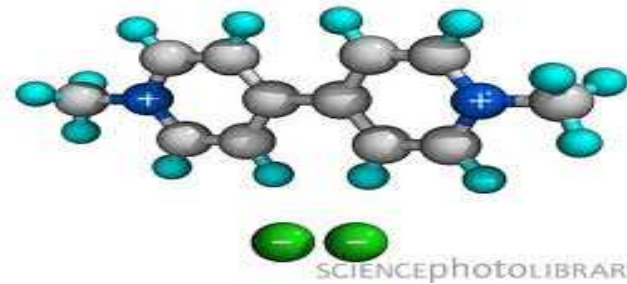


Paraquat

The most highly
acutely toxic
herbicide



- ⊕ Paraquat was first synthesised in 1882
- ⊕ Its herbicidal properties were discovered in 1955
- ⊕ Registered in England in 1962
- ⊕ First introduced in Malaysian rubber plantations in 1961



Paraquat

- ⌘ marketed over the last 60 years
- ⌘ The most widely used herbicide
- ⌘ Used on more than 100 crops in about 100 countries
- ⌘ Gramoxone is the most common trade name
- ⌘ China is now the world's largest manufacturer of paraquat, producing more than 100,000 tonnes per years



Thailand (ton/year)

	Insecticide	Fungicide	Herbicide
2009	19,709	8,485	85,821
2008	25,332	11,255	68,825
2007	21,590	10,626	79,239
2006	20,487	9,383	62,129
2005	18,529	9,052	48,841

Now Paraquat has been **banned**,
or use disallowed in **32 countries**
(including the countries of the
European Union 27 countries)



EU countries had already banned paraquat :-

Sweden (1983)

: high acute toxicity, irreversible toxic effects and risk of accidents during handling and use

Finland (1986)

: very toxic even in small doses, resulting in death



- **Hungary (1991)** : First severely restricted, then the only registered use was cancelled.

Accidental poisoning; the mortality rate was unacceptably high



- **Austria (1993)** : high acute toxicity, irreversible effects (especially on lungs) and numerous fatal accidents

- **Denmark (1995)**

: persistence in soil; very toxic to non-target organisms and death had occurred in hares and rabbits eating or walking on spraying grass



- **Slovenia (1997)**

: human and environmental toxicity; deadly toxic in small amounts with no antidote; concern about high rate of suicide

Other countries to have **banned** paraquat

- **Kuwait (1985)** : banned for all uses, for health and environmental reasons
- **Cambodia (2003)** : all uses banned
- **Ivory Coast (2004)** : prohibition of import, manufacture and use in agriculture
- **Syria and United Arab Emirates (2005)** : Banned all uses



- **Malaysia** banned in 2002
- However in 2006 the ban was reversed, and restricted use allowed in oil palm plantations

- **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**

Non-authorisation

- Norway (1981) : voluntarily withdrawn and registration cancelled.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

Restrictions

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

- **Columbia (1989)** : banned for aerial application
- **Philippines (1989)** : restricted

- **Indonesia (1990)** : severely restricted, use only for certain estate crops by professional applicators possessing special permit.
- **S Korea (1987)** : severely restricted because of high acute toxicity, must contain emetic, colourant and stenching agent

- **Uruguay (1992)** : limited concentration of active ingredient (<28%p/v), size of container (1-30 litres), and colour (blue)
- **Belize (2003)** : restricted to ground application
- **Chili (2003)** : prohibited for aerial application

- **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)

- **Costa Rica (2005)** : restriction on aerial application, in 2007 aerial was banned as was low volume and ultra-low volume spraying, and all sales of paraquat required a "professional prescription"
- **Sri Lanka (2007)** :
 - all formulation to have their paraquat ion concentration reduced to 6.5% with effect from 1st of January, 2008.

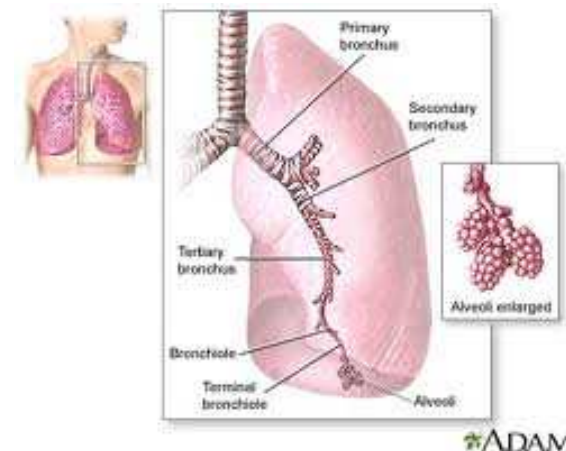
- Phase out the use of paraquat in three years.
- Annual quantity of paraquat formulations sold in 2008 shall not exceed the present level.
- Existing stocks of paraquat formulation with higher than 6.5% of paraquat ion concentration in the country are to be allowed to deplete through the regular marketing channel.

- Paraquat was due to be phased out altogether in Sri Lanka by end of 2009.
- In 1991, paraquat was banned in the Dominican Republic. However, now, its regulatory status was reduced to "restricted" and the herbicide is widely used to out the country.

In 2007 The European Court of first Instance annulled the EU-wide authorisation of paraquat

⊕ 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.

- Paraquat can **crosses the placenta**, level in fetal and cord blood higher than in the maternal blood 2-6 times.
- Exposure during the early stages of pregnancy have nearly always been fatal



Chronic effects

- ② Survivors of paraquat poisoning are usually left with **pulmonary fibrosis**
- ② 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

DM type II

1. Oxidative stress → development of insulin resistance
2. Inhibit insulin action
3. Inhibit insulin - dependent glucose uptake through oxidative stress
4. Cause hyperglycemia



- ☀ Paraquat has the ability to **cross the blood-brain barrier**
- ☀ Animal studies : 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

Parkinson's disease

- Paraquat may cause the onset, or accelerate the development, of Parkinson's disease; the longer the exposure the greater the risk
- Early exposures are the most deleterious
- The unborn fetus and children are most at risk

- ❖ Paraquat is known to cause production of “**reactive oxygen species**”, such as suproxide, which cause oxidative damage in brain mitochondria
- ❖ Cause dose-dependent loss of dopamine neurons and degeneration of the nigrostriatal dopamine system



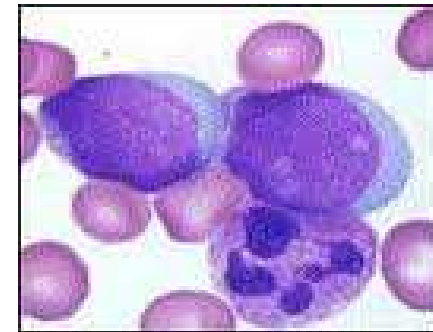
Cancer

- Increased oxidative stress leads to cancer
- FAO (2008) reported paraquat to have been mutagenic in **human lymphocyte**
- The California Environmental Protection Agency (Cal EPA 1993) concluded there was evidence of genotoxicity



Cancers from Paraquat

- Acute lymphocytic leukemia
- Squamous cell carcinoma
- Melanoma
- Non-Hodgkin's lymphoma
- CA brain
- CA breast



Pseudofeminization

- Paraquat **inhibited** the production of testosterone in the testis and 17-beta-estradiol in the ovary of the frog
- When injected paraquat 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”

- There was a **reduction** in the number of gonocytes in both males and females (germ cells responsible for formation of ova or spermatids)
- Study in rats (exposure to paraquat 5 mg/kg and 20 mg/kg) ⇒ decreased organ weight; **decreased** diameter of semiferous tubules; **degeneration** of the epididymal epithelium; decreased spermatogonia, spermatocytes, spermatids and Leydig cells

- Increased sperm mortality and **abnormal sperm morphology**
- **Decreases** in testosterone, follicle-stimulating hormone, luteinizing hormone and prolactin



Birth defects (teratogenicity)

- Embryotoxic and teratogenic to frogs
- Maternal exposure resulting in higher embryo and tadpole mortality, **growth retardation, abnormal** tail flexure and gut coiling, and stunted growth rate in surviving tadpoles



A study of children with **congenital malformations** in Spain revealed a possible association with paternal exposure to paraquat (relative risk of 2.77)



Suicide

- Paraquat is the one of the **most common pesticides causing death from suicide**
- **Has 60-70% mortality rate**
- **A Sri Lankan study found that 85% of self-poisoning patients cited easy availability; more than 50% ingested the poison less than 30 minutes after deciding to self-harm**

Environmental Effects

Acute effects on fish include :-

- excessive gulping of air
- erratic swimming
- restlessness, excessive secretion of mucus
- loss of movement
- loss of equilibrium, swimming on the back
- paralysis

- Genotoxic to amphibia
- Dose-dependent DNA damage in the tadpoles of Chinese toad
- Adversely effects freshwater shrimps causing reduced feeding, body weight and oxygen consumption
- Adversely affected aquatic microorganisms including bacteria and zooplankton

- Moderately toxic to birds, can **affect** reproduction or hatchability of eggs
- Caused **pseudofeminization** of male chicken and quail embryos
- **Bees** direct exposure caused 55% mortality within 2 days of exposure and 99% mortality after 3 days

- **Toxic** to the beneficial nitrogen-fixing blue - green alga *Cylindrospermum* sp. found in rice paddy

