

PARAQUAT

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Summary

Paraquat is the most highly acutely toxic herbicide to be marketed over the last 60 years. Yet it is one of the most widely used herbicides in the world, and in most countries where it is registered it can be used without restriction. It is used on more than 100 crops in about 100 countries.

Gramoxone, manufactured by Syngenta, is the most common trade name for paraquat, but the herbicide is also sold under many different names by many different manufacturers. China is now the world's largest manufacturer of paraquat, producing more than 100,000 tonnes per year.

Paraquat has been banned, or use disallowed, in 32 countries (including the countries of the

European Union), mainly for health reasons. But there has been strong industry resistance to including paraquat in the Rotterdam Convention on Prior Informed Consent and it remains outside the PIC list. Many international organisations, such as Rainforest Alliance, Fairtrade, Forest Stewardship Council, and food giants like Dole have voluntarily banned it from their production systems.

Poisonings

Paraquat is highly acutely toxic and enters the body mainly by swallowing, or through damaged skin, but may also be inhaled. Thousands of deaths have occurred from ingestion (often suicide) or dermal exposure (mainly occupational) to paraquat. Paraquat is corrosive

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to the skin and once the skin is damaged it is easily absorbed into the body. One farmer died after just 3.5 hours spraying diluted paraquat with a leaking knapsack. Others have died from spilling the concentrate on their skin. Thousands more have suffered severe acute and chronic effects from occupational use.

It represents a severe public health problem in many countries despite the fact that paraquat is considered safe by its manufacturers, who believe they have no responsibility for the suicides. Yet experience has shown that where paraquat is banned or restricted deaths from suicides drop dramatically.

In developing countries paraquat is often applied under hazardous conditions that result in high dermal exposure. These conditions include high temperature and humidity, lack of protective clothing, leaking knapsack sprayers, lack of awareness of hazard, lack of control over the workplace, lack of facilities for washing, or medical treatment, and repeated exposure. In Malaysia women sprayers can spray herbicides, commonly paraquat, 262 days of the year. It was banned there in 2002 because of the unacceptable risk of adverse health effects, but industry pressure caused a reversal of the ban in 2006.

As little as a teaspoon of concentrated paraquat can result in death. Death is by respiratory failure and may occur within a few days after poisoning or as long as a month later. There is no antidote. Paraquat damages the lungs, heart, kidneys, adrenal glands, central nervous system, liver, muscles and spleen, causing multi-organ failure, as well as damaging the skin and eyes.

Acute toxicity

The European Commission has described the acute hazard of paraquat as:

- very toxic by inhalation
- toxic in contact with skin and if swallowed
- danger of serious damage to health by prolonged exposure if swallowed
- irritant to the eyes, respiratory system and skin.

The World Health Organisation classifies

paraquat as Class 2, moderately toxic; but PAN believes it should be reclassified as Class I because of its acute toxicity, delayed effects and lack of antidote.

Common exposure symptoms include burns to the mouth, acute respiratory distress, loss of appetite, abdominal pain, thirst, nausea, vomiting, diarrhoea, giddiness, headache, fever, muscle pain, lethargy, shortness of breath and rapid heartbeat. There can be nosebleeds, skin fissures, peeling, burns and blistering, eye injuries, and nail damage including discolouration and temporary nail loss.

Chronic effects

Paraquat causes extensive damage to the mitochondria of cells through the production of free radicals and oxidative stress, resulting in the interruption of important biochemical processes and causing cell death.

There is considerable evidence that paraquat may cause the onset, or accelerate the development, of Parkinson's disease; that the longer the exposure the greater the risk; that there may be a lag time between exposure and development of symptoms; and that early exposures are the most deleterious. The unborn foetus and children are most at risk. Pregnant women and children should not be exposed to this chemical. Paraquat crosses the placenta and can cause acute poisoning including death of the foetus or chronic effects that can persist for the lifetime.

The California Environmental Protection Agency states that paraquat can penetrate the nervous system, is a neurotoxicant, and impacts brain functions. Exposure to paraquat, even in relatively low doses, during critical periods in childhood may adversely affect the development of brain functions.

Regulators generally state that paraquat is not carcinogenic, despite it causing nasal and squamous cell carcinomas in rats; but there are a considerable number of independent studies showing it to be genotoxic, and some epidemiological evidence linking it to cancer, especially skin cancer.

Paraquat can cause endocrine disruption. It decreased testosterone, follicle-stimulating hormone, luteinizing hormone and prolactin in male rats. One epidemiological study linked paraquat exposure to hypothyroidism.

Regulatory assessments generally conclude paraquat does not cause reproductive effects, but independent studies show that it can cause reproductive problems in rodents and hens. It crosses the placenta and also concentrates in the placenta. Foetal death in pregnant women poisoned by paraquat, and neonatal death after induced delivery, has been reported.

Similarly, regulatory assessments generally conclude paraquat is not a teratogen, but independent studies show that it can cause birth defects in rodents and frogs, prompting some scientists to state that it should be classified as a teratogen. An epidemiological study has linked congenital malformations in children with paternal exposure to paraquat.

There is some evidence of effects on the immune system, and it may also be implicated in type II diabetes.

Environmental effects

Paraquat is described by US Environmental Protection Agency as “extremely biologically active and toxic to plants and animals”; and by the Environmental Risk Management Authority of New Zealand as “very ecotoxic to the aquatic environment”. It has caused teratogenic malformations in fish and amphibia, disrupted hormones in frogs, and is genotoxic in tadpoles. Amphibia are at risk from paraquat, through residues in plants, reduction in food sources and habitat, spray drift from up to 300m away, and downstream transport of paraquat in sediment. Aquatic plants can concentrate high levels of paraquat. Planktonic algae are very sensitive to paraquat and it can cause significant ecological disturbances in freshwater ecosystems through alterations in species composition, potentially resulting in loss of biodiversity, harmful algal blooms, disease, and decline in fisheries. The European Commission’s Scientific Committee on Plants expressed concern about the effects of paraquat on hares and birds. They

concluded that it “can be expected to cause lethal and sublethal effects and this is confirmed by field reports”. Freshly sprayed foliage can induce death in rabbits, and especially the hare.

The US EPA concluded that paraquat is moderately toxic to birds, and it can affect reproduction or hatchability of eggs when adult birds are exposed. It also causes endocrine disruption in birds.

Paraquat is toxic to some soil fungi and bacteria, but can also increase populations of some soil pathogens.

Poisoning incidents include fish, dogs, hares, cattle and sheep; there have also been many deliberate poisonings of dogs.

Environmental fate

Paraquat binds strongly to soil particles and tends to remain strongly bound for a long time in an inactive state, although it can also desorb again and become biologically active. Half-life in soil can be up to 20 years.

In water it is adsorbed on to particles and sediment, with a half-life under mid-European conditions estimated to be between 2 and 820 years depending on sunlight and depth of water. It has been found in surface waters, drinking water, and in groundwater although it is believed to be immobile in the soil and not to leach to groundwater.

Herbicide resistance

There are 22 different species of weeds in 13 countries that have become resistant to paraquat.

Alternatives

There are numerous design, management, mechanical and cultivational practices, as well as some plant extracts, that can be used instead of paraquat, depending on the weed species and the situation.

1. Chemical Profile

1.1 Identity

Common name

Paraquat, paraquat dichloride

Common trade name

Gramoxone

Chemical names and form

1,1'-dimethyl-4,4'-bipyridinium

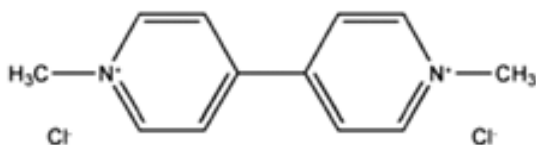
White crystalline solid, aqueous solution or granules; typically available as 10-30% concentrated solutions coloured a dark blue-green.

Molecular formula and structure

Paraquat: $C_{12}H_{14}N_2$

Paraquat dichloride: $C_{12}H_{14}N_2Cl_2$

It is a quaternary nitrogen compound.



Chemical group

Bipyridyl

Other related chemicals

paraquat dichloride trihydrate

paraquat bis(methyl sulfate)

paraquat bistribromide

CAS numbers

paraquat 4685-14-7

paraquat dichloride 1910-42-5

paraquat dimethyl sulphate 2074-50-2

Synonym

Methyl viologen

Other trade names

Because paraquat is manufactured in many countries, it is sold under numerous trade names, including:

Action, Agroquat, Agroxone, Almoxone, Cap Pelanduk, Capayam, Cekuquat, Crisquat,

Cropoquat, Cyclone, Crysquat, Delta-quat, Dextrone X, Dexuron, Dragocson, Efoxon, Esgram, Erazone, Express, Esgram, Firestorm, Galokson, Goldquat, Granafin, Gramex, Gramix, Gramixel, Halexone, Herbatop, Herboxon, Herbikill, Inferno, Kapid, Katalon, Kemozone, Kendo, Ken-tec, Kingxone, Marman Herbiquat, Methyl viologen, Methyl viologen dichloride, Multiquat, Nuquat, Osaquat, Paquat, Para, Parable, Paraco, Para-col, Parakill, Parakwat, Paranox, Paraquato, Paratone, Paratroop, Parawin, Parazone, Pillarquat, Pillarxone, Plusquat, Priquat, Prelude, R-Bix, Revolver, Scythe, Secaquat, Shirquat, Sparkle, Speeder, Speedway, Starfire, Swat, Sweep, Sunaquat, Surefire, Total, Toxer, Uniquat, Weedless.

Paraquat may also be found in compounds with other herbicides such as diquat (Actor, Dukatalon, PDQ, Preeglox, Preglone, Priglone, Seccatuto, Speedy, Weedol), simazine (Terraklene), linuron, metolachlor, and urea herbicides (Anuron, Dexuron, Gramocil, Gramonol, Gramuron, Tota-col). Pathclear contains paraquat, diquat, simazine and amitrole.

1.2 Inerts and contaminants

To reduce the chance of poisonings many countries require herbicides containing paraquat to include a stinking agent, an emetic to make people vomit, and a coloured dye so that it cannot be mistaken for a drink.

A new formulation – Gramoxone Inteon – contains a gelling agent to reduce fatality when ingested. The gel is activated at the pH of stomach acid, and is intended to slow the passage of paraquat to its site of absorption in the small intestine. This allows more time for the increased levels of emetic to remove the paraquat via vomiting, and hence reduce absorption. This new formulation is claimed by Syngenta to improve survival after ingestion by 25-35% (Dinis-Oliveira et al 2006). However experience in Sri Lanka does not support this claim – see section on Poisonings.

The concentrate may also contain an aliphatic detergent to assist entry into plant cells and hence enhance its toxicity (Dinis-Oliveira et al 2006).

Emetic

PP796, 2-amino-4, 5-dihydro-6-methyl-4-propyls-triazole-[1,5-a]pyrimidin-5-one (FAO 2008)

Its molecular formula is: $C_9H_{13}N_5O$. No information could be found about its health effects other than causing vomiting.

Contaminants

Free 4,4'-bipyridyl; terpyridines (FAO 2008)

4,4'-bipyridyl is the precursor of paraquat and there is evidence linking it to skin cancer (see Toxicology, Cancer). Little information appears to be available on the health effects of terpyridines.

1.3 Metabolites

Paraquat is excreted largely unmetabolised, along with small quantities of monoquat (1.9%), paraquat monopyridone (3.2%), and paraquat dipyrindone (1.1%) (INCHEM 1986).

1.4 Mode of action in weeds

Paraquat is a fast-acting, non-selective contact herbicide that is absorbed by the foliage. It destroys plant tissue by disrupting photosynthesis and rupturing cell membranes, which allows water to escape leading to rapid desiccation of foliage (Dinis-Olivera et al 2006). It can also be translocated within the plant, increasing the likelihood of residues.

1.5 Uses

Paraquat is used as a herbicide, desiccant, defoliant, and plant growth regulator (US EPA 1997). It is used for controlling broadleaf weeds and grasses in more than 100 different crops, including plantations (Paraquat Information Centre 2010a). According to industry sources, between 1995 and 2001 3.9% of total global sales were to oil palm plantations, 3.1% to banana plantation and 2.5% to tea estates – in all 9.5% of total sales to just 3 plantation crops mainly in developing countries (Gochez 2009).

Other major crop uses are for maize, orchards, soybeans, vegetables, potatoes, rice, and cotton. It is used for wheat, apples, oranges, coffee,

cocoa, and rubber. It is used as a pre-harvest defoliant or desiccant on crops such as cereals, cotton, beans, hops, sugar cane, pineapple, soy, potatoes, and sunflowers; and as a post-harvest desiccant to speed up removal of spent plants such as tomato plants. It is applied to pine trees to induce turpentine production. Paraquat is employed in no-till agriculture, killing grasses and weeds to minimise ploughing and help prevent soil erosion. It is used for weed control in non-agricultural areas such as roadsides, airports, around commercial buildings, drains, irrigation ditches, and waterways. It has been employed for killing illegal marijuana crops in the U.S. and in Mexico. It has also been reported as used in shrimp and prawn farming (PAN UK 2003).

Most use takes place in developing countries, where the conditions of use (hot often humid climate, lack of protective clothing, leaking equipment, continuous use, lack of control over the workplace, lack of awareness of hazard, and lack of medical facilities) make its use particularly hazardous.

Paraquat is now being promoted as an alternative to glyphosate to overcome the increasing problem of glyphosate resistance in countries with widespread use of Roundup on GM crops (Paraquat Information Centre 2010b). In the US paraquat is recommended for use in conservation tillage programmes, mixed with up to 3 other herbicides, each with a different mode of action, because of the advent of superweeds like Palmer amaranth (Ho 2010).

Paraquat is also put to a number of illegal uses. It is believed to have been used to catch mud lobsters in Fiji, which were linked to the death of a woman who consumed some (Fiji Times 2010a).

1.6 Manufacturers

Syngenta (formerly Zeneca, ICI), the world's largest agrichemical corporation, is the major manufacturer (with plants in UK and China), selling the product under the trade name Gramoxone. It is produced in many other countries under different trade names.

China is reported to be the world's largest manufacturer of paraquat, and production is

increasing. In 2006 China had 19 active ingredient producers and another 118 formulators – at that stage with a production capacity of 21,000 tonnes (Jing undated). By 2009 it was producing 109,000 tonnes/year and exporting 53,000 tonnes (Anon 2009). Construction began on another plant in March 2010, which will increase China's paraquat capacity by another 20,000 tonnes/year (Poupard 2010).

1.7 Regulatory status

Paraquat was first synthesised in 1882. Its herbicidal properties were discovered in 1955 by ICI, and registered in England in 1962 (US EPA 1997). However, it was first introduced in Malaysian rubber plantations in 1961 (Isenring 2006). It is now approved for use in about 100 countries, according to industry information (Paraquat Information Centre 2010a).

Regional and national bans

Paraquat is banned in 32 countries, including the 27 countries of the European Union.

In 2007 the European Court of First Instance annulled the EU-wide authorisation of paraquat, after a successful legal challenge launched by Sweden. The Court ruled that a 2003 Directive authorising the use of paraquat within the European Union failed to satisfy the requirement of protection of human health, particularly relating to operator exposure. It also failed to assess the risk of Parkinson's disease, and to properly assess risk to animals (Court of the First Instance 2007). Prior to this decision a number of EU countries had already banned paraquat—

- Sweden (1983): high acute toxicity, irreversible toxic effects and risk of accidents during handling and use (Kemi 2006).
- Finland (1986): very toxic even in small doses, resulting in death (UNEP 1999).
- Hungary (1991): first severely restricted, then the only registered use was cancelled. Accidental poisoning; the mortality rate was unacceptably high (UNEP 1999).
- Austria (1993): high acute toxicity, irreversible effects (especially on lungs) and numerous fatal accidents (UNEP 1999).
- Denmark (1995): persistence in soil; very toxic to non-target organisms and deaths

had occurred in hares and rabbits eating or walking on spraying grass (UNEP 1999).

- Slovenia (1997): human and environmental toxicity; deadly toxic in small amounts with no antidote; concern about high rate of suicide in Slovenia (UNEP 1999).
- Germany (1991): not a ban, but a severe restriction because of extreme persistence in soil (half-life of 17 years) (UNEP 1999).

Other countries to have banned paraquat—

- Kuwait (1985): banned for all uses, for health and environmental reasons (UNEP 1999).
- Cambodia (2003): all uses banned from December 15, 2003 (MAFF 2003); however there are reports of illegal use of paraquat smuggled in from Vietnam and Thailand (verbal report to Pesticides Task force, Pesticide Action Network Asia and the Pacific, March 13, 2010).
- Ivory Coast (2004): prohibition of import, manufacture and use in agriculture (Ministère d'Etat & Ministère de l'Agriculture 2004).
- Syria (2005) (MSEA 2005).
- United Arab Emirates (2005). Banned all uses (UNEP 2005a).

Malaysia banned paraquat in 2002, with all use to be phased out by 2005, and all advertising to cease. Reasons: acutely toxic with irreversible effects and no known antidote; high annual statistics of human poisoning; long experience and the associated poisoning shows that risk of handling and using paraquat under local conditions is unacceptably high; there are plenty of cost-effective less hazardous alternative herbicides (UNEP 2005b). However in 2006 the ban was reversed, and restricted use allowed in oil palm plantations (UNEP 2006), ostensibly to allow a comprehensive study of its uses. In November 2007, the Malaysian government announced that the ban was postponed until further notice. In 2009 the Pesticide Board announced they were waiting for a study on Integrated Weed Management and alternatives on paraquat, commissioned by the Roundtable on Sustainable Palm Oil (RSPO) before they make the final decision on paraquat. Paraquat is still on the market in Malaysia, theoretically restricted for use on oil palms less than 2 years old (Tenaganita 2009)

In 2008, Saudi Arabia notified the Secretariat of the Rotterdam Convention of its final regulatory action against paraquat, but it is unclear if this is a ban of all uses or restricted use (UNEP 2008).

Non-authorisation

- Norway (1981): voluntarily withdrawn and registration cancelled (Berne Declaration 2010a).
- Switzerland (2002): not registered for use due to acute toxicity and misuse (SFC 2002).

Restrictions

Paraquat is also severely restricted or restricted in at least 10 other countries.

- Columbia (1989): banned for aerial application (Berne Declaration 2010a).
- Philippines (1989): restricted (Berne Declaration 2010a).
- Indonesia (1990): severely restricted, use only for certain estate crops by professional applicators possessing special permit. May induce symptoms in affected humans too late to cure (UNEP 1999).
- S Korea (1987): severely restricted because of high acute toxicity; must contain emetic, colourant and stenching agent (UNEP 1999).
- Uruguay (1992): limited concentration of active ingredient (<28% p/v), size of container (1-30 litres), and colour (blue) (Lombardi 2009).
- USA: can only be sprayed under the supervision of a certified applicator. Its use is prohibited in homes, schools, recreational parks, golf courses, and playgrounds. There is a requirement to wait 12 or 24 hours before re-entering any area where paraquat has been sprayed (US EPA 1997).
- Belize (2003): restricted to ground application (Berne Declaration 2010a).
- Chile (2003): prohibited for aerial application (Berne Declaration 2010a).
- Costa Rica (2005): restriction on aerial application (Berne Declaration 2010a); in 2007 aerial application was banned, as was low volume and ultra-low volume spraying, and all sales of paraquat required a "professional prescription" (Pers comm Fernando Ramirez, RAPAL Costa Rica, 19th Jan 2008).

- Sri Lanka (2007): considering the very high rate of deaths due to paraquat poisoning, the Pesticide Technical and Advisory Committee functioning under the control of Pesticides Act No 33 (1980) decided at its 44th meeting held on the 9th Nov. 2007 that it poses unacceptable risk and therefore to enforce the following regulatory measures:
 - all formulations to have their paraquat ion concentration reduced to 6.5% with effect from 1st of January, 2008;
 - phase out the use of paraquat in three years, the phasing out scheme of the product to be worked out at the end of 2008;
 - annual quantity of paraquat formulations sold in 2008 shall not exceed the present level;
 - existing stocks of paraquat formulations with higher than 6.5% of paraquat ion concentration in the country are to be allowed to deplete through the regular marketing channel (Manuweera 2009).

Paraquat was due to be phased out altogether in Sri Lanka by the end of 2009, but risk of the reduced strength formulation is to be re-evaluated (CRC 2009).

In 1991, paraquat was banned in the Dominican Republic. However agrochemical companies successfully argued that the herbicide posed no serious health effects and was necessary because of high labor costs. Its regulatory status was reduced to "restricted" and the herbicide is now widely used throughout the country (PANNA 2002).

International

Paraquat is not yet included in the Rotterdam Convention on Prior Informed Consent (PIC), although 14 countries (and the EU as a whole) have notified the Secretariat of bans and restrictions. Heavy industry lobbying, primarily by Syngenta, has so far ensured paraquat is not listed.

Paraquat was identified by the Intergovernmental Forum on Chemical Safety (IFCS) as one of the pesticides that has caused fatal poisonings (IFCS 2003).

1.8 International standards

PAN International

Paraquat is on PAN International's Dirty Dozen (1985) and Highly Hazardous Pesticides (2009) lists for global phase-out.

Voluntary standards

In the face of the so-far failure of international regulatory action on paraquat, a number of non-regulatory organisations have taken action to prohibit paraquat use (Berne Declaration 2010b).

- **UTZ Certified:** a leading coffee certification program worldwide, now expanding to become a multi-commodity program including cacao, tea and palm oil. In 2008 approximately 77,000 coffee farmers in 19 countries were UTZ-certified. The code of conduct for coffee, tea, and cacao production prohibits the use of pesticides that are banned in the European Union and/or the USA and the pesticides listed as PAN Dirty Dozen.
- **Rainforest Alliance:** certifies sustainable production on 129,097 hectares in Latin America: mainly banana plantations (including all Chiquita plantations) with 46% of the total area, followed by coffee (42%), cacao (7%) and citrus (5%). In 2009 Chiquita announced that 90% of its pineapple supplies will be certified by the Rainforest Alliance by the end of 2009, with a long-term target of 100% pineapple certification. Rainforest Alliance prohibits pesticides listed by Stockholm and Rotterdam Conventions, PAN Dirty Dozen, and products banned by the US Environmental Protection Agency (US EPA) or the European Union.
- **International Organisation for Biological and Integrated Control of Noxious Animals and Plants International (IOBC):** an international organisation that aims at promoting the development of biological control. It is affiliated with the International Union of Biological Sciences. Paraquat is explicitly banned.
- **Fairtrade Labelling Organizations International (FLO):** sets worldwide standards for fair trade and carries out certification.
- **FLO fair trade standards exist for coffee, tea, cocoa, sugar, honey, banana, fresh fruit and vegetables, dried fruit, fruit juice, rice, wine, nuts and oilseed, cut flowers, ornamental plants, cotton, and footballs.** By the end of 2008 there were 872 Certified Producer Organizations in 58 developing countries, representing more than 1.5 million producers (about 7.5 million people including dependents) benefiting directly from Fairtrade in Africa, Asia, and Latin America. FLO prohibits the use of pesticides that are either in WHO Class Ia or Ib, PAN Dirty Dozen, or listed under the Rotterdam Convention.
- **The Common Code for the Coffee Community (CCCC):** a joint initiative of coffee producers, trade and industry (including Nestlé, Kraft Foods, Sara Lee and others), trade unions, and social or environmental NGOs. Paraquat has to be substituted within a period of 3 to 5 years. The recommendations state explicitly that paraquat should be banned as soon as possible.
- **Forest Stewardship Council (FSC):** an international network for promoting more sustainable management of timber plantations and forests. Over the past ten years 50 million hectares in more than 60 countries have been certified on the basis of FSC standards, while several thousand products made from FSC-certified wood carry the FSC label. Paraquat is prohibited.
- **World Bank:** The World Bank Operational Manual on pest management defines the criteria for pesticide selection and use. In Bank-financed agriculture operations, pests are normally controlled through IPM approaches, such as biological control, cultural practices, and the development and use of crop varieties that are resistant to or tolerant of the pest. Pesticides used in projects financed by the World Bank must have negligible adverse human health effects. The technical background regarding the selection and procurement of pesticides provided by the World Bank clarifies that paraquat is excluded from Bank financing: "The products on the 'Dirty Dozen List' are excluded from Bank financing because they do not meet the selection criteria of OP 4.09."

- Dole Food Company announced in October 2007 that it was discontinuing the use of paraquat worldwide in its operations (Dole 2008).
- Chiquita has also stopped using paraquat in banana plantations (Gochez 2009).
- United Plantations has announced it will cease use of paraquat on all its plantations by January 1st, 2011 (UP 2010). United Plantations is one of the largest oil palm plantation companies in Malaysia; it also has some coconut plantations, and oil palm in Indonesia.
- The Danish company AarhusKarlshamn, a leading producer of speciality vegetable oils and fats and a founding member of the Roundtable for Sustainable Palm Oil has stated that paraquat should be minimised or phased out “as soon as possible” (Frank 2010).

2. Toxicological Assessment

2.1 Absorption and distribution

Paraquat can be rapidly absorbed by inhalation and through the intestine after ingestion. Absorption after oral intake is about 10% (EC 2003).

Absorption through intact skin is generally low, 0.5% according to EC (2003), but is substantially increased if the skin is damaged, and has led to death in humans (Kemi 2006).

After oral intake, there is high initial concentration in the liver and kidneys, which then reduces. Plasma concentration is relatively stable for 30 hrs, and concentration in the lungs increases. It is actively concentrated in the lungs (Kemi 2006).

Low levels of paraquat may be retained in muscle tissue after skin exposure and slowly released into the blood (Lee 2008a).

Metabolism of paraquat is limited, and it is largely (69-96%) excreted in the faeces unchanged. One study showed a degree of microbial degradation in the gut (US EPA 1997).

2.2 Acute toxicity

WHO (2010) Recommended Classification of Pesticides by Hazard: Class II Moderately toxic. However, it is argued that paraquat, because of its acute toxicity, delayed effects, and absence of an antidote should be in WHO Class 1a or 1b (Isenring 2006).

US EPA (1997) Hazard Classification:

- Acute toxicity by inhalation = Category I, highly toxic
- Acute toxicity from oral intake = Category II, moderately toxic
- Systemic toxicity from dermal absorption = Category III, slightly toxic
- Eye irritation = Category II, moderate to severe
- Skin irritation = Category IV, minimal

Lethal doses

The lethal dose, LD₅₀, is the dose that kills 50% of test animals.

A wide variety of lethal doses have been reported, some expressed in terms of paraquat ion and some technical grade paraquat dichloride, others not identifying which but presumed to be in terms of paraquat ion.

Oral:

FAO (2008):

- Oral LD₅₀ rat, male = 113.5 mg/kg body weight (paraquat ion), which is 344 (range 246-457) mg/kg bw of paraquat dichloride technical
- Oral LD₅₀ rat, female = 93.4 mg/kg bw (paraquat ion), 40-200 mg/kg bw of paraquat dichloride technical

Kemi (2006):

- Oral LD₅₀ rat = 40-200 mg/kg
- Oral LD₅₀ mouse = 120 mg/kg
- Oral LD₅₀ guinea pig = 22-80 mg/kg
- Oral LD₅₀ rabbit = 49-150 mg/kg
- Oral LD₅₀ sheep = 50-75 mg/kg
- Oral LD₅₀ cat = 26-50 mg/kg
- Oral LD₅₀ dog = 25-50 mg/kg
- Oral LD₅₀ monkey = 50 mg/kg
- Oral LD₅₀ human = 40-60 mg/kg

Dermal

- Dermal LD₅₀ rat = >660 mg/kg bw (paraquat ion) (FAO 2008)

Inhalation

- Inhalation LC₅₀ rat = 0.6-1.4 mg/kg³ (EC 2003)
- Inhalation LC₅₀ rat = 0.83-1.93 mg/kg³ (FAO 2008)

Paraquat has higher toxicity to humans than it does to rats. The lowest fatal dose recorded for humans is 17 mg/kg, but even lower doses may be fatal for children (Wesseling et al 2001a).

The lung is the primary target for toxicity, both acute and chronic, with alveolar damage from oral intake and upper respiratory tract damage from inhalation (EC 2003). Toxicity is characterised by initial development of pulmonary oedema, damage to the lung membranes, and then development of fibrosis (IPCS 1984). Death is usually due to respiratory failure from lung oedema or lung fibrosis depending on the dose (Wesseling et al 2001a). Higher doses, such as 5-10 gm are “always lethal via a progressive development of respiratory dysfunction through lung fibrosis, often in combination with renal failure, painful mucosal ulcerations and lung haemorrhage” (Kemi 2006). Death may occur 2 weeks after exposure (Kemi 2006). There is no antidote.

Acute sublethal effects

Acute sublethal effects include cramps, central nervous system disorder, and respiratory symptoms in animals (Kemi 2006).

US EPA (1997) reported the following symptoms:

- Oral exposure: decreased activity, dehydration, hypothermia, irregular breathing, bloody tears, piloerection, sides pinched in, stains around nose and mouth, upward curvature of spine, reduced splay reflex.
- Dermal: skin irritation, scabbing and thickening of skin.
- Inhalation: pale and swollen kidneys, lung congestion and haemorrhages.

Skin and eye irritation

Paraquat causes moderate to severe eye

irritation (class 5 on a 1-8 scale) and slight but persistent skin irritation (FAO 2008).

US EPA (1997) reported corneal opacity, redness and discharge in eyes; and redness of the skin, with thickening, scabbing, swelling, and shedding of the outer layers.

2.3 Sub-chronic / intermediate toxicity

No & Lowest Observed Adverse Effects Levels

The No Observed Adverse Effects Level (NOAEL) is the lowest dose of the chemical given to a test animal at which no harmful effects are observed, and the Lowest Observed Adverse Effects Level (LOAEL) is the lowest dose of the chemical at which a harmful effect is observed.

- Lowest relevant NOAEL, oral = 0.45 mg/kg bw/day in dogs, 1 year study (EC 2003)
- Lowest relevant NOAEL, inhalation = 10 µg/m³ in rats, 15 exposures (EC 2003)
- NOEL, dermal = 1.15 mg/kg bw/day in rabbits, 21-day study (EC 2003)

Subchronic effects

US EPA (1997) reports the following adverse effects from subchronic toxicity testing:

- Oral: increased lung weight, large lesions in the lungs, alveolar collapse, shortness of breath, and harsh rattling noises with breathing; slow or irregular heartbeat; decreased food intake; and weight loss.
- Dermal: minimal to severe inflammation, pre-cancerous cell proliferation, thickening, ulceration and exudation; and decreased weight of testes.
- Inhalation: nasal discharge; epithelial cell proliferation, ulceration, necrosis, and inflammation in the larynx; and in the lungs thickening of alveolar walls, and aggregation of white blood cells.

2.4 Chronic toxicity

The chronic NOEL and LOEL are (FAO 2008):

- NOEL = 1.25 mg/kg bw/day paraquat ion (rat)
- LOEL = 3.75 mg/kg bw/day paraquat ion (rat)

Mode of action in animals

Oxidative stress occurs when the production of 'reactive oxygen species', such as free radicals and hydrogen peroxide, exceeds the body's ability to neutralise and eliminate them, overwhelming antioxidant defences such as glutathione, and resulting in DNA damage, and cell and tissue death. Oxidative stress is involved in many human diseases, including Parkinson's disease, cancer, Alzheimer's disease, diabetes, and heart failure. Commonly used measures of the extent of oxidative stress in laboratory studies are the levels of glutathione and associated enzymes of the antioxidant system such as glutathione reductase, glucose-6-phosphate dehydrogenase, glutathione-S-transferase, glutathione peroxidase, catalase, and superoxide dismutase. Alterations in the components of the antioxidant system can be used as biomarkers for paraquat poisoning (Ray et al 2007).

Paraquat causes extensive damage to the mitochondria of cells through the production of free radicals and oxidative stress, resulting in the interruption of important biochemical processes, cell death, and multi-organ failure (Suntres 2002; Mohammadi-Bardbori & Ghazi-Khansari 2008; Cocheme & Murphy 2009). Effects have been measured in rats in the mitochondria of brain cells (e.g. Castello et al 2007; Dreschel & Patel 2009), in brain neurons (Yang & Tiffany-Castiglioni 2005; Zaidi et al 2009), in blood, liver, lung and kidney cells (Ray et al 2007); and in the hippocampus of mice brain (Chen et al 2010a).

Systemic effects

Paraquat alters the levels and activity of various enzymes in liver and kidney (Dere & Polat 2000); and in serum, including acetylcholinesterase (El-Demerdash et al 2001).

US EPA (1997) reported decreased red blood cells, haemoglobin, white blood cells, and serum protein; increased polymorphonucleocytes (types of white blood cells); altered ratios of liver enzymes; increased potassium and glucose; and decreased weight of a number of organs (heart, liver, brain, kidneys, urinary bladder, ovaries, thyroid, and adrenals) varying between male and female rodents. IPCS (1984) reported increased plasma concentrations of corticosteroids.

Diabetes

Paraquat is implicated in the development of diabetes. Oxidative stress, a key effect of

paraquat, is thought to play an important role in type II diabetes, through the development of insulin resistance (Kimura et al 2007, 2010; Shibata et al 2010). Paraquat has been shown to inhibit insulin action in laboratory tests on rat liver cells (it impaired the suppressive effect of insulin on insulin-like growth factor-binding protein-1 gene expression) (Kimura et al 2007, 2010). Another study showed that paraquat inhibits insulin-dependent glucose uptake through oxidative stress (Shibata et al 2010). Paraquat has also been shown to cause hyperglycaemia in sheep (Webb 1982-83).

Eyes

US EPA (1997) reported clouding of the lens, and cataracts in rodents.

Lungs

US EPA (1997) reported chronic inflammation of lungs, increased lung weight, deeper breathing, thickened alveolar walls, fibrosis, oedema, and alveolar haemorrhage in rodents.

It is clear that paraquat causes the development of lesions in the lungs, although these appear generally to be non-cancerous. According to the Japanese pesticide industry (ICI Ltd Japan & Otuska Chemical Ltd 1988), paraquat "can induce a chronic proliferative and hyperplastic lung lesion", although "it was not tumorigenic in this study" (referring to a study carried out by Nippon Experimental Medical Research Institute). The same study also reported a higher incidence of lung adenomas in female rats but denied their significance (they were "within historical range").

Rats exposed to sublethal doses of paraquat experienced decreases in aerobic performance and mechanical efficiency, as well as increased oxygen consumption during exercise (Lacerda et al 2009).

Liver

US EPA (1997) reported cell proliferation and fibrosis of the bile duct in rodents.

Kidneys

US EPA (1997) reported rough surface and nephritis, and renal tubular degeneration in rodents.

Adrenals

US EPA (1997) reported adrenal cysts in rodents.

Thymus

US EPA (1997) reported atrophy of the thymus gland in rodents.

Cardiac and haematolymphatic system

Effects at high dose rates in laboratory animals include damage to the myocardium and haemolytic anaemia (IPCS 1984).

Paraquat caused myocardial contractile dysfunction in mice (Ge et al 2010).

Paraquat inhibits the synthesis, and accelerates the breakdown, of haeme, the iron-containing component of haemoglobin in blood (Noriega et al 2002).

US EPA (1997) reported swelling of the spleen, swelling and inflammation of the mesenteric lymph node, and leukaemia in rodents.

Cancer

There is some evidence that paraquat may cause cancer, particularly skin cancer, and a considerable amount of controversy over whether or not it does.

The US EPA (1997) concluded that paraquat does not pose a risk of cancer to humans (Category E: evidence of non-carcinogenicity in humans). This was based on four studies, two on rats and two on mice. However, in 1986 the US EPA had classified paraquat as a possible carcinogen (Category C: limited evidence in animals, no evidence in humans), based on evidence in rat studies of an excess of adenomas and carcinomas in the lung, and squamous cell carcinomas in the forehead. But there was scientific disagreement (especially by the industry) about the significance of the effects, and when the data was reviewed in 1988 paraquat was reclassified as having evidence of being non-carcinogenic to humans (Category E). Then in 1989, a different body (the FIFRA SAP) considered that the nasal carcinoma provided “equivocal evidence of carcinogenicity” and placed it in Category D. Back again to EPA in 1989: it decided to retain Category E classification. The US EPA’s on-line Integrated Risk Information System (IRIS) retains the

1993 classification of paraquat as a possible carcinogen based on the forehead carcinomas (US EPA 1993), as does the National Library of Medicine’s Hazardous Substances Data Bank (HSDB 2009).

US EPA (1997) also reported studies that showed dose-related increases in adenomas and carcinomas in the thyroid gland, and tumours (pheochromocytoma) in the adrenal gland, but discounted these as within the range reported for controls historically. Another study showed evidence of tumours in pituitary and thyroid glands, but these were discounted as either not dose-related or ‘similar’ to controls. Another study found frequent leukaemia in male and female rodents.

The International Agency for Research on Cancer (IARC) has not evaluated paraquat for carcinogenicity.

The International programme on Chemical Safety (IPCS 1984) concluded that paraquat is not carcinogenic, as also did the European Commission (EC 2003) and FAO (2008).

A number of epidemiological studies have associated paraquat exposure with skin cancers in humans. Wesseling et al (2001a) drew a link between paraquat and skin cancer in the following 3 studies:

- squamous cell carcinoma was associated with combined exposure to sunlight and bipyridines, the precursors of paraquat, among workers in 28 paraquat factories in Taiwan (Jee et al 1995);
- a geographic study in Costa Rica found an excess of different skin cancers (lip, penile, melanoma, and non-melanomous skin cancer) in the coffee growing regions, and of melanoma in banana regions, both crops involving extensive paraquat use (Wesseling et al 1999);
- a cohort study in Costa Rica found increased risk of skin melanoma in banana workers (Wesseling et al 1996).

Additionally a 52-year old strawberry farmer in the UK developed about 100 skin lesions on his back, suspected to be squamous cell and basal cell carcinomas. One ulcerated lesion was confirmed as squamous cell carcinoma. The

man had repeated direct contact with paraquat on his back. He sprayed paraquat and demeton-S-methyl using a leaking backpack sprayer and recalled that his clothes would be soaked in chemicals after a spray session (Anderson & Scerri 2003).

Laboratory studies have shown that paraquat causes oxidative stress and damage in mouse skin cells (Black et al 2008), and oxidative stress is known to contribute to the development of cancer (Valko et al 2006), so this may in part explain the proposed associations between paraquat and skin cancer.

An earlier study of paraquat workers had also found an association between exposure to the bipyridine precursors of paraquat, and squamous cell carcinoma and Bowen's disease (an early stage of squamous cell carcinoma) (Bowra et al 1982).

In a case-control study of parental occupational exposure to pesticides and risk of childhood leukaemia in Costa Rica, the mother's exposure to paraquat particularly during the second trimester of pregnancy but also during the year before conception was associated with leukaemia, especially acute lymphocytic leukaemia. There was also a small increased risk from fathers' exposure to paraquat during the year before conception (Monge et al 2007).

An epidemiological study of 24,667 pesticide applicators found a possible link between paraquat exposure and non-Hodgkin's lymphoma, although there was inconsistency in exposure level trends (Park et al 2009).

A third epidemiological study, in Nebraska USA, found a "significant positive association" between exposure to paraquat and brain cancer – an 11-fold increase – although the number of cases was small (Lee et al 2005).

Breast cancer

The US EPA (1997) reported mammary gland cysts, adenomas, fibromas, fibroadenomas and adenocarcinomas in a trial on rats, although they concluded they "did not appear to be treatment-related".

Women with the inherited breast cancer susceptibility gene BRCA1 appear to be at

greater risk for breast cancer from paraquat exposure, as the gene confers sensitivity to oxidative stress, a key effect of paraquat (Bae et al 2004).

Among the symptoms reported by women sprayers using paraquat in Malaysian plantations are breast pain, swelling and/or the development of pus in their breasts (Joshi et al 2002). Although these symptoms themselves are not indicative of breast cancer, evidence suggests that inflammation may be a key event in cancer development (Lu et al 2006; Berasain et al 2009; Schetter et al 2010).

The USA Agricultural Health Study (Engel et al 2005) found a slightly increased risk of breast cancer associated with women whose husband's used paraquat. The authors examined the association between pesticide use and breast cancer incidence among 30,454 farmers' wives in a large prospective cohort study in Iowa and North Carolina, in which 309 breast cancer cases were identified. However the small number of cases precluded firm conclusions.

Genotoxicity / mutagenicity

A pesticide is genotoxic if it causes damage to a gene that could result in cell death or change in the structure or function of the gene. The damage can be mutagenic (heritable) or non-mutagenic. Mutagenic means causing a change in the genetic structure usually through base-pair substitution (change in amino acid sequence), deletion, or addition of gene fragments, or some other mechanism. Mechanisms involved include causing damage to the chromosome such as loss, breaks or rearrangements of chromosomal segments. Genotoxicity also includes sister chromatid exchanges, interchanges and re-attachments of strands in the chromosome during DNA replication, and induction (increase) in the frequency of micronuclei (small fragments formed when chromosomes break). One of the main health implications of genotoxicity is cancer.

The evidence on mutagenicity is inconclusive, but there is evidence that paraquat may contribute to cancer through this mechanism. EC (2003) concluded that paraquat was not genotoxic in *in vivo* studies (i.e. whole living organisms), but it was in some *in vitro* studies (tissue studies). The IPCS (1984) also concluded that *in vitro* studies are suggestive of weak potential mutagenic activity, but *in vivo* studies are not. FAO (2008) reported paraquat

to have been mutagenic in human lymphocytes and Chinese hamster lung fibroblasts, but not in rat liver cells and mouse lymphocytes. The California Environmental Protection Agency concluded there was evidence of genotoxicity (Cal EPA 1993).

In 1979 Thomas Haley, of the United States Food & Drug Administration, reported that “paraquat is mutagenic or antimutagenic depending on experimental conditions”.

Genotoxicity has been demonstrated as follows:

- human lymphocytes: micronuclei induction, DNA damage, chromosomal aberrations, sister-chromatid exchange
- human embryo epithelial cells: unscheduled DNA synthesis
- Chinese hamster lung cells: sister chromatid exchange and chromosomal aberrations
- rat bone marrow: micronuclei induction
- barley root tip cells: chromosomal aberrations and micronuclei induction
- mice skin cells: increased frequency mutation in harlequin prematurely-aged mice
- erythrocytes of Chinese toad (*Bufo bufo*) tadpoles: DNA damage
- algae: reverse, forward, and auxotrophic mutations
- yeast cells, *Saccharomyces cerevisiae*: mitotic recombination or gene conversion
- the bacteria *Salmonella typhimurium*: forward mutations
- mouse lymphoma: forward mutations
- fruit fly: mutagenic
- wheat seeds: chromosomal aberrations
- Welsh onion/scallion (*Allium fistulosum*): weakly mutagenic

(Haley 1979; Vaishampayan 1984; US EPA 1993; el-Abidin Salam et al 1993; US EPA 1997; Ribas et al 1997; Yin et al 2008; Jovtchev et al 2010; Van Osch et al 2010).

Paraquat caused genotoxic effects (chromosome damage) in rat bone marrow even when the exposure was via the skin (D'Souza et al 2005).

Other cancer-causing mechanisms

Oxidative stress

There is abundant evidence that paraquat causes oxidative stress, and there is growing evidence that increased oxidative stress leads to cancer (Mukherjee et al 2006).

Endocrine disruption

Paraquat's potential for endocrine disruption has not been assessed for regulatory purposes. However there is evidence that it can interfere with hormones. The study by Zain (2007), reported below in the section on reproduction, showed that paraquat decreased testosterone, follicle-stimulating hormone, luteinizing hormone and prolactin in male rats. Conversely hormonal status can influence the effects of oxidative stress caused by paraquat (Huang et al 2006).

Paraquat also inhibited the production of testosterone in the testis and 17beta-oestradiol in the ovary of the frog *Rana esculenta* (Quassinti et al 2009).

Paraquat may also affect the thyroid hormones. A significant association was found in the Agricultural Health Study (1993 to 1997 in Iowa and North Carolina, USA) between hypothyroidism in women, and having used paraquat. Thyroid adenomas have been observed in rats exposed to paraquat, and detectable levels of paraquat have been found in the thyroid gland in poisoning victims, with higher amounts in women, suggesting that “the thyroid could be susceptible to the effects of paraquat” (Goldner et al 2010).

Reproductive & developmental effects

Despite regulatory assessments that paraquat has no effects on reproduction, a number of independent studies indicate that it does.

- Lowest relevant reproductive NOAEL = 2.5 mg/kg/ bw/day, based on lung lesions in parents
- Lowest relevant development NOAEL = 3 mg/kg bw/day (EC 2003).

On the basis of these, EC (2203) concluded that paraquat has no specific effects on reproduction and is embryotoxic only at levels that are also toxic to the mother. FAO (2008) concluded paraquat has no effect on reproductive parameters.

US EPA (1997) reported necrosis and atrophy of the testes, atrophy of the ovaries, and uterine cysts and polyps, with chronic exposure.

According to Wesseling et al (2001a), animal studies revealed no reproductive effects at doses of paraquat lower than the maternal toxicity dose. Reproductive effects that were found at high rates included foetal mortality in rats, increased percentage of abnormal eggs in hens (Exttoxnet 1996), and increased resorption rate and postnatal mortality rate in mice (IPCS 1984; Cal EPA 1993). Hence paraquat is not expected to cause damage to reproduction at levels humans are normally exposed to (Exttoxnet 1996).

However, recent *in vitro* laboratory studies have demonstrated that paraquat, even at very low levels of exposure, may affect reproduction.

Pre-implantation exposure of mouse embryos to concentrations of paraquat as low as 8 μM (the lowest concentration tested) resulted in significant reduction in their development (Hausberg et al 2005). And exposure to concentrations of paraquat 800-fold less than these injured mouse stem cells, stalling cell proliferation and increasing cell death. These effects occurred at the equivalent of the first 4-6 days of pregnancy and at concentrations so low (e.g. 0.014 μM) that adverse health effects are not expected (Perla et al 2008).

Additionally, in 2007 Anuar Zain concluded that paraquat is in fact "toxic to male reproductive function both by oral and dermal routes of exposure". His study showed that, in rats, medium to high levels of exposure to paraquat (5 mg/kg and 20 mg/kg) resulted in decreased organ weight; decreased diameter of seminiferous tubules; degeneration of the epididymal epithelium; decreased spermatogonia, spermatocytes, spermatids and Leydig cells; increased sperm mortality and abnormal sperm morphology; and decreases in testosterone, follicle-stimulating hormone, luteinizing hormone and prolactin.

Haley (1979) reported that, when injected into fertile hen eggs, "paraquat caused pseudofeminization of male chick and quail embryos, the testes showed intersexual

phenomena, and regression of the Mullerian ducts was inhibited (these normally develop in females but degenerate in males). There was a reduction in the number of gonocytes in both males and females" [germ cells responsible for formation of ova and spermatids].

Paraquat is known to cross the placenta: in Crete, it was found in higher concentrations in the placenta than in the mother's blood (Tsatsakis et al 1996). Foetal death in pregnant women poisoned by paraquat, and neonatal death after induced delivery, have been reported (Wesseling et al 2001a).

Birth defects (teratogenicity)

There is also controversy over whether or not paraquat is a teratogen: regulatory assessments say it is not, but a number of independent studies show it is.

Animal studies revealed no teratogenic effects at doses of paraquat lower than the maternal toxicity dose, according to Cal EPA (1993). FAO (2008) concluded paraquat is not teratogenic.

Teratogenic effects in rodents at high dose levels include reduced foetal body weight; delayed ossification of forelimb and hindlimb digits, and of the occipital (lower back part of skull); non-ossification of hind limb bones (astragalus); delayed or partial ossification of the sternabrae; and changes to the spine (US EPA 1997). According to Exttoxnet (1996), the weight of evidence suggests that paraquat does not cause birth defects at doses theoretically experienced by humans.

Several studies have shown paraquat to be embryotoxic and teratogenic to frogs, with maternal exposure resulting in higher embryo and tadpole mortality, as well as growth retardation, abnormal tail flexure and gut coiling, and stunted growth rate in surviving tadpoles (Vismara et al 2000, 2001a, 2001b; Osano et al 2002), prompting Osano et al to conclude that paraquat should be classified as a teratogen.

A study of children with congenital malformations in Spain revealed a possible association with paternal exposure to paraquat (relative risk of 2.77) (Garcia et al 1998).

Nervous system

Neurotoxicity tests were not required by the US EPA (1997) because of the chemical nature of paraquat and the fact that it did not inhibit cholinesterase or damage the structure of the nervous system. Yet there is considerable evidence from animal studies, supported by clinical experience and pathology findings from human poisonings, to show that paraquat is neurotoxic.

As far back as 1984 it was known that, at high doses, paraquat produced symptoms of neurological disturbance in rats, including decreased motor activity, lack of co-ordination, ataxia, and dragging of the hind limbs (IPCS 1984).

Since then a number of studies have shown that exposure of laboratory animals to paraquat causes reductions in neurotransmitters in the brain (Endo et al 1988; Miranda-Contreras et al 2005), resulting in significantly disturbed or reduced motor activity including walking, drinking, rearing, and rotational activity (Chanyachukul et al 2004; Müller-Ribeiro et al 2010; Songin et al 2010), and increased anxiety (Littlejohn et al 2008).

Paraquat also kills neurons in the brain – both mature and immature cerebellar granule neurons (Stelmashook et al 2007) – and damages the hippocampus region of the brain, reducing learning and memory (Chen et al 2010a).

Kriscenski-Perry et al (2002) demonstrated that thermal stress and paraquat have a synergistic effect in damaging spinal motor neurons.

Now, in 2010, the California Environmental Protection Agency (Cal EPA 2010) has raised real concerns about the effects of paraquat on the developing brains of children. It concluded that “paraquat is a neurotoxicant and impacts brain functions”. It also stated “there is direct evidence that paraquat can penetrate the central nervous system. Paraquat may affect different systems of the brain including the nigrostriatal dopaminergic system. The developing brain may be particularly sensitive to oxidative insults, a mechanism of action of paraquat”. Exposure to paraquat, even in relatively low doses, during critical periods in childhood may alter biochemical factors that result in “re-programming of the signal

transduction pathways”, which may adversely affect the development of brain functions. The immature brain is highly susceptible to the oxidative stress caused by paraquat.

Parkinson's disease

Available epidemiological studies suggest there is an association between the degenerative neurological condition Parkinson's disease and exposure to:

- pesticides (Fall et al 1999; Ritz & Yu 2000; Engel et al 2001; Priyadarshi et al 2001; Zorzon et al 2002; Baldi et al 2003; Firestone et al 2005; Ascherio et al 2006; Frigerio et al 2006; Dick 2007; Dick et al 2007; Fong et al 2007; Kamel et al 2007; Bronstein et al 2009); or
- specifically herbicides (Seidler et al 1996; Hancock et al 2008).

Several studies found a 7-fold elevation of risk (Golbe et al 1990) including in women in Hong Kong (Chan et al 1998). More commonly the increased risk has been in the range of 1 to 4 fold for both pesticides (Hubble et al 1993) or more specifically herbicides (Gorell et al 1998; Semchuk et al 1992; Butterfield et al 1993). In 2005 a 3-fold increase in risk of Parkinson's disease associated with pesticides was reported in China (Ma et al 2005), and in 1998 a 2.3 times increased risk had been found in a study in Australia (Menegon et al 1998). One study found a 70% increased risk with use of insecticides in the home and 50% increased risk with use in the garden (Stephenson 2000).

Semchuk et al 1993 concluded that occupational herbicide use was the 3rd strongest predictor of risk of Parkinson's disease after family history and head trauma.

A meta-analysis by Priyadarshi et al (2000), of studies between 1989 and 1999, found an approximate doubling of risk of Parkinson's disease with exposure to pesticides.

Other studies too have found a strong association between increased risk of Parkinson's disease and:

- work in the agricultural sector (Hertzman et al 1990; Granieri et al 1991; Tüchsen & Jensen 2000; Kirkey et al 2001; Petrovich et al 2002; Bronstein et al 2009);

- living in rural areas (Ho et al 1989; Golbe et al 1990; Butterfield et al 1993; Liou et al 1997); and/or
- drinking well water (Smargiassi et al 1998; Gatto et al 2009; Willis et al 2010).

Medical cases add to the evidence. Two individual cases were reported by Bocchetta & Cosini (1986) “in relation with the direct use of pesticides”. Both were early onset cases, one a 41-year-old farmer using pesticides extensively, and the other a 38-year-old worker at a chemical plant making petroleum derivatives and pesticides.

So there is substantial evidence linking Parkinson’s disease with exposure to pesticides. The question now is whether paraquat is one of the causative pesticides.

There are three individual pesticides particularly linked to Parkinson’s disease: rotenone, maneb, and paraquat (Hatcher et al 2008).

Paraquat and Parkinson’s: laboratory studies

Numerous laboratory studies demonstrate the plausibility of paraquat as able to cause the onset, or accelerate the development, of Parkinson’s disease (Hatcher et al 2008).

Animal studies have shown that paraquat causes degenerative brain changes that are the pathological hallmarks of Parkinson’s disease. Parkinson’s is characterised by a progressive loss of dopamine neurons in the substantia nigra region of the brain, the presence of ubiquitin- and α -synuclein-positive cytoplasmic inclusions known as Lewy bodies, depigmentation of the locus ceruleus, and autonomic dysfunction (Hatcher et al 2008). Dopamine is a neurotransmitter involved in the control of muscular movement.

Paraquat has been shown to cause dose-dependent loss of dopamine neurons and degeneration of the nigrostriatal dopamine system; aggregation of α -synuclein and formation of Lewy bodies; and decreased or altered locomotor activity (e.g. Liou et al 1996; Brooks et al 1999; Uversky et al 2001; Manning-Bog et al 2002; McCormack et al 2002; Mollace et al 2003; Chanyachukul et al 2004; Peng et al

2004; Li et al 2005; Ossowska et al 2005; Dinis-Oliveira et al 2006; Purisai et al 2007; Yang & Tiffany-Castiglioni 2007; Somayajulu-Niṭu et al 2009; Choi et al 2010; Songin et al 2010).

Although the mechanism by which paraquat causes these effects in the brain is not fully understood, there are indications that it may be via oxidative stress and the formation of free radicals (Mollace et al 2003; Yang 2005; Castello et al 2007; Li et al 2007; Kang et al 2009; Chen et al 2010a). Paraquat is known to cause production of ‘reactive oxygen species’, such as superoxide, which cause oxidative damage in brain mitochondria (Dreschel & Patel 2009).

Paraquat has the ability to cross the blood-brain barrier (Shimizu et al 2001; Dinis-Oliveira et al 2006) and enter the brain (Lee 2008a). It persists in mouse midbrain tissue with a half-life of 28 days, and this persistence may contribute to prolonging adverse effects (Prasad et al 2007).

The uptake of paraquat into the brain is age-dependent, with higher concentrations found in very young and very old in animal studies (Thiruchelvam et al 2002).

The effect of paraquat in inducing Parkinson’s disease or symptoms is heightened by synergistic interaction with the fungicide maneb, and the adverse effects of the combination occur at low doses in animal studies (Thiruchelvam et al 2000a, 2000b; Thrash et al 2007). Males have shown greater vulnerability to this combination, and aging increases vulnerability (Dinis-Oliveira et al 2006; Thiruchelvam et al 2003). Vulnerability is also increased in people with certain genetic variations relating to dopamine transport: males with 2 or more of the susceptible alleles of the gene, and who were occupationally exposed to maneb and paraquat, had an almost 3-fold risk of Parkinson’s compared to those without the genetic variation (Ritz et al 2009). In other words there is an interaction between genetics and the pesticides.

Another dithiocarbamate fungicide closely related to maneb – nabam – has a similar synergistic effect on paraquat, increasing tissue concentration and altering dopamine transport (Barlow et al 2003).

Paraquat and Parkinson's: epidemiology and cases

The evidence from animal studies showing that paraquat may cause or promote Parkinson's disease is supported by a number of case studies and epidemiological studies linking the two.

- A 32-year-old citrus farmer developed Parkinson's after working with paraquat for 15 years (Sanchez-Ramos et al 1987).
- A case-control study in California, USA, found that exposure to both paraquat and maneb greatly increased the risk of Parkinson's disease, particularly in people who would have been children, teenagers, or young adults during the period of exposure – the risk was 2-fold when exposed to just paraquat or maneb alone but 4-fold when exposed to both of them (Costello et al 2009).
- Occupational use of pesticides was associated with an 80% increased risk of Parkinsonism, with the risk rising to 280% for paraquat, in a recent US study (Tanner et al 2009).
- A case-control study in Texas, USA, found a 3.5-fold increase in risk of Parkinson's disease associated with exposure to paraquat (Dhillon et al 2008).
- In 2005, Firestone et al reported a 67% increased risk of Parkinson's disease with exposure to paraquat in Washington State, USA.
- A Taiwanese study found that using paraquat was associated with a 4.7 fold increase in Parkinson's disease, the risk increasing with duration of use (Liou et al 1997).
- Unusual clustering of Parkinson's disease in 3 kibbutzim in Israel was thought to be linked to pesticide use, including maneb and paraquat (Goldsmith et al 1990).
- In Hong Kong, previous use of herbicides gave a 3.6 times increased risk of developing Parkinson's, and the author commented that paraquat was widely used (Ho et al 1989).
- In 1985 Barbeau et al reported a high correlation between Parkinson's disease incidence and pesticide use in Quebec, Canada, postulating paraquat as the cause (Barbeau et al 1985,1986).

Early exposures

There may be a considerable lag time between

exposure to paraquat and development of Parkinson's disease, with early exposures being pivotal. Hertzman et al (1990), in their study on occupational exposures, commented "our findings suggest that if paraquat were a causal factor, the damage might occur only a decade before diagnosis, or that some damage may occur early in life, and subsequent exposure to paraquat, serves to bring out [Parkinson's disease]. Golbe et al (1990) found that early life use of pesticides was associated with a 7-fold increased risk of Parkinson's disease.

Several animal studies have linked adult onset Parkinson's disease to neonatal exposure to paraquat. Neonatal exposure to paraquat, even at low doses can induce permanent brain function changes, and neurochemical and behavioural changes in the adult mouse, including reduced dopamine (Fredriksson et al 1993). Previous exposure, and particularly developmental exposure, to paraquat enhances vulnerability to neurotoxins, and there is progressive neurotoxicity with continuing exposure leading to earlier onset of Parkinson's disease than is the norm (Thiruchelvam et al 2002). Foetal exposure in mice led to adult onset (Barlow et al 2004). Developmental exposures led to "progressive, permanent, and cumulative neurotoxicity of the nigrostriatal dopamine system and enhance[d] vulnerability to subsequent environmental insults (Cory-Slechta et al 2005a). Neurotoxicity as a result of developmental exposures can remain "silent" until unmasked later in life by another challenge (Cory-Slechta et al 2005b).

In summary, there is a considerable amount of evidence that paraquat may cause the onset, or accelerate the development, of Parkinson's disease; that the longer the exposure the greater the risk; that there may be a lag time between exposure and development of symptoms; and that early exposures are the most deleterious. The unborn foetus and children will be most at risk. Pregnant women and children should not be exposed to this chemical.

Immune system

Very little research appears to have been carried out on the effect of paraquat on the immune system of mammals. However available results do show adverse effects.

Repetto & Baliga (1996) reported a rat study

showing a decrease in macrophages (cells that destroy bacteria, viruses, and tumour cells) as a result of exposure to paraquat (Styles 1974). Another study, of chronic exposure of rats to low levels of paraquat, showed suppression of the T lymphocytes (Caroleo et al 1996).

Paraquat has also been found to increase the release of histamine from mast cells in rats and therefore can exacerbate allergic diseases (Sato et al 1998).

Recently paraquat has been demonstrated to cause immune-based inflammatory effects in umbilical cells (Yu & Nie 2010).

At high doses it suppresses both the cellular and humoral activity of the immune system of rats (Riahi et al 2010).

2.5 Toxic interactions

The addition of copper enhanced the toxicity of paraquat to the malarial parasite *Plasmodium falciparum* (Marva et al 1991) and the bacterium *E. coli* (Kohen et al 1985). Iron also enhanced toxicity of paraquat to *E. coli* (Korbashi et al 1986).

Prior exposure to paraquat enhanced the inhibition of brain acetyl cholinesterase by the insecticide fenthion (Wijeyaratne & Pathiratne 2006).

2.6 People at heightened risk

People at heightened risk from exposure to paraquat include those with impaired pulmonary function (HSDB 2009); those with selenium-deficient diets, as selenium deficiency increases the toxicity and lethality of paraquat (Glass et al 1985); and children.

3. Human Health Effects

3.1 Exposure guidelines

- Acceptable Daily Intake (ADI) = 0.004 mg/kg/day (EC 2003)

- Acceptable Operator Exposure Level (AOEL) (long term) = 0.0004 mg/kg/day (EC 2003)
- Acceptable Operator Exposure Level (AOEL) (short term) = 0.0005 mg/kg/day (EC 2003)
- Acute Reference Dose = 0.005 mg/kg/day (EC 2003)
- Child Reference Dose (draft) = 7×10^{-5} mg/kg/day (CAL EPA 2010)

As little as a teaspoon, or a mouthful, of a 20% solution may be fatal – equivalent of 17 mg/kg (Wesseling et al 1997; Dinis-Oliveira et al 2006).

3.2 Health effects

Acute effects

Severe paraquat poisoning is fatal; death may be very rapid or delayed up to several weeks.

The main target organ of paraquat poisoning is the lung, but paraquat is also distributed to the heart, liver, and kidney. The brain is now recognised as another target organ: after a single injection paraquat is clearly seen in the brain (Cal EPA 2010). Systemic paraquat poisoning is characterised by burns to the mouth, throat, oesophagus, and stomach (when ingested); acute respiratory distress; and multi-organ failure. Less frequently there may be effects on the central nervous system; adrenal glands; kidney; heart; and muscles including necrosis, excitability, convulsions, lack of coordination; and coma. There may be loss of appetite, thirst, nausea, vomiting, abdominal pain, diarrhoea, giddiness, headache, fever, muscle pain, peripheral burning sensations, lethargy, shortness of breath, rapid heartbeat, sore and congested lungs, coughing up of frothy sputum, cerebral oedema and brain damage, and renal failure. Pancreatitis may cause severe abdominal pain, and liver damage may cause jaundice. Death is by respiratory failure (Grant et al 1980; Extoxnet 1996; Reigart & Roberts 1999; Wesseling et al 2001a; Gawarammana & Dawson 2010).

Clinical reports identify acute lung injury and pulmonary hypertension; leucocytosis; metabolic acidosis; increased levels of blood amylase, glucose, and creatinine (Jun & Kang 2009); enlarged heart (Im et al 1991); acute kidney injury (Kim et al 2009); and generalized oedema,

haemorrhages, and meningeal inflammation in the brain (Grant et al 1980).

Mild to severe topical injuries have been observed in up to 50% of exposed workers in a number of studies (Wesseling 2001a).

Topical injuries include:

- frequent nose bleeds;
- skin problems ranging from mild irritation, fissures, peeling, and dermatitis to severe chemical burns and blistering on hands, legs, back, buttocks, genital area, and ulceration; paraquat breaks down the natural skin barrier greatly increasing absorption of the chemical;
- eye injuries, ranging from blepharitis (inflamed eyelids) and conjunctivitis to ulceration or keratosis (wart-like growth) of the cornea; protracted or permanent blindness; in Sweden one boy suffered permanent eye damage after getting concentrated paraquat in the face;
- nail damage, ranging from localised discolouration, and horizontal ridging to breakdown of the nail bed, transverse bands of white discolouration, and nail loss; and
- mouth ulcers.

(Botella et al 1985; Reigart & Roberts 1999; US EPA 1997; Wesseling et al 2001a; Kemi 2006).

According to the US EPA (1997) the worse effects “typically result when protective clothing is not worn, skin has abrasions or open cuts, and/or when extensive exposure is allowed to persist without washing”.

Symptoms reported by women sprayers using paraquat in Malaysian plantations include blindness, frequent nose bleeds, breathing difficulties, coughs, burns, peeling fingernails, and toe nails, generalised muscle aches, vomiting, vaginal itching and infections (Fernandez & Bhattacharjee 2006); and breast pain, swelling and/or the development of pus in their breasts (Joshi et al 2002).

The consequences of paraquat exposure in the malnourished may need to be considered, as animal studies have showed that dietary deficiency of magnesium and/or potassium can enhance paraquat toxicity (Minakata et al 1998). Vitamin C has been found to diminish paraquat’s embryotoxicity in frogs (Vismara et al 2001b).

Paraquat exposure in pregnant women usually also affects the infant. It crosses the placenta and has been measured at levels 2-6 times higher in the foetal and cord blood than in the maternal blood (Talbot et al 1988; Tsatsakis et al 1996). Exposures during the early stages of pregnancy have nearly always been fatal, and also often following ingestion during the 3rd trimester of pregnancy: out of seven reported cases only one infant survived. When a young woman in Thailand ingested a non-fatal dose of paraquat at 36 weeks of gestation, her infant (delivered by emergency caesarean) developed chronic lung disease still evident at birth and 10 months later (Chomchai & Tiawilai 2007).

Chronic effects

Survivors of paraquat poisoning are usually left with pulmonary fibrosis resulting in long-term pulmonary dysfunction (Yamashita & Ando 2000; Tung et al 2010), although one author says lung function changes are reversible by treatment (Huh et al 2006).

Eye and nail damage can be permanent.

Epidemiological studies show that chronic effects almost certainly include Parkinson’s disease, and possibly also cancer (skin, leukaemia, non-Hodgkin’s lymphoma, brain, and breast), and these are reported in detail in the section 2.4 *Chronic toxicity*.

3.3 Occupational Poisonings

The early fatal paraquat poisoning cases mainly resulted from decanting paraquat into beer, wine or soft-drink bottles; then suicides became prominent (IPCS 1984). By 1977, there were 600 reported fatalities (IPCS 1984). By 1984 acute paraquat poisoning had been reported from many countries, including Bulgaria, Denmark, Germany, France, Hungary, Japan, the Netherlands, Poland, Switzerland, UK, USA and Yugoslavia. Since then, thousands more paraquat poisonings and fatalities have been reported. Including from occupational exposure.

Records do not always differentiate between suicidal, accidental, and occupational poisonings. This section focuses only on known occupational poisonings, and probably grossly under-represents the real situation. Work-

related paraquat poisonings are believed to be significantly underreported and suicides over-represented in surveillance data (Murray et al 2002), including misclassification of occupational cases (Wesseling et al 1997). Non-occupational poisonings – equally important – will be addressed in the following sections.

Most occupational poisonings occur in developing countries where deficient working conditions, improper maintenance of equipment, climatic conditions, illiteracy, and poverty make controlled and ‘safe’ use of paraquat extremely difficult.

Occupational exposure

Paraquat can enter the body when swallowing, breathing, or by contact with the skin or eyes. The main route of exposure in agriculture is through the skin. Exposure occurs primarily through splashing during preparation of the spray and its transport, or when filling a knapsack sprayer; deposition of spray mist; leaking of a knapsack sprayer; adjusting spray equipment; and walking through sprayed vegetation. Hence the most exposed areas are hands, wrists, legs, back, and genitals (Wesseling et al 2001a).

Paraquat is a contact herbicide; plant growth is rapid in humid, hot climates; and spraying occurs with high frequency (every 6 to 8 weeks) in many tropical countries: these factors can cause frequent occupational exposure (Wesseling et al 2001a).

Dermal

Although dermal absorption is low through intact skin, it is considerably higher through damaged skin including skin that may be initially irritated by the paraquat, and a number of deaths have been reported from such exposure, including to the diluted spray solution.

Studies carried out in collaboration with Syngenta (and its forebears) concluded that paraquat is unlikely to cause serious occupational health problems, despite several of the studies showing 40-50% of workers experience topical effects. Other researchers have concluded that paraquat sprayers are continuously at risk of high exposures that can lead to severe injury and poisoning (Wesseling et al 2001a). One recent study of paraquat use in Malaysia showed that manual knapsacks resulted in high

levels of dermal exposure (Mohd Rafee et al 2010). Earlier studies had found lower levels, but nevertheless four out of six studies found paraquat in urine of users at the end of the working day (Wesseling et al 2001a). Sprayers using knapsacks are more likely to be exposed to high levels of paraquat; and heavy prolonged dermal exposure as from a leaking knapsack sprayer can result in severe poisoning or death (US EPA 1997). One farmer died after spraying correctly diluted paraquat for 3.5 hours with a leaking knapsack (Wesseling et al 2001a).

A study of exposure to paraquat from knapsack spraying in Costa Rican banana plantations found that the sprayers were “continuously at risk of high exposures that could lead to severe intoxication”. Health problems recorded included blistering and burns on hands, thighs, back, testicles and legs; redness and burning of eyes from splashes; and nosebleeds (van Wendel de Joode et al 1996).

Motorised knapsacks can also result in unsafe exposure. A study of exposure levels in pesticide sprayers in Egypt’s cotton fields showed that exposure was occurring on 3.6% of the head, 23.7% of the body, and 29.1% of the legs. This was considerably more than for manual non-leaking knapsacks (head 0.76%, body 4.8%, legs 5.8%) (Elhalwagy et al 2010).

The US EPA (1997) concluded, after field studies on workers, that exposure was unacceptable for backpack applicators who mixed, loaded and applied paraquat, and for those who used low pressure sprayers, even when they wore long pants, long-sleeved shirt, socks, shoes, and chemical-resistant gloves.

The EU reported estimates from exposure models showing that the exposure of knapsack sprayers to paraquat may exceed the short term AOEL by 60 times when protective equipment is worn and 100 times when it is not worn (EC 2002).

Wearing of protective clothing and equipment can reduce exposure, but it is frequently not worn in developing countries for a variety of reasons including its expense, lack of availability, and unsuitability for hot humid climates. Studies have shown that, even when it is worn, exposure still occurred in areas with

movement or that became wet with perspiration or pressure of knapsack (knees, elbows, wrists, armpits, shoulders) and hands still became contaminated with taking gloves off and on. Under such conditions absorption may actually be increased (Wesseling et al 2001a).

Inhalation

Industry does not consider inhalation to be an issue as paraquat is non-volatile and sprayed droplets are reputedly too large to enter small airways. However several studies suggest inhalation may be important under some climatic conditions, and when motorised backpacks are used increasing the respirable fraction of paraquat (Wesseling et al 2001a). Additionally, spray droplets from manual sprayers are deposited in the nose where they irritate the mucosal tissue and cause nosebleeds; they may also be absorbed through the mucosa and/or swallowed, contributing an internal dose (Wesseling et al 1997).

Inhalation may have been the cause of fatal poisonings in several Costa Rican banana plantation workers (Wesseling et al 1997). The frequently reported nosebleeds are evidence of the acute effects of inhalation, but it is unclear if the level of inhalation causing these effects is relevant for systemic uptake and poisoning (Wesseling et al 2001a).

Ongoing subclinical exposure to paraquat via inhalation affects the lungs. A South African study of 126 fruit farm workers exposed to paraquat found their lung capacity to be 10-15% lower than that of a reference population, as demonstrated by decreased arterial oxygen uptake during exercise. None of the workers had reported being poisoned, and only 4 had a history of skin burns (Dalvie et al 1999). Among Nicaraguan banana workers, a threefold increase in wheeze and shortness of breath was associated with more intense paraquat exposure (Castro-Gutierrez et al 1997). A cohort study of 20,468 pesticide applicators ranging in age from 18 to 88 years in Iowa and North Carolina, USA, found a significant relationship between respiratory wheeze and exposure to paraquat (Hoppin et al 2002). Even a Syngenta-funded study found "a significant independent association of shortness of breathe with wheeze with cumulative paraquat exposure and a small increase in chronic cough with paraquat

exposure", and oxygen desaturation which, they said, suggests a subclinical abnormal gas exchange (Schenker et al 2004).

Oral

Oral exposure can occur when the operator swallows the "run-off" on her/his face when working in a spray mist, or when swallowing paraquat inhaled into the nose. Three fatalities have resulted from sucking on a blocked sprayer jet (Wesseling et al 1997, 2001a).

Vulnerable workers

Exposure can be especially high for plantation workers who are employed as sprayers. In Malaysia, women are the major workforce in plantations, with about 30,000 employed (Whittle 2010). There most sprayers are women, and herbicides can be used on average 262 days per year. Paraquat was the most frequently used herbicide prior to its temporary ban in 2002 (Fernandez et al 2002). In 2008 a community-based monitoring survey found it was still the most popular herbicide in Sarawak, but although still commonly used it had been overtaken by glyphosate and 2,4-D in Perak. Only 19% of sprayers were using protective clothing in the Sarawak survey. It was also the most popular herbicide in a survey in Yunnan (Whittle 2010). On Indonesian palm oil estates, where again the sprayers are mainly women, paraquat is sprayed approximately once every two days (Madeley 2002).

Workers in paraquat formulation factories are also at risk, with 78% of workers in a UK survey and 50% in a Malaysian survey having experienced symptoms (Wesseling et al 2001a). The International Code of Conduct on the Distribution and Use of Pesticides states: "Pesticides whose handling and application require the use of personal protective equipment that is uncomfortable, expensive or not readily available should be avoided, especially in the case of small-scale users in tropical climates" (FAO 2003, article 3.5). This is clearly the situation with paraquat.

Cases of Occupational poisoning

The following section gives some examples of occupational poisonings: it should not be considered as comprehensive.

Through skin exposure

In the 20 years between 1974 and 1994, 11 fatalities as a result of dermal exposure to paraquat were recorded (Gear et al 2001). More have occurred since. The poisonings have occurred in a variety of ways, but appear to require that the exposure was prolonged, or to undiluted concentrate, or that the skin was abraded such as by scratches, dermatitis, burns, or lesions from scabies or lice (Gear et al 2001).

In 1983 a farmer died within a week of 3.5 hrs spraying a 0.5% solution of paraquat with a leaking knapsack (Wesseling 2001a).

In 1993, a man in the UK died after being splashed in the face when he dropped an open container of paraquat (PAN UK 1993).

An 81-year-old man in Greece died after accidental paraquat exposure. He suffered minimal skin burn, but slept overnight in trousers on which the paraquat had been spilt, prolonging the exposure through the skin burn. He developed severe breathlessness after 4 days, followed by acute renal and respiratory failure (Soloukides et al 2007).

A 55-year-old crop-dusting pilot died from respiratory and renal failure after flying his plane into power lines. His plane exploded and the pilot sustained 37% burns, but it was the concomitant exposure to paraquat that killed him 4 days later (Gear et al 2001).

In Thailand a worker in a rubber plantation died after exposure to a mixture of paraquat and glyphosate. He sprayed from dawn to dusk, the employer did not provide protective clothing, and he was regularly soaked. He developed a cough, skin disease, became ill, lost his hair and vision, and eventually died 3 months later (Bartlett & Bijlmakers 2003).

There were at least 3 known fatal cases following occupational skin absorption in Papua New Guinea between 1969 and 1981 (Wohlfahrt 1982); and Wohlfahrt (1981) cautioned that "because reporting systems are inadequate many other cases of paraquat poisoning have not been recorded".

An analysis of 15 deaths from occupational exposure to paraquat in Costa Rica revealed

that 5 died from dermal exposure: one from spilling concentrate on his legs, one from working in a sprayed plantation with minor skin lesions on his leg, and three from spraying, one of these with a leaking backpack. This last one is of particular concern as it reflects conditions common in many developing countries. The plantation worker sprayed for 3 consecutive days; he received chemical burns on his back, scrotum and inner thighs, and died 21 days later (Wesseling et al 1997).

Non-fatal poisonings via dermal exposure have also occurred. A 60-year-old farmer in Spain was admitted to hospital with severe liver toxicity resulting from use of a mixture of paraquat and diquat applied by knapsack sprayer in high temperature and humidity and without any protective clothing – conditions that increase skin absorption (Peiro et al 2007) and which are common in developing countries.

Another Spanish male suffered liver problems (blocked bile duct) 2 years after being hospitalised as a result of paraquat exposure. He had used paraquat without protection for 3 weeks. After 2 weeks he had developed severe dermatitis with superficial ulcers. A further week of spraying resulted in breathlessness, high fever, and liver damage (Bataller et al 2000).

A 65-year-old agricultural worker in Spain suffered intense itching, redness of skin and papules on face, neck, forearms and hands, made worse by exposure to sun, and then developed acute toxic hepatitis from which he eventually recovered (Vilaplana et al 1993).

A 57-year-old Greek farmer developed breathlessness, high fever and lung fibrosis after dermal exposure to paraquat (Papisiris et al 1995).

A 26-yr old Sri Lankan man suffered a burnt face when he was accidentally hit in the face with paraquat spray solution on opening the spray tank (Whittle 2010).

Wesseling (undated) provides testimonies of 8 Costa Rican workers interviewed in 2002, all suffering from dermal exposure to paraquat, 6 because of leaking backpack sprayers. They ranged in age from 17 to 53. They suffered burns to arms, back, buttocks, testicles, and

thighs; nausea, vomiting, dizziness, shortness of breath, headache, abdominal pain, and fever; lost and damaged toenails; eye damage; nose bleeds; and lack of appetite, and general malaise.

Through inhalation

In Japan, a 44-year-old man died from apparent inhalation of paraquat when spraying in a vinyl greenhouse. He was hospitalised for general fatigue but died from respiratory failure (Kishimoto et al 1998).

Accidents to the eyes

A Malaysian plantation worker suffered pain and blurred vision for two years after she slipped and accidentally sprayed paraquat in her face. Then she became blind in one eye, the other still affected by pain, burning sensations and excessive tears. She also experienced severe head, back and throat pain after the accident (Fernandez & Bhattacharjee 2006).

Some surveys of occupational poisonings

- Two surveys of Malaysian paraquat sprayers showed that 44% and 50% respectively experienced skin or eye injuries (Wesseling et al 2001a).
- Between 1978 and 1985, paraquat accounted for 66% of 1,442 occupational pesticide poisoning cases in Malaysia, with 64% of workers reporting poisoning symptoms (Fernandez & Bhattacharjee 2006). Then from 1986 to 1996, it caused nearly 700 poisoning cases in Malaysia. Of these, about 27% were a result of accidental and occupational exposures (Majid 1997).
- In October 2002, 153 textile workers in the Dominican Republic were poisoned by paraquat sprayed on nearby grounds. Hospital officials confirmed that the workers had experienced headaches, nausea, dizziness, exhaustion and dehydration from their exposure (PANNA 2002).
- In Costa Rica hundreds of paraquat injuries occur each year, most of them in the banana-producing Atlantic Region. In 1993 and 1996, paraquat was the pesticide most frequently associated with injuries, mostly skin and eye lesions (Wesseling et al 2001b). A survey of pesticide poisoning found that 60% of victims suffer from skin burns or dermatitis and 26% from eye injuries. The remaining 14% had

systemic poisonings, nosebleeds, and nail damage (Wesseling et al 2001a). During 1986, of the 1800 occupational accidents caused by pesticides, paraquat caused 21% of the accidents, 24% of hospitalizations and 60% of deaths (Wesseling et al 1993). Between 1996 and 2001, 40% of 3,865 pesticide-related deaths were due to occupational exposure. In 33% of deaths the circumstances were not identified, 14% were suicides and 13% accidents; paraquat accounted for 68% of all deaths (Isenring 2006).

- A survey of 96 families in a rural region of Honduras showed paraquat was the most used pesticide, and that every worker who used paraquat had at least one symptom potentially related to its use (Cantor & Young-Holt 2002).
- In Nicaragua, one study reported chronic occupational paraquat exposure among 134 workers. Nail damage was the most frequent symptom reported (58%), followed by skin rash or burn (53%), paraquat splashed in the eyes (42%), and bleeding nose (25%). There was also a high prevalence of respiratory symptoms (shortness of breath and wheezing) (Castro-Gutierrez et al 1997).
- In California, USA, 231 cases of paraquat poisoning were reported between 1998 and 2000, with 4 more in 2001, 3 in 2002, and 4 in 2003 (Isenring 2006).
- Paraquat was identified as the cause in 18 occupational incidents (3 fatal) in Chile in 2005 (PAN UK 2006b).

3.4 Suicide

By far the biggest cause of non-occupational poisonings is intentional self-poisoning, i.e. suicide. This problem is central to the problem of paraquat: if paraquat were banned worldwide and so no longer available, many thousands of lives would be saved, whether from occupational poisoning, suicide, or accidents to children.

Paraquat is the one of the most common pesticides causing death from suicide. It has a 60-70% mortality rate (Seok et al 2009), much higher than many other agents – for example the overall case fatality for self-poisoning in Sri Lanka is reported to be 18% (van der

Hoek & Konradsen 2005). Yet a study in Korea in 2007, of 250 attempted suicides with paraquat, revealed that only 38% of people had intentionally selected paraquat as the agent, indicating that if paraquat was not available the survival rate from attempted suicide would be significantly higher (Seok et al 2009). This is very important, given that in countries such as Sri Lanka intentional self-poisoning is “often a result of impulsive behaviour rather than the result of long-standing psychiatric problems”. Sudden anger and grief are common triggers (van der Hoek et al 1998). A Sri Lankan study found that 85% of self-poisoning patients cited easy availability as their basis for choice of poison; more than 50% ingested the poison less than 30 minutes after deciding to self-harm (Eddleston et al 2006). Experience has shown that restrictions on availability of paraquat (e.g. in Samoa) and other highly toxic pesticides have reduced deaths from poisoning (Roberts et al 2003; Gunnell et al 2007) – see also Figure 1.

Most intentional self-poisoning occurs via ingestion, although injection with fatal consequences has been reported in Korea (Kim et al 2000; Choi et al 2008) and Taiwan (Hsu et al 2003; Chen et al 2009).

Numerous cases of intentional paraquat self-poisoning have been reported in Malaysia, South Korea, Taiwan, Thailand, and Sri Lanka. It is reported to be less common in India – 6% of 84 poisoning cases admitted to a Respiratory Intensive Care Unit in North India between 1998 and 2006 involved paraquat (Agarwal et al 2006). In 1993 Fiji and Japan were reported to be countries with high rates of paraquat poisoning, with the rate in Fiji being 47 deaths per million people per year, and in Japan 11 deaths/million/year, compared with the USA rate of 0.004/million/year (Tinoco et al 1993).

Sri Lanka

Thirty-two cases of paraquat poisoning, including 10 deaths, were recorded in just 2 rural hospitals in Sri Lanka in a 1-year period in 1998-99 (van der Hoek & Konradsen 2005). Over a 2-year period, 2004-5, 774 paraquat patients were registered with 9 rural hospitals. Syngenta ran a study on these to compare the outcome of the poisoning with their new formulation Gramoxone INTEON, touted as a partial solution to the suicide problem. Although

the rate of survival with the new formulation was 35.6% compared with 25.5% for the original formulation, still 186 people died after ingesting INTEON (Wilks et al 2008). Between 6 and 7 out of every ten people who ingested the new formulation still died (Bateman 2008). A second study of 533 paraquat poisonings in 10 hospitals in Sri Lanka, from October 2006 to August 2008, failed to show any beneficial effect of the INTEON formulation (Wilks et al 2010).

South Korea

In South Korea, where paraquat has been used for 3 decades, it is estimated to cause 2,000 poisonings annually, with a 40-50% mortality rate. An investigation of 154 cases with 34% fatality in 1999, found that 73.3% were intentional ingestion (Hwang et al 2002). The total number of pesticide poisoning deaths from 1996 through 2005 was 25,360. 84.8% of these were from intentional self-poisoning. Paraquat was the most frequent cause, accounting for 538 (35.5%) of all pesticide-related deaths (Lee & Cha 2009). In 1999, the Korean Agricultural Promotion Agency estimated that there were 800 deaths due to paraquat poisoning annually in Korea. In 2005, that number had fallen to 256 cases in 9 months (Yoon 2009).

Thailand

Paraquat was responsible for 23.7% (376 cases including 150 deaths) of all poisoning cases in Thailand between the years 2001 and 2004. This includes intentional and unintentional, adult and child figures for pesticide poisoning in Thailand, although the majority of all poisoning cases were adult intentional (89.9%) (Wananukul et al 2007).

Japan

From 1998 to 2002, paraquat was responsible for 20% of the 345 cases of pesticide poisoning seen at hospitals affiliated with the Japanese Association of Rural Medicine, with a mortality rate of 70%. Suicide accounted for 70% of all pesticide poisoning cases (Nagami et al 2005). In 1990 Eisler reported that, in Japan, more than 1,000 persons each year are reportedly poisoned by paraquat, but didn't identify what proportion of these were occupational poisonings.

Malaysia

During the period 1986-96, paraquat was

the source of nearly 700 poisoning cases in Malaysia. Out of these, about 73% were due to suicide while the remainder were a result of accidental and occupational exposures (Majid 1997).

According to the National Poison Centre, the number of poisonings caused by paraquat has been rising in recent years. Malaysia banned paraquat in 2002, but then lifted it again in 2006, and since then the reported poisoning cases have more than doubled until in 2008 they were 7 times the level in the year the herbicide was banned. It is not specified how many of these were occupational or self-poisoning.

Table 1: Paraquat poisoning cases reported in Malaysia

Year	No. Cases
2002	10
2003	15
2004	16
2005	36
2006	31
2007	39
2008	71

Source: Whittle 2010

China

From the first reports of paraquat poisoning in China in 1991 until the first quarter of 2006, 3,020 cases were reported in medical science journals. 99% of these were suicide, with 0.6% unintentional drinking, and 0.4% occupational poisonings (Jing 2007). An analysis by Yin et al (2006) for the period 2002-2005 found that occupational poisonings accounted for 14.29% of cases, with 8.16% unintentional drinking and 77.14% suicide. Most of the suicide cases are women, and the occupational poisonings men (PEAC 2007).

Taiwan

Paraquat was the leading cause of poisoning-induced death in Taiwan between 1985 and 1997 (Lang et al 2010); and again in a study of poisoning cases at the emergency departments of two medical centres in southern Taiwan between January 2001 and December 2002 (Lee et al 2008b).

Hong Kong

In Hong Kong's New Territories paraquat was responsible for 80% of acute pesticide poisoning deaths between 1998 and 1992 (Chan et al 1996).

Samoa

Paraquat was responsible for 70% of all suicide-related deaths in Samoa after its introduction in the mid-1970s until 2000, with a peak of 94 poisonings (49 deaths) in 1981. A tireless campaign to ban the herbicide there failed in the face of industry pressure (Stewart-Withers & O'Brien 2006).

Fiji

Paraquat is reported to be used often in rural Fiji as a suicide agent (Szmedra 2002).

Trinidad

In 1998 Daisley & Hutchinson reported that paraquat caused most of the fatal poisonings in Trinidad, resulting in an estimated 80 deaths per year over the previous 5 years.

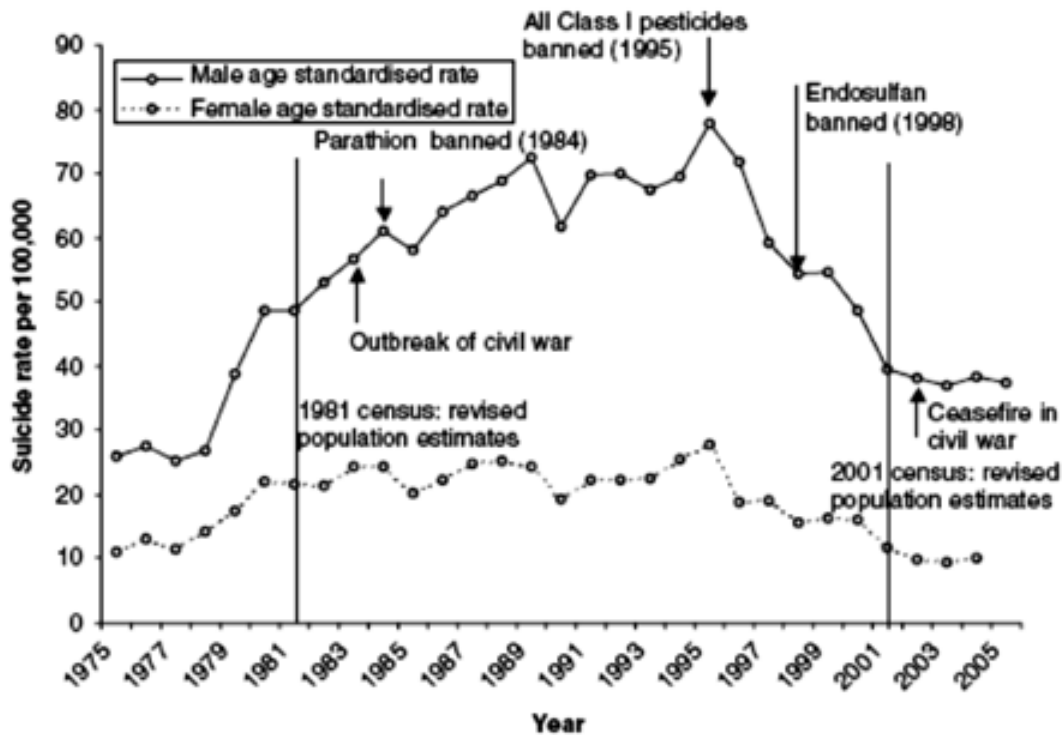
Costa Rica

In Costa Rica, paraquat was the main cause of 283 deaths due to pesticide poisoning registered by the Forensic Medical Department between 1980 and 1987. Of the 198 deaths where the cause was defined 62% were suicides, 26% were fatalities due to non-occupational accidents (confusion of paraquat with beverages or medicine, children handling the container/equipment or present in the field, consumption of recently sprayed food), and 11% were fatalities during work in Hong Kong's New Territories paraquat was responsible for 80% of acute pesticide poisoning deaths between 1998 and 1992 (Chan et al 1996).

Mexico

There were 25 paraquat poisoning cases, with 16 deaths, amongst a population of 315,000 people in Southern Mexico between January 1988 and April 1990. Nine of the cases were suicidal intent, and another 4 involved intoxication with alcohol (Tinoco et al 1993).

Figure 1: Age standardized suicide rates for males and females, Sri Lanka 1975–2005 D (Gunnell et al 2007)



3.5 Accidental poisonings

Other exposures can occur through accidental ingestion when paraquat is stored in refreshment, liquor, or medicine bottles, and even homicide. Severe and fatal poisonings have occurred with children playing with rinsed spray jets and bottle tops, and empty bottles (Wesseling et al 2001a).

There has always been a particular problem with accidental poisoning with paraquat, especially of children, usually as a result of the herbicide being stored in inappropriate containers and being mistaken for a drink. The first fatalities from paraquat occurred in 1964 (IPCS 1984), only 2 years after paraquat was first registered. They involved a child in Ireland, followed by 2 men in New Zealand. The later had apparently accidentally drunk a 20% solution of paraquat at a party from a bottle that had previously contained stout. One died 7 days later and the other 15 days later (Bullivant 1966). Despite all regulatory efforts such poisonings are still happening, even in developed countries: in 2008 a 2-year-old died in Australia after drinking paraquat from an unlabelled sports drink bottle (Stevens 2008), and in 2010 in the United States there was a report of an 8-year-old who died as a result of a similar accident (Chen et al 2010b).

An 18-year old boy from Shaxian County, China, was hospitalised after drinking paraquat, having mistaken it for a very similar looking medical tonic (Jing 2010).

Even adults are still dying in this manner: in 2004, in the UK, a 66-year-old man died when he mistakenly consumed paraquat stored in mineral water bottles at a bowling club (McDonald 2008); and in the same year a second man died after drinking paraquat decanted into a drink bottle by a City Council employee (PAN UK 2006a).

One child died after using an empty Gramoxone bottle to drink water from a water tank (Wesseling et al 1997).

In 2005, 50 men from rural Sri Lanka drank illicit alcohol, kasippu, that had been contaminated with unusually high levels of paraquat. Five died between 9 and 30 days later, from renal and respiratory conditions. Survivors suffered fever, headache, cough, shortness of breath, abdominal pain, lung problems, and enlarged livers (Beligaswatte et al 2008). Brewers of kasippu are said to commonly hang a bottle of paraquat with the lid pierced over the distilling liquor in the belief that the pesticide evaporates but condensed particles of it act as a catalyst, increasing the concentration and quality of the

kasippu. In this instance the bottle slipped and fell into the illicit brew but, as there was no change to taste or smell of the kasippu, only the colour, it was still sold. This practice of using paraquat to make illicit alcohol is reported to be widespread in Sri Lanka (Dias 2010).

Other deaths have been reported as a result of using paraquat to kill body lice and scabies (Wohlfahrt 1982; IPCS 1984).

One unintentional death resulted from vaginal absorption (Wesseling et al 2001a).

A 44 year-old Thai farmer suffered renal and respiratory failure and liver damage from dermal exposure of the scrotum, after mistakenly using Gramoxone stored in a toilet container to clean his perineum. He survived and left hospital after 53 days (Tungsanga et al 1983).

3.6 Other exposures

Homicidal poisoning by intramuscular injection of paraquat has been reported in Sri Lanka (Chandrasiri et al 1999); and four cases of homicide with paraquat have been reported in the US (Stephens & Moormeister 1997).

There are also reports that paraquat has been used to torture victims in Zimbabwe; it reputedly has been applied to wounds after beating, increasing the pain and slowing the healing (Anon 2008).

Paraquat was recently used in a domestic violence case in Fiji: a husband flung it in his estranged wife's face (Fiji Times 2010b).

Residues in Food

The main concern with residues is when paraquat is used as a desiccant and sprayed directly on mature food crops. Field trials have shown that residues may also occur in fruit fallen onto paraquat-sprayed grass beneath fruit trees; when paraquat is used in tea, vegetable, legume and pulse cultivation; and when it is used as a desiccant for cotton-seed and sunflower seed production (JMPR 2004).

Residues of paraquat have been found in potatoes treated with paraquat as a desiccant, and boiling the potatoes did not reduce the

residue (IPCS 1984). They have also been found in onions (Wigfield et al 1993), and when used as a desiccant in barley, wheat, rice, sorghum, and cotton (IPCS 1984).

Residues in food are stable and degrade only very slowly in storage: there was no decrease in residue levels in ground samples of prunes, banana, cabbage, potato, carrot, tomato, maize (grain, forage, fodder and silage), wheat grain, or coffee beans stored in a deep freezer at a temperature < -15 °C over 46 months; and no decrease in the levels of residues in meat, milk and eggs under storage for up to 28 months (JMPR 2004).

The Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues (JMPR) estimated that the short-term dietary intake for children up to 6 years may be as high as 50% of the Acute Reference Dose of 0.006 mg/kg, and for the general population up to 20% (JMPR 2004).

Yet in one agricultural area in South Africa (Vaalharts), the intake of paraquat in food was found to be 3 times the Acceptable Daily Intake (Raschke & Burger 1997).

Table 2: Some poisoning data: occupational and non-occupational

Country	Date	No.	Deaths
Malaysia	1980-82	94	61
Fiji	1983	59	34
USA	1984	153	1
UK	1980-84	931	190
Ireland	1982-84	166	30
Japan	1985	?	>1,900
Surinam	1985-6	82	58
Sri Lanka (4 districts only)	1986	322	103
England, Wales	1990-91	--	33
Mexico, Chiapas	1988-90	25	16
Trinidad & Tobago	1996	?	39 (suicides)
Samoa	1979-00	?	363 (suicides)

Country	Date	No.	Deaths
El Salvador	1998-00	923	94
Nicaragua	199-00	570	?
Costa Rica	1980-86	749	257
Costa Rica	1992-98	835	477

Data in Table 1 is taken from Wesseling et al (2001a). Many of the incidents in the table are suicidal poisoning. In Costa Rica 1980-86, for example, 75% were unintentional, mostly accidental ingestion but also occupational exposure.

4. Environmental Effects

Paraquat is described by US EPA (2009) as “extremely biologically active and toxic to plants and animals”.

4.1 Aquatic toxicity

The Environmental Risk Management Authority of New Zealand described paraquat as “very ecotoxic to the aquatic environment” (ERMANZ undated).

Fish

US EPA (2009) classifies paraquat as “slightly toxic” to freshwater fish, the 96 hr LC₅₀ varying with species from 13 to 156 mg/L. At a concentration of 500 µg/L, which is below the recommended application rate, paraquat adversely affects sensitive species of freshwater carp (Eisler 1990).

Acute toxicity – LC₅₀ (96 hr):

- Rainbow trout = 19 mg/L (FAO 2008)
- Mirror carp = 98 mg/L (FAO 2008)
- Bluegill sunfish = 13 mg/L (US EPA 2009)

Chronic toxicity – NOEC:

- Rainbow trout = 8.5 mg/L (FAO 2008)

Acute effects of paraquat on fish include abnormal stress behaviour such as excessive gulping of air, erratic swimming, restlessness, loss of movement, loss of equilibrium, increased beating of the flap covering the gills, excessive

secretion of mucus, swimming on the back, and paralysis (Omitoyin et al 2006).

Sublethal effects on fish include adverse effects on the immune system, with the effect enhanced by elevated temperatures (Salazar-Lugo et al 2009); alterations to gonads likely to affect reproductive activity particularly in males (Figueiredo-Fernandes et al 2006); and oxidative stress (Stephensen et al 2002).

Paraquat-induced teratogenic malformations have been reported in the embryos of *Oryzias latipes* (Medaka or Japanese killifish) (Dial & Bauer Dial 1987).

Amphibia

At a concentration of 500 µg/L, which is below the recommended application rate, paraquat adversely affects frog tadpoles (Eisler 1990).

As reported in the section on Toxicology, several studies have shown paraquat to be embryotoxic and teratogenic to frogs. Maternal exposure results in higher embryo and tadpole mortality, as well as growth retardation, abnormal tail flexure and gut coiling, and stunted growth rate in surviving tadpoles (Vismara et al 2000, 2001a, 2001b; Osano et al 2002), prompting Vismara et al (2000) to describe paraquat as highly embryotoxic for amphibia, and Osano et al to conclude that paraquat should be classified as a teratogen. Dial & Bauer (1984) also reported teratogenic effects in young developing *Rana pipiens* tadpoles after treatment, at paraquat concentrations as low as 0.5 mg/L.

Mussi & Calcaterra (2010) found that exposure to paraquat reduced the ability of embryos of the toad *Chaunus arenarum* to develop normally, leading to arrested development and severe malformations such as tail abnormalities, abdominal edema, reduced head development, and curved dorsal structures.

Paraquat inhibited the production of testosterone in the testis and 17beta-oestradiol in the ovary of the frog *Rana esculenta* (Quassinti et al 2009).

In a study in which tadpoles of the Rio Grande Leopard frog (*Rana berlandieri*) were fed plants with ‘field-level’ residues of paraquat absorbed from water, the following effects were reported: significant mortality, abnormal tails (flexed or

short), abnormal swimming behaviour, and differences in feeding behaviour (Bauer Dial & Dial 1995).

Paraquat is also genotoxic to amphibia: it caused significant dose-dependent DNA damage in the tadpoles of Chinese toad (*Bufo bufo gargarizans*), a common inhabitant of Chinese rice fields (Yin et al 2008).

The US EPA (2009) considered that the Californian Red-Legged frog was at risk from paraquat use in California, through its ingestion of invertebrates and small mammals affected by acute exposures to paraquat, as well as through reduction in algal food sources, and habitat reduction as a result of spray drift from up to 300m away. It may also be affected, directly or indirectly, by downstream movement of paraquat when streams travel through treated areas, up to 300 km for forest land cover, 258 km for cultivated crops, and 88.7 km for 'developed land cover'.

Invertebrates

At concentrations of 0.9-5.0 $\mu\text{g/L}$, which are below the recommended application rate, paraquat adversely affects larvae of crustaceans (Eisler 1990).

The US EPA (2009) classifies paraquat as 'moderately toxic' to the water flea, *Daphnia*.

Acute toxicity – EC₅₀ (48hr):

- *Daphnia magna* = 1.2 mg/L (US EPA 2009); 2.2 mg/L (FAO 2008)

Chronic toxicity – NOEC:

- *Daphnia magna* = 0.12 mg/L (FAO 2008)
- *Chironomus riparius* (a sediment dweller) = 0.367 mg/L (EC 2003).

Paraquat adversely affects freshwater shrimps, causing reduced feeding, body weight, and oxygen consumption (Yuan et al 2004); and reducing their ability to respond to chemical attractants (Chu & Lau 1994).

It has a teratogenic effect on sea squirt larvae, involving malformation of the nervous system and decreases in dopamine (Zega et al 2010).

Aquatic plants

The US EPA (1997) concluded that paraquat dichloride can pose a risk to non-endangered and endangered non-target aquatic plants. At a concentration of 250 $\mu\text{g/L}$, which is below the recommended application rate, paraquat adversely affects sensitive species of freshwater algae and macrophytes (Eisler 1990).

Acute toxicity – EC₅₀ (14 day):

- *Lemna gibba* = 0.037 mg/L (EC 2003); 0.071 mg/L (US EPA 2009)

Acute toxicity – EC₅₀ (96hr):

- *Naviculla pelliculosa* (algae) = 0.00023 mg/L (EC 2003)

Chronic toxicity – NOEC:

- *Selenastrum capricornutum* (algae) = 0.016 mg/L (FAO 2008)

Algae are highly vulnerable to the effects of paraquat. For example, a study by Jamers & De Coen (2010), on the acute toxicity of paraquat to algae, found the median effective concentration (EC₅₀) to be 0.26 μM for the green freshwater algae *Chlamydomonas reinhardtii*. They also found sublethal effects on gene expression at exposure levels as low as 0.05 μM .

Plants can concentrate high levels of paraquat from water, with residues of 2,300 mg/kg and 1,300 mg/kg reported in *Chara* sp. and *Spirogyra* sp. (Bauer Dial & Dial 1995).

Plankton

In a study of freshwater reservoirs in western Africa, paraquat adversely affected aquatic microorganisms including bacteria at concentrations as low as 5.7 $\mu\text{g/L}$, phytoplankton at 57 $\mu\text{g/L}$, and zooplankton at 57.7 $\mu\text{g/L}$ (Leboulanger et al 2009). Another study found adverse effects on microalgae at concentrations above 0.05 μM (Prado et al 2009). These results indicate that paraquat can cause significant ecological disturbances in freshwater ecosystems through alterations in species composition, potentially resulting in loss of biodiversity, harmful algal blooms, disease, and decline in fisheries.

4.2 Terrestrial toxicity

Paraquat is moderately toxic to mammals and birds (US EPA 2009).

The European Commission's Scientific Committee on Plants expressed concern in 2002 about the effects of paraquat on wildlife welfare, especially on hares and birds. They concluded that it "can be expected to cause lethal and sublethal effects and this is confirmed by field reports" (EC 2002).

Mammals

Acute toxicity – LD₅₀ (US EPA 1997):

- male rat = 334 mg/kg bw
- female rat = 283 mg/kg bw
- rabbit = 110 mg/kg bw
- Belgian hare = 35 mg/kg bw

Based on toxicity to rodents, US EPA (1997) concluded that paraquat is moderately acutely toxic to small mammals, and lethal below 25 ppm after 12 weeks exposure. Freshly sprayed foliage can induce death in rabbits, and especially the hare.

Birds

Paraquat is generally less toxic to birds than it is to mammals. Nevertheless exposure, especially chronic exposure, remains a risk and especially to reproduction. Eisler (1990) reported that some birds are very much more sensitive than others, with adverse effects at 10 mg/kg bw in nestlings of the American kestrel (*Falco sparverius*) causing reduced growth; 20 mg/kg in the diet of northern bobwhite (*Colinus virginianus*) causing reduced egg deposition; and 40 mg/L in the drinking water of domestic chickens (*Gallus* sp.) increasing the number of abnormal eggs produced. The lowest doses of paraquat causing measurable adverse effects in sensitive species of birds were 0.2 mg/kg bw administered by single intravenous injection to Japanese quail, causing anemia; and 0.25 mg/kg applied in oil solution to the surface of mallard eggs, producing reduced survival, reduced growth, and increased frequency of developmental abnormalities (Eisler 1990). These are considerably lower values than LD₅₀s reported by FAO.

Acute toxicity – LD₅₀ (96 hr):

- unspecified = 35 mg/kg (EC 2003)

- Bobwhite quail = 127 mg/kg bw (FAO 2008)
- Mallard duck = 144 mg/kg bw (FAO 2008)

Acute toxicity – NOEL:

- Bobwhite quail = 72 mg/kg bw (FAO 2008)

Dietary toxicity – LC₅₀ (FAO 2008):

- Bobwhite quail = 711 mg/kg diet
- Mallard duck = 2,932 mg/kg diet
- Japanese quail = 703 mg/kg diet

Reproductive toxicity – NOEC

- Unspecified = 30 mg/kg diet (EC 2003)
- Bobwhite quail = 100 mg/kg (FAO 2008)
- Mallard duck = 30 mg/kg (FAO 2008)

Signs of oral paraquat intoxication in birds include excessive drinking and regurgitation, usually within 10 min of exposure. Other signs appearing after 3 hours include diarrhoea, ruffled feathers, lack of coordination, imbalance, wing drop, slowness, weakness, running and falling, constriction of pupils, and terminal convulsions. Additional signs reported after dermal exposure include blistering and cracking of skin, lacrimation, wingspread, and wing shivers. Death usually occurred between 3 and 20 hours (Eisler 1990).

The US EPA (1997) concluded that paraquat is moderately toxic to birds on both an acute and sub-acute dietary basis; and that it can affect reproduction or hatchability of eggs when adult birds are exposed.

The European Commission's Scientific Committee on Plants stated that "the possible effects on the reproduction from spray solutions reaching eggs in nests and resulting in reduced hatching and abnormalities could be of serious concern" (EC 2002).

At concentrations less than the recommended application rate, paraquat is embryotoxic to developing eggs of migratory waterfowl (0.056 kg/ha) (Eisler 1990).

Paraquat has caused pseudofeminization of male chicken and quail embryos; testes showed intersexual phenomena and Mullerian duct abnormalities; both sexes had a reduction in the number of gonocytes (germ cells responsible for spermatogenesis in males, and oogenesis in

females (Haley 1979; Eisler 1990).

Bees

US EPA (2009) described paraquat as “practically non-toxic” to honeybees, with an acute contact LD₅₀ (48 hr) of > 34 µg/bee, a value considerably higher than those of the EC and FAO for 120 hr:

Acute oral toxicity – LD₅₀ (120 hr):

- *Apis mellifera* = 9.06 µg/bee (EC 2003)
= 11.2 µg/bee (FAO 2008)

Acute contact toxicity – LD₅₀ (120 hr):

- *Apis mellifera* = 9.26 µg/bee (EC 2003)
= 50.9 µg/bee (FAO 2008)

Direct application of paraquat dichloride with a surfactant caused 55% mortality in bees within 2 days of exposure and 99% mortality after 3 days (US EPA 1997).

There have been a number of incidents in the UK in which bees have been poisoned by paraquat. During one dry spell of weather paraquat spraying in a field resulted in small puddles to which bees were attracted and subsequently died. In another incident oilseed rape crops accidentally contaminated with GM rape seeds was sprayed out with paraquat; many bee colonies were affected and even though one bee keeper kept his colonies closed for 18 hours after spraying his hives were still seriously affected (PAN UK 2002; Fletcher & Barnett 2003).

Earthworms

Acute toxicity – LC₅₀ (FAO 2003):

- *Eisenia foetida* = >1,000 mg/kg dry soil

Paraquat is not significantly accumulated by earthworms or soil invertebrates, but delayed toxic effects, including death of birds and mammals, is common according to Eisler (1990).

Plants

The US EPA (1997) concluded that paraquat dichloride can pose a risk to non-endangered and endangered non-target terrestrial plants.

Micro-organisms

Paraquat is toxic to soil fungi and bacteria causing a reduction in some populations (Sahid et al 1992). It has also been found, in combination with diquat, to increase populations

of some pathogens, such as *Gaeumannomyces graminis* var. *tritici*, the causal agent of take-all disease of wheat (Sims 1990).

It was found to be toxic to 29 out of 35 strains of the nitrogen-fixing bacteria *Rhizobium*, which play an important role in maintaining soil fertility (Martani et al 2001; Marino et al 2008). Paraquat is also toxic to the beneficial nitrogen-fixing blue-green alga *Cylindrospermum* sp. found in rice paddy (Kaur et al 2002).

4.3 Poisonings

Aquatic incidents reported for paraquat dichloride in the US include (US EPA 2009):

- death of 54 fish (1 largemouth bass, and 53 sunfish) due to runoff June 4, 1981 in Virginia;
- death of fish (bass, bluegill, and crappie) in Indiana, June 2, 1997;
- death of an unknown amount of bass, bluegill, and crappie in Indiana, January 1, 1997;
- death of 200 bass and bluegills found on June 3, 1999.

Terrestrial incidents include:

- Paraquat was found in the urine of a pack of foxhounds in UK showing symptoms of acute and sub-acute poisoning (Quick et al 1990).
- At least seven dogs in Portland, Oregon, USA died after exposure to paraquat in a park (Cope 2004).
- In July 2010 3 dogs died from suspected paraquat poisoning in Cayman; “vets in Cayman say dog poisonings by paraquat have been happening for many years” (Anon 2010).
- Paraquat has been used for intentional poisoning of wild and domestic animals in southeastern Spain (Motas-Guzmán et al 2003).
- More than 700 sheep died on a farm in New South Wales, Australia, between Nov 1990 and January 1992 from paraquat introduced into their drinking water. Symptoms of affected sheep included depression, head held low, uncoordinated gait, reluctance to move, yellow diarrhoea, and dehydration (Philbey & Morton 2001).
- Cattle and sheep have been poisoned by paraquat whilst grazing on pasture; and

pigs have been accidentally or intentionally poisoned by paraquat (Philbey et al 2001).

- In the UK there have been numerous poisonings; for example in 2001 there were 6 intentional poisonings of dogs and one of a cat (Barnett et al 2002); and in 2006 dogs, hares, a cat, and a fox were affected (Barnett et al 2007). There were two incidents, in 1976 and 1990, in which 70-80 hares were killed following the spraying of paraquat on grass (ERMANZ undated).

5. Environmental Fate

5.1 Soil

Paraquat is very persistent in soil (US EPA 2009). It binds readily to both clay and organic matter, with adsorption increasing with clay content. The soil K_{oc} (sorption coefficient) ranges from 8,400 to 40,000,000 (EC 2003).

Paraquat is assumed to be strongly adsorbed to clay particles, however the US EPA (2009) notes that “the potential for desorption does exist”. In Thailand, 5.83% desorption was found in sandy loam soils (only 0.17% in clay soils) (Amondham et al 2006). A trial using vineyard soils in Spain found 70-90% of paraquat was adsorbed, but 11% was desorbed again (Pateiro-Moure et al 2010).

Adsorption increases with increasing pH, and decreases with increasing acidity (Muhamad et al 2010).

In highly organic soils, adsorption is weaker and paraquat remains herbicidally active for longer, up to 29 days in one trial on soils with 98% organic matter (IPCS 1984). Certain clay minerals also adsorb paraquat less strongly. For example in kaolinite clay the paraquat slowly became available to plant roots and killed cucumber seedlings, whereas in soil with 1% montmorillonite it was not available. At the same time adsorption of paraquat onto clay minerals affects their capacity for holding water and nutrients (Weber & Scott 1966).

The strong adherence to soil limits the availability of paraquat to plants or other organisms; hence

it is very slowly biodegraded. According to the US EPA (2009), it is resistant to microbial degradation under both aerobic and anaerobic conditions: no microbial degradation was seen after 180 days of aerobic incubation or after 60 days of anaerobic incubation following a 30 day aerobic incubation. However other authors report that paraquat can be significantly degraded by bacteria, fungi, actinomyces and yeast, using the paraquat as a nitrogen source (Amondham et al 2006).

Paraquat does not photodegrade, even when exposed to natural sunlight for 85 weeks, according to the US EPA (1997). However Amondham et al (2006) claim that it does, and Eisler (1990) states that 50% of paraquat in the surface soils photodecomposes in 3 weeks whilst that in subsurface soils does not.

Field studies have found a half-life (DT_{50}) of 7-8 years in the UK and 10-20 years in the USA. DT_{90} values (i.e. 90% degradation) were never reached. Monitoring for residues in the soil in Europe found residues of between <0.2 and 15 mg/kg (EC 2003). In field studies in Thailand, only 25% of the paraquat remained after 3 months; the faster degradation is attributed to higher temperatures and intensive solar radiation causing photodegradation (Amondham et al 2006).

Field dissipation studies showed paraquat to accumulate slightly with repeated applications (US EPA 2009).

5.2 Water

Paraquat is resistant to hydrolysis (FAO 2008). Solubility in water at 20°C, pH 7.2 = 620 g/L (EC 2003).

Paraquat is adsorbed onto suspended matter in water, and onto sediment, with “no evidence of desorption ... back into the water phase” (EC 2003). According to Eisler (1990), loss of paraquat from the water phase is rapid: about 50% in 36 hr and 100% in 4 weeks from freshwater ecosystems; and in marine ecosystems, 50-70% loss of paraquat from seawater was usually recorded within 24 hr. It moves from the water itself onto aquatic weeds, sediment and suspended solids.

However the environmental half-life in water (including solids) under mid-European conditions is estimated to be between 2 and 820 years depending on seasonal sunlight and depth of water (FAO 2008).

Paraquat is likely to enter surface waters bound to soil particles as a result of erosion and run-off, and subsequently be redeposited onto the beds of surface water bodies or lowland areas that receive eroded sediments from uplands (e.g. riparian zones, wetlands) (US EPA 2009).

In a study of surface waters in a wetland in Spain, paraquat was found in 6.6% of samples from a lagoon (maximum level 3.95 $\mu\text{g/L}$), and in 9.35% of samples from a marsh (maximum level 1.45 $\mu\text{g/L}$), (Fernández et al 1998).

Paraquat was the most commonly found pesticide in the sediment of watershed areas for Davao City, Philippines. It was found at levels of 0.31-2.80 ppm (Interface Development Interventions 2008).

Paraquat has been found in drinking water sampled from taps in the Caribbean Island of St Lucia at levels 50 times greater than that permitted in the EU. In 1995 it was found at concentrations of 5.3 $\mu\text{g/L}$. It was also found in a number of rivers and dams at a maximum concentration of 1 μg (Boodram 2002).

Groundwater contamination

Because paraquat is rapidly and tightly bound onto soil particles, it is thought to be immobile in the soil and hence leaching is not thought to be problem. According to US EPA (1997), field studies found that it did not leach below 9 cm in loamy sand soil, although in one plot it was found at the detection limit of 0.05 mg/kg in the soil segment of 11.4 to 25.4 cm after 296 days. Another long-term field study found that, although most of the paraquat had remained in the top 5 cm, "significant amounts" had penetrated to the 25-36 cm layer of soil (Fryer et al 1975).

The USGS has not looked for paraquat contamination of groundwater, so very little data are available. However, it has been detected in drinking water wells in at least two US states (US 1997). One out of 399 samples taken in California in 2006 did contain a low level (0.24

ppb) of paraquat (US EPA 2009). In Thailand it has been found in groundwater at levels up to 18.9 $\mu\text{g/L}$ (Amondham et al 2006).

It has also been found in groundwater in the Pacific island of Guam (Morrison & Brodie 1985).

5.3 Air

Paraquat has low vapour pressure ($<10^{-8}$ kPa at 25°C) and is non-volatile (EC 2003). It is likely to exist predominantly in the particulate phase in the atmosphere. Because of its high water solubility, paraquat in the particulate and vapor phases may be partially removed from the air by rain and snow. Particulate paraquat may also be removed from the atmosphere by dry deposition (HSDB 2009).

US spray drift modelling indicates that the buffer zone needed to prevent ecological effects from drift resulting from aerially applied paraquat is greater than 300m as effects on non-target plants can be expected at distances of $>300\text{m}$ (for ground-based application it is 110m) (US EPA 2009).

Drift problems have been reported. In California, in 1991, applications of paraquat in two fields resulted in drift over the nearby community, with a number of health effects reported. A survey of health effects found an increase in coughs, eye problems, diarrhoea, irritation, headache, nausea, rhinitis, throat infections, breathing problems, wheezing, and unusual tiredness (Ames et al 1993).

5.4 Bioaccumulation

US EPA (1997) concluded that bioaccumulation is unlikely, because of a low K_{ow} .

- $\log K_{ow} = -4.5$ at 20°C.

HSDB (2009) reports an estimated bioaccumulation factor of 0.05-1.21.

However, as referred to earlier, aquatic plants can concentrate high levels of paraquat, sufficient to cause toxic, behavioural, and teratogenic effects in tadpoles (Bauer Dial & Dial 1995).

6. Herbicide Resistance

Resistance to the effects of paraquat has been recorded since 1980, when it appeared in Japan, Canada, USA, Belgium, Taiwan, Malaysia, and Sri Lanka. By June 2010, 22 species of weeds in 13 countries had developed resistance to paraquat. Malaysia (6) and Japan (5) are the countries with the highest number of resistant weeds. Some weeds are developing multiple resistance – for example resistant to glyphosate as well as paraquat (hairy fleabane and horseweed in USA; and rigid ryegrass in South Africa, which is also resistant to haloxyfop-methyl and tepraloxymethyl) (Heap 2010).

Table 3: Weed resistance to paraquat

Weeds	Countries
<i>Amaranthus lividus</i> (Livid amaranth)	Malaysia
<i>Bidens pilosa</i> (Hairy beggarticks)	Kenya
<i>Conyza bonariensis</i> (Hairy fleabane)	Egypt, Japan, South Africa, USA
<i>Conyza canadensis</i> (Horseweed)	Japan, Canada, USA, Belgium
<i>Conyza sumatrensis</i> (Sumatran fleabane)	Japan, Taiwan, Malaysia, Sri Lanka
<i>Crassocephalum crepidioides</i> (Redflower ragleaf)	Malaysia
<i>Cuphea carthagenensis</i> (Tarweed cuphea)	Fiji
<i>Eleusine indica</i> (Goosegrass)	Malaysia, USA
<i>Epilobium adenocaulon</i> (American willowherb)	Belgium, UK
<i>Erigeron philadelphicus</i> (Philadelphia fleabane)	Japan
<i>Hordeum glaucum</i> (Wall barley)	Australia
<i>Hordeum leporinum</i> (Barley grass)	Australia
<i>Ischaemum rugosum</i> (Saramollagrass)	Malaysia

Weeds	Countries
<i>Landoltia punctata</i> (Dotted duckweed)	USA
<i>Lepidium virginicum</i> (Virginia pepperweed)	Canada
<i>Lolium rigidum</i> (Rigid ryegrass)	South Africa, Australia
<i>Mitracarpus hirtus</i> (Small square weed)	Australia
<i>Poa annua</i> (Annual bluegrass)	UK, Belgium
<i>Solanum americanum</i> (American black nightshade)	USA
<i>Solanum nigrum</i> (Black nightshade)	Malaysia
<i>Vulpia bromoides</i> (Silvergrass)	Australia
<i>Youngia japonica</i> (Asiatic hawkbeard)	Japan

Late in October 2010, another case of resistance was found: annual ryegrass, a major weed of crops in Australia and already known to be resistant to glyphosate has now been found to be resistant to paraquat as well (Hemphill 2010).

7. Alternatives to Paraquat

7.1 Alternative herbicides

All other herbicides on the market have lower acute toxicity than paraquat. However most of these have a range of other adverse health or environmental effects, such as endocrine disruption, cancer, groundwater contamination, etc. Hence their use is not recommended here as replacements for paraquat. There are some herbicides derived from natural plant extracts, such as pine oil or coconut oil, and these appear to have no or minimal health effects. However their relatively high initial purchase price generally puts them out of the financial reach of small holders. If these products were used instead of paraquat and other herbicides in plantations it may be feasible that the higher initial cost would be offset by improved worker health and productivity.

7.2 Alternative weed management

There are many alternatives to the use of herbicides in managing weeds. These usually involve biological, mechanical, and cultivational techniques that may vary from weed to weed and with the growing system. Sustainable weed management is more complex than herbicide use. It requires recognition that weeds are an integral part of the whole agri-ecosystem, and form a complex with insects and diseases as well as the crop(s). Usually a mix of methods is required and many of these have the added bonus of increasing soil health and fertility; and providing animal forage, improved crop yields, and additional food sources; as well as controlling weeds. The emphasis is on preventative approaches and cultivational methods of management, and tailoring the solutions to the situation. A sustainable weed management system aims to make the use of herbicides such as paraquat unnecessary, at the same time as it improves soil structure and fertility, and the total yield of the land – whether that is from the primary crop alone, or a combination of crops and even livestock.

Preventative measures include:

- appropriate design of orchards, plantations, fields, gardens, and even roads, to provide less weed habitat and to improve ease of control by mechanical means;
- having healthy, biologically active soil;
- good selection of seeds to minimize weed contaminants;
- thorough manual/mechanical land preparation before sowing, including making sure the seed bed is free of weeds;
- using a high seeding rate; the extra plants allow the crop to shade weeds and make it more difficult for them to access nutrients and water; and narrow row spacing makes the crop more competitive than the weeds;
- applying fertilizer when the main crop has access to it but the weeds do not, for example after weeding; this enables the crop to be more competitive with weeds;
- maintaining clean irrigation canals;
- keeping the surroundings of the farm free of weeds, unless they are maintained and intended as habitats for natural enemies, fodder or food.

Sustainable management practices include:

- regular monitoring of weed status of the crops;
- introducing and fostering natural enemies and pathogens used as biological controls;
- soil tillage, either conventional or conservation in which the crop is sown in the stubble of the previous crop;
- cultivation techniques that aim to suppress weed germination and growth: crop rotation, cover crops or green manure crops, intercropping (growing two or more crops side by side in the same area), adjusting the time of planting, manipulating soil temperature and moisture;
- planting weed-suppressing or weed-tolerant varieties, varieties that show quick emergence, fast growth, and rapid soil cover in the early stages;
- mulching: using cut grass, straw, chipped plant material, seaweed, etc, to smother weeds (also helps acts as a barrier against pests and diseases, retain soil moisture, lessen the impacting of soil from heavy rain, maintain a more even soil temperature, and reduce erosion);
- solarisation to prevent weed seed germination, and to kill some weeds in some situations, e.g. through use of black plastic covers;
- mechanical techniques that range from hand weeding to line trimmers, thermal weeders, and tractor mounted cultivators or mowers;
- fertility and soil structure improvement, and management of soil pH and moisture so that conditions favour the crop over the weed;
- using animals to graze orchards and plantations, with mixed species grazing of pastures;
- use of hot water or steam vegetation control systems on roadsides and in orchards;
- aquatic weeds can be controlled by alternative flooding and drying out, and by certain fish;
- the need for pre-harvest defoliation can be avoided by use of appropriate varieties and management systems.

Madeley (2002) reported on a study in Costa Rica where oil palm plantations in which legume ground covers are used generally showed better growth and yield of the palm oil than monocropped systems.

Chemical-free weed management in coffee crops in Ethiopia involves growing under shade trees to suppress weeds, use of mulches, animal manures, and leguminous cover crops (Madeley 2002).

Paraquat's use in no-tillage systems can be completely replaced by mechanical processes. Not only is the process of rolling and crimping as effective as herbicides, but it is also considerably cheaper and does not suffer the disadvantage of weed resistance (Ashford & Reeves 2003).

The proof that paraquat is not necessary lies, at least in part, in millions of hectares of farmland on which paraquat is not permitted to be used. This includes the 32.2 million hectares of certified organic land worldwide (at the end of 2007) (IFOAM 2009). The real area farmed organically, i.e. without using synthetic chemical herbicides, will be very much greater than this now, as the certified area continues to escalate and additionally large areas are farmed organically without certification. There are also millions of hectares farmed under the voluntary schemes that have banned paraquat referred to in the section *International Standards*, such as the Forest Stewardship Council, Rainforest Alliance, and Fairtrade Labelling Organisations.

In a survey of 11 palm oil growers with a combined total of 364,834 ha in Indonesia, Brazil, Papua New Guinea, Ecuador, and Guatemala, 6 of the growers said they do not use paraquat or were ceasing to do so, citing instead other herbicides, mowing, legume cover crops, and manual weeding as their methods of weed management. Chiquita and Dole, who have 50% of the global banana trade, prohibit the use of paraquat on their own plantations and on the plantations of supplier farms. Unilever, which buys about 12% of the world's black tea, prohibits the use of paraquat (Gochez et al 2009).

More detailed and crop specific information on alternatives to paraquat can be found in the publication *How to Grow Crops without Paraquat: Field Guide to Non-chemical Management of Grasses, Sedges and Broadleaf weeds for small scale farmers* published by PAN Germany in 2008 (http://www.oisat.org/downloads/field_guide_without_paraquat.pdf); and the *Online Information Service for Non-chemical Pest*

Management in the Tropics (OISAT) (<http://www.oisat.org>) hosted by PAN Germany.

For on-going up to date information check [http:// www.stop-paraquat.net](http://www.stop-paraquat.net)

8. References

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Pesticide Action Network Asia and the Pacific (PAN AP) is one of the five regional centres of PAN, a global network dedicated to eliminating the harm caused to humans and the environment by pesticides and promoting biodiversity-based ecological agriculture.

PANAP's vision is a society that is truly democratic, equal, just, and culturally diverse; based on the principles of food sovereignty, gender justice and environmental sustainability. It has developed strong partnerships with peasants, agricultural workers and rural women movements in the Asia Pacific region and guided by the strong leadership of these grassroots groups, has

grown into a reputable advocacy network with a firm Asian perspective. PAN AP's mission lies in strengthening people's movements to advance and assert food sovereignty, biodiversity-based ecological agriculture, and the empowerment of rural women; protect people and the environment from highly hazardous pesticides; defend the rice heritage of Asia; and resist the threats of corporate agriculture and neo-liberal globalization.

Currently, PAN AP comprises 108 network partner organizations in the Asia Pacific region and links with about 400 other CSOs and grassroots organizations regionally and globally.



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