

Czech Republic

Gramoxone - herbicide

CAS 4685-14-7

Chemical name: 1,1-dimethyl-4,4-bipyridinium

Empirical formula: C₁₂H₁₄N₂

Molecular weight: 186.3

The chemical formulation of a commercial herbicide requires an active ingredient, which in the case of Gramoxone is Paraquat.

Trade names: *Gramoxone plus, Gramoxone super, Gramoxone X, Gramoxone max,*

Composition:

EC-No. : 217-615-7 Paraquat dichloride

EC-No. : 248-383-5 Paraquat Emetic (aminopropyltriazopyrimidone)

EC-No.: 269-929-9 Pyridine Bases

Classification according to Directive 67/548/EEC:

Hazard symbols:

Paraquat dichloride CAS 1910-42-5: T+, N, R24/25-26-R36/37/38-R48/25-R50/53 200 g/l as paraquat ion

Paraquat Emetic CAS 27277-00-5: T, R25 < 1 g/l

Pyridine Bases CAS 68391-11-7: Xn, R10-R20/21/22 5 g/l

Alkylphenol Ethoxylate CAS 68412-54-4: Xn, R22-R36/38-R53 < 100 g/l

Hazard identification: very toxic by inhalation, harmful in contact with skin and if swallowed, irritating to eyes, respiratory system and skin. Toxic – danger of serious damage to health by prolonged exposure if swallowed. Very toxic to aquatic organisms may cause long-term adverse effects in the aquatic environment.

Physical –chemical properties:

Form: liquid

Colour: dark-blue/green

Odour: characteristic of pyridine bases

Boiling point: approx 100 °C aqueous solution

Melting point: not available

Flash point: does not flash

Explosive properties: non – explosive

Vapour pressure: not available

Density: 1.08 g/ml

Solubility: soluble in/with water

pH-value: 6.5-7.5

Oxidizing properties: non-oxidizing

Stability and reactivity:

- Hazardous reactions – paraquat is highly corrosive to most metals – aluminium, zinc, iron;

- Hazardous decomposition products – combustion or thermal decomposition will evolve toxic and irritant vapours.

Biodegradation

This herbicide is part of a group of bioresistant (persistent) compound, which is not biodegradable by the environment or by conventional treatment in water purification plants. In generally, when a pesticide enters the soil, some of it will adhere to soil organic matter through the process of

adsorption, and some will dissolve in water between soil particles. By rain or irrigation, the adsorbed pesticide may become detached from soil by desorption, because the solubility of a pesticide and its adsorption capacity to soil is inversely proportional.

Gramoxone has a persistent half-life of more than 100 days and partition coefficient of 4.46. Therefore, this compound has a high groundwater contamination potential (Bicki, Thomas J. Pesticides and groundwater, Illinois, USA, May 1989, No. 12 cited 5 December 2001).

Paraquat, which is also called gramoxone, is a kind of pyridine compound that can be solved in water easily but slightly solved in acetone or ethanol. It is un-volatilizable and is unstable in alkali mediate. It is a quickly effective contact....

Mutagenity

The possibility mutagenity of the herbicide Gramoxone was evaluated using five different living systems: *Allium cepa*, *Vicia faba*, yeast, *Drosophila melanogaster* and human lymphocytes. The results indicate that Gramoxone has mutagenic activity at the cytological level in *Allium cepa*, *Vicia faba* and human lymphocytes. All doses were effective in inducing chromosomal abnormalities and a clear dose-response relationship was observed in the various cytological tests. Analysis of chromosomal abnormalities revealed that this herbicide displays clastogenic and turbagenic activities. At the gene mutation level Gramoxone induced gene conversion at the trp-5 locus and reversion at the ilv locus in *Saccharomyces cerevisiae*. In *Drosophila melanogaster*, proved to be mutagenic to germ cells and induced a high frequency of sex-linked recessive lethal (SLRL). At the protein level, Gramoxone had detectable mutagenic effects on the genetic background of two enzymes, Adh and Est-6. Gramoxone should be considered a mutagenic herbicide. (*Electronic Journal of Biotechnology, Mutation Research/Genetic Toxicity, volume 319, issue 2, October 1993, pages 89-101*).

Toxicology

Toxicological investigations demonstrated rapid elimination of poison the blood, as well as prolonged fixation of parquat in the lung, kidney, liver and spleen tissues. Historical examinations showed multiorgan failure from renal tubular necrosis and pulmonary hemorrhage with epithelial injury.

Pulmonary proliferative changes were present in only two cases who survived 7 and 10 days and in which artificial ventilation was utilized (*Harsanyi, L. 1987, American Journal of Forensic Medicine and Pathology*).

Toxicological information:

Acute toxicity (lethal doses):

LD50 oral male rats: 707 mg/kg

LD50 oral female rats: 612 mg/kg

Harmful if swallowed.

LD50 dermal male rats: 590 mg/kg

LD50 dermal female rats: 735 mg/kg

Harmful - in contact with skin.

Inhalation – nose bleeding and soreness of the throat may result from spray mist or dust trapped on the nasal mucosa.

Acute toxicity (irritation, sensitization, etc.):

Eye irritation: moderate irritant to rabbit eyes, may cause eye irritation in man.

Skin irritation: moderate/severe irritant to rabbit skin

Chronic toxicological effects/long term exposure:

Long term exposure: ocular effects (cataracts) have been reported following long term oral exposure of laboratory animals.

Ecological information:

Liquid, with low volatility. Inform applies to: Paraquat ion. The substance is soluble in water, paraquat is rapidly adsorbed and de-activated by soil.

Ecotoxicity:

Harmful if drunk by livestock.

Toxicity to fish: LC50 96 hours, Rainbow trout: 8.3 mg/l

Toxicity to daphnia: EC50 24 hours, Daphnia magna: 6 mg/l

Toxicity to algae: EbC50 72 hours, hours green algae: 0.11 mg/l

ErC50 72 hours : 0.34 mg/l

Very toxic to aquatic organisms may cause long-term adverse effects in the aquatic environment.

Indications of use the main substance of Gramoxone - epizootic paraquat

Paraquat a poisonous dipyrilidium compound is one of the few nonselective herbicide still available in the United States. Because paraquat is fast-acting, can be effectively used in wet environments, and has limited potential for environmental contamination and low rates of weed resistance, it is still widely use in various crop production systems. However, paraquat is highly toxic to domestic animals if ingested (*Cope, R.B.: Toxicology Brief - Helping animals exposed to the herbicide paraquat, Veterinary Medicine, Sep. 1, 2004*).

Sources : within the United States, paraquat is a restricted –use herbicide with the exception of pressurized formulation that contain no more than 0.44% paraquat bis (methyl sulfate) and liquid fertilizer formulation that contain no more than 0.04% paraquat dichloride. Current active U.S. registered brand names include Gramoxone Super, Gramoxone Max, Cyclone Max, Marman Hebicquat Herbicide and Surefire Herbicide. Because paraquat has been available for agricultural use since 1962 outdated stocks are relatively easy to obtain. Older, outdated domestic garden herbicides often contained a 50:50 (Wt:Wt) mixture of diquat's and paraquat, and supplies of this mixture can still be found in the United States. Despite paraquat's restricted-use status, intentional paraquat poisoning animals remains a problem.

Exposure and toxico-kinetics: most cases of paraquat in people and animals involve ingestion of concentrated formulations. In dogs, only about 25% to 28% of orally administrated parquat is adsorbed; the remainder is excreted unchanged in the feces. In experiments in rodents, paraquat was detected in the feces up to seven days after exposure. The oral LD50 of paraquat in cats is 35 to 50 mg/kg. The oral LD50 in dogs is unknown but is higher than in cats, and the intravenous LD50 in dogs is 7.48 mg/kg.

Many of the current commercial paraquat preparations (e.g. Gramoxone) deliberately incorporate emetics and bitters in their concentrate formulation to reduce the dose absorbed after suicide-related oral poisoning in people. This protective measure fasting and nonfasting dogs to vomit 61 to 86% of an orally administered dose and reduces blood paraquat concentrations by about 170 times. Unfortunately, older concentrates are less likely to incorporate this key safety feature.

Irrespective of the administration route, absorbed and circulating paraquat is rapidly, selectively and actively sequestered in type I an type II alveolar cells and Clara cells by an energy-dependent diamine/polyamine transport mechanism that follows saturation kinetics. The lungs have the greatest paraquat retention and, thus, the highest concentration of paraquat of any of the tissues four after ingestion. At four hours, the paraquat concentration in the lungs is about 10 times higher than at other selective accretion sites (e.g. kidneys, brain, adrenal glands). By four to 10 days after exposure, the paraquat concentration in the lungs is about 30 to 80 times higher than plasma. The half-life of paraquat in the lungs is about 24 hours. Because of paraquat's rapid excretion, the paraquat concentration in the lungs and other tissues may fall below detectable limits in animals that die of this agent's delayed effects.

Mechanism of action –although paraquat is excreted largely unchanged, it undergoes extensive cyclic oxidation-reduction reactions in mammalian tissues in vivo. This redox cycling produces oxygen and hydroxyl, and the ensuing free-radical-mediated damage to cellular macromolecules, particularly membrane lipids, is primarily responsible for paraquat's toxic effects. Tissue damage is typically confined to selective paraquat accumulation (e.g. type I and type II alveolar cells, Clara cells, renal proximal tubular epithelia). Contact of mucosal surfaces and skin with concentrated paraquat solutions may also result in marked tissue damage.

Typically, early clinical signs of paraquat toxicosis involve acute gastrointestinal upset, particularly vomiting, since paraquat is a gastrointestinal irritant. Other common clinical signs include anorexia, inapretence, and lethargy. These clinical signs, frequently combined with history of consumption of unknown food items, often lead to an initial misdiagnosis of acute gastroenteritis. The inclusion of emetics in concentrated paraquat formulations may increase the risk of misdiagnosis. Clinical experience gained during the recent outbreak in Portland demonstrates that elevated serum lipase activities common at presentation. This elevation may lead to an initial presumptive diagnosis of acute pancreatitis. Stasis of the pancreatic duct, pancreatic failure, and elevated serum amylase activities

have been detected in cases of paraquat poisoning in people. In people, the severity of pancreatic injury at the time of initial treatment helps to predict survival from acute paraquat poisoning. However serum lipase activities are also commonly increased in dogs compromised renal function. Thus, hyperlipasemia may be a secondary consequence of paraquat-induced acute renal failure rather than the result of direct damage to the exocrine pancreas. Concentrated paraquat solutions cause severe irritation to the skin and mucous membranes; oro-pharyngeal pain and swelling followed by ulceration and mucosal sloughing a few days later are common. In extreme cases, complete sloughing and perforation of the esophagus can occur.

Evidence of compromised renal function (i.e. increased blood urea nitrogen and creatinine concentrations) and mild systemic hypertension are also often present at admission. Death after paraquat ingestion is typically caused by an insidious and irreversible form of respiratory failure. The time of onset of the respiratory syndrome after paraquat poisoning is dose-related and may occur a few days to more than week after exposure.

Paraquat toxicosis is usually diagnosed through a combination of clinical history, the results of a histological examination of affected tissues, and detection of paraquat in tissue or bait samples. Spectrophotometry, gas liquid chromatography, and radioimmunoassay have all been used to measure paraquat concentrations in biological fluids+ however, because prompt recognition of paraquat toxicity is a key factor in this treatment, using fast qualitative tests based on the dithionite reaction (i.e. dithionite spot test) may offer an important advantage. In the acute stages of paraquat toxicity, vomits, gastric contents, bait or concentrate samples, feces, and lung and renal tissue are ideal samples. Blood or plasma may be tested, but circulating paraquat concentrations are much lower in blood and plasma than concentrations in the lungs.

Treatment - because systemically absorbed paraquat is eliminated primarily through renal excretion and the presence of oliguric renal failure markedly contributes to paraquat accumulation in the lungs, maintaining urine production is critical when treating an animal with paraquat toxicosis. Forced diuresis can remove large quantities diuresis of circulating paraquat if it is initiated within a day or so of ingestion. However, forced diuresis carries with it the risks of electrolyte disturbances and exacerbation of paraquat – induced pulmonary edema. Particular caution is required during the first 24 hours after ingestion, especially if oliguric is present.

Antioxidant therapy has been extensively studied in experimental models and cases involving people with paraquat toxicosis with variable results. Recent studies using trimetazidine (an anti-ischemic), S-carboxymethylcysteine (a respiratory drug), propofol, and epigallocatechin gallate (from green tea) have shown promising results, but clinical experience with these agents is limited, and little controlled clinical trial data are available. Because of the risk of enhanced oxidative effects, oxygen administration in parties with paraquat toxicosis should be avoided except when necessary of comfort (e.g. parties in respiratory distress). Collagen synthesis inhibitors may offer some control or prevention of pulmonary fibrosis, but their use has not been extensively studied in field conditions. Corticosteroids, immunosuppressants, vitamins, blockers, alkylating agents, chlorpromazine hydrochloride, tocopherol, superoxide dismutase, glutathione peroxidase and nitric oxide inhalation have all been used to treat paraquat toxicosis with little clearly documented effectiveness. Currently available immune-antidotes are ineffective.

Prognoses and prevention

Despite treatment, the overall prognosis for paraquat toxicosis is poor. Situational factors associated with higher survival rates in people include inhalation or dermal exposure, ingestion of less than 35 mg/kg a young age at the time of toxicity, the time between paraquat ingestion and the last meal (because paraquat is adsorbed and neutralized by foodstuffs), accidental ingestion rather than homicidal intention, ingestion of diluted materials rather than liquid concentrates or granular formulations, and aggressive treatment within two to five hours of ingestion. In people, a lack of caustic gastric lesions; urine and plasma paraquat concentrations; lesser degrees of leukocytosis acidosis, and respiratory distress; and absence of renal, hepatic and pancreatic failure at the time of administration are all considered to be good predictors of survival.

Because of the severe consequences of paraquat toxicosis, early diagnosis and aggressive treatment are paramount if the survival prospects of a severely toxic –impacted patient are to be improved.

Given the limited effectiveness of current treatment modalities, the best solution to the problem of paraquat poisoning in companion animals is to prevent exposure.

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