally

Table 13. Paraquat LD_{50} (mg/kg body weight) after parenteral treatment

Species/Sex	Subcutaneous	Intraperitoneal	Intravenous
Rat (F)		19[a]	
Rat	22[b]		
Mouse		30[c]	50[d]
Guinea-pig (F)		3[a]	
Guinea-pig	5[b]		
Turkey		100[e]	20[e]

[a] Clark et al. (1966).
[b] Makovskii (1972).
[c] Smalley (1973).
[d] Ecker et al. (1975).
[e] Bus et al. (1975).

administered paraquat and preventing its absorption from the gastrointestinal tract. Staiff et al. (1973) reported the high adsorption capacity of Amerlite. Smith et al. (1974) found considerably reduced plasma-paraquat levels after the combined treatment of rats with purgatives and bentonite suspension; these rats survived a dose that normally killed 90 - 100% of the animals. The absorption capacities of six absorbent materials were tested by Okonek et al. (1982) who demonstrated that activated charcoal was the most successful in absorbing ingested paraquat in rats.

Another way of decreasing paraquat absorption is to introduce an emetic in the concentrated formulations. Kawai et al. (1980) examined the protection this provided in fasting and non-fasting male and female dogs that were given paraquat containing an emetic. The amount of paraquat eliminated by vomiting was 61 - 86% of the orally-administered dose. In the group given paraquat only, the blood level averaged 44 mg/litre; in the group given paraquat and emetic, it was 0.26 mg/litre.

7.5 Relation Between Age, Sex, and Toxicity

There is no evidence that paraquat is more toxic to either sex of adult experimental animals (section 7.3) Young rats were more resistant than older rats, and some authors have paralleled this resistance with that of young rats to oxygen toxicity. Smith & Rose (1977b) found a more than 40% increase

in cumulative mortality in 180 g rats compared with 50 g rats, after oral dosing with paraquat at 680 µmol/kg body weight. According to Smith & Rose (1977b), the difference in renal function between young and mature rats accounted for the difference in paraquat toxicity.

8. EFFECTS ON MAN

8.1 Accidental and Suicidal Poisoning

8.1.1 Case reports

The first fatalities from acute paraquat poisoning occurred in 1964 and were reported in 1966 (Bullivant, 1966). By 1977, 600 deaths had been reported following accidental or intentional ingestion of paraquat. The number of accidental cases of poisoning is small relative to instances of suicide. Because of different requirements or practices for notification or reporting of cases of poisoning in the many countries in which paraquat is used, the magnitude of the problem is difficult, if not impossible, to determine. Some representative reports on acute paraquat poisoning are summarised in Table 14.

The earlier cases of paraquat intoxication were mostly accidental (Fennelly et al., 1968; Matthew et al., 1968; Masterson & Roche, 1970; Malone et al., 1971). These cases seemed to have resulted mainly from the habit of decanting the liquid formulations into small unmarked or incorrectly labelled containers such as beer, wine, or soft-drink bottles.

An increased ratio of suicidal to accidental poisoning has been noted in recent years (Fletcher, 1975; Carson & Carson, 1976; Fitzgerald et al., 1978a; Bramley & Hart, 1983). This change from accidental to suicidal poisoning was also reflected in the enhanced percentage of fatal cases, shorter survival times, and significantly higher tissue and body fluid levels (Connolly et al., 1975; McGeown, 1975; Park et al., 1975; Carson & Carson, 1976; Howard, 1979a; Sugaya et al., 1980; Bismuth et al., 1982).

While the vast majority of poisoning cases are due to swallowing, a small number of fatal cases of accidental paraquat poisoning via the skin have been reported when liquid concentrates (200 g/litre) have been applied in order to kill body lice (Ongom et al., 1974; Binns, 1976). A few other fatal and non-fatal cases have been reported following skin-contamination (McDonagh & Martin, 1970; Kimura et al., 1980).

8.1.2 Distribution of cases of paraquat poisoning

Cases of acute paraquat poisoning have been reported in: Bulgaria (Mircev, 1976), Denmark (Pederson et al.,1981), England, Ireland, Scotland, and the Netherlands (Fletcher, 1975), the Federal Republic of Germany (Grundies et al., 1971; Hofman & Frohberg, 1972; Fletcher, 1975; Fischer & Kahler,

Table 14. Case report data on accidental and suicidal acute paraquat poisoning

Number of cases		Fatal	Non-fatal	Fatality	Reference
19		12	7	63%	Malone et al. (1971)
24	3 accidental 19 suicidal 2 homicidal	10	14	42%	Connolly et al. (1975)
25	10 accidental	17	8	68%	McGeown (1975)
31	7 accidental 21 suicidal 3 homicidal	18	13	58%	Park et al. (1975)
33	7 accidental 19 suicidal	26	7	79%	Carson & Carson (1976)
16		7	9	44%	Wright et al. (1978)
136	77 suicidal	92	44	68%	Fitzgerald et al. (1978)
10		10	0	100%	Natori et al. (1979)
188		69	119	37%	Higginbottom et al. (1979)
79		28	51	35%	Proudfoot et al. (1979)
68	68 suicidal	41	27	66%	Howard (1979)
6	6 suicidal	5	1	83%	Sugaya et al. (1980)
28	12 suicidal	17	11	61%	Bismuth et al. (1982)
262	95% deliberate intent	94 (36%)	168 (64%)	36%	Bramley & Hart (1983)

1979), France (Faure et al., 1973; Gervais et al., 1975; Bismuth et al., 1982; Efthymiou, 1983), Hungary (Farago et al., 1981), Poland (Firlik, 1978), Switzerland (Schlatter, 1976), the USA (Kimbrough, 1974; Dearden et al., 1978; Stephens et al., 1981), and in Yugoslavia (Vucinovic, 1978). Recently, a number of cases of paraquat poisoning, mainly suicidal, have also been reported in Japan (Takahashi et al., 1978; Natori et al., 1979; Tomura et al., 1979; Kimura et al., 1980; Matsumoto et al., 1981). No attempt has been made to make this list exhaustive, in fact the distribution is worldwide.

8.1.3 Route of entry

By far the most frequent route of poisoning has been ingestion. An unusual case of subcutaneous injection of 1 ml paraquat by a mentally disturbed farmer was reported in Israel (Almog & Tal, 1967). Cases of dermal poisoning have been mentioned in section 8.1.1. There is no evidence of fatal poisoning as a result of inhalation.

8.1.4 Formulations

Paraquat trade names are listed in Table 3. Concentrated liquid formulations have been responsible for most (and more severe) poisonings than granular forms, which contain less paraquat (McGeown, 1975; Park et al., 1975; Fitzgerald & Barnville, 1978; Wright et al., 1978; Higginbottom et al., 1979; Howard, 1979a).

8.1.5 Dose

The minimum lethal dose of paraquat is stated to be about 35 mg/kg body weight for human beings (Pederson et al., 1981; Bismuth et al., 1982).

Symptoms of poisoning depend on the dose absorbed. It is difficult to estimate the dose absorbed from case histories since in many cases the patients spat out part of the paraquat concentrate or vomited profusely after swallowing the herbicide. Some patients have survived after apparently ingesting 50 - 100 ml Gramoxone® (10 - 20 g paraquat), whereas some died after taking as little as 2 sachets of Weedol (2.5g paraquat) (Table 15).

Howard (1979) demonstrated the relationship between the dose of paraquat ingested, the time elapsing between ingestion and institution of treatment, and the ultimate outcome in 68 cases of intentional paraquat poisoning.

Table 15. Recovery from paraquat poisoning involving lung dysfunction

Dose of paraquat ingested	Major organ damage	Notes	Reference
50 ml	kidney, liver, lung	vomiting; pains in stomach; changes in urine and serum	Grundies et al. (1971)
15 ml approx.	lung	nausea; buccal lesions; chest X-ray: poor aeration at lung bases	Lloyd (1969)
10 ml approx.	kidney, lung	oliguria; changed renal function; basal rales; chest X-ray: small bilateral, pleural effusions; limited atelectasis; functional lung change	Fisher et al. (1971)
not specified	kidney, liver, lung	oliguria; serum, and urine changes; minimal deviations in the respiratory function	Fennelly et al. (1971)
30 ml approx.	kidney, liver myocardium, lung	nausea; oliguria; ECG changes; chest X-ray: increased vascular markings	Galloway & Petrie (1972)
granular paraquat	kidney, liver, lung	14 cases with mild oral, renal, lung, and liver impairment	Fitzgerald & Barniville (1978)
50 ml	kidney, liver, lung	vomiting; diarrhoea; abdominal pain; serum and urine changes; dyspnoea, decreased forced vital capacity; chest X-ray: extensive perivascular changes	Rose (1980)

8.1.6 Clinical and pathomorphological data relating to fatal paraquat poisoning

Cases of fatal poisoning can be sub-divided into cases of:

(a) acute fulminant poisoning from a massive dose leading to generalized systemic poisoning and death from a combination of acute pulmonary oedema, oliguria, hepatocellular and adrenal failure and biochemical disturbances (death usually occurs within 1 - 4 days);

(b) less overwhelming poisoning with slower onset of organ failure and death from pulmonary oedema, mediastinitis, and complications of therapy (McGeown, 1975; Fitzgerald et al., 1978a); and

(c) late pulmonary fibrosis (death ensuing 4 days to several weeks later).

8.1.6.1 Respiratory system

(a) Clinical data

Soon after ingestion, there is oropharyngeal pain and swelling, followed within a few days by exudation, ulceration, and mucosal sloughing, sometimes with pseudomembrane formation, which on occasion leads to total sloughing of the oropharynx and oesophagus (Malone et al., 1971). In severe poisoning, pulmonary oedema rapidly ensues with clinical and functional deterioration until death. Less intense, but ultimately fatal, poisoning causes progressive pulmonary fibrosis over days or several weeks, with gradually increasing dyspnoea and hypoxaemic pulmonary failure. Pulmonary oedema may occur from fluid overload in oliguric patients. Mediasteinitis and pneumothorax are occasionally seen (Dearden et al., 1978; Kimura et al., 1980).

Pulmonary function tests reflect the underlying pathology, with hypoxaemia, reduction in lung volume, high alveolar-arterial gradient, and impaired gas transfer (Cooke et al., 1973, Higginbottom et al., 1979). Chest radiographs may show bilateral pulmonary oedema, coalescing consolidations, and later, sequential changes of pulmonary fibrosis (Davidson & McPherson, 1972).

(b) Pathology

At autopsy, the lungs do not collapse properly and the pleural cavity contains a small amount of fluid. In cases of lung fibrosis, the lungs are heavy, firm, dark purple, and

rubbery. Consolidation and decreased aeration are found predominantly at the bases. Emphysema and atelectasis are often found.

Histological studies following lung biopsy and necropsy show pulmonary oedema, haemorrhages, and atelectasis due to pulmonary infiltrates, loss of alveolar epithelial cells and, at a later stage, interstitial and intra-alveolar fibrosis (Smith & Heath, 1976).

During the first 7 days of paraquat poisoning in man, loss of alveolar epithelial cells has been seen with alterations in, or detachment of, the type I and II cells, proliferation of fibroblasts and polymorphous cells, loss of surfactant secretion, and thickening of the alveolar septa by interstitial fibrosis (Toner et al., 1970). The later findings (2 - 3 weeks) involved pulmonary fibrosis and endothelial abnormalities. Dearden et al. (1978) reviewed the histological and electron-microscopic findings in human lungs. Capillary permeability seemed to be enhanced either by vesicles forming transendothelial channels or by disruption of endothelial cells.

8.1.6.2 Renal system

Acute oliguric renal failure is common in severely poisoned patients. Less severe manifestations include impaired renal function, which may disappear before the pulmonary fibrosis progresses (Beebeejaun et al., 1971; Fisher et al., 1971; Fletcher, 1975; Natori et al., 1979; Grant et al., 1980). Other manifestations include proteinuria, with hyaline casts, white and red blood cells. Tubular damage is reflected in glycosuria, aminoaciduria, and excessive leaking of phosphorus, sodium, and uric acid (Vaziri et al., 1979).

Soft, pale, swollen kidneys with extensive tubular necrosis, compatible with toxic injury, are found at necropsy (Beebeejaun et al., 1971). Sometimes necrosis of the proximal tubules is found together with extreme dilatation of the distal tubules of the kidney (Shuzui, 1980).

8.1.6.3 Gastrointestinal system, the liver, and the pancreas

The initial symptoms after oral ingestion of paraquat are nausea, vomiting, upper abdominal pain, and diarrhoea. Perforation of the oesophagus is uncommon (Ackrill et al., 1978; Natori et al. 1979).

The ingestion of large doses of paraquat has resulted in severe liver damage (Ward et al., 1976; Grant et al., 1980) with progressive metabolic acidosis (Shuzui, 1980; Sugaya et al., 1980). Fatty degeneration of periportal hepatocytes and sporadic cellular necrosis in the central region of the liver

lobules have been described (Matsumoto et al., 1980). Cholestasis and portal inflammation may occur (Matsumoto et al., 1981). Oedematous degeneration or necrosis of both the intra-hepatic and extra-hepatic bile ducts, and of the gall bladder, have also been noted (Mullick et al., 1981).

Takayama et al. (1978) noted stasis of the pancreatic duct, with increased serum amylase levels after severe paraquat poisoning.

8.1.6.4 Cardiovascular system

Occasionally, toxic myocarditis after paraquat ingestion has been described (Bullivant, 1966; Malone et al., 1971; Copland et al., 1974; Grant et al., 1980).

Takahashi et al. (1978) found fibrinoidal necrosis of the small arteries in the pancreas, kidney, and liver on days 3 - 6 following ingestion.

8.1.6.5 Central nervous system

The ingestion of very high doses of paraquat provoked anxiety, convulsions, ataxia, and semi-consciousness (Grant et al., 1980; Mukada et al., 1978). Haemorrhagic leukoencephalopathy was present throughout the central nervous system, involving almost exclusively the white matter. Focal haemorrhage and demyelinization were present at various stages together with haemorrhagic meningitis.

8.1.6.6 Adrenal glands

Adrenal cortical necrosis may contribute to death in severe paraquat poisoning and the severity of the damage appears to be dose-related (Nagy, 1970; McGeown, 1975; Fitzgerald et al., 1977a; Takahashi et al., 1978).

8.1.6.7 Pregnancy

A woman, who accidentally swallowed paraquat in the 28th week of pregnancy (Fennelly et al., 1968), died 20 days later. Gross pathological examination did not reveal any abnormalities in the fetal organs.

A woman, in the 7th month of pregnancy, intentionally ingested about 60 ml of technical paraquat (Takeuchi et al., 1980) and vomited approximately half that amount. Oliguria, jaundice, and cough with sputum production progressed; fetal heartbeat disappeared on the 13th day and the next day the dead fetus was delivered. The mother died on the 17th day

after poisoning. The lungs of the dead fetus were filled with the debris of amniotic fluid; the fetus had begun intrauterine respiration to compensate for the insufficient oxygen supply. No symptoms of paraquat poisoning were noted in the body of the neonate.

A case report published by Musson & Porter (1982) concerning paraquat ingestion by a 20-week pregnant woman, confirmed the lack of teratogenic risk in human beings. The pregnancy was allowed to continue after the treatment of the mother. The infant was followed up to the age of 3 years and did well clinically, with normal laboratory tests, development, and behaviour.

8.1.7 Recovery from paraquat poisoning

In the largest series reported (68 - 188 cases) (Fitzgerald et al., 1978a; Higginbottom et al., 1979; Howard, 1979a; Proudfoot et al., 1979), survival rates varied from 32% to 65% (Table 14) Factors determining recovery from paraquat poisoning, reviewed by Fletcher (1975), McGeown (1975), Fitzgerald & Barniville (1978), Howard (1979a), and Bismuth et al. (1982), are shown in Table 16.

Victims of paraquat poisoning, who escape major pulmonary complications, usually recover fully within a few weeks of ingestion. Renal, gastrointestinal, and hepatic manifestations return to normal (Fisher et al., 1971; Beebeejaun et al., 1971; Grundies et al., 1971; Galloways & Petrie, 1972).

Minor pulmonary functional and radiographic abnormalities may be transient and are of doubtful relationship to paraquat lung injury. Some patients have recovered despite major pulmonary abnormalities (Table 15). Among 5 survivors, Schlatter (1976) reported no signs of lung residual disorders. Fitzgerald et al., (1979a) followed, for at least a year, 13 survivors of paraquat poisoning to determine the prevalence of residual pulmonary disability. Of 11 adults, 5 (all non-smokers) did not have any clinical, radiological, or functional evidence of pulmonary dysfunction; 4 others (all smokers) were considered normal on clinical and chest X-ray examination, but had a mild deficit in pulmonary function, while the remaining 2 adults were known to have suffered from respiratory disability before the paraquat poisoning. Only 1 patient showed new and persistent lung infiltrates that could be ascribed to permanent paraquat lung damage. No abnormalities were discovered in the 2 children studied.

Table 16. Factors determining recovery from paraquat poisoning

No.	Factor	Notes
1.	Route of entry	Most paraquat poisonings have occurred following ingestion; ingestion following a meal usually has less serious consequences; skin contamination with liquid concentrate formulations is dangerous; poisoning through inhalation is usually benign
2.	Dose	Dose rarely known, but usually, for survivors, less than 6 g paraquat, often, spat out or vomited after ingestion
3.	Intention	High mortality rates established in suicidal or homicidal poisoning; many more survivors reported among cases of accidental poisoning
4.	Formulation ingested	High mortality rate registered after ingestion of liquid concentrates; survivors have more often than not ingested dilute or granular formulations
5.	Time of starting treatment	Treatment should start as soon as possible; delay of more than 2 - 5 h reduces chances of survival; patients hospitalized several days after paraquat ingestion have minimal chance of recovery
6.	Decreased gastrointestinal absorption	Occurs when there is vomiting, use of emetics stomach washout, application of adsorbents (such as Fuller's Earth or bentonite), single or repeated, and forced diarrhoea; such treatment should be as prompt as possible; a delay of more than 5 h adversely affects the safe and effective elimination of paraquat; care should be taken to avoid complications (aspiration of Fuller's Earth, oesophagal perforation)
7.	Blood paraquat concentrations	Fig. 6 (section 6.2.3) demonstrates importance of paraquat plasma concentrations for prognosis
8.	Urine paraquat concentrations	Patients excreting more than 1 mg paraquat/h, 8 h or more after ingestion, unlikely to recover
9.	Renal function	Patients with severe renal damage or renal failure usually die
10.	Forced diuresis	Should not be instituted when renal damage with oliguria present; caution needed during the first 24 h
11.	Haemodialysis	Important if forced diuresis cannot be carried out

8.2 Occupational Exposure

8.2.1 Epidemiological studies and case reports

8.2.1.1 Spraying personnel

Paraquat has been in agricultural use since the early 1960s and several surveys have been conducted on spray operators (Swan, 1969; Hearn & Kier, 1971; Makovskii, 1972; Staiff et al., 1975; Seiber & Woodrow, 1981; Howard, 1979b, 1980, 1982; Chester & Ward, 1981; Howard et al., 1981; Chester & Woollen, 1982; Wojeck et al., 1983). Some of these studies were aimed at clinically evaluating possible adverse effects, others at estimating inhalatory and dermal exposure. Some of the latter studies have been summarised in Table 17 from which it can be seen that:

(a) the main route of exposure of agricultural workers to paraquat is via the skin; respiratory exposure is negligible.

(b) The worst case of exposure (of those examined) was via knapsack spraying.

Table 17. Comparision of dermal and inhalation exposure resulting from various methods of application

Method of application		Dermal exposure (mg/h)	Respiratory exposure (mg/h)
Hand-held knapsack[a]		66 (12.1 - 169.8)	$(0.45 - 1.3) \cdot 10^{-3}$
Vehicle mounted[b]		0.4 (0.1 - 3.4)	$0 - 2 \cdot 10^{-3}$
Aerial[c] -	a) Flagman	0.1 - 2.4	$0 - 47 \cdot 10^{-3}$
	b) Pilot	0.5 - 0.1	$0 - 0.6 \cdot 10^{-3}$
	c) Mixer/loader	0.18	$1.3 - 1.5 \cdot 10^{-3}$

[a] From: Chester & Woolen (1982).
[b] From: Staiff et al. (1975).
[c] From: Chester & Ward (1981).

In Malaysian rubber plantations, exposure is likely to be greater than in most other situations (Swan, 1969). Weed control is required continuously for 10 months of the year, and the herbicide is applied by knapsack sprayers during the

entire working day, 6 days a week. The high temperature and humidity together with the light clothing of the sprayers increase the potential risk of dermal exposure. In 1965, a study was carried out on a team of 6 sprayers, and in 1967 on 4 teams, to estimate the efficacy of protective measures. The operators used spray dilutions containing paraquat at 0.5 g/litre, for 12 weeks. Attention was paid to personal hygiene. Each man was given a thorough physical examination, and urine samples were taken before spraying began and at weekly intervals throughout the study. Paraquat analyses were carried out using the method of Calderbank & Yuen (1965). Chest X-rays were taken before the study started and at the end of the 6th and 12th weeks.

In the course of the 2 studies, a total of 528 urine samples were examined. Paraquat was found on 131 occasions, the maximum concentration detected being 0.32 mg/litre in the first study and 0.15 mg/litre in the second. Average urine levels of paraquat of 0.04 mg/litre were found in the 1965 study, and of 0.006 mg/litre in the 1967 study. After spraying ceased, these levels declined steadily to become undetectable within a week - with one exception. It was concluded that the workers were not subjected to hazardous levels of paraquat.

Both trials showed that about half of the men had suffered mild irritation of the skin and eyes, but had recovered rapidly with treatment. Two cases of scrotal dermatitis occurred in workers wearing trousers that were continuously soaked by the spray solution. There were also 2 cases of epistaxis. All chest radiographs were normal.

Studies over a period of several years on 296 workers were performed by Hearn & Keir (1971) on a Trinidad sugar estate. This survey drew attention to nail damage following gross contamination with paraquat at 1 - 2 g/litre that ranged in severity from localized discoloration to nail loss. The typical distribution of the lesions - affecting the index, middle, and ring fingers of the working hand - suggested that they had occurred through leakage from the knapsack sprayer, and inadequate personal hygiene. Apart from 2 cases of contact dermatitis of the hands, no skin, eye, or nose irritation was reported, nor were there any systemic effects.

Similar data were obtained by Makovskii (1972), who examined several groups of workers spraying paraquat as a herbicide and dessicant in cotton fields during the hot season. These workers were exposed to paraquat aerosol concentrations of 0.13 - 0.55 mg/m^3 air. Dermal exposure was low, not more than 0.05 - 0.08 mg paraquat on the hands and face. There were no complaints, nor did the clinical and laboratory examinations of the workers demonstrate any significant deviations from the matched control groups.

In the USA (Staiff et al., 1975), the exposure of field workers operating tractor-mounted spray equipment in orchards was determined. About 4.6 litre paraquat liquid concentrate (291 g/litre) was used in 935 litre water per h. In addition, exposures from yard and garden applications were studied in volunteers using pressurized hand dispensers containing paraquat solution (4.4 g/litre). Dermal contamination was measured by adsorbent cellulose pads attached to the worker's body or clothing, and by hand-rinsing in water in a polyethylene bag. Special filter pads were used in the filter cartridges of the respirators worn by the subjects under study.

In all, 230 dermal and respiratory exposure pads, 95 samples of hand-rinse water, and 130 urine samples, collected during and following the spray, were analysed. This involved 35 different paraquat application situations. The exposure of field workers was found to range from about 0.40 mg/h (dermal) to less than 0.001 mg/h (inhalation). As for individuals spraying the yard or garden, exposure ranged from 0.29 mg/h (dermal)to less than 0.001 mg/h (inhalation).

In almost all cases, dermal exposure affected the hands. The respiratory paraquat values were generally below the sensitivity level of the analytical method. No detectable paraquat concentrations were found in the urine samples (lower limit 0.02 mg/litre). This study confirmed the general safety of paraquat under correct conditions of use.

The potential long-term hazard associated with the use of paraquat has also been studied. Howard et al. (1981) studied the health of 27 spraymen who had been exposed to paraquat for many months per year for an average of 5.3 years, and compared them with two unexposed control groups consisting of 24 general workers and 23 factory workers. There were a few skin lesions resulting from poor spraying techniques and 1 case of eye injury. The workers were given full clinical examinations and lung, liver, and kidney function tests were carried out. There were no significant differences in all health parameters measured between the groups, which led the authors to suggest that the long-term use of paraquat was not associated with harmful effects on health.

A paraquat formulation (240 g/litre) diluted 300 times by volume with water was sprayed for 2 h on weedy ground (Kawai & Yoshida, 1981). No irritation of the eyes and the skin was reported. The urine of the workers who wore gauze masks contained 1.4 - 2.7 µg paraquat, 24 h after the spraying. The urine of workers who had worn a high-performance mask did not contain detectable levels of paraquat. During the spraying operations, the concentration of paraquat aerosol was 11 - 33 µg/m^3 air. The total dermal exposure was about 0.22 mg. The authors discussed the need for protective

equipment to decrease skin contact with paraquat and to avoid aerosol inhalation.

Quantitative estimates of dermal and respiratory exposure of 26 plantation workers in Malaysia (Chester & Woollen, 1982) have shown a mean dermal dose of 1.1 mg/kg body weight per h. The highest individual total exposure was equivalent to 2.8 mg/kg body weight per h; the mean respiratory exposure was 0.24 - 0.97 µg paraquat/m^3 air. Spray operators and carriers were exposed to an order of 1% or less of a TLV of 0.1 mg/m^3 for respirable paraquat. Urine levels of paraquat were generally below 0.05 mg/litre.

A study was carried out on a group of 14 spray men in Thailand using conventional high-volume knapsack sprayers and low-volume spinning disc applicators with paraquat ion concentrations of 1.5 g/litre and 20 g/litre, respectively (Howard, 1982). Irritation of unprotected skin was found, and this was severe in workers using high spray concentrations (caustic burns on the feet after work with spinning disc applicators and paraquat solution (20 g/litre)). Urinary paraquat levels after 14 days spraying were significantly higher (10.21 - 0.73 mg/litre) in unprotected men using both concentrations, and there was evidence that urinary levels of paraquat increased as the trial progressed. No evidence of systemic toxicity was discovered among the spray men undergoing clinical and radiographic examination 1 week after spraying ended. The author concluded that spray concentrations in hand-held equipment should not exceed 5 g paraquat ion/litre.

After tomato spraying in the USA, the total body exposure to paraquat was determined to be 168.59 mg/h (Wojeck et al., 1983). The use of enclosed tractor cabs or a high clearance tractor reduced total body exposures to paraquat to 26.91 mg/h or 18.38 mg/h, respectively. The authors reported that the total body exposure of tractor spray men working in two citrus locations was proportional to the tank concentrations (paraquat dilutions of 1.1 g/litre and 0.7 g/litre were applied); exposure levels of 28.50 mg/h and 12.16 mg/h were found for workers using the higher and the lower concentrations, respectively. In all situations studied, the respiratory exposure was consistently a small fraction (< 0.1%) of the total body exposure. Exposure was mainly through the skin.

8.2.1.2 Formulation workers

Groups of workers exposed to formulations were examined by Howard (1979b). The first group of 18 workers in England comprised subjects exposed to dust and liquid paraquat formulations during a 37.5 h working week, the mean length of

exposure being 5 years. The second group also comprised 18 males, from Malaysia, exposed to liquid concentrate formulations during a 42-h working week, the mean length of exposure being 2.3 years. Partly protective clothing was worn. However, in Malaysia, no gloves, rubber aprons, or goggles were used. The medical records and the dermatological examinations revealed acute skin rashes, nail damage, epistaxis, blepharitis, and delayed wound healing in 12 - 66% of these workers. Delayed caustic effects were often found among the Malaysian formulation workers where a lower level of safety and hygiene was apparent. Clinical examination did not reveal any evidence of chronic contact dermatitis, hyperkeratosis, or eczematous lesions.

8.2.2 Cases of occupational poisoning and local caustic effects

Hayes & Vaughan (1977) reviewed deaths from pesticides in the USA. From 1956 - 1973, no deaths attributable to paraquat were registered among agricultural workers, but in 1974, 4 fatal cases were associated with this herbicide, although it was not clear whether they were accidental, suicidal, or occupational. Conso (1979) reported 17 cases of skin and eye irritation, not accompanied by epistaxis or other signs of systemic effects, in paraquat-exposed workers in France. Bismuth et al. (1983) discussed a few cases of paraquat poisoning due to skin contamination and eye irritation.

The available evidence indicates that, at the recommended dilution rates and correctly used, systemic oral, inhalation, or dermal effects should not be expected. Skin and eye irritation have occurred only when protective measures were disregarded.

However, it should be emphasized that carelessness in handling paraquat may have serious consequences. Fitzgerald et al. (1978a) summarized the clinical findings and pathological details concerning 13 accidents involving paraquat among agricultural workers, 6 of which were fatal. In 5 of these cases, swallowing was involved.

8.2.2.1 Oral ingestion

The ingestion of paraquat may occur accidentally, if liquid concentrates are decanted into unlabelled containers near the working areas (Kawatomi et al., 1979), and dangerous ingestion can occur if operators suck or blow out the blocked pipes or nozzles of spray apparatus. Of the 6 fatalities studied by Fitzgerald et al. (1978a), 3 swallowed Gramoxone® after sucking the outlet of a sprayer. In one non-fatal case, the man had sucked out a nozzle containing diluted paraquat,

while in another case, the man who had blown into the jet, to clear it, escaped with only minor signs of poisoning. Dilute solution blown into the face by the wind and splashes of concentrate that get into the mouth probably explain the resultant signs in the mouth, on the tongue, and in the throat. Smoking with paraquat-contaminated hands has been reported to result in a farmer's developing oropharyngeal irritation, nausea, and muscular weakness (Mourin, 1967).

8.2.2.2 Dermal absorption

Acute dermal paraquat poisoning has been described by Fitzgerald et al. (1978a). The use of a leaking sprayer by a worker with severe extensive dermatitis probably resulted in fatal absorption of paraquat through the damaged skin. Jaros (1978) has described how the use of concentrated solutions of paraquat (50 g/litre instead of 5 g/litre), with an old leaking knapsack sprayer, resulted in paraquat contamination of the neck, back, and legs of a worker. After 4 h of work, he complained of a burning sensation on the neck and scrotum. On admission to hospital 6 days later, cough and respiratory difficulties were recorded. Three days later the patient died of renal and respiratory failure. This author has stressed the need for careful handling of paraquat. Jaros et al. (1978) have discussed several other cases of paraquat poisoning in the CSSR related to paraquat application.

Severe skin damage, followed by death due to respiratory insufficiency, occurred in a woman (Newhouse et al., 1978), 8 weeks after initial contact with paraquat. The toxic dermatitis started with scratches on the arms and legs from the branches of fruit trees. The patient had often failed to wear protective clothing or to shower after spraying. During the 4 weeks preceding her first admission to hospital, she developed ulcers and respiratory complaints combined with anorexia. Damaged and broken skin was thus exposed to paraquat. A chest X-ray and needle biopsy of the lung revealed pulmonary lesions. Seventeen days after discharge from hospital, without a specific diagnosis, she was re-admitted, and died 2 weeks later with progressive lung, hepatic, and renal dysfunction. More recently, Levin et al. (1979) described the clinical and pathomorphological investigation of a patient who died of hypoxia after repeated dermal exposure to paraquat (28 g/litre) and diquat (29 g/litre) in a water-oil dilution - contrary to accepted practice. The worker had used a leaking sprayer. A characteristic ulcer developed at the site of paraquat contact. There was also lung damage. Waight & Weather (1979) reported a fatal case of dermal poisoning with paraquat after prolonged contact with a concentrated formulation following

spillage from a bottle in the back trouser pocket. Wohlfahrt (1982) discussed the factors related to severe paraquat poisoning due to dermal absorption in tropical agriculture. Three fatal incidents followed skin contamination; one victim used paraquat to treat scabies infestation, and one to treat lice. In all cases, the skin was blistered and ulcerated. The patients died of progressive respiratory failure, 4 - 7 days after the accidents. However it has been pointed out that each of these three spraymen showed skin lesions much more severe than would be expected had recommended and customary dilutions been used and that, in one of these cases, the presence of mouth and throat ulceration strongly suggested that ingestion might also have occurred (Davies, 1982).

8.2.2.3 Local skin and nail effects

Paraquat has a delayed effect on the skin. Brief contact with liquid formulations, as well as repeated exposure to dilute solutions, produced skin irritation, desquamation, and, finally, necrosis at the site of contact (Ongom et al., 1974; Binns, 1976; Newhouse et al., 1978; Waight & Wheather, 1979; Levin et al., 1979; Horiuchi et al., 1980). Harmful dermal effects have been reported (Howard, 1982) among spray men who worked without protective clothes and with naked feet. The blistering and ulceration of the skin were due to excessive contact and inadequate personal hygiene. Horiuchi & Ando (1980) carried out patch testing on 60 patients with contact dermatitis due to Gramoxone®. In 8 patients (13.3%) positive allergic reactions were established. In another survey with 52 persons, a positive photo-patch response was reported in 11 patients.

Nail damage has also been reported after frequent exposure to paraquat concentrates during the formulation of the herbicide or the preparation of working dilutions (Samman & Johnston, 1969; Howard, 1979b). Leakage from sprayers may cause nail damage only if there is gross contamination (Hearn & Keir, 1971). Asymmetric discoloration and softening of the nail base appears together with an infection, that usually persists after the loss of the nail, but a few months after cessation of paraquat exposure, the nails re-grow satisfactorily.

8.2.2.4 Ocular damage

A number of studies have demonstrated the hazard from splashes of concentrated paraquat that come into contact with the eye (Swan, 1969; Schlatter, 1976; Howard, 1979b, 1980; Deveckova & Myalik, 1980). Apart from irritation of the eye and blepharitis, a week later more serious ocular damage may

occur such as destruction of the bulbar and tarsal conjunctiva and of the corneal epithelium (Cant & Lewis, 1968). Anterior uveitis was also noted. Joyce (1969) reported a case of conjunctival necrosis after paraquat had been splashed into the eyes during spraying in windy weather. In a second case, there was progressive keratitis with gross corneal opacity. Severe conjunctival injuries with keratitis and decreased visual acuity were reported in 3 workers by Watanabe et al. (1979) and in another by Okawada et al. (1980). The eyes were washed with water immediately, but the damage progressed and required treatment for more than 3 weeks.

8.2.2.5 Inhalation

The inhalation of droplets in normal paraquat spraying does not appear to represent a significant health hazard (Howard, 1980), and the effects of occupational inhalation have been limited to nose bleeds, and nasal and throat irritation (Swan, 1969; Howard, 1979b). Standard spraying equipment failed to produce significant levels of droplets in the respirable range of < 5-7 µm diameter, and chemical analyses of paraquat aerosols or particulate matter, sampled from working areas, have usually shown them to be well below the TLV. However, there have been some reports (Malone et al., 1971; Mircev, 1976; Bismuth et al., 1982) of adverse effects as a result of inhalation exposure.

8.3 Use of Marijuana Contaminated by Paraquat

In the USA, it has been found that marijuana sprayed with paraquat (in an attempt to destroy the plant) may become available for smoking by drug users. Concentrations of paraquat in marijuana of up to 461 mg/kg have been reported (Liddle et al., 1980). Understandably, concern has been expressed that smoking this contaminated marijuana may be more harmful than smoking marijuana itself. The available data do not justify an absolute conclusion. However, paraquat is known to pyrolyse at 300 °C and it has been established (Smith 1978) that in marijuana cigarettes contaminated with 1000 mg paraquat/kg (1 mg, assuming a 1 g cigarette), only 0.26 µg of paraquat escaped pyrolysis and was available to be inhaled. On this basis, the amount of paraquat inhaled by a heavy user of contaminated marijuana will be insufficient to cause injury. In the absence of exhaustive toxicological studies, it cannot be stated categorically that all the pyrolysis products of paraquat do not damage the lung. However, there has been no confirmed injury attributable to the smoking of contaminated marijuana.

8.4 Guidelines for the treatment of paraquat poisoning

The most important measures are the immediate neutralisation of ingested paraquat by 15% Fuller's earth, bentonite, or activated charcoal and urgent removal of the poison by vomiting or, when possible, gastric washout. The urgency of these measures is such that where transfer to hospital may involve delay of an hour or more, this emergency treatment may need to be given by a paramedical person, e.g., a nurse or a medical assistant. The delay should not be more than 4 - 5 h. Furthermore, Fuller's earth should be given together with a strong purgative such as magnesium sulfate or mannitol.

Admission to a hospital either directly or after emergency treatment elsewhere is essential.

Where a person has swallowed a lethal dose, the most important single determinant of survival is the early commencement of treatment.

Depending on local facilities, patients who reach hospital after the initial treatment will have further treatment aimed at neutralizing paraquat in the gastrointestinal tract (Fuller's earth, bentonite, activated charcoal) or its excretion in the faeces (purgatives, 10% mannitol, gut lavage). In addition, attempts to remove absorbed paraquat from the circulation (haemoperfusion, haemodialysis) or aid its excretion by the kidney (forced diuresis) can be instituted.

In centres where facilities for analytical procedures are available, measurement of urinary, or ideally plasma levels of paraquat may give guidelines for the required intensity of treatment or likely prognosis.

Many other therapies including corticosteroids, immunosuppressive treatment, vitamins, β-blocking and alkylating agents, α-tocopherol, superoxide dismutase and/or glutathione peroxidase (Autor, 1974, 1977) proved to be of no significant importance in human paraquat poisoning (Fletcher, 1975; Fairshter et al., 1976; Schlatter, 1976; Brown et al., 1981; Bismuth et al., 1982). The administration of oxygen should be avoided except where vital for the patient's comfort.

It should be noted that, as with the great majority of chemicals, there is no specific antidote.

Care must be exercised in the administration of most of these treatments, as the following serious complications may occur: perforation of the oesophagus during gastric intubation; serious blood chemistry disturbance when severe diarrhoea is induced; fluid overload during forced diuresis (McGeown, 1975).

Despite such an array of both simple and sophisticated measures, the response to therapy in paraquat poisoning is disappointing and the mortality rate remains high.

In cases of skin and eye contamination, irrigation with water (preferably running water) should be commenced urgently and must be continued uninterrupted for at least 10 min (timed by the clock). Eye cases should always be taken for medical treatment. In cases of skin contamination by the concentrate or extensive and/or prolonged contamination by the diluted material (particularly where signs of skin irritation are present) the patient must be assessed at hospital for systemic poisoning.

9. EVALUATION OF RISKS FOR HUMAN HEALTH AND EFFECTS ON THE ENVIRONMENT

9.1 Exposure

Introduction

Paraquat is a contact herbicide or dessicant that is used to destroy weeds in various agricultural situations. It is used in the form of an aqueous spray, which means that potential human exposure may occur as a result of its presence in air, on plants, in soil, or in water.

Degradation of paraquat

Photochemical degradation takes place when paraquat-treated plants are exposed to normal daylight and continues after the plants are dead (section 4.1.1). The products formed have been identified and found to be of a lower order of toxicity. Ultraviolet degradation on soil surfaces also occurs, but photodecomposition of paraquat in the soil is insignificant in comparison with adsorption on clay particles. Microorganisms can degrade free paraquat rapidly, but chemical degradation of adsorbed paraquat is relatively slow.

Soil

Paraquat is rapidly and tightly bound to clay materials in soils. The adsorbed paraquat is biologically inactive and in normal agricultural use no harmful metabolic or breakdown products are to be expected (section 4.3 and 5.1). In multiple spray trials, paraquat residues in soil varied from 22 to 58 mg/kg. Under field conditions, the residual paraquat is slowly re-distributed. Long-term field studies have shown degradation rates of 5 - 10% per annum, which is sufficient to prevent saturation of soil deactivation capacities. At normal and high rates of application, no adverse effects are expected in the soil microflora and other soil organisms, or on crop growth (section 4.3.1).

Water

Following the use of paraquat as an aquatic herbicide at a normal application rate of 1 mg/litre, the concentration was found to decrease to about one half of the initial level within 36 h and to below 0.01 mg/litre in less than 2 weeks (section 4.3.2). Phytotoxic damage to crops irrigated with treated water is unlikely to occur, if an interval of 10 days

is observed between treatment of the water and its use, because of the rapid decrease of paraquat residues in the water.

Normal application of paraquat for aquatic weed control is not harmful for aquatic organisms. However, care should be taken in the application of paraquat to water containing heavy weed growth, since oxygen consumed by subsequent weed decay may decrease oxygen levels in the water to an extent that is dangerous for fish or other aquatic organisms.

Air

Paraquat is not volatile so inhalation of paraquat vapour is not a problem, in practice. However, droplets of paraquat solution can be present in the air as a consequence of aerial, knapsack, or tractor-mounted spraying. Paraquat aerosol concentrations (total airborne) ranged up to 0.55 mg/m^3 in the work situation, depending on the method of spraying. The amount of respirable airborne paraquat was found to be insignificant under normal conditions of use (section 8.2.1).

The amount of paraquat present in airborne dust was found to range from 0.0004 to 0.001 mg/m^3. The binding of paraquat to the dust was so tight that it did not exert any toxicological effect on rats, when given by inhalation.

Food

Examination of paraquat-treated plants (section 4.3.4), or of materials from animals fed paraquat-treated crops (section 4.3.5), revealed low residues, so that no hazard should be expected from paraquat residues in food when used as a herbicide or as a desiccant. Paraquat is not subject to bioconcentration (section 5) and has not been found to accumulate in food chains.

Environmental contamination

Exposure to paraquat from spray drift may occur in windy weather, though field studies suggest that the airborne paraquat concentration declines markedly within a few metres of the sprayed area (section 4.3.3). Because of the rapid and complete binding of paraquat to clay particles in the soil, contamination of water supplies either from field runoff or percolation through soil to the water table is not an environmental problem (sections 4.3.1 and 4.3.2). Paraquat has also been shown not to have any harmful effects on birds (sections 5.3 and 5.4).

9.2 Poisoning by Paraquat

Misuse of paraquat has led to many deaths throughout the world, mainly due to the swallowing of undiluted preparations.

9.2.1 Suicidal ingestion

The majority of paraquat poisonings are due to swallowing liquid concentrates with suicidal intent and the mortality rate is high. Ingestion of granular paraquat is less common and usually causes milder poisoning, though fatalities have occurred. Paraquat has been used to commit homicide (section 8.1).

9.2.2 Accidental poisoning

Poisoning by accidental swallowing is less common than intentional swallowing and is usually the result of storing liquid concentrates in inappropriate containers, particularly beer or soft drink bottles. The mortality rate is lower than in suicidal cases. Childhood poisoning is usually accidental. Legislation on the control of the sale of liquid concentrates has reduced accidental ingestion in some countries (section 8.1).

A small number of fatal cases of accidental paraquat poisoning via the skin have been reported following the application of liquid concentrates (200 g/litre) to kill body lice.

9.2.3 Occupational Poisoning

Cases of severe poisoning following inappropriate behaviour or accidents while handling paraquat occur. Fatal and non-fatal ingestion of paraquat has occurred when hand-spray operators have attempted to clear the spray outlet by sucking on the spraying nozzle or outlet pipes. In some of the severe cases, the authors noted their suspicion of concealed suicidal intent. Fatal poisoning by dermal soaking with dilute paraquat has been reported in one operator who had severe dermatitis and had been using a leaky sprayer (section 8.2.2).

Fatal systemic poisoning may result from continuous contact with paraquat-soaked clothing or splashes of liquid concentrate on the skin. Splashes of liquid concentrate may lead to severe ocular and skin damage (sections 8.2.1, 8.2.2). Spraying with inadequately diluted paraquat (e.g., with ultra low volume application) may result in similar problems.

9.3. Occupational Exposure

There are several studies on paraquat exposure in normal agricultural use. Occupational exposure may be oral, dermal, or by inhalation. The spray aerosol and dust particles are relatively large and are mostly deposited in the upper respiratory tract (section 8.2.1).

The potential dermal exposure of field workers (section 8.2.1) is closely related to working conditions. Workers on tractors were found to have a paraquat exposure of 12 - 168 mg/h while spraying tomatoes and citrus. In other studies, field workers were dermally exposed to paraquat at approximately 0.40 mg/h, and individuals spraying the garden to 0.29 mg/h. In all trials, respiratory exposure was not higher than 0.01 mg/h. Urine concentrations in occupationally-exposed workers were often lower than 0.01 mg/litre, but concentrations up to 0.73 mg/litre were determined after improper paraquat application in tropical agriculture use.

Local skin effects (contact, irritative, or photoallergic dermatitis) delayed wound healing, and nail damage has been observed among formulation workers or among individuals handling the herbicide improperly. Blepharitis and epistaxis may result due to delayed irritative action of paraquat. Such incidents illustrate the need for strict personal hygiene and rigorous adherence to safe handling procedures.

9.4 Effects

9.4.1 Paraquat toxicity in animals

The acute lung-directed toxicity of paraquat in man has been confirmed in numerous studies in animals. At high doses of paraquat, minor toxic effects have been noted primarily in liver and kidney, and in other organ systems, including nervous, cardiovascular, blood, adrenals and male reproductive systems. However, toxic effects have not been reported at low doses of paraquat. Concentrated solutions of paraquat have been found to be irritating to both skin and eyes. The FAO/WHO (1976) has determined no-observed-adverse-effect levels of 30 mg/kg diet, equivalent to 1.5 mg/kg body weight per day for rats and 50 mg/kg diet, equivalent to 1.25 mg/kg body weight per day, for dogs exposed to paraquat dichloride. Additional animal studies have indicated that paraquat is neither teratogenic nor carcinogenic (sections 7.1.6 and 7.1.8). *In vitro* mutagenicity studies have been inconclusive, though generally suggesting weak potential activity, while *in vivo* studies have given negative results (section 7.1.7). Thus, the results of animal studies suggest that low-level exposure to paraquat is unlikely to induce toxic effects in man.

9.4.2 Paraquat determinations in biological fluids and tissues

Determination of paraquat levels in stomach washings, serum, and urine is useful for the management of poisoning (section 6.2). The urinary levels decline rapidly during the 24 h following exposure and may remain low for some weeks. Determination of urinary levels of paraquat may be useful in the conduct of epidemiological studies.

9.5. Earlier Evaluations by International Bodies

The Joint Meeting on Pesticide Residues (JMPR) has reviewed residues and toxicity data on paraquat on several occasions (FAO/WHO 1971, 1973, 1977, 1979, 1982, 1983). In 1972, it estimated the acceptable daily intake (ADI) for man 0 - 0.002 mg/kg body weight, on the basis of no-observed-adverse-effect levels of 1.50 mg/kg body weight per day in the rat and 1.25 mg/kg body weight in the dog. Because of concern relating to lung and kidney toxicity, this ADI was changed in the 1982 meeting to a temporary ADI of 0 - 0.001 mg paraquat dichloride/kg body weight (or 0.0007 mg paraquat ion/kg body weight). The no-observed-adverse-effect level for the rat remained, however, at 1.5 mg/kg body weight/day (FAO/WHO 1983).

The same JMPRs have recommended maximum residue levels (tolerances) for paraquat in food commodities of plant and animal origin.

The WHO/FAO (1978) in its series of "Data sheets on chemical pesticides" issued one on paraquat. Based on a brief review of use, exposure, and toxicity, practical advice is given on labelling, safe-handling, transport, storage, disposal, decontamination, selection, training and medical supervision of workers, first aid, and medical treatment.

Regulatory standards established by national bodies in 12 different countries (Argentina, Brazil, Czechcoslovakia, the Federal Republic of Germany, India, Japan, Kenya, Mexico, Sweden, the United Kingdom, the USA, and the USSR) and the EEC can be found in the IRPTC (International Register of Potentially Toxic Chemicals) Legal file (IRPTC 1983).

9.6. Conclusions

On the basis of the above findings, it can be concluded that:

General population

Residue levels of paraquat in food and drinking-water, resulting from its normal use, are unlikely to result in a health hazard for the general population.

This likely lack of hazard in normal usage of dilute paraquat is in strong contrast with the potential serious hazard that may result from handling concentrated paraquat.

Accidental paraquat poisoning results mainly from swallowing liquid concentrate that has been decanted into unlabelled bottles or other containers and stored inappropriately.

The number of suicides by means of paraquat is of great concern. The total number of such suicides is unknown. Notwithstanding the facts that the reasons for suicide may be manifold and complex, and that paraquat is one among many means towards that goal, the prolonged and painful way of dying from paraquat suggests that every effort within reason should be made to diminish the attractiveness and availability of paraquat for this purpose.

Occupational exposure

With reasonable work practices, including safety precautions, hygiene measures, and proper supervision, occupational exposure during manufacture, formulation, and application will not cause hazard. However the undiluted concentrate must be handled with great care because improper work practices may result in contamination of eyes and skin (with possible consequent dermal absorption).

Spray concentrations should not exceed 5 g paraquat ion/litre in order to avoid skin damage and absorption of the herbicide through the skin. Its use in hand-held ultra-low volume application should be discouraged.

Environment

Paraquat in soil binds rapidly and tightly to clay particles and residual phytotoxicity from freely-available paraquat is unlikely. The toxicity of the compound for birds has been shown to be of low significance. Under normal conditions of use, paraquat shows low toxicity to aquatic organisms although resulting depletion of water-oxygen because of weed decay may pose a problem. Paraquat does not seem to represent an environmental hazard.

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DIQUAT

DIQUAT

1. SUMMARY AND RECOMMENDATIONS

1.1 Summary

1.1.1 General properties

Diquat (1,1'ethylene, 2,2'bipyridyl) is a non-selective contact herbicide. It is sold primarily as a 20% w/v solution in many countries and is manufactured in the United Kingdom. It is exclusively manufactured as a dibromide salt and is usually formulated to contain wetters.

The herbicidal property of diquat depends on its ability to undergo a single electron addition to form a radical that reacts with molecular oxygen to reform diquat and concomitantly produce a superoxide anion. This oxygen radical may directly or indirectly cause cell death.

It is possible to detect the compound because of its ability to form a radical. Analytical procedures are available.

1.1.2 Environmental distribution and transformation environmental effects

Diquat undergoes rapid photochemical degradation in aqueous solution and on surfaces. The major degradation products produced in water have been identified and are of lower acute oral toxicity for rats than diquat itself. The photochemical degradation of diquat on plants is more complex than that in water. On diquat-desiccated wheat and barley, diquat itself normally constitutes the most important single compound. The most important photochemical degradation products have been identified, they are of low mammalian toxicity. No other well-defined major degradation product is formed.

Ruminants excrete diquat and its photochemical products rapidly and very little is transferred to milk and tissues. Consequently, residue levels in products of animal origin are very low. Ingestion of diquat and its photochemical products at higher levels than would be found in practice did not induce ill effects in ruminants.

Diquat reaching the soil becomes rapidly and strongly adsorbed to clay minerals in soil. This process inactivates the herbicidal activity of diquat. While free diquat is degraded by a range of soil microorganisms, degradation of strongly adsorbed diquat is relatively slow. In plot studies,

the rate of degradation of diquat in soil is very slow or non-detectable. However, in long-term field studies, degradation rates of the order of 5 - 10% per year have been shown. This is greater than the rate required in normal practice to prevent saturation of the deactivation capacity of agricultural/horticultural soils. Strongly-bound diquat has no adverse effects on soil microfauna or soil microbial processes.

Diquat residues disappear rapidly from water by adsorption on aquatic weeds and by strong adsorption on bottom mud. Diquat is of low toxicity for fish and is not accumulated in them. Normal applications of diquat for aquatic weed control are not harmful to aquatic organisms. However, care should be taken in applying diquat to water containing heavy weed growth to treat only a part of the weed growth, since oxygen consumed by subsequent weed decay may decrease dissolved oxygen levels to an extent that may be dangerous for fish. Treated water should not be used for overhead irrigation until a period of 10 days has elapsed following treatment.

Diquat is not volatile and the concentrations of airborne diquat during spraying have been shown to be very low.

1.1.3 Kinetics and metabolism

Diquat is poorly absorbed from the intestinal tract and skin. Diquat monopyridone is the major metabolite of diquat in the body; of lesser importance is diquat dipyridone. Both metabolites are considerably less toxic than diquat itself. Depending on species and route of administration, less than 20% of the dose is metabolized. The gastrointestinal microflora appear to be mainly responsible for the metabolism of diquat.

Compared with paraquat, accumulation of diquat in the lungs is far less marked, but diquat shows a certain preference for the kidneys. The kidneys are the major route of excretion, but a considerable amount of diquat can also be excreted in the bile, varying with the animal species.

1.1.4 Effects on animals

Diquat is less toxic than paraquat and does not give rise to the specific lung disease that is so typical of paraquat poisoning. Gastrointestinal disturbances, with vomiting, greenish diarrhoea, and abdominal distension from the significant accumulation of water in the lumen of the intestines, are typical of diquat poisoning, together with progressive haemoconcentration, which may progress to lethargy, coma, and death. At high doses, minor toxicity has

been noted in the liver, kidney, and the nervous and endocrine systems.

Diquat has induced cataracts after prolonged oral exposure although this effect has not been reported in man. It is less irritant to the skin, mucous membranes, and the eye than paraquat, and is not known to be a sensitizer.

Diquat is not teratogenic or carcinogenic.

In vitro mutagenicity studies were inconclusive, though generally suggesting only weak activity, while the results of *in vivo* studies have been negative. A no-observed-adverse-effect level of 0.75 mg diquat ion/kg body weight per day has been established from long-term feeding studies on rats.

1.1.5 Effects on man

Occupational exposure to diquat does not pose a health risk if the recommendations for use are followed and there is adherence to safe working practices.

Diquat poisoning by suicidal or accidental ingestion is much less common than paraquat poisoning. It produces a similar severe clinical syndrome with two notable differences: (a) diarrhoea is a prominent feature, and (b) pulmonary fibrosis has not been described.

Accidental cases are usually due to ingestion of decanted diquat.

The lethal dose for man appears to be approximately 6 - 12 grams of diquat dibromide. In agricultural workers, inflammation and bleeding of the nasal mucosa have been reported, as well as nail changes and delayed wound healing.

1.2 Recommendations

1.2.1 General

Where practical and reasonable, the availability and use of the 20% liquid product should be limited to *bona fide* agriculturalists, horticulturalists, and professional users who work with trained personnel, properly maintained equipment, and adequate supervision.

Every effort should be made to prevent the practice of decanting or rebottling of the product into containers that have not been properly labelled.

1.2.2 Prevention and treatment

Attention should be drawn to the fact that persons with skin lesions (either pre-existing or following contamination with diquat) should not be permitted to take any part in spraying procedures until skin condition has resolved.

It must be stressed that treatment of persons with diquat poisoning should be instituted as early as possible. The likelihood of recovery from a fatal dose is greatest when therapy begins within 5 - 6 h of poisoning.

1.2.3 Experimental work

Results of existing mutagenicity and carcinogenicity studies generally suggest that diquat is unlikely to induce genotoxic effects in man, but more detailed information is required.

2. PROPERTIES AND ANALYTICAL METHODS

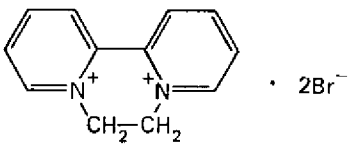
2.1 Physical and Chemical Properties

Diquat is a non-selective contact bipyridylium herbicide and desiccant. The herbicide is supplied mainly as an aqueous solution of the dibromide (1,1'-ethylene-2,2'-bipyridylium dibromide, $C_{12}H_{12}N_2$ Br_2), with a relative molecular mass of 184.2 based on the cation. The commonly available analytical standard is diquat dibromide monohydrate, which is an odourless, pale yellow, crystalline powder. Some of the other physical properties of diquat dibromide are listed in Table 1. It is slightly soluble in alcohol, and practically insoluble in non-polar organic solvents (Summers, 1980). Diquat is non-explosive and non-inflammable in aqueous formulations.

Table 1. Physical properties of diquat dibromide

Specific gravity at 20 °C	1.200
Melting point	180 °C
Boiling point	approximately 300 °C with decomposition
Solubility in water at 20 °C	700 g/litre
pH of liquid formulation	6.0 - 7.0
Evaporation rate	not applicable
Vapour pressure	not measurable

Diquat is stable in neutral or acid solutions but is hydrolysed by alkali. It is inactivated by inert clay and by anionic surfactants. Diquat dibromide has the following chemical structure:



Diquat is generally marketed as an aqueous solution of the dibromide salt Reglone® (200 g ion/litre). It is a dark reddish-brown liquid containing wetting agents that remains stable in the original polyethylene containers, for a long time, under normal atmospheric conditions.

Water-soluble granules containing 2.5% diquat and 2.5% paraquat are used in home gardens. Diquat is sold under several different trade names: Deiquat, Aquacide, Dextrone, Reglox, Weedtrim-D (Vanholder et al., 1981). Fletcher (1975) listed the commercial forms of diquat, many of which are combinations containing paraquat or other herbicides.

2.2 Analytical Procedures

The detection of diquat depends on its reduction to the free radical with sodium dithionite (Summers, 1980). Calderbank & Yuen (1966) developed a column chromatographic procedure for colorimetric diquat determinations in food and biological tissues. The sensitivity of the method varied down to 0.01 mg/kg. An immunological assay of diquat was published by Williams et al. (1976). The minimum detectable quantity of diquat was 60 pg/ml. Pyl & Giebelmann (1978) proposed a thin-layer chromatographic method for diquat determinations with a detection threshold of 0.5 - 1 µg diquat.

Soil

Diquat residues in soil have been determined using spectrophotometric analysis (ICI, 1972), the detection limit being approximately 0.1 mg/kg, depending on the sample. An extraction technique for the spectrophotometric measurement of diquat has been published by Leary (1978).

Water

Diquat residues in water have been determined spectrophotometrically with a limit of detection < 0.001 - 0.01 mg/litre (ICI, 1972a). Benecke (1977) used the inhibition of algal trichome movements by diquat involving photoelectric detection of their inhibition. A concentration of 1 µg diquat in the test sample was satisfactorily detected. A Lemna minor bioassay was reported by O'Brien & Prendeville (1978) for diquat determination in water. The minimum diquat concentration that could be detected ranged from 1.8 µg/ml after 3 h of treatment to 0.00018 µg/ml after 72 h of treatment.

Plants and food

The method of Calderbank & Yuen (1966) has been used for determining diquat in crops and animal tissues with detection limits of 0.1 mg/kg to 0.01 mg/kg, depending on the sample (ICI, 1972b). Leary (1978) developed a spectrophotometric procedure for diquat determination in crops and animal tissues (but not for whole blood). The detection limit was 0.01 mg/kg when a 50 g sample was taken.

A gas-chromatographic method for determining diquat residues was published by King (1978). The detection limit was 0.01 mg/kg. The application of gas chromatography in the analysis of food for diquat has been discussed by Dickes (1979).

Biological tissues

The analytical method for diquat residues in milk is spectrophotometry (ICI, 1972a), with a detection limit of 0.01 mg/litre. Tompsett (1970) reported a cation exchange technique for colorimetric diquat determination in biological fluids and tissues of patients with diquat poisoning. This technique is similar to those applied for paraquat determination but more time-consuming. A spectrophotometric procedure for diquat determination in serum, urine, and biological tissues has been published by Leary (1978).

Gas-chromatographic analysis of herbicides containing diquat dibromide and paraquat dichloride in forensic toxicology was proposed by Ukai et al. (1977). The procedure was found to be well suited for assaying diquat and paraquat simultaneously at 10 - 90 mg/litre.

3. SOURCES IN THE ENVIRONMENT

3.1 Production and Uses

Diquat is manufactured in the United Kingdom and does not occur naturally. It is produced by the oxidative coupling of 2 molecules of pyridine over a heated Raney nickel catalyst to 2,2'-bipyridyl. It is then reacted with ethylene dibromide in water to give diquat.

Formulations of diquat dibromide are used in more than 100 countries all over the world, mainly as a desiccant but also as a herbicide. In many countries, diquat is formulated locally on the basis of the imported active ingredient. Data on world production and uses are not available.

It is used to control both broad-leaved weeds among crops and submerged and floating weeds in water bodies, for potato haulm destruction, and for seed crop desiccation (rice, sunflower, etc.). Application rates are usually of the order of 0.56 - 0.84 kg/ha for potato haulm destruction, 0.42 - 1.96 kg/ha for seed crop desiccation, pre-harvest rice desiccation, and pre-crop weed control (beans, beetroots, cabbages, onions, etc.), 0.42 - 1.12 kg/ha for aquatic weed control, and 0.28 - 0.84 kg/ha for pre-plant weed control. Working dilutions vary between 1 and 5 g/litre water. It is applied by ground sprayers (not mist-blowers) in 200 - 500 litres of the solution per hectare and in some countries aerially in 40 - 50 litres of solution per ha.

Conning et al. (1969) summarized the mechanism of the herbicidal effect of diquat. Light and oxygen are required for the damage, which affects only the green parts of the plant. The blockage of photosynthesis is due to disturbed photosynthetic electron transport resulting from a single-electron redox cycling reaction, as described for paraquat (Paraquat, section 3.3).

4. ENVIRONMENTAL DISTRIBUTION, LEVELS, AND EXPOSURE

4.1 Photochemical and Microbial Degradation of Diquat

4.1.1 Photochemical degradation

In agricultural practice, most of the diquat spray is initially deposited on plant surfaces and part of it on the soil surface. According to Black et al. (1966), photochemical degradation is responsible for the rapid decrease in the concentration of diquat following the spraying of herbage. Application of 0.284 kg/ha resulted in 12 - 48 mg diquat/kg dry herbage on the first day, 2.5 - 10.9 mg/kg after 3 - 4 days, and 1.0 - 5.7 mg/kg, 7 days after treatment. Photochemical degradation appears to occur more rapidly in the case of diquat than in the case of paraquat. The light absorption maximum for diquat occurs at a longer wavelength (310 nm) than for paraquat (256 nm), and this partly explains the high rate of photochemical decomposition in the case of diquat. The major degradation products have been identified; they appear to be of low oral toxicity for rats and seem unlikely to produce adverse environmental effects (Black et al., 1966). Cavell (1979) monitored the photochemical degradation of ^{14}C-diquat in aqueous solutions aerated for 40 h. Decomposition of diquat continued after the plants were dead and the degradation products were not translocated from the desiccated leaves of the plants. Diquat photochemical degradation products (Cavell, 1979) are shown in Fig. 1.

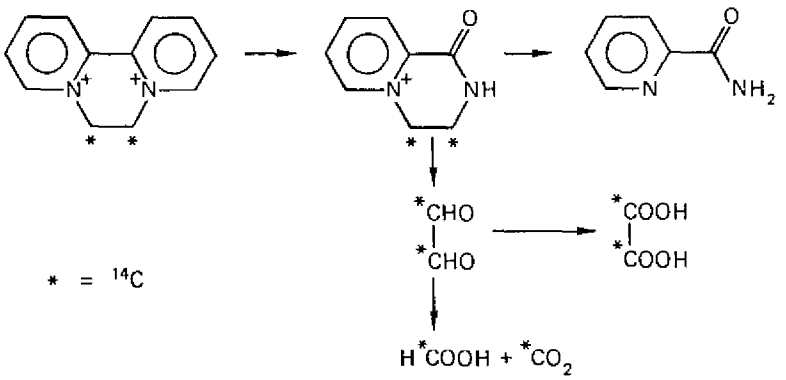


Fig. 1. Photochemical degradation of diquat.

4.1.2 Microbial degradation

Photochemical degradation of diquat on plants is quicker than microbial degradation in soil. Microbial degradation of strongly-bound diquat in soil is slow, but is faster in culture. The degradation of diquat by soil fungi was studied by Smith et al. (1976). The degradation of ^{14}C-diquat to $^{14}CO_2$ by Aspergillus niger was tested by 4 different fungal test systems. High intracellular herbicidal levels and inability to grow in the presence of low diquat concentrations in the media characterized the species unable to decompose diquat. Under laboratory conditions, diquat degradation by Pseudomonas started after 3 days (Tchipilska, 1980). Under field conditions, degradation started after 10 days, and was related to the ambient temperature, and the aeration and type of soil.

The fact that no significant hazard has been observed for ruminants from diquat-treated herbage, or for the general population from crops and water, is explained by the rapid photochemical degradation of diquat.

4.2 Diquat Adsorption, Residue Levels, and Exposure in Soil

4.2.1 Diquat adsorption on soil particles

Diquat binds readily to clay particles in the soil. The rate of adsorption depends on the degree of contact of diquat with adsorbent minerals, the type of soil, and the initial herbicide concentrations tested. Weber et al. (1965) studied the effects of temperature and exposure time on diquat adsorption by montmorillonite, kaolinite, charcoal, and an anionexchange resin in pH 6.0 phosphate buffer. Diquat was preferably adsorbed on the clay particles by a process of ion exchange. Adsorption was limited by the cation-exchange capacity of the test systems examined. Coats et al. (1966) showed the adsorption capacity of kaolinite to be about 2 g/kg and that of bentonite 80 - 100 g/kg.

A diquat soil concentration of 0.1 mg did not produce any significant reduction in the dry weight of wheat grown in the soil (Coats et al., 1966). The diquat appeared to be too tightly adsorbed to the surface and between the lattices of bentonite to be available to the wheat plant, at a soil treatment rate of 50 g/kg. Data for diquat adsorption on sandy soils (Tucker et al., 1967) showed that the herbicide was bound to different extents, according to the structure of the soil particles.

4.2.2 Residue levels of diquat in soils

Makovskii (1972) reported on diquat residues in soils from different plots, treated every year for a period of 7 years. There were 3 - 4 treatments per season, at approximately 27.5 kg diquat/ha. Samples were taken at 0 - 10 cm, 10 - 20 cm, and 20 - 30 cm depths in the soil; total diquat residues were shown to be about 5.4 mg/kg soil, the mean values being 3.9 mg/kg, 1.3 mg/kg, and 0.2 mg/kg in the respective soil layers. No diquat residues were discovered in plants and citrus fruits sampled at different times from the treated plots. In other studies, soil was analysed for diquat residues on the 1st, 8th, and 15th days after applying Reglone® at 0.8 litre/ha and 0.4 litre/ha (Tchipilska, 1980). On the 1st day, residues of 0.400 mg/kg and 0.126 mg/kg were detected; on the 8th and 15th days residues in the treated plots were lower than 0.1 mg/kg.

As summarized in section 4.1.2, free diquat is degraded by a range of microorganisms. While degradation of strongly-absorbed diquat is relatively slow, results of long-term field studies have nevertheless shown degradation rates of the order of 5 - 10% per year. This is greater than the rate required to prevent saturation of the deactivation capacity of soils.

In a long-term trial on a loamy soil, plots were treated with 0, 90, 198, and 720 kg diquat/ha, which was incorporated to a depth of 15 cm. These rates were equivalent to 0, 50, 110, and 400% of the soils strong absorption capacity (Gowman et al., 1980; Wilkinson, 1980; Riley 1981). Over the 7 years, diquat residues declined by 5% per year (sig $P = 0.05$) on the 90 kg/ha plots and by 7% per year (sig $P = 0.01$) on the 198 and 720 kg/ha plots. The rate of decline on the 198 and 720 kg/ha plots were significantly greater ($P = .01$) than on the 90 kg/ha plots.

4.2.3 Effect of residual diquat on soil biological activity, on plants, and crop yields

A literature review and an extensive study of the effects of different concentrations of diquat on microorganisms (saprophyte and pathogenic microflora, and fungi) were carried out by Tchipilska (1980). Staphylococcus aureus growth was inhibited while Scenedesmus acutus was stimulated. Smith et al. (1981) examined the effects of diquat applied at 0.5 - 32 times the concentration recommended in agricultural practice on vesicular arbuscular endophyte spore abundance in the soil and on the infection of wheat roots. No measurable deviations in endomycorrhiza formation and function were noted at normal application rates. Loss of potassium and phosphate from fungi was recorded at higher concentrations of diquat.

Coats et al. (1966) studied the uptake and translocation of ^{14}C-diquat from soil into wheat. No metabolites were found in the plants.

Diquat does not appear to have any significant influence on the normal microbial activity that is important for soil fertility. Nor is there any evidence that the recommended application rates for diquat lead to residual effects on crop growth. Moreover, tightly adsorbed diquat in soil is not reactivated into a biologically active form, so that, in practice, accidental spillage is probably the only cause of local high phytotoxic levels of residual herbicide.

4.3 Diquat Transformation, Residue Levels, and in Effects on Aquatic Organisms and Crops

4.3.1 Transformation and residue levels of diquat in water

In static water, initial diquat concentrations of 0.5 - 1.0 mg/litre fell rapidly to 0.1 - 0.3 mg/litre after 4-7 days (Calderbank, 1972; Calderbank & Slade, 1976). In field experiments, initial concentrations of 1.0, 0.8, and 0.5 mg/litre decreased to 0.03 - 0.003 mg/litre after 7 - 14 days. This rapid loss of diquat from treated waters was due to rapid uptake by aquatic weeds. Two weed species (Myriophyllum spicatum and Callitriche stagnalis) were immersed in water containing 1.0 mg diquat/litre. The concentration of the herbicide decreased rapidly to 0.14 - 0.03 mg/litre during a period of 6 - 14 days after treatment. At the end of the experiment, the residue levels in the weeds ranged from 6.2 - 17.4 mg/kg. In addition to uptake by weeds, loss of diquat from treated waters was due to photodegradation at the water surface and adsorption by bottom mud. In field experiments carried out in 1010 m^2 ponds with an initial concentration of diquat of 2 mg/litre water, there were no residues of diquat in the water after 8 days (Calderbank, 1972; Calderbank & Slade, 1976).

In pond water that had been treated with diquat at 2.5 mg/litre (Grzenda et al., 1966), residues of 0.01 - 0.08 mg/litre were found, 7 - 9 days after applying the herbicide, and no residues could be determined after 14 - 30 days. The authors concluded that, compared with other herbicides, diquat appeared to have the greatest potential for use in sources of potable water.

The data obtained from studies in ponds, large and small lakes, canals, and reservoirs demonstrate the fast disappearance of diquat from treated waters (Calderbank, 1972). Absorption by aquatic weeds explains the high efficacy of the herbicide. Decomposition of the dead weeds is rapid, and diquat is not released from the bottom mud back into the

water. Applications of paraquat and diquat each at a dose level of 1.1 kg/ha (Grover et al., 1980) proved very effective for the control of weeds in irrigation ditches, and the residual levels of both herbicides decreased rapidly.

4.3.2 Effects of residual diquat on aquatic organisms and crops

The toxicity of diquat for fish varied with the species, the size of the fish, and the softness or hardness of the water. The LC_{50} values range from 12 to 90 mg/litre (24 h), 6 to 44 mg/litre (48 h), and 4 to 36 mg/litre (96 h) (Calderbank, 1972). Reviews of the effects of diquat on fish, aquatic invertebrates, microbiological organisms in the soil of lakes, and phytoplankton demonstrate that the herbicide, applied at the rates used for aquatic weed control, did not affect estuarine fauna, oysters, shrimps, water insects, or fish-food organisms (Calderbank, 1972; Atkinson, 1973). At concentrations of 1 - 100 mg/litre, diquat appeared to be less toxic for carp fingerlings than paraquat, diuron, simazine, and dalapon (Singh & Yadev, 1978). Reish et al. (1979) reviewed the effects of diquat on marine organisms; no bioaccumulation by estuarine and marine organisms was found. The toxicity of diquat for fish is low, and the main risk for aquatic organisms and fish from its use as an aquatic weed killer is the decreased oxygen concentration following the decay of weeds.

Trout exposed to 1 mg diquat/litre for 7 days contained residues of 0.3 - 0.4 mg/kg in the gut, liver, and kidney, and of 0.1 - 0.3 mg/kg in the skin and gills. Residues were below the limit of detection in muscle, spleen, and heart (Calderbank, 1972). Trout exposed to 1 mg diquat/litre for 16 days contained residues of 0.5 - 0.6 mg/kg, which disappeared when the fish were returned to fresh water.

Because of irreversible adsorption, low residues in water will be lost on contact with soil. The herbicide is thus unavailable to plant roots. However, in overhead irrigation experiments, the use of water containing diquat at 0.1 - 0.5 mg/litre (Calderbank, 1972) resulted in diquat residues in the crops (tomato, lettuce, sugar beet) ranging from less than 0.01 mg/kg to 0.04 - 0.07 mg/kg. Thus, before using herbicide-treated waters for overhead plant irrigation, it is advisable to allow 10 days for the diquat aquatic residues to drop to acceptable levels.

The maximum diquat residues in water ultimately to be used for drinking were 0.03 - 0.01 mg/litre, at the points of entry into the public distribution system, 2 - 4 days after treatment; no residues were detectable on the 10th day after applying diquat as an aquatic herbicide. More often than not,

residue levels were below the detection limits of the analytical methods used.

4.4 Diquat Exposure and Residue Levels in Plants and Animals

4.4.1 Plants

Diquat is largely used as a desiccant in silage production. At the recommended rates of 1.5 - 3.0 litre Reglone®/ha, diquat residues were very low (Riley & Gratton, 1974). Following pre-harvest desiccation of fodder crops, they ranged from below 0.05 mg/kg to 50 mg/kg, most of the levels determined being below 25 mg diquat/kg (FAO/WHO, 1971, 1973). Diquat residues in the treated herbage, sampled at different intervals after spraying with 0.258 - 0.515 mg/ha, were relatively high after 1 day (12 - 65 mg/kg), but after 7 days had markedly decreased (1.0 - 6.5 mg/kg) (Black et al., 1966). The levels of diquat found in silage during a 4-year trial, with application rates of 0.190, 0.258, and 0.540 mg/ha, varied from 1.4, 3.6, 9.3, and 13.3 to 26.8 mg/kg. The differences were due to the atmospheric conditions at the time of desiccation and the consequent degree of photochemical degradation of the diquat. For this reason, diquat residues in treated herbage should be expected to vary by an order of magnitude (10 times).

Pre-harvest desiccation of rape-seed with diquat did not result in any detectable residues in the extracted oil and only low residues (0.3 - 2 mg/kg) in the meal cake. Rape plants were sprayed with ^{14}C-diquat at 0.3 - 1.1 kg/ha, 3 - 14 days before harvesting. There were no detectable residues of diquat or of its photodegradation products in the rape-seed oil when the seeds were harvested 7 days after desiccation, and very low diquat residues (0.02 - 0.003 mg/kg) were determined when the seeds were harvested 14 days after treatment with diquat. The diquat residues in the meal cake varied from 1.49 to 10.2 mg/kg, 14 days after treatment, a large proportion being unchanged diquat (FAO/WHO, 1973). Dembinski et al. (1971) reported diquat residues of 2 mg/kg in sunflower seeds desiccated with Reglone®.

Makovskii (1972) reported the diquat residue levels in weeds treated with Reglone®. After applications of Reglone® at 0.5, 1.0, and 1.3 litre/ha, the residues in dry weeds ranged from 34 to 74 mg/kg, 1 h later; from 15 to 26 mg/kg after 1 day; from undetectable to 10 mg/kg after 4 days; from 2.8 to 3.5 mg/kg after 2 weeks; from 1.9 to 2.3 mg/kg after 4 weeks; and from undetectable to 1.7 mg/kg after 6 weeks. The degradation of diquat in plants was more rapid than the degradation of paraquat. The residues in potatoes did not exceed 0.08 mg/kg, when diquat was used to

destroy potato haulm, and levels in fruits (apples, pears, plums, citrus), tea, and cereals were undetectable (< 0.01 mg/kg), when diquat was applied as a herbicide for weed control. Samples of potatoes purchased from shops (Andersson & Josefsson, 1982) were analysed for diquat residues. Residues in the range of 0.004 - 0.039 mg/kg were found in 20 of 23 samples obtained from commercial growers. None of the samples contained more than the residue tolerance of 0.1 mg/kg accepted for potatoes in Sweden.

Residue levels of diquat have been discussed in more detail by the Joint Meeting on Pesticides Residues (FAO/WHO, 1971, 1973). Residue levels of diquat in plants were summarized and published by FAO/WHO (1977a). Some of these data are given in Table 2.

Data on diquat residues in desiccated wheat collected from 6 countries showed a mean of 0.5 mg/kg (FAO, 1979).

Table 2. Diquat residues in plants[a]

Plants	Dose of diquat (kg/ha)	Mean value of residues (mg/kg)
Wheat (grain, flour)	0.6 - 1.0	0.61, 0.22
Rice (with husk, polished)	0.2 - 0.4	0.89, 0.07
Sorghum (grain)	0.4 - 0.6	0.81
Cotton (grain)	0.4 - 1.0	0.37
Potato	0.6 - 1.0	0.03
Beans	0.3 - 1.0	0.10
Peas	0.3 - 1.0	0.05
Sugar beet (juice)	0.3 - 0.8	< 0.01

[a] From: FAO/WHO (1977a).

4.4.2 Animals

Sheep and cattle fed silage containing diquat residues of up to 13 mg/kg were studied by Black et al. (1966). The total diquat excreted in the urine was 0.19 - 0.65 mg over an 8-day period. No diquat residues were detected in the brain, liver, and kidney of sheep, or in the meat or organs of cattle fed diquat-treated silage for one month. Milk collected on alternate days for 2 weeks was free of diquat residues (< 0.003 mg/litre).

Feeding trials with sunflower seed containing approximately 0.20 mg diquat/kg were reported by Dembinski et al. (1971). Although the amount of diquat consumed by the cattle over 257 days ranged from 11.2 mg to 184.2 mg, no residues were found in any of the milk samples analysed. Wethers fed ground sunflower seed containing approximately 0.20 mg diquat/kg for 141 days were estimated to have consumed a total of 14.1 mg diquat per sheep. No residues were found in brain, liver, or kidney, nor were there any residues in the meat, lungs, and kidney of steers treated with diquat-desiccated sunflower forage. In long-term feeding trials with silage, desiccated grass, lucerne, clover hay, barley straw, and sunflower seeds containing diquat residues ranging from 0.2 to 50 mg/kg, the residues in milk and meat were determined to be less than 0.007 mg/litre and less than 0.0006 mg/kg, respectively (FAO/WHO, 1971, 1973, 1977a,b). Calderbank (1972) reviewed the effects on farm animals of diquat in the drinking-water and on herbage; there were no adverse effects on cattle and sheep and only very low residue levels in milk, meat, and the organs analysed.

Lavaur et al. (1979) studied the effect of treated lucerne on rabbits. Immediately after spraying, a concentration of 211 mg diquat/kg dry weight was determined in the lucerne. After 24 h and 48 h, diquat residues were 97 mg/kg and 25 mg/kg, respectively. No signs of poisoning or gastrointestinal damage were found in the rabbits fed with different levels of diquat residues in the lucerne. However, in some circumstances, lack of careful organization may result in adverse effects of diquat on animals. Intoxication of sheep, cattle, and swine has been reported (Schultz et al., 1976) after the aerial application of Reglone® as a rapeseed desiccant. The clinical course and the causes of the accident stressed the need for proper diquat application by air.

For a more detailed discussion of the fate of diquat residues in exposed animals, refer to FAO/WHO (1977a,b).

4.5 Diquat Levels in Air and Exposure of Workers

Experiments with ^{14}C-diquat demonstrated that it was not volatile (Coats et al., 1966). Diquat levels in air after spraying with aerosols were determined by Makovskii (1972), using the method of Calderbank & Yuen (1966). The application rates were 1.0 - 1.3 kg diquat/ha in working dilutions of 2.5 g and 3.3 g active ingredient/litre, the highest diquat concentrations being found in the tractor cabin when the door was open and spraying was in progress in the direction of the wind (Table 3). The diquat concentrations in air decreased rapidly 10 - 20 min after completion of the treatment.

Table 3. Total airborne diquat concentrations in the air of working areas[a]

Place of sampling		Number of samples	Mean concentrations (mg/m³ ± SE)
Working area	sprayer loading	20	0.12 ± 0.03
	tractor cabin (in direction of wind)	8	0.56 ± 0.10
	tractor cabin (against the wind)	8	0.17 ± 0.04
	manual spraying	16	0.25 ± 0.04
Treated field	after 5 min	8	0.20 ± 0.03
	after 10 min	24	0.06 ± 0.01
	after 20 min	8	ND
Distance from treated field	200 m	8	0.09 ± 0.01
	400 m	8	ND

[a] From: Makovskii (1972).

Wojeck et al. (1983) reported that diquat was determined in air samples taken near the breathing zone of workers during its application for aquatic weed control. The respiratory exposure levels were below the limits of quantitation of the chemical analysis.

In Bulgaria and the USSR, the proposed MAC (maximum allowable concentration) for diquat is 0.1 mg/m³ aerosol. The TLV for diquat in workroom air in the United Kingdom and the USA is 0.5 mg diquat/m³ (1982), a level that will not be reached under normal conditions of application.

5. KINETICS AND METABOLISM

5.1 Animal Studies

5.1.1 Absorption

Oral absorption

Daniel & Gage (1966) studied the absorption of ^{14}C-diquat dibromide and ^{14}C diquat dichloride following oral and subcutaneous single-dose administration to rats. About 90 - 97% of the oral diquat dibromide and 84 - 90% of the diquat dichloride were found in the faeces and 4 - 11% of both diquat salts in the urine. Following subcutaneous injection of ^{14}C-diquat (10 mg/kg body weight) in rats, 87% of the administered dose was excreted in the urine and 5% in the faeces within 4 days. The urine contained mainly unchanged diquat (75% of the dose) together with diquat monopyridone (about 3% of the dose) and diquat dipyridone (about 6% of the dose) (FAO/WHO, 1978).

The poor absorption of diquat from the gastrointestinal tract was confirmed by Litchfield et al. (1973) in the rat, and by Black et al. (1966), Stevens & Walley (1966), and Dembinski et al. (1971) in farm animals.

Pulmonary absorption

The uptake of ^{14}C-diquat by perfused rat lung, following intratracheal injection, was examined by Charles et al. (1978) and Charles & Menzel (1979). Removal of ^{14}C-diquat from the airways was rapid, initially, but slowed down with time. The results indicate 2 phases of absorption and removal of diquat from the airways in the rat.

Dermal absorption

There are no data on the rate of diquat absorption through the skin. Studies on the dose-related percutaneous toxicity of diquat suggest that it may be dermally absorbed.

5.1.2 Distribution

Although paraquat and diquat have similar chemical, physical, and herbicidal properties, only paraquat has been shown to damage the lung. According to Sharp et al. (1972), diquat concentrations in lung and muscle were much lower than the levels attained with equal 20 mg/kg body weight iv doses

of paraquat. Table 4 shows the distribution of both in the main internal organs.

Table 4. Ratio of concentration of paraquat/diquat in the tissues of the rat[a]

Organ	Days after intravenous administration				
	1	3	5	7	10
Lung	8	33	12	10	20
Muscle	2	13	10	7	16
Kidney	0.9	0.9	0.9	0.3	0.25
Liver	0.4	0.7	0.7	0.5	0.2

[a] From: Sharp et al. (1972).

Diquat concentrations were higher in the kidney and the liver but significantly lower in the lung (Table 4). In addition, the concentrations of paraquat were 2-8 times higher than those of diquat in the heart, adrenal glands, spleen, stomach, ileum, testes, and thymus. Plasma levels were similar for both bipyridylium herbicides.

Litchfield et al. (1973) injected ^{14}C-diquat cation at 50 mg/kg body weight iv into mice. Whole-body autoradiographs were prepared after 10 min, 1 h, 24 h, and 72 h. Radioactivity was selectively located in the gall bladder and was also present in cartilaginous tissue, liver, and the gastrointestinal tract. Low radioactivity was found in the brain and spinal cord. One h after dosing, the amount in the urine and intestinal epithelium had increased. After 24 h, the excretion of diquat was virtually complete, although radioactivity continued to be detected in the small and large intestine and the bladder.

Litchfield et al. (1973) also determined diquat levels in various tissues of male and female rats fed a diet containing diquat dibromide monohydrate at 250 mg/kg for 2, 4, and 8 weeks. High levels (0.18 - 1.17 mg/kg) were found in the kidney and the large intestine; levels in the lung ranged from < 0.05 to 0.53 mg/kg; those in the liver from 0.07 - 0.22 mg/kg, while levels in the brain, muscle, and blood were very low. At all stages of the study, diquat lung levels were lower than those for paraquat, the average paraquat content in the lung (at a dose of 250 mg/kg diet) over the 8-week period being 1.7 mg/kg and the average diquat level, 0.2 mg/kg. No

sex differences were found. Within 1 week of return to a normal diet, diquat was below the detectable limit in all tissues examined.

Rats given paraquat or diquat orally at 680 µmol/kg had high kidney levels of diquat throughout the 30 h period after dosing (Rose & Smith, 1977, 1977a). There was no significant time-dependent increase in diquat levels in the lung, liver, brain, adrenal glands, muscle, and plasma. These results confirmed that, following oral dosing, the lung does not accumulate diquat. Rose & Smith (1977) also incubated rat lung slices in 10^{-5}M paraquat and diquat. In contrast to paraquat, diquat did not accumulate in the lung slices, and the compound did not accumulate significantly in any tissue slices with the exception of those from the kidney. These observations were confirmed by Lock (1979).

Matsuura et al. (1978) studied the distribution of orally administered LD_{50} doses of diquat and paraquat in rats. Two and 24 h after dosing, there were higher concentrations of diquat in kidney, liver, and lung than in brain, heart, the gastrointestinal system, and blood. At equitoxic doses, levels of diquat in the lung appeared to be lower than those of paraquat. In a similar distribution study of the LD_{50} and 0.5 LD_{50} doses of diquat and paraquat, Kurisaki & Sato (1979) determined the tissue concentrations from 2 to 48 h and from 2 to 9 days after treatment. Distribution in the lung, heart, brain, liver, and kidney of the rats agreed with previously published data.

The results of the above studies demonstrate that diquat does not persist as long as paraquat in the body of the rat and that it does not accumulate in the lung.

5.1.3 Metabolic transformation and excretion

Daniel & Gage (1966) reported that the amount of ^{14}C-diquat excreted in rat bile during the 24 h following oral doses of 1.2 - 64 mg/kg body weight represented 1.1 - 4.8% of the dose. Small amounts were detected in the urine, but about 70% of the diquat was present in the faeces. In other studies (FAO/WHO, 1978), the rate of diquat metabolism in the rat was considerably lower than previously reported by Daniel & Gage (1966). The biliary, urinary, and faecal excretion of ^{14}C-labelled bipyridylium herbicides was studied by Hughes et al. (1973) in the rat, guinea-pig, and rabbit. ^{14}C-diquat dichloride was injected ip at dose levels of 40 µmol/kg body weight in the rat, 13 µmol/kg in guinea-pig, and 14 µmol/kg in the rabbit. Most of the injected diquat (82% - rat, 64% - rabbit) was found in the urine. Rabbits metabolized 18% of the dose, guinea-pigs 5%, and rats less than 1%. The metabolites were similar for the 3

species. The rat excreted approximately 1.4% of the dose in the bile, the guinea-pig 4.8%, and the rabbit 2.9%.

Stevens & Walley (1966) treated cattle orally with ^{14}C-diquat dibromide in doses of 4, 8, and 20 mg/kg body weight. The radioactivity levels in the milk of the cows indicated that 0.04 - 0.15% of the ingested dose was excreted in this way. Very low levels of diquat (0.01 mg/kg) were present in muscle tissue, 2 - 8 days after dosing. A bull calf was dosed orally with ^{14}C-diquat dibromide at 10 mg/kg. About 2.6% of the 10 mg/kg dose was excreted in the urine, but the major part of the dose was excreted via the faeces. In the calf, 24 h after dosing, the residues were 0.66 mg/kg in kidney, 0.20 mg/kg in heart and skin, 0.19 mg/kg in liver, 0.03 mg/kg in lung, testes, and serum, and 0.006 mg/kg in muscle.

Studies on rats dosed orally with ^{14}C-diquat at 45 mg/kg body weight or subcutaneously (sc) with 10 mg/kg body weight were reported by FAO/WHO (1978). Rats given the oral dose excreted 6% and 89% in the urine and faeces, respectively, within 4 days and mainly within the first 2 days. Unchanged diquat was the major component in both urine (5% of the dose) and faeces (about 57% of the dose). About 5% of the oral dose was excreted as diquat monopyridone, mainly in the faeces, while diquat dipyridone appeared to be the major urinary metabolite. Following sc injection, rats eliminated 87% of the dose in the urine and 5% of the dose in the faeces within 4 days. The urine contained 75% of the dose as diquat, about 3% as diquat monopyridone, and about 6% as diquat dipyridone. In vitro studies have shown that the caecal microflora of the rat can metabolize about 10% of the diquat added in a 24-h incubation period, with the formation of some diquat monopyridone. This observation, together with the paucity of metabolites following ip injection, suggests that diquat is metabolized by the gastrointestinal tract bacteria.

The oral LD_{50} of diquat monopyridone in the rat was more than 4000 mg/kg body weight. Oral administration of diquat monopyridone at 1000 mg/kg body weight per day for 2 weeks did not induce any clinical, haematological, biochemical, or histopathological deviations in the rat. In other studies, no adverse effects were noted after sc injection of diquat monopyridone or diquat dipyridone in rats, but 9 animals out of a group of 10 injected with the equivalent dose (16 mg/kg body weight) of diquat were dead by the 14th day following dosing (FAO/WHO, 1978).

5.2 Observations on Man

Feldman & Maibach (1974) studied the dermal penetration of twelve ^{14}C-labelled insecticides and herbicides. Diquat

showed a very low rate of dermal absorption in man. No other studies on the kinetics of diquat in volunteers have been published, but observations are available on accidental and suicidal ingestion (section 7). Toxicological analysis, at the time of admission, of the serum of a patient who had ingested 20 ml Reglone®, showed a diquat level of 0.4 mg/litre (Vanholder et al., 1981). At postmortem examination on the 5th day after ingestion, approximately 0.20 mg diquat/kg was determined in liver, kidneys, muscle, and eye liquid.

6. EFFECTS ON ANIMALS

6.1 Effects on Experimental Animals

6.1.1 Gastrointestinal system and liver

Investigation of the clinical signs of acute oral intoxication by diquat (Verbetskii & Pushkar, 1968; Clark & Hurst, 1970; Crabtree et al., 1977; Cobb & Grimshaw, 1979) have established gastrointestinal disturbance as the major syndrome of poisoning and as a cause of death. In both rats and guinea-pigs, the clinical signs of acute oral poisoning (Verbetskii & Pushkar, 1968) were dose-dependent. At doses greater than the LD_{50}, signs of poisoning appeared after 6 - 12 h; at lower levels, the signs were less obvious and appeared after 1 - 2 days. Most deaths occurred on the 3rd - 9th day after oral administration. The animals lost 7 - 35% of their initial body weight. During the first 24 h following the oral dosing of rats with 900 µmol diquat/kg body weight (LD_{50}), a reduction in water intake was noted (Crabtree et al., 1977). The animals were subdued, showed pilo-erection and loss of appetite. At 24 h, they excreted mucoidal, ropy faeces of a characteristic greenish-yellow or grass-green colour, this colour being due to the reduction of diquat by intestinal bacterial metabolism. This colour can be reproduced *in vitro* with fresh intestinal contents and actively growing bacterial isolates from them (Clark & Hurst, 1970).

A significant dose-dependent accumulation of water in the lumen of the intestines and progressive haemoconcentration were reported (Crabtree et al., 1977) following acute diquat intoxication in rats. It was concluded that diquat had an adverse effect on water distribution in the body. Rapid fluid excretion following oral diquat poisoning suggested a direct action on the stomach and intestinal mucosa. Monkeys dosed orally with diquat ion at 100, 200, 300, and 400 mg/kg body weight (Cobb & Grimshaw, 1979) vomited within 2 h and showed diarrhoea within 12 h of dosing. The most severely affected became lethargic and comatose, and finally collapsed and died, 12 - 84 h after dosing. An increased number of polymorphonuclear leukocytes as well as increased levels of serum urea, plasma glucose, and serum GOT and GPT activities were determined in monkeys that died during the study. Histological examination revealed a distended gastrointestinal tract and a swollen caecum; the mucosa of the stomach was ulcerated and the small and large intestines congested. Large areas of the stomach and intestines showed necrosis and exfoliation of the epithelium from the mucosa. The submucosa

was infiltrated with lymphocytes, and polymorphonuclear and mononuclear cells. These changes were most severe in the intestinal villi. The death of the monkeys was due to destruction of the epithelial lining of the gastrointestinal tract in combination with kidney damage.

Liver

The liver was not severely affected in acute and repeated diquat poisoning of experimental animals. High doses sometimes resulted in histological lesions (Verbetskii & Pushkar, 1968; Bainova, 1975), but signs of toxic hepatitis were not described. Cage (1968a) reported stimulated NADPH oxidase activity in rat liver microsomes in vitro after exposure to diquat.

6.1.2 Renal system

The major route of diquat elimination is through the kidneys. High doses of diquat provoke histological and biochemical changes in the kidneys, but the most severe damage occured in relation to renal excretion function (Lock & Ishmael, 1979).

Kidney damage following acute and repeated diquat poisoning was reported by Verbetskii & Pushkar (1968), Bainova (1969), Cobb & Grimshaw (1979), Lock (1979), and Lock & Ishmael (1979). Rats, guinea-pigs, and monkeys were investigated after oral poisoning with the herbicide. Diquat, orally administered at 680 µmol/kg to rats, induced a significant increase in diuresis, proteinuria, and glucosuria after 6 - 24 h. Biochemical tests in vitro revealed a decrease in N'-methylnicotinamide, but not 4-aminohippurate, accumulation by renal cortical slices suggesting competition for the base transport system. Stimulation of the pentose phosphate pathway and inhibition of fatty acid synthesis were found when diquat was added to renal cortical slices in vitro. No such changes were noted when the renal cortical slices were prepared from rats previously treated with diquat (Lock, 1979).

Lock (1979) also investigated the changes in several variables and the clearance of diquat by the rat kidney after oral administration of toxic doses (680 and 900 µmol/kg body weight). Diquat was not bound to the proteins of the rat plasma. Active renal secretion was confirmed by the fact that diquat was cleared by the kidney at a slightly higher rate than inulin. In rats treated orally with diquat at 540 µmol/kg body weight, renal clearance decreased after 24 h. However, the reduction in renal function induced by

diquat (Lock 1979) was considered to be secondary and due to water redistribution caused by acute poisoning.

Histopathological changes have been reported in the kidneys of animals poisoned with high doses of the herbicide (Verbetskii & Pushkar, 1968; Cobb & Grimshaw, 1979; Lock & Ishmael, 1979). The renal papillae were hyperaemic, degeneration and necrosis of the epithelium of the proximal and distal convoluted tubules were noted, the epithelial cells were exfoliated, and the nuclei pycnotic.

6.1.3 Eyes and skin

Eye irritation

The local irritation caused by diquat is less pronounced than that caused by paraquat. One drop of 20% solution gave rise to slight conjunctival irritation of the rabbit eye, which persisted for 2 days (Clark & Hurst, 1970). A 40% diquat solution induced moderate conjunctival irritation.

Eye cataract

Both rats and dogs fed diets containing diquat developed cataracts (Howe & Wright, 1965). However, rats fed 7.5 mg diquat/kg diet over a life-span did not develop cataracts, while 70 mg diquat/kg diet appeared to be the no-observed-adverse-effect level for dogs. According to Clark & Hurst (1970), rats on diets containing 50 mg diquat/kg or more developed cataracts in the course of the study. In another group fed a diet containing 1 g diquat/kg, eye opacities were discovered within 6 months, while a few animals on diets of 100 mg/kg and 50 mg/kg showed slight opacities at the end of the study period. A 2-year test with a diet containing diquat at 10 mg/kg did not induce cataracts in rats.

Bilateral cataracts were discovered in all dogs 10 - 11 months following oral administration of diquat at 15 mg/kg body weight per day . The dose of 5 mg/kg body weight per day induced eye opacities after 17 months, and doses of 1.7, 0.8, and 0.4 mg/kg body weight per day were ineffective after 3 - 4 years of treatment.

A 2-year feeding study was carried out with diquat levels of 15, 25, and 75 mg/kg in the diet of rats. Only the 25 and 75 mg/kg levels caused cataracts (FAO/WHO, 1978).

Pirie & Rees (1970) confirmed that rats fed diquat dibromide at 0.5 - 0.75 g/kg in the diet developed cataracts. In vivo observations showed that, invariably, the first change seen was an opacity in the posterior cortex, immediately under the posterior capsule of the lens. The next stage was a defined nuclear cataract that could be seen with the naked

eye. Finally, shrinkage and complete opacity occurred. This histological study revealed that the first posterior cortical opacity was formed from damaged epithelial cells. The level of diquat in the blood of these rats was less than 2.2 µM. No diquat accumulation was registered in the lens of these rats. The mechanism of the specific cataractogenic action of diquat is not clear, although *in vitro* studies demonstrated that reduction of diquat by the lens was enzymatically catalysed by glutathione reductase (EC 1.6.4.2) with NADPH as the source of reducing equivalents. The loss of ascorbic acid from the lens and the ocular fluids of treated rats was proposed as a factor for maintaining the normal glutathione level in the rat lens.

Local skin effects

Single diquat applications on the skin of mice (Bainova, 1969a) and rabbits (Clark & Hurst, 1970) did not cause any local irritation. Daily applications of 1% diquat solution in water to the skin of rats provoked slight erythema at the site of contact during the first 10 days, while daily applications of diquat at 20 mg/kg body weight to the skin of rabbits caused mild erythema, thickening of the skin, and some scabbing (Clark & Hurst, 1970). Diquat has not been found to be a sensitizer (Bainova, (1969a).

6.1.4 Respiratory system

The effect of diquat on the respiratory system has been studied after parenteral (Hawkins et al., 1979; Lam et al., 1980), oral (Verbetskii & Pushkar, 1968; Bainova, 1969; Bainova & Vulcheva, 1978), intratracheal (Lam et al., 1980), and inhalation exposure (Gage, 1968; Bainova et al., 1972). Unlike paraquat, no specific effects on the lung were reported, though difficulties in breathing occurred after severe acute poisoning of the animals with diquat.

6.1.5 Nervous system

General depression and lethargy were most commonly seen following the administration of high doses of diquat to guinea-pigs and rats (Verbetskii & Pushkar, 1968; Clark & Hurst, 1970; Crabtree et al., 1977), and to monkeys (Cobb & Grimshaw, 1979).

6.1.6 Effects on reproduction, embryotoxicity, and teratogenicity

6.1.6.1 Effects on reproduction

Male rats were dosed orally with diquat dibromide at 6.5 mg/kg body weight per day, for 60 days, and the testes were then examined biochemically and histologically (Bainova & Vulcheva, 1974). There were no significant changes in the sperm count, sperm motility, the testicular tubules, the basal cells, or in the activity of several enzymes.

A 2-generation study on rats was carried out with dietary levels of 125 and 500 mg diquat/kg. The 500 mg/kg dose resulted in reduced body weight for F_{1a}, F_{1b}, F_{2a}, and F_{2b}, and increased cataracts in F_{1b} and F_{2b} after 91-280 days of exposure. The 125 mg/kg dose resulted in decreased body weight in F_{1b} and F_{2b}, but no lens opacities were noted (FAO/WHO, 1973).

6.1.6.2 Embryotoxicity and teratogenicity

Diquat was reported to have induced deviations in the prenatal development of rats (Khera et al., 1968). Bus et al. (1975) studied the fetal toxicity and teratogenicity of diquat in rats by administering 15 mg/kg body weight iv on days 7 - 21 of gestation. This resulted in 57% fetal resorption compared with 7.6% for paraquat. The incidence of maternal deaths was essentially the same. When ^{14}C-diquat and ^{14}C-paraquat were administered to rats, iv, in a dose of 15 mg/kg body weight on days 13, 16, and 21 of gestation, paraquat increased radioactivity in fetal lung whereas diquat appeared to have a stronger embryotoxic action than paraquat. In the review published in 1979 by FAO/WHO, it was reported that diquat dibromide monohydrate, administered orally to pregnant rabbits at doses of 1.25, 2.5, and 5.0 mg/kg had no adverse effect on the fetuses. In groups of pregnant rats kept on diets containing 125 and 500 mg diquat cation/kg throughout gestation, reduced body weight was noted only in the fetuses of mothers from the 500 mg/kg group. A slightly increased incidence of subcutaneous haemorrhages was also noted.

Teratogenicity studies in mice have been reported by Selypes et al. (1980). Single ip doses of diquat at 2.7 and 11 mg/kg body weight were injected on days 9, 10, 11, and 12 of gestation. The number of dead fetuses, as well as post-implantational lethality, increased significantly: average embryo weight was lower and, though no congenital malformations were noted, there were signs of skeletal retardation such as large fontanelles, wider cerebral sutures,

flat-shaped ventral nuclei of the vertebrae, and delayed ossification in the sternum and phalanges. The embryotoxic effect in mice of high doses of diquat was thus confirmed, but no chromosomal aberrations were noted in the liver cells of the embryos from diquat-treated female mice.

6.1.7 Mutagenicity

Studies on the genotoxic potential of diquat are rather contradictory. Diquat was negative in the Ames test, with and without metabolic activation (Anderson et al., 1972; Benigni et al., 1979; Levin et al., 1982). Dominant lethal assays in mice performed by various authors with several doses of the herbicide gave negative results (Pasi et al., 1974; Pasi & Embree, 1975; Anderson et al., 1976). Selypes et al. (1980) injected mice ip with 22 mg/kg (LD_{50}) diquat, while another group of mice was dosed orally with 90 mg/kg (0.5 LD_{50}). After 24 and 38 h, preparations of bone marrow were examined for chromosome aberrations; no statistically significant changes were determined.

On the other hand, diquat was found to induce slight gene conversion in Saccharomyces cerevisiae (Siebert & Lemperle, 1974). Ahmed et al. (1977) reported that diquat induced DNA changes in cultured SV-40-transformed human cells, with and without metabolic activation, and the induction of 8-azaguanine resistance in the Salmonella typhimurium assay was positive (Benigni et al., 1979; Bignami & Crebelli, 1979). Benigni et al. (1979) also found that diquat was positive in an S. typhimurium repair test. It was further reported by these authors that diquat induced gene mutations in Aspergillus nidulans, and increased unscheduled DNA synthesis in human epithelial-like cells. They commented that diquat may have an effect on a number of different genetic endpoints.

6.1.8 Carcinogenicity

In 2-year feeding studies on rats (Clark & Hurst, 1970), diquat at levels of up to 720 mg/kg diet did not induce tumours. The daily ingestion of 2 and 4 mg diquat per kg body weight in water for a period of 2 years did not have any significant effects on the health and mortality rate in rats (Bainova & Vulcheva, 1978). Some histological changes related to chronic interstitial infiltration and pulmonary adenomatosis in the lungs were found, especially after the higher dose, but there were no indications of malignancy.

6.2 Effects on Farm Animals

The effects of diquat on farm animals was studied in relation to its application as an aquatic herbicide and desiccant (Howe & Wright, 1965; Black et al., 1966; Stevens & Walley, 1966) (section 4.4). Little variation in diquat toxicity in the various animal species was found, but cattle appeared to be the most sensitive (LD_{50} for cattle approximately 30 mg/kg, LD_{50} for rat 230 mg/kg). Single oral doses up to 8 mg/kg produced no signs of toxicity in cows (Stevens & Walley, 1966), and the continuous exposure of animals via the forage to doses ranging from 0.2 to 330 mg/kg in the diet (Calderbank, 1972) did not induce any clinical or pathological changes in farm animals.

Calderbank (1972) recommended that domestic animals should not be allowed to enter fields newly treated with diquat, nor be given water recently treated with the herbicide. When edible crops are treated with diquat, as desiccant, at least 4 days should elapse before the crops are fed to stock, and when diquat is used for aquatic weed control, at least 7 days should elapse before the treated water is used for field irrigation. Recommended levels for weed control must be observed (Calderbank, 1972).

Sheep given doses of 1, 5, 10, and 20 mg diquat/kg per day in their drinking-water for 1 month and calves similarly exposed to 5 and 20 mg diquat/kg per day did not show any adverse toxicological effects as evidenced by growth, food consumption, and observation.

6.3 Dose-Effect of Diquat

The acute LD_{50} values of diquat in various species were published by Howe & Wright (1965) and Clark & Hurst (1970). The acute toxicity of diquat salts (Table 5) does not differ significantly and is similar for both sexes.

Table 6 summarizes the acute oral, dermal, and inhalation LD_{50} and LC_{50} values of diquat in various experimental and domestic animals. There are no marked species differences but cattle, guinea-pigs, and monkeys appear to be the most sensitive species. The few cases of acute diquat poisoning in man have not furnished sufficient data to determine the lethal dose for man.

The dose-effect relationship of repeated diquat exposure, from various studies, is summarized in Table 7. Rats, guinea-pigs and dogs were subjected to oral and dietary administration of diquat. Guinea-pigs appeared to be rather sensitive (Makovskii, 1972), but the herbicide did not induce cumulative toxic effects (Bainova, 1969, 1975; Makovskii,

Table 5. LD_{50} (mg/kg) of diquat salts in rats

Diquat	Route of entry	Sex	LD_{50} (mg/kg)
Diquat dibromide	oral		215[b]
Diquat dibromide	oral		210[b]
Diquat dibromide	subcutaneous	F	11[a]
Diquat dichloride	subcutaneous	F	10[a]
Diquat dichloride	subcutaneous	M	11[a]
Diquat dibromide	subcutaneous		22[b]

[a] From: Clark & Hurst (1970).
[b] From: Makovskii (1972).

1972), because of its relatively rapid elimination from the organism and the absence of deposits in the tissues.

Table 6. Diquat LD_{50} (mg/kg) and LC_{50} (mg/m³) in various species

Species	Oral (mg/kg)	Dermal (mg/kg)	Inhalation[a] (mg/m³)
Rat	400[b]	650[f]	35[f]
Rat	281[c]		83[h]
Rat	231[e]		
Rat	215[f]		
Rat	130[g]		
Mouse	170[b]	430[d]	
Mouse	125[e]		
Rabbit	190[b]		
Rabbit	101[e]	> 400[e]	
Guinea-pig	123[c]	400[f]	38[f]
Guinea-pig	approximately 100[e]		
Guinea-pig	100[f]		
Hen	400 - 800[b]		
Hen	200 - 400[e]		
Dog	> 200[b]		
Dog	100 - 200[e]		
Cow	approx. 30[f]		
Cow	30[e]		
Monkey	100 - 300[i]		

[a] Respirable diquat aerosol.
[b] From: Howe & Wright (1965).
[c] From: Verbetskii & Pushkar (1968).
[d] From: Bainova (1969a).
[e] From: Clark & Hurst (1970).
[f] From: Makovskii (1972).
[g] From: Bainova (1975).
[h] From: Bainova & Vulcheva (1977).
[i] From: Cobb & Grimshaw (1979).

Table 7. Effect of repeated oral, dermal, and inhalation exposure to diquat in experimental animals

Species	Dosage	Duration	Results obtained	Reference
Rat	87.5, 175, and 350 mg diquat ion/kg of diet	2 years	cataract at all dietary levels	FAO/WHO (1971)
Rat	7.2, 36, 72, 180, 360, and 720 mg diquat ion/kg diet	2 years	no deaths; reduced growth in males at highest dietary level; cataract at dietary levels of 36 mg diquat ion/kg diet and above; no cataract at 7.2 mg/kg	FAO/WHO (1971)
Rat	15, 25, and 75 mg diquat ion/kg diet	2 years	no deaths; "no effect" level for cataractogenesis 15 mg diquat ion/kg diet	FAO/WHO (1978)
Rat	oral - 6.5, 13, and 40 mg/kg body weight per day	30 days	dose-related biochemical and histological changes in kidney, liver, gastrointestinal system, and lung; no haematological changes; increased G-6-P-isomerase serum activity; histological changes at 4.3 mg/kg body weight per day	Bainova (1969, 1975)
	2.1 and 4.3 mg/kg body weight per day	4 1/2 months		
Rat Guinea-pig	oral - 0.2, 2.1, and 5.3 mg/kg body weight per day 0.1, 1.0, and 2.5 mg/kg body weight per day	1 year	the higher doses were toxic for the 2 species; no-observed-effect levels 0.2 and 0.1 mg/kg body weight per day for rat and guinea-pig	Makovskii (1972)
Dog	10, 20, 50, 140, and 420 mg diquat ion/kg of diet	up to 4 years	no cataracts at dietary levels up to and including 50 mg/kg; cataract at 2 higher dietary levels; no mortality; no effects on growth	FAO/WHO (1971)

Table 7 (contd).

Rat	oral - 2 and 4 mg/kg per day	1 and 2 years	no increase in mortality rates; histological changes in lungs after treatment with 4 mg/kg per day in drinking-water; minimal effective dose 2 mg/kg per day	Bainova & Vulcheva (1978)
Rat	dermal - 5, 10, 20, 60, and 120 mg/kg per day	20 days	slight skin irritation; death and toxic effects at 10 - 120 mg/kg per day; dilation of the gastrointestinal system at toxic levels; histological changes in kidney, gastro-intestinal system, liver, and lung at toxic levels, LD_{50} 35 mg/kg per day without occlusion; no-observed-effect dose 5 mg/kg per day	Bainova (1969a)
Rabbit	dermal - 20 and 40 mg/kg per day	20 days	mild skin irritation; toxic effects at 40 mg/kg per day; no clinical signs of toxicity at 20 mg/kg per day; LD_{50} between 20 and 40 mg/kg per day	Clark & Hurst (1970)
Rat	inhalation[a] - 0.50, 1.60, and 2.0 mg/m³, 6 h daily	15 days	clinical signs of irritation and histological changes in lungs at 2 mg/m³; no clinical, haematological, and histological deviations at 0.50 mg/m³; minimum effective concentration 1.0 mg/m³ diquat aerosol	Gage (1968)
Rat	inhalation[a] - 0.32 and 1.90 mg/m³, 6 h daily	4 1/2 months	biochemical and histological changes in lungs at 1.90 mg/m³; minimal effective concentration 0.32 mg/m³ diquat aerosol	Bainova (1972)
Rat	inhalation[a] - 0.4, 0.7, and 1.9 mg/m³, 4 h daily	4 months	clinical signs of irritation and toxic effects at 1.9 mg/m³; 0.7 mg/m³ produced changes in some rats; minimal effective concentration 0.4 mg/m³ diquat aerosol	Makovskii (1972)

[a] Respirable diquat aerosol.

7. EFFECTS ON MAN

7.1 Case Reports

Several cases of acute diquat poisoning among the general population have been reported in the literature. Fitzgerald et al. (1978) found 5 cases from 1967 to 1977 in Ireland. Vanholder et al., (1981) summarized the clinical outcome and the treatment of 11 patients with diquat poisoning (6 fatal and 5 non-fatal).

(a) Suicidal diquat poisoning

Schönborn et al. (1971) reported the fatal case of a man who drank 2 - 3 mouthfuls of Reglone® (estimated 15 - 22 g diquat) with the intention of committing suicide. Severe vomiting occurred after 2 h and, 2 h later, watery diarrhoea, the stools having a peculiar yellow-greenish colour. During the next 6 h, the patient lost about 3.5 litres of liquid through faeces and 4 litres of liquid through vomiting. The urine was very concentrated, the haematocrit was 55%. Serum enzyme activity showed toxic liver damage, and proteinuria and metabolic acidosis were registered. On the 2nd day, there were ulcers and severe oropharyngeal inflammation, on the 3rd day, increasing restlessness, optical hallucinations, and delirium and stridulous breathing developed. During the 4th - 6th days, anuria, raised body temperature, generalized convulsions, and coma were registered, and the patient died on the 7th day of cardiac insufficiency and thrombocytopenia.

The autopsy revealed extensive necrosis of the pharynx and oesophagus, and petechial bleeding and erosions in the gastrointestinal tract; pulmonary oedema with haemorrhages, hyaline membrane production, and bronchopneumonic foci were noted in the lungs; fatty degeneration was found in the liver and heart, and severe degeneration of the tubulus epithelium with necrosis in the kidneys, while the signs of circulatory failure with oedema and haemorrhagic diapedesis of the brain explained the central nervous system effects. The diquat concentrations measured on the 1st day after ingestion were 1.85 mg/litre in the urine and 0.47 mg/litre in the blood. Higher diquat levels were determined post mortem in the kidneys, spleen, and lungs (1.19, 1.04, and 0.56 mg/kg, respectively).

In a second case of suicide, the subject had taken unknown quantities of Reglone® during a period of 3 days (Okonek & Hofmann, 1975). One day after the second ingestion, she was admitted to hospital - shocked, sleepy, anuric, with haemorrhagic mucosal necrosis in the mouth, throat, and

eosophagus. Four h after admission to hospital, the diquat serum level was 1.038 mg/litre. This decreased to 0.30 mg/litre following dialysis. Death from cardiovascular collapse ensued 46 h after admission.

Vanholder et al. (1981) concluded, from their review of 11 cases, that the lethal dose of Reglone® is 30 - 60 ml or approximately 6 - 12 g diquat dibromide.

An unusual case of diquat poisoning was described by Narita et al. (1978). A clerk, after drinking heavily, swallowed about 200 ml 30% diquat dibromide formulation. Vomiting was accompanied by great thirst, severe irritation of the mouth, diarrhoea, and a temperature of 39 °C. After 24 h, the patient became anuric and developed acute renal failure; he was comatose and inarticulate, and had meiosis and unclear light reflexes. He died from dyspnoea 38 1/2 h after ingestion of diquat. Autopsy revealed renal failure with tubular necrosis, lung haemorrhages, haemorrhagic ulcers, and erosions in the stomach, and severe congestion of the lungs, kidneys, liver, gastrointestinal system, and adrenal glands. High diquat residues were determined in the kidneys, liver, lungs, and intestines. Vanholder et al. (1981) reported 2 cases of Reglone® ingestion (50 ml and 20 ml) in suicide attempts. Because of vomiting and diarrhoea, they were admitted to local hospitals, but no specific treatment was given and the patients were released in satisfactory clinical condition. However, because of the development of progressive oliguria several h later, the patients returned to the hospital. The diquat serum levels were found to be 4.5 and 0.4 mg/litre, respectively. The patients died 1 and 5 days after the ingestion of diquat.

(b) Accidental diquat poisoning

Oreopoulos & McEvoy (1969) described a patient who accidentally took a mouthful of Reglone® from a soft drink bottle. He spat out part of it. After 8 - 10 h, he had diarrhoea and 2 ulcers in the mouth, but there was no clinical evidence of respiratory, renal, or central nervous system effects on examination in hospital, and all laboratory and biochemical examinations were within the normal physiological limits. The patient continued to excrete diquat in the urine for 11 days after ingestion. He underwent forced diuresis and left the hospital in good condition.

Another case of acute poisoning following the accidental ingestion of less than a mouthful of diquat was reported by Fel et al. (1976). Nausea, vomiting, and diarrhoea were the first effects. The patient then developed uraemia, oliguria, and anuria despite forced diuresis for 2 - 3 days after the accident. Haemodialysis proved more successful. Bilateral

pneumonia was noted during the 2nd week, but was cured with antibiotics, and the patient was discharged on the 26th day in good health.

7.2 Effects on Agricultural Operators

A few studies have been performed on workers spraying diquat. Air concentrations of diquat aerosol were measured by Makovski (1972) (Table 3). The dermal exposure of the spraymen ranged from 0.05 mg to 0.08 mg on the face and hands after 2 - 3 h of daily work. The spraymen did not have any complaints, and the clinical and laboratory examinations did not reveal any significant differences in comparison with control groups. Wojeck et al. (1983) studied the exposure of workers applying 1.76% diquat by hand-operated spray against water hyacinths or using direct injection of 4.41% spray mixture into the water for hydrilla control. The spray crews applied diquat 2 - 5 h daily for 4 days weekly. The inhalatory exposure was found to be < 0.01 mg/h. The dermal exposure of the spraymen and the airboat drivers were estimated to be 1.82 and 0.20 mg diquat/h, during the treatment of water hyacinths. The dermal exposures of the spraymen and the mixer of diquat for the treatment of water hydrilla were 0.17 and 0.47 mg/h, respectively. The results of urine analysis of all workers involved in the study were negative (< 0.047 mg/litre). The dermal exposure to diquat was closely related to the concentrations used in the working solutions.

Inflammation and bleeding of the nasal mucosa were observed in people handling crystalline diquat powder in the laboratory or under field conditions (Clark & Hurst, 1970). Epistaxis during agricultural diquat application is related to the inhalation of droplets or splashes from the careless mixing of liquid concentrates. A worker who spent some considerable time in an aerosol spray drift developed irritation of the upper respiratory tract.

According to Clark & Hurst (1970), if a 20% diquat solution comes into contact with the nail base, nail growth disturbances may result, and discoloured spots, white bands, and shedding of the nail were seen after prolonged contact with concentrated diquat. The nail re-grew normally once exposure was discontinued. No adverse effects on the nails were observed following the use of diluted diquat spray solutions in agriculture. Concentrated diquat formulations have also been reported to delay the healing of superficial cuts on the hands of spray workers.

Cataracts have never been observed in man following exposure to diquat (FAO/WHO, 1978; Hayes, 1982).

7.3 First Aid and Medical Treatment

These are essentially the same as those given for paraquat (section 8.4, p. 91). See also WHO/FAO (1979).

8. EVALUATION OF RISKS FOR HUMAN HEALTH AND EFFECTS ON THE ENVIRONMENT

8.1 Exposure

8.1.1 Relative contributions of soil, water, air, and food sources to total diquat uptake

Introduction

Diquat is a contact herbicide and dessicant that is used to destroy weeds in various agricultural situations. It is used in the form of an aqueous spray, which means that the potential exposure of man may occur as a result of its presence in air, on plants, in soil, or in water.

Degradation of Diquat

Photochemical degradation takes place, when diquat treated plants are exposed to normal daylight, and continues after plants are dead. The products formed are of lower toxicity than diquat. The rapidity of photochemical degradation on plant and soil surfaces minimizes the hazard of diquat for the environment.

Soil

Diquat is rapidly and tightly bound to clay particles in the soil, and is thereafter inert. In normal agricultural use, no toxic breakdown products are to be expected in the soil (section 4.2) where diquat is less persistent than paraquat. Total diquat residues in the soil after repeated spraying ranged from 0.2 to 3.9 mg/kg. On the 15th day after a single application of diquat, residues were less than 0.1 mg/kg in field studies. Even at high rates of application, no specific adverse effects are found on soil microorganisms, fungi, or invertebrates, and no phytotoxic effects have been reported on crops.

Water

Following its use as an aquatic herbicide at normal application rates, diquat residues in water have been found to decrease rapidly to essentially undetectable levels within 7 - 14 days (section 4.3). Toxic effects on fish and other living organisms in the water are unlikely, because diquat is rapidly photodegraded, absorbed by aquatic weeds, or adsorbed to soil particles at the bottom. However, caution should be taken in the application of diquat to water containing heavy weed

growth, since oxygen consumed by subsequent weed decay may decrease the oxygen content of the water to such an extent that it is dangerous for fish or other aquatic organisms. No phytotoxic damage should occur on crops irrigated with diquat-treated water, if at least 10 days is allowed to elapse between treatment and irrigation.

Air

Diquat is not volatile. Inhalation exposure can occur via spray aerosols or contaminated dust but, if correctly applied, diquat should not give rise to significant inhalation exposure of the sprayers (section 4.5). Total airborne aerosol concentrations of diquat in the air in working areas ranged from 0.06 to 0.56 mg/m^3, depending on the method of application and the period of time after the spraying.

Food

Extensive studies on forage desiccated with diquat have demonstrated that the residues are very low within some days of the application of the desiccant. Diquat residues in the treated herbage following pre-harvest desiccation ranged from 0.02 to 25 mg/kg at different intervals after spraying. Trials in which such forage was fed to cattle and sheep have demonstrated insignificant residue levels in the milk, meat, and internal organs (section 4.4). Residues found in vegetables, fruits, and cereals have been low. There is no bioaccumulation.

8.1.2 General population exposure

Inhalation exposure of the general population to diquat may occur from spray drift off the treated fields, but this is thought to be insignificant. There are no published data on total diquat intake among the general population but this again is expected to be insignificant on the basis of known residue levels. Studies on its environmental distribution point to a low environmental hazard. Due to diquat's rapid and complete binding to clay minerals in soil, contamination of water supplies either from field runoff or percolation through soil to the water table is not expected (section 4.2).

Few cases of diquat poisoning have been reported (section 7.1). Most cases are due to the intentional ingestion of concentrated formulations, but accidental ingestion has occurred. The decanting of liquid concentrate formulations into beer, wine, or soft drink bottles, and subsequent inappropriate storage, is very dangerous.

The acute lethal dose of diquat dibromide is considered to be 6 - 12 g for man. Recovery from diquat poisoning depends on the cause of ingestion, the dose absorbed, the renal damage, and prompt initiation of therapy. No long-term adverse effects have been reported in those who have survived acute diquat poisoning.

8.1.3 Occupational exposure

There may be inhalation, dermal, and to some extent oral occupational exposure. Spray aerosols and dust particles settle in the upper respiratory tract. Diquat aerosol concentrations range from 0.06 to 0.56 mg/m^3, according to the spraying method. At a distance of 200 - 400 m from the treated field, they decrease to 0.09 mg/m^3 and less than 0.01 mg/m^3. Inhalation exposure was found to be very low in comparison with dermal (0.17 - 1.82 mg/h) exposure to diquat during application for aquatic weed control. Skin irritation, epistaxis, nail damage, and delayed wound healing have been reported. However, no data on severe or fatal cases of occupational intoxication, acute ocular damage, or occupational contact dermatitis caused by diquat were found in the literature.

8.2 Effects

8.2.1 Diquat toxicity in animals

Diquat is less toxic than paraquat and does not cause the specific lung disease so typical of paraquat exposure.

The primary toxic effect of diquat in animals is gastrointestinal damage resulting in diarrhoea with consequent dehydration. After high doses of diquat, minor toxic effects have been noted in the liver, kidney, and the nervous and endocrine systems. High concentrations of diquat are irritating to the skin, although less so than paraquat. Development of eye cataracts has been reported in rats and dogs following long-term treatment with diquat (section 6.1.3). This observation has not been reported in man. Diquat is embryotoxic but it has not been found to be teratogenic in rats and mice or carcinogenic in long-term feeding studies on rats given diquat at levels up to 720 mg/kg diet (sections 6.1.7 and 6.1.8). *In vitro* mutagenicity studies have been inconclusive, although generally suggesting weak activity, while the results of *in vivo* studies have been negative (section 6.1.8). Thus, the results of animal studies suggest that low-level exposure to diquat is unlikely to induce toxic effects in man. The no-observed-effect level in

rats has been estimated to be 0.75 mg diquat ion/kg body weight per day (FAO/WHO, 1978).

8.3 Earlier Evaluations of Diquat by International Bodies

The Joint Meeting on Pesticide Residues (JMPR) reviewed and published residue and toxicity data on diquat in 1970, 1972, 1976, 1977, 1978 (FAO/WHO 1971, 1973, 1977a,b, 1978, 1979). In 1977, it estimated the acceptable daily intake (ADI) for man as 0 - 0.008 mg/kg body weight expressed as diquat ion (FAO/WHO 1978).

The same JMPRs have recommended maximum residue levels (tolerances) for diquat in food commodities of plant and animal origin.

Regulatory standards established by national bodies in 12 different countries (Argentina, Brazil, Czechoslovakia, Federal Republic of Germany, India, Japan, Kenya, Mexico, Sweden, the United Kingdom, the USA, and the USSR) and the EEC are available from the IRPTC (International Register for Potentially Toxic Chemicals) legal file (IRPTC 1983).

A data sheet on diquat has been prepared by WHO/FAO (1979) in a series of "Data sheets on chemical pesticides". Based on a brief review of use, exposure, and toxicity, practical advice is given on labelling, safe-handling, transport, storage, disposal, decontamination, selection, training and medical supervision of workers, first aid, and medical treatment.

8.4 Conclusions

On the basis of the above findings, it can be concluded that:

General population

Residue levels of diquat in food and drinking-water, resulting from its normal use, are unlikely to result in a health hazard for the general population;

Diquat has caused some fatalities following suicidal ingestion. Occasional accidental fatalities have followed ingestion of decanted diquat. Ill-effects similar to those caused by paraquat occur, but the characteristic fibrosis of the lungs is not a feature.

Occupational exposure

With reasonable work practices including safety precautions, hygiene measures, and proper supervision, occupational exposure during the manufacture, formulation, and

application of diquat will not cause a hazard. However, the undiluted concentrate must be handled with great care, because contamination of eyes and skin (with possible consequent dermal absorption) can result from improper work practices.

Environment

Diquat in soil binds rapidly and tightly to clay particles and residual phytotoxicity from freely available diquat is unlikely. Under normal conditions of use, the toxicity of diquat for aquatic organisms is low, though resulting depletion of water oxygen due to weed decay may pose a problem. Diquat does not seem to represent an environmental hazard.

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