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Att. Stacie Johnston

Statens tilsyn for planter, fisk, dyr og næringsmidler

Mattilsynet

INFORMATION FROM NORWAY REGARDING PARAQUAT

Evaluation of paraquat during the re-registration process for the Plant protection product Preeglone, containing the active ingredients paraquat and diquat, in 1993 resulted in a de-registration decision by the Norwegian Board of Pesticides. However, after an appeal by the industry, the decision was revoked and the product was placed on the market until 1996. After that, there have not been any applications for products containing paraquat. It is not legal to place pesticides on the Norwegian market which have not been evaluated/registered by the Norwegian authority for Pesticides.

Paraquat has never been produced in Norway and all amounts used up until December 31, 1997 (last date it was allowed to be sold) were imported.

Attached please find our latest evaluations of Paraquat – Ecotoxicological and Toxicological (including information on incidents) Evaluations from the Norwegian Pesticide Inspectorate from 1992 and 1993, and also a pesticide label for the product from 1993 which specifies the handling/applicator restrictions (in Norwegian only).

Yours Sincerely

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Plantevernmiddeltilsynet
Pesticide Inspectorate of Norway
Saksbehandler A. Tobiesen
December 1992

ECOTOXICOLOGICAL EVALUATION

PARAQUAT - PREEGLONE

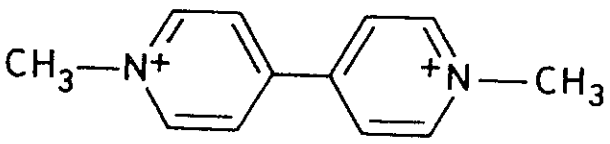
1 INTRODUCTION

Paraquat is a widely used nonselective herbicide. In Norway its main application is in mixtures with Diquat as total weed controller in a variety of cultures in addition to walkways, greenhouses under trees a. o. The recommended dosages of Paraquat in mixtures with Diquat are between 0,2 kg/ha to 0,35 kg ai/ha. In other countries it also used for control of aquatic weeds. The mechanism of herbicidal effect depends on the presence of light and oxygen which only affects the green parts of the plant. Paraquat in plant form free radicals which react with oxygen to reform the cation and concomitantly produce a superoxide anion. This oxygen radical may directly or indirectly cause cell death. ~~Grotesket~~

Paraquat was reviewed by the IPCS in 1984 together with Diquat, however the evaluation has already been outdated by much more recent studies and did not add significantly to the amount of information compared to the documentation reviewed below.

2 CHEMICAL AND PHYSICAL PROPERTIES

Chemical name (IUPAC) : 1,1-dimethyl-4,4-bipyridinium
Commen name : Parakvat, Paraquat dicloride, Methyl viologen
Formulations : Gramaxone, Dextrone, Esgram, Preeglone, Weedol CASno 4685-14-7
Empirical formula : $C_{12}H_{14}N_2Cl_2$
Chemical structure



Molecular weight : 257,2 (salt) og 186,3 (Cation)

Appearance : Technical substance is a dark redbrown oderless liquid
Melting point decomposes at 325 °C
Solubility : in water 618 g/l at pH 7 20 °C
methanol 143 g/l
Acetone <0,1 g/l
other organic solvents <0,1 g/l

Vapour pressure : << 10^{-8} Pa 20 °C
Partition koefficient n-octanol/water : log P estimated to -4 to -5
Henrys constant:
Stability : Stable in dry and liquid state in the dark, may decompose in direct sunlight.
Pollution i technical product : Minimum 94,4 % pure equal to 30 % paraquat ion on a w/v basis. Maximal impureities are:

1	%	1-methyl-4,4-bipyridinium ion
0,25	%	1-methyl-2,4-bipyridilium ion
0,5	%	monopyridone
0,25	%	1,1dimethyl-2,4-bipyridinium ion
1	%	sodium chloride
1	%	methanol
0,5	%	digylone
2	%	sulphated ash
55	%	water

3 EXPOSURE

3. Transformation and Turnover

Hydrolysis was studied in 1985 in buffered sterile solutions at pH 5, 7 and 9 containing 91 mg/l of Paraquat and incubated at 25 °C or 40 °C in the dark for 30 days. No hydrolysis were determined.

The dissipation of Paraquat from pools were studied in water from natural pools 1967. Ten plastic aquaria with sediment and plants were treated Paraquat to give different concentrations of between 1000 and 3000 ppm. The concentration was measured after 24 hours and found to be between 16-31 % of initial. Another sett of concentration were tried directly in the pools and found the concentration reduced to 20 to 72 % of initial. The dissipation was somewhat slower than for Diquat. Ponds treated with Paraquat also showed unexplainable increases at different time intervals.

Photochemical decomposition of Paraquat was studied in 1965, 1966 and 1967 all of these studies utilize light in the far UV region after it was found that Paraquat absorbency peak in the region of 265 nm, only a very small part of the natural light has any irradiance in this region and usually photochemical degradation studies are done at irradiances above 300 nm. When a 0,1 % solution of Paraquat dichloride with oxygen passed

Alle fotolysestudier med nedbrydning er udført med [illegible] ca U.V. lys

through was exposed to unfiltered Hanovia lamp. After 3 days no Paraquat was left. Chromatography of the solution at different time interval showed first the production of N-methyl betaine isonicotinic acid (II) and then methylaminehydrochloride (III). In the absence of Oxygen these products are not formed and paraquat decompose to polymeric resin of II. Paraquat adsorbed to a surface will also degrade in sunlight however an aqueous solution will not. In an other study radioactive labelled Paraquat aqueous solution of 1 or 5 ppm was irradiated with UV light down to 240 nm. Very little paraquat is left after 48 hours. When ^{14}C-labelled Paraquat adsorbed to aluminium planchettes were exposed to UV light, radioactivity disappeared with half-time of 12-18 hours. Dark controls had no loss. When ^{14}C-labelled Paraquat adsorbed to soil or two different clays were exposed to UV light 25 % of the radioactivity disappeared after 14 days in soil, about 20 % disappeared in kaolinite clay and nothing in montmorillinite. The studies with UV-light has no relevance in field usage.

The possible photochemical degradation of Paraquat applied to sandy soil surface was investigated in 1981 under natural sunlight. The soil was treated with 17,6 mg/kg 14C-labelled Paraquat. The soil had a SAC value of 13 mg/kg. The soil samples were incubated outside in quartz bottles, similar bottles were stored in the dark. At intervals during the next 85 weeks the bottles were sampled. After 85 weeks the unchanged Paraquat had been reduced to 86-89 % compared with 95 % in bottles incubated in the dark. Degradation product II and III were found and accounted 1,4-2,4 and 1,2-1,3 % respectively. In addition a non characterized compound accounted for 1,8-2,4 % of the radioactivity.

IPCS refers to studies on Photochemical breakdown on plant surfaces. Paraquat was applied to maize, tomato and beanplants. Determination done at 100 day intervals showed photochemical decomposition but no metabolism on plants. Degradation products were Product II and III. The degradation continued after the plants were dead and no movements of degradation products were seen. The rate of decomposition was related to the sun intensity and the radiation between 285 and 310 nm and 2/3 of applied Paraquat could be decomposed after 3 weeks of intense sunlight.

A long term field study (1980) was started at Frensham (U.K.) in 1972. The plots which had a Strong Adsorption Capacity (SAC) of 120 mg Paraquat per kg (capacity to immobilize and make unattainable to plants) were treated with paraquat to give 50, 100 and 400 % and the SAC value. The soil was a loamy sand with 9 % clay 83 % sand and 2,0 % org. matr. The plots were therefore treated with 90, 198 and 720 kg/ha and mixed down 12 cm (deep). Other plots were treated with 15, 22 and 120 kg and mixed down to 2,5 cm (shallow). The plots were direct drilled with barley between 1972 and 1977. After some transitory effect in all treated plots the first year, only the highest treatment gave effects the following years. Several weedplants grew well even at the highest treatment. Shallow incorporation showed that barley could grow through a layer containing Paraquat residues above the soils SAC. Carrots grown at plots with highest treatment died, while carrots grown in plots treated with 90 and 198 kg/ha grew well and contained less than 0,07 mg/kg. Some plots were in addition given an annual treatment of Paraquat to con-

trol weeds during the next 14 years which in sum gave an addition of 8,9 kg/ha. Residue analysis of these plots annually gave a mean decrease of 5 % decrease per year at plots treated with 90 kg/ha an 7 % decrease in plots treated with 198 and 720 kg/ha. A higher loss from plots treated with highest concentration may have been due to more Paraquat being available to degradation by microorganisms. Samples taken from further down and adjacent to treated area show no vertical or horizontal movement.

A more simple version of the study above was carried out in Netherlands in 1987 by treating three different areas with 15, 30, 60 and 120 % of the previously determined SAC vales of the soils. The three soils were; Peaty fine sand (SAC=65), very fine sand (SAC=300) and Sand (SAC=80). All soils having quite low SAC values and therefore expected to be worst case approximation. In peaty sand and very fine sand there were a clear dose response on the growth of wheat the first year though without affecting the yield of grain before the soil residue reached 38 % of the SAC value. The conclusion in this study is that the soil can be allowed to reach at least 38 % of the SAC value before there is any phytotoxic effect. As the study only covers one year it expected that a better equilibrium is reached later giving an even higher safety percentage level. In Netherlands the authorities has applied a safety factor of 10 on SAC values with concern to phytotoxicity.

A follow up on the Frensham high rate long term trial were conducted 8-12 years after application. Possible vertical movement was studied by comparing the concentration at different depths with time. Although there to some extent is a relative increase at lower depths compared to the top, the change is very small and is probably due to factors such as soil rotovation and earthworm activity. Also sampling of plots adjacent to the high rate treated plots showed neither increase or decrease any movements must therefore be very small and be balanced by a degradation or further horizontal movement. While there is a clear decrease in soil residues at 720 kg/ha the other two dosages have very slow decreases giving half-times of approximately 20 years, based on a 25 % decrease after 10 years. Except ~~for the~~ at the highest dosage there was no difference i vegetation cover in treated plots compared to the control. In plots treated with 720 kg/ha there was less Lolium perenna and more Trifolium repens.

A follow up of the Frensham trial was made in 1989, soil from treated plots were used in wheat bioassays and compared to newly treated soil. it was found that aged residues gave less effect than comparable new residues. Even aged residues above SAC had become deactivated. Soil previously treated with paraquat at 40-170 mg/kg had higher SAC values (old remains excluded) than soils with little or no Paraquat residue history.

In a short article Hance et al (1980) the fate of Paraquat i 4 field plots were followed after an annual application of 4,5 kg/ha/year or four applications of 1,12 kg/ha/year. The plots are given different maintenance. Some of the plots receiving an annual application of 4,5 kg/ha were hoed, or rotavated or left alone. There was no difference between plots with concern of total residues in the soil. In these plots the residues had reached a steady state with a mean concentration of 50-60 mg/kg after 10 years. They suggested a 10 %

degradation per giving a mean half-time of 7 years, though the fit to data was non significant in several instances. The range of half-times was 2,5-16 years. In a study preceding this, in the same plots (Fryar, 19875) had found that essentially all applied Paraquat was present after the first 5 years.

In New Jersey plots were treated with Paraquat at rates of 1100, 3300 and 5500 kg/ha. The soil residues were monitored for 12 years and the data fitted to a first order equation giving half-times of 26, 26 and 15 years respectively for the three treatments. Very little vertical or horizontal movement was observed. No effect was seen at the lowest dose wit concern to effect on apple trees, beans, potato or carrots, there was some effect at 3300 kg/ha and severe effect at 5500 kg/ha. All crops at 1100 kg/ha had less than 1 ppm of residues.

A similar study as the one above was made in California with plots treated with 330, 1500 and 3300 kg/ha. Half-times were calculated to 13, 5 and 6 years respectively. No effect was seen at 330 kg/ha while 1500 kg/ha gave some effects and gross effects were noted at 3300 kg/ha. Cotten and weeds contained less than 0,1 ppm at the lowest treatment.

Microbial degradation (IPCS) of Paraquat has been identified for several microorganisms isolated from the soil. Bacteria such as Corynebacterium and Clostridium, and fungus such as Lipomyces could degrade Paraquat however in soil this would only be possible before Paraquat became immobilized by the soil.

A test was undertaken to see if Paraquat undergos chemical degradation by incubating in soil slurries at high temperature (speeding up the chemical process while excluding biological. No degradation was measured.

3.2 Volatilization

No likely, IPCS refers to tests were dry deposits of Paraquat show no loss after 64 days. Spray exposure give less than 0,001 mg/h, for people working in the field. Spray drift measurements show 4,3-10,7 µg/m³ air. Samples taken 2-4 h later had 1-10 % of amount dispersed and no detectable amount after 5-7 hours. Germany has a maximal air tolerance limit of 20 µg/m³.

3.2 Transport and Distribution

3.2.1 Adsorption and Desorption

An adsorption study was done on four soils (Table 3) in 1988 attempting to follow guidelines however having to depart from these because of the properties of Paraquat. In order to be able to have measurable concentrations of Paraquat in the equilibrium solution enough Paraquat had to be added to overcome the SAC value of the soils. When enough Paraquat was given to give about 0,01 µg/ml Kd values could be calculated

(Table 3). When the equilibriated soil was resuspended in 100 ml of 0,01 M CaCl2 no measurable desorption was detected in any of the soils.

The SAC values for 7 German soils were determined by wheat bioassays and were found to vary between 70 mg/kg and 250 mg/kg. The soils had all a sand content of 84 % or more and a clay content of 12 % or less. In another study from Germany 120 soils from several types agricultural uses were tested with concern to SAC level and residues. Some of the soils had been treated with Paraquat for up to 18 years. The loam soils had a clay content of 11-37 % and SAC values of 90-1250 mg/kg, highest SAC saturation 4,6 %. Sandy soils from potato plots had a clay content of 2-9 % and SAC values of 10-380 mg/kg, the highest SAC saturation was 2,2 %. Soils from nurseries (sand/peat) treated for at least 5 years had SAC values of 25-160 mg/kg and residues of up to 60 % of the SAC value in peats and 18 % in the sands. In one plot which had been treated for 12 years the top 5 cm had a residue of 39 mg/kg which was 39 % of the SAC value of this soil, however wheat bioassay of this soil did not give significant stunting of roots or other effects.

Table 1. Soiltype used for measuring adsorption and desorption

Soiltypes	pH	Org. Matr. %	Granulation %			Kd	Koc
			sand	clay	silt		
Loam	7,2	3,7	62	21	17	42000	1135135,1
Loamy sand	6,3	1,9	81	8	11	5900	310526,3
Silty clay loam	6,5	4,8	14	29	57	9400	195833,3
Coarse sand	5,4	0,8	94	2	4	480	60000

The SAC values of 4 U.K. soils were determined by wheat bioassay and were found to vary between 30 mg/kg for muck and 1440 mg/kg for the soil with 21 % clay. 3 of the soils had a clay content of 11 to 21 %, the forth was muck (42 % organic matter).

The SAC values of 16 soils in the Netherlands were determined and found in the range of 25-1740 mg/kg, these soils had a clay content (2-33 %). Nine of the 16 soils were chosen because they were representative of extreme situations with low clay content and high sand content. The sites were treated individually with formulated Paraquat (Gramoxone 25 % Paraquat dichloride), By adding up total applied Paraquat a theoretical residue level was calculated and these values were compared to measured residues. In two cases the measured concentration was higher than the theoretical. Of the 9 extreme plots 7 had residues in excess of 1 % of the SAC value of the soil, with a mean value of 3,5 %. Of the plots chosen by ICI all had less than 1 % and residue levels were less than 2,4 ppm.

The SAC values of 21 soils from Denmark were determined by the wheat-bioassay method. The soils had a clay content of 4-19 % and the corresponding SAC values was 23-1100 mg/kg. The sites were treated with Paraquat in the range of 0,2 kg/ga to 6,0

kg/ha. Measured residues were higher than theoretical calculated in 5 instances. In only four cases was the measured residue above 1 % of the SAC value. The highest was 4,5 % found in loamy sand.

SAC values have been estimated for 250 different soils. The general levels found could be classified according to types of soil. Clays had values in the range of 300-3000 mg/kg loams 100-1000 mg/kg, sands 20-200 mg/kg and organic soils 30-100 mg/kg. A few soils with negligible clay had values of 10 mg/kg.

3.2.2 Mobility and Leaching

Helling (1972) categorize Paraquat as immobile on the bases of soil thin layer chromatography.

A field study in New Jersey applied 1250, 3750 and 6250 kg/ha of paraquat to plots and mixed this down 15 cm into the soil (sandy loam with 14 % clay). The SAC value of the soil was 2800 kg/ha mixed 15 cm deep. The plots were irrigated with water (amount ?) and water samples taken from the drainage pipes underneath showed no detectable (<0,005 mg/l) of Paraquat within 96 hours. In column studies with the same soil given the maximal field treatment and watered with 250 mm gave 0,02 mg/l of Paraquat in the leachate. The column consisted of 15 cm of treated soil (2500 ppm) above 5 cm of non treated soil.

3.3 Bioaccumulation

No studies

3.4 Uptake, Metabolism and residues in Plants

In a review article the result of plant metabolism of Paraquat is described. 14C-labelled Paraquat were directly administered to alligator weed or given in a nutrient solution to bean plants. at various intervals up to 3 weeks shots of these plants were analyzed with respect to metabolism of Paraquat. No metabolites or 14CO2 was found.

The transportation of Paraquat in plant is dependent on time of application relative to irradiance. A plant sprayed at midday in the sun will only show transport to leaves at close proximity, leaves sprayed in darkness and left in darkness for 24 hours show no transport while if the plant are put in 24 hour of light after a period of darkness the transport is extensive. Plant sprayed with Paraquat and exposed to sunlight show some degradation of Paraquat, however only paraquat not absorbed by the plant will be susceptible to photodegradation and only at high intensity.

Duckweed showed an increase in respiration when treated with Paraquat, while photosynthesis was inhibited. Atrazin caused inhibition of the Hill reaction at concentration lower than for Paraquat. Diquat was a more effective inhibitor than Paraquat. No metabolism of Paraquat was noted in alligatorweed or snap bean.

Tomato, maize and broad leved beans were treated with Paraquat on the leaves. Some degradation was found, however this was the result of photochemical degradatio, not the effect of plantmetabolism. The degradation product found were 4-carboxy-1-methyl-pyridinium chloride and methylamine hydrochloride.

Residues
The codex have established a ADI value of 0,004 mg/kg paraquat cation per day. MRL values for fruit and berries have not been established however closely related crops have MRL values of 0,1-0,2. No new data have been admitted and old data give none detectable residues for berries and no residue measurements for fruit.

3.6 Summary Comments to Exposure

Paraquat deposits on plant surfaces exposed to bright sunshine undergo Photochemical degradation to compounds that have little or no toxicity, however no documentation of measured rates have been received.

On reaching the soil Paraquat becomes rapidly and strongly adsorbed to clay minerals present. This process inactivates the herbicidal effect of the compound. While Paraquat in medium may be degraded by microorganisms the strong adsorption hinders any breakdown in the soil. For the same reason Paraquat does not pose any threat to soil living organisms. Even assuming a annual degradation of only 1 % per and an annual application of 1,0 kg ai/ha Paraquat, the residues in soil will not exceed 65 mg/kg. This concentration will be reached after about 200 years. A 1% degradation per year gives a half life of 69 years. Field trials indicate half-lives of 6-20 years.

Paraquat in water disappear rapidly from the waterphase being taken up by plants, adsorbed to sediment and suspended particles. No documentation on bioconcentration in fish has been forwarded however it is likely that it behaves as Diquat with Maximal BCF values of 5-8.

4 EFFECTS

4.1 Terrestrial Organisms

4.1.1 Microorganisms

At the Frensham site an investigation was also carried out in order to evaluate the long term effect of high dosage rates in soil on microorganisms. Organisms investigated were fungus, actinomycetes, bacteria and algae. Numbers and biomass were not affected 7 years after treatment when compared to nontreated areas. The only significant effect was an increase in the number of the fungus Lipomyces starkeyi which showed an increase at the highest treatment (720 kg/ha). Microbial activities such as CO2 production from glucose, soil matter and wheat material were unaffected. Nitrogen mineralization and nitrification were unaffected as were dehydrogenase and phosphatase activity.

Bacterial isolates from soil has been found which seem able to degrade Paraquat in media containing 1000 ppm Paraquat. After 4 days incubation a demethylated compound was found and later also a compound with a negative charge was found probably 1-methyl-4-carboxypyridinium ion. No rates were measured.

4.1.2 Earthworms

The possible effect of earthworm was studied at the high rate long term study at Frensham. Counts were made before treatment, one year after treatment and 6 years after treatment. Significant reduction in total earthworms both in numbers and weight was seen at the highest level 920 both with concern of shallow incorporation and deep incorporation. For immature worms all treatments showed reduced populations after one year. After 6 years there was only a few cases of particular species showing significant reduction at the highest rate. In comparison Diquat showed no significant differences between treated and non treated in all cases.

In the trials from Frensham the residues of Paraquat within Lumbricus terrestris was investigated 6 years after the application. There was a clear dosage dependent residue concentration in earthworm with gut soil content intact of 4,6, 8 and 37 mg/kg earthworm (wet weight) from the plots treated with 90, 198 and 720 kg/ha (deep incorporation) the plots had soil residue concentrations of 47, 66 and 252 mg/kg (shallow incorporation) respectively. Comparable Diquat residues in soils were 47, 66 and 252 mg/kg. When the soil gut content was removed the tissue content of Diquat and Paraquat were measured to be <0,1 mg/kg even from plots with the highest treatment.

The effect on Lumbricus in soil plots treated with 1,2 kg was studied in 1985. Some plots were also treated with an emetic. The plots were samples 7 weeks before treatment and 1, 6 and 12 months after. No negative effects were seen in any of the plots at any time. Some significant increases in treated plots were seen compared to untreated plots, these were probably explained by increased food availability due to destruction of grass coverage.

4.1.4 Honey bee toxicity and non target arthropods

Acute 5 day contact and oral toxicity of Paraquat (both technical and formulated Gramoxone) to Honey bees were tested in 1987 in order to uncover eventual delayed effects. The doses offered were the same as given in the standard 48 hour test. Oral doses were given at 8 intervals in the range 0,7 to 144 µg/bee (technical) or 1 to 200 µg/bee (formulated) of Paraquat cation. There was a clear decrease in the LD50 dose from 24 hours to 5 days Oral LD50 decreased for 154 µg/bee (technical) or 72 µg/bee (Gramoxone) to 11 µg/bee or 9 µg/bee, after 5 days. Similar for contact toxicity were >150 µg/bee (technical) or 207 µg/bee (Gramoxone) after 1 day to 51 µg/bee or 9 µg/bee after 5 days. The results indicate that Paraquat should be labelled as toxic to bee.

Paraquat was tested at concentration between 0,125 % and 4,0 % in honey fed to bees in 4 trial, in one trial there was 100 % mortality at all concentrations. LC50 was at about 0,125 %. Calculation give an oral LD50 of 48 µg/bee. Contact toxicity showed that a concentration of 2,3 % gave 50 % mortality. These results agree with the study above.

A review of Honey bee poisoning in U.K. in the last 20 years made in 1977 have gathered information on incidents and their possible relation to pesticide use. An assessment of acute oral and contact toxicity showed Paraquat to have an oral LD50 of >48 µg/bee and a contact LD50 of >25 µg/l. No bee poisoning incidences were related to Paraquat use.

In a Italian journal for beekeeping Paraquat was estimated to bee highly toxic to bees on the bases of laboratory studies. In another study by Moffet et al (1972) bees were sprayed with a 2,5 % solution (recommended dose i Norway is 0,09%) of Paraquat in the field while inside cages. Test showed that 25 % of the spray reached the inside of the cage. There was after 1 day a rapid increase in toxicity to near 100 % mortality after 3 days.

Anderson & Atkins have in 1968 categorized Paraquat as relatively nontoxic to bees on the bases of laboratory dusting tests and field trials.

Morten et al (1974) gave a bee colony a 0,1 % solution of Paraquat as only water source and observed the mortality. After 1 week more than half of the colony were dead and by 5 weeks all were dead.

The toxicity of Paraquat (as formulated in Gramoxone) to a carabid beetle and a spider was tested in 1991 following OECD-guidelines. Loamy coarse sand was sprayed at maximal recommended doses (1 kg ai/ha) and spiders or beetles were released within an hour. There was no mortality. Beetles showed an increased activity (feeding) the two first days compared to the control which normalized after 6 days. Treated spiders were feeding somewhat less than controls however not significantly so.

4.1.5 Avians

The acute toxicity of Paraquat to mallards were studied among other pesticide in order to compare these with LD50 for rat. Paraquat was administered both orally and percutanous (on the feet). The oral LD50 was 199 mg/kg, and percutanous LD50 was 600 mg/kg.

The toxicity of Paraquat to turkeys was studied in 1972 by administering Paraquat orally, dermally interperitonally and intravenous. Oral doses above 30 mg/kg gave toxic symptoms. Oral LD50 was 250 mg/kg. Mortality incurred 2-5 days after administration. Dermal mortality incurred at 250 mg/kg and above. Dermal LD50 was about 400 mg/l. Intraperitonal and intravenous gave about the same LD50 of 15-20 mg/kg, mortality occurred almost immediately with convulsions and respiratory distress. Turkeys were also exposed to grass treated with either 80 g/ha or 8 kg/ha cation of Paraquat one day after

treatment. They were in addition given uncontaminated feed and water. There were no mortalities at either dose within 30 days.

An investigation on the toxicity of Paraquat to Geese was initiated after a suspected case of paraquat poisoning in tame birds after foraging in a treated field. A small part of the field not usually foraged by geese were treated with approximately 240 g/ha Paraquat. On day one 4 of 84 birds died the next 43 birds and then 14 bird totalling 72 % of the birds. In order to check weather they had died of Paraquat poisoning 2 of the bird still alive and 3 new bird were all given 120 mg/kg. All the birds died within 10 hours. Analysis for Paraquat in organs revealed significantly higher concentration in liver and kidney of the two birds from treated field compared to new birds. Especially one of the birds had nearly 10 times the amount in internal organs. The symptoms of toxicity in lab test compares well with those seen in the field and these geese therefore clearly died of Paraquat poisoning.

The dietary toxicity of Paraquat to bobwhite quail, japanese quail, pheasant and mallard was studied in 1976 by the bureau and wildlife in USA. The birds were divided into 5 dosage groups and given treated food for 5 days and observed an additional 3 days. Birds were 9 to 14 days old at initiation of study. No sex discrimination was performed. The study compromises 89 different agents. The LC50 were 981, 970, 1468 and 4048 ppm respectively. Comparison with Diquat shows Paraquat to be 2-3 times more toxic to birds.

(IPCS) Pheasant eggs were sprayed with spray concentration equivalent to spraying a field with 2 kg/ha without any effect. I similar study with quail eggs gave no effect up to 3 kg/ha. Population of wild birds have been monitored in areas where Paraquat was extensive over several years without being able to detect any effect on birds of which several were ground nesting ones.

4.2 Aquatic Organisms

4.2.1 Algae and plants in water

Growth inhibition of Selenastrum capricornutum by Paraquat was studied in 1990 following OECD-guidelines at 7 concentrations between 0,025 and 1,6 mg/l of Paraquat dichloride. Mean measured concentrations were 47 to 68 % of nominal. Significant reduction was seen at a measured concentration of 0,12 mg/l. EC50 after 4 days was 0,22 mg/l. NOEC was 0,047 mg/l. The effect was relatively constant during the test period.

4.2.2 Daphnids

In an article by Crosby & Tucker (1966) the toxicity of Paraquat to Daphnia magna was tested. Paraquat gave a 50 % immobilization within 24 hours at a concentration of 8 mg/l. All daphnids died within 22 days at 6 mg/l (lowest concentration tested.

The toxicity of Paraquat on Daphnia magna was tested in 1990 following guidelines at 6 concentrations between 0,78 and 10 mg/l. Measured concentrations were 106-123 % of nominal. EC50 after 48 hours was calculated to 4,4 mg/l The NOEL value was 2,16 mg/l. NOEC was 1,3 mg/l.

4.2.3 Fish

Acute toxicity in rainbow trout was studied in 1990 according to OECD-guidelines at 8 concentrations between 1,57 mg/l and 200 mg/l. Verified concentrtions were 55-80 % of nominal. 100 % mortlity was found down to 78 mg/l, no mortality was found below this after 96 hours. LC50 after 96 hours was calculated to be 55 mg/l. All exposed fish showed toxic symptoms after 96 hours. most commen symptom was sounding and dark colouration. There was a clear log/log relationship between exposure time and LC50 concentration.

A chronic toxicity study over 21 days on rainbow trout was performed in 1990 at 5 doses with a mean measured concentrations of 7,9, 13, 25, 47 and 85 mg/l of Paraquat dichloride, which was 64 to 75 % of nominal. The main mortality occurred within 7 days and no morality occurred after 14 days. LC50 after 21 days was 42 mg/l. With no mortality at 25 mg/l. No toxic symptoms or effect on weight were observed at 25 mg/l and below. NOEC is therefore 25 mg/l.

In an article about the fate of Paraquat in water a reference is made to a acute study on rainbow trout. LC50 was found to be 32 mg/l after 96 hours. In addition a 30 % mortality was found after 16 days of exposure to 1 ppm and median survival time was 13 days in fish exposed to 10 ppm.

4.2.4 Field studies

The potential effect of Paraquat treated alfalfa on Hares was tested by releasing Hares onto treated plots directly or after a few hours (spray mixture had dried). The plots were treated at the recommended dose of 0,6 kg/ha, this gave a initial concentration on the alfalfa of 30 ppm and 60 ppm in grass. Half the animals were dead 72-100 hours after being released. The hares were only exposed to treated alfalfa for 48 hours after which they were transferred to nontreated plot. The surviving animals were killed after 2 weeks and showed pulmonary lesions, emphysema and ulceration of lingual mucous membrane. Paraquat was hardly found (<0,3 ppm) in the hare except in the caecum and the urine had very low concentrations. Although more hares died in plot were hares was released directly after treatment than after spray had dried the difference is not significant due to low number of animals.

A follow up study has showed than treatment with ammonium sulphate mixed together with Paraquat result in a repellent effect on hares of treated vegetation. When 2/3 of available food was treated with the mix the released hares preferred to forage in non-treated area, while if a plot was treated only with Paraquat (or Diquat) no discrimination was seen. Actual mortalities in this study was not given.

A field study was undertaken to see if Paraquat treatment of weed beneath spruce would have any effect on the number of small rodents (voles and shrew). The working hypothesis was that elimination of grass would lead to emigration of rodents from treated areas into nontreated. There was no significant reduction, the rodents seemingly preferring to wait until new grass grew after 4 months. Although the rodents were fairly sensitive to Paraquat with LD50 down to 25-50 mg/kg, no effects were noted on live trapped individuals. The herbicide treatment of weed in order to get rid of rodents in treplanting may therefore actually be disadvantageous as loss of grass food may lead to increased forage on wood by the rodents.

A field study was initiated in 1966 in order to evaluate the ecological effects of Paraquat treatment of small lakes for weed control. A chain of 5 small lakes stocked with brown trout and with a large population of Elodea (water weed). Paraquat were applied in May at a nominal concentration of 0,5 ppm from a boat with a watering can. The residues in water fell from 0,37 mg/l after one day to 0,01 mg/l on day two (detection limit was 0,01 mg/l). The residues in plants was 46 ppm on day one and varied considerably from sample day to sample day on day 16 plant residues was 38 ppm. After 16 days all water plants were dead, while plant in the above control lake grew profusely. Even 65 weeks after treatment hardly any new waterweeds were observed. After 2 years some scattered patches were seen of different waterweeds. Fish appeared sluggish 2 days after treatment, after 4 days fish were obviously distressed gulping air at the surface. 7 dead roach were found until day 11, most of the fish were concentrated near the inlet of the lake however no more dead fish was found. Except on days 8 when 36 animals from 15 taxa were found dead no dead invertebrates or tadpoles were found. Residue analysis of the sediment showed an increase to approximately 17,7 ppm after 6 months and then a reduction to 8 ppm after 1 year, in the top 25 cm. The reduction was not due to an increase at lower depth as this also was sampled. The rapid decrease in Paraquat Concentration in water and the lack of effect on fauna has also been found in other field studies were ponds have been treated to give a initial concentration of 0,5 ppm.

4.3 Summary Comments on Effects

Paraquat seem to be toxic to a wide range of organisms, however rapid adsorption will in most instances make applied Paraquat inaccessible to a degree that effects will be minor or none. The exceptions are those cases were animals are directly exposed as i.e. bees or when animals forage on treated vegetation i.e. hares and geese. In a review of wildlife poisonings due to pesticide use from U.K., only 1 incidence of 127 proved incidences of poisoning was due to Paraquat. 99 of the cases were due to either mevinphos, strychnine or alfachloralose often in connection with deliberate use as bait poisoning.

Aquatic organisms will not be at risk with the present use of Paraquat. Algae had an EC50 of 0,2 mg/l, effective waterweed eradication is achieved at 0,5 mg/l. Daphnids has a LC50 of 4,4 mg/l and fish 42 mg/l.

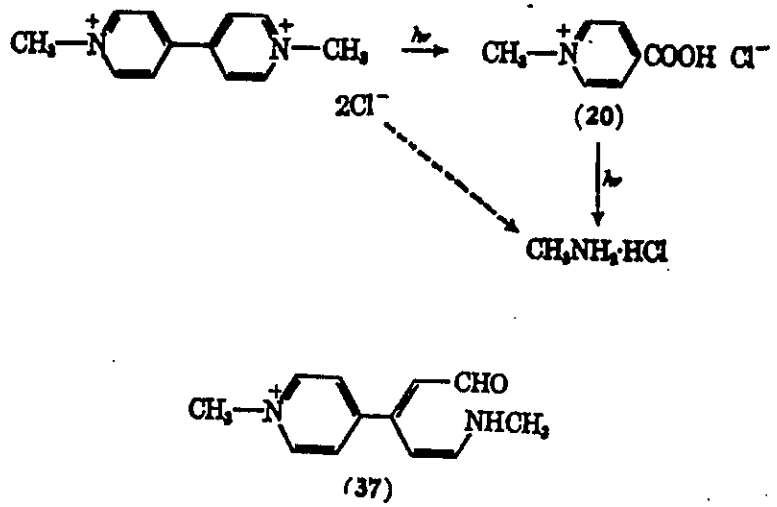
5 DISCUSSION AND EVALUATION

Paraquat is an old non-selective herbicide, which in Norway mainly is used for total eradication in non agricultural areas or beneath fruits and berries.

The recommended use in Norway is 420 g/ha and is only found in the preparation Preeglone which includes Diquat with recommended dose 560 g/ha. Most soils can immobilize 100 mg cation/kg soil, and even if there was no dissipation and degradation it would take 100 years of continuous annual use to saturate the soil. Field studies indicate half-lives of Paraquat in soil in the range of 6-20 years. While being extremely persistent in soil studies have shown microbial degradation of Paraquat in solution and photochemical breakdown on plant surfaces.

Paraquat has been shown to toxic to hares and geese when these forage on newly treated alfalfa or grass. While other animals seem not to be affected. Honey bees are susceptible if sprayed directly. Aquatic organisms and soil organisms are not at risk with the present use of Paraquat.

Figure 1. Possible photochemical degradation route is shown. The compound 37 may be an early intermediate



PARAQUAT

TOXICOLOGICAL EVALUATION OF PARAQUAT (a.i.) AND THE FORMULATION PREEGLONE CONTAINING 25G PARAQUAT AND 25G DIQUAT AS IONS/KG

Contents:

For The Advisory Board on Pesticides
Written by Cand. scient. Marianne Rudfoss
February, 1993

Toxicological Evaluation of

PARAQUAT

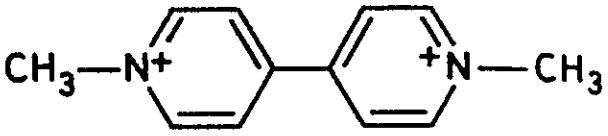
1. Introduction

Like Diquat, paraquat is a bipyridyl compound. They were both described by R.C. Brian in 1958. Hundreds of cases of accidental or suicidal fatalities resulting from paraquat poisoning have been reported during the past decade. The lung is the target organ of paraquat, and degeneration/hypertrophy of Type II alveolar epithelial cells, interstitial edema and fibrosis are the main histopathological changes induced.

This evaluation contains additional information which is mainly taken from FAO plant production and protection paper 78/2 (1986), Environmental Health Criteria 39 (1984) and Handbook of Pesticide Toxicology (Hayes Jr. & Laws Jr., 1991), referred to as Hayes. All results are given with statistical significance, $p<0.05$. Paraquat was tested as the dichloride salt, but doses are normally referred to as amount of paraquat ion.

2. Chemical and physical properties of paraquat,

Common name: Paraquat
Chemical name (IUPAC): 1,1`-dimethyl-4,4`-bipyridinium (dichloride)
Norwegian name: Parakvat
Non-official name: Methyl viologen
Molecular formula: $C_{12}H_{14}Cl_2N_2$ (paraquat)
Molecular weight: 186.3 (cation), 257.2 (dichloride salt)
Code: AT-5, PP148 (dichloride), [PP910 bis(methylsulphate)]
Formulations: Gramoxone, Dextrone X, Esgram, Galgo-quat, Longlife Plus, Prelude, mixtures with diquat: Preeglone (Weedol), Cleansweep
CAS RN: 4685-14-7 (paraquat), 1919-42-5 (paraquat dichloride)
2074-50-2 (paraquat dimethylsulphate)



Chemical structure

Technical paraquat is an aqeous liquid with dark red-brown colour and no odour. The boiling point is ~100°C, density is 1.13 - 1.15 at 20°C and vapour pressure is negligible, at or below the limits of detection (10^{-7} mm Hg).

The pure ingredient is crystalline hygroscopic white powder, also odourless. The melting point is >300°C, with decomposition. It does not boil. Density is 1.5 g/ml and vapour pressure is at or below the limits of detection.

Solubility:

Solvent	technical	pure paraquat
water	700 g/l	618 - 620 g/l, pH 7.2 - 9.2
fat	insoluble	insoluble
organic solvents	Insoluble in non-polar organic solvents. In methanol 143 g/l. <0.1 g/l in hexane, dichlormethane, acetone, toluene and ethyl acetate.	

Paraquat is highly water soluble and so does not partition.

Formulation of Preeglone (G), (CAS RN given in brackets):		g/kg
active ingredient:	paraquat, as ions	25
	diquat, as ions	25
Emulsifier:	Nonyl phenyl ethylene oxide condensate (009016-45-9),	0.540
Wetter:	C13/C15 cut synthetic amine ethylene oxide condensate,	0.127
Dye:	Heliogen blue 6930,	0.008
Antifoam agent:	Polysiloxane suspended silica (063148-62-9),	0.010
Emetic:	PP796 Guanazol (27277-00-5),	0.002
Filler:	Magnesium sulphate (7487-88-9),	to 1 kg

Toxicology of additives is low to moderately and given in enclosure no. 1. The technical grade used in the toxicological studies contains minimum 94.4% a.i.. Impurities are given in enclosure no. 2.

3. Toxicokinetics of paraquat in animals

3.1 Studies

Paraquat is generally poorly absorbed from the gut, so after oral intake maximum 20 % is eliminated in the urine. The proposed biochemical mechanism is shown in enclosure no. 3. The time related distribution is shown in enclosure no. 4, and shows a storage pool in lungs possibly responsible for the pulmonary toxicity of paraquat. In several cases the efflux of 14C-paraquat was diphasic, with a rapid phase half life and afterwards a slow. (EHC 39).

In the lung paraquat is probably accumulated by the energy-dependent uptake system for diamines and polyamines located in the Type I and Type II alveolar epithelial cells. Putrescine (a diamine) effectively inhibited the uptake of paraquat in rat lungs (publ., 1982). Monoamines, like 5HT, does not affect the uptake of paraquat. The higher and more prolonged levels of paraquat in the

lungs than in other organs seems to be the cause for the differences between the clinical action of paraquat and diquat on the lung.

In rats there are two phases of intoxication. First, the destruction phase lasting a few days with damage to the Type I and II alveolar epithelial cells, oedema and haemorrhage, and the second phase; a reparative phase with regeneration of the epithelium and proliferation of fibroblasts. In both phases death results from anoxia. In lung cells, paraquat produces superoxide anion. This radical may lead to the formation of lipid peroxides and hence to cell death.

IN VITRO: ABSORPTION OF PARAQUAT THROUGH HUMAN SKIN
STUDY 1: This study consists of two parts; *a)* application of 0.5% ^{14}C-paraquat dichloride aqeous dilution of four different formulations, including Gramoxone, to human skin (dermis and epidermis), corresponding to spray strength formulations, and *b)* application of 1,0 mg ^{14}C-paraquat dichloride/ml destilled water to both human skin and to isolated epidermis.

Initially (up to 24 hours) the absorption rate of ^{14}C-paraquat dichloride in formulations was appr. 0.52 µg/cm^2 skin surface/hour. Thereafter the rate was reduced to <0.1µg/cm^2/hour. These rates correspond to the results with the aq. solution containing 1.0 mg/ml. The difference in absorption through skin and isolated epidermis was not statistic significant. (ICI, 1983). The rates are similar to rates for diquat absorption in human skin in vitro.

STUDY 2:
^{14}C-paraquat ion dilutions were made from the formulation "Gramoxone". The tested dilutions contained 20% and 0.5% (spray strength) paraquat ion, respectively. The dilutions were applied to human epidermis in vitro. The 20%-dilution caused an absorption rate of 23.88µg ion/cm^2 skin/hour, and the 0.5% was at 0.69µg ion/cm^2 skin/hour, which is equal when the concentrations are being taken into the consideration. (ICI, 1985).

STUDY 3:
In an in vitro study permeability constants for paraquat were determined to be approx. 40-270 times higher in different species of lab animals (e.g. rat and guinea pig) than in human skin. For hairless mice the constant was > 1000. This should be regarded when extrapolation to man is done. (Publ., 1983).

3.2 Discussion

Spray strength of Preeglone contains 0.06% diquat and 0.06% paraquat (w/v). Without protection, the absorption of paraquat through human skin will be probably be less than 0.69µg ion/cm^2/hours.

4. Acute toxicity

The time from dosing to death varies both an inter- and intraspecific. In rats death seems to be concentrated in an early and a late peak.
Paraquat intoxication is fought biochemically with antibody (to NADPH-cytochrome *b* reductase), superoxide dismutase (SOD) and probably to a certain degree antioxidants like vitamine C .
Oxygen enhances the toxicity of paraquat, or paraquat enhances the toxicity of oxygen. [the attack is thought to be on the polyunsatured lipids of cell membranes.] The absorbents bentonite and fuller`s earth have prevented deaths due to paraquat in rats and reduced absorption in cats. These

clays are also recommended after ingestion of paraquat by humans, together with evacuation of the GI-tract.

4.1 Paraquat (stated as mg paraquat ion)

Route	Strain and sex	LD50, LC50	
oral	rat	112-150 mg/kg	(Hayes)
dermal	rat	80-90 "	-"-
oral	monkey	50 "	-"-
oral	cat	35 "	-"-
intraper.	guinea pig	3 "	-"-
1oral	Ald. Park rat, M+F	~1 ml/kg	JF6924
2dermal	"	~0.35 "	"
3inhalation	Wistar, M+F	0.6-1.4 mg/m³	4 h, nose only
4"	"	>=3.5 mg/m³	"

M: males, F: females
JF6924 is a formulation containing 200 g paraquat/l.
Signs of toxicity:
Study 1 and 2: Subdued behaviour, piloerection, respiratory difficulties, signs of urinary incontinence and staining around the eyes, nose and mouth.
Study 3: The aerosols were highly respirable. Irritation of the respiratory tract and general body weakness. Increase in lung weight and macroscopic evidence of acute lung damage
Study 4: Aerodynamic diameter was large: 21.5-23µm, with only 0.12-0.25% respirable particles. Irritation of the respiratory tract and general body weakness, especially in males. Increase in lung and kidney weigh.

Lung of rabbit was highly sensitive to paraquat intrabronchial instillation in doses ranging from 0.1g - 1pg, moderately sensitive to intravenously administered paraquat (25 mg/kg bw), resistant to the herbicide when given intraperitoneally or subcutaneously (25 mg/kg bw). (Publ., 1978, from EHC 39).

4.2 Preeglone (Weedol)

Route	Strain and sex	LD50/LC50	Comments
oral	JCL-SD-rats, M+F	5.250 mg/kg bw	Weedol, 1979
dermal	" "	>4.000 mg/kg bw	---------"----------

The oral adm. of Weedol gave the following symptoms of intoxication: hair bristling, vomiting, salivation and diarrhea were noted after 24 h. Hyposthenia and hypohydration. Congestion in the stomach, repletion of gas. Some had haemorrhage in the intestines or around the eyelids.
After dermal application the rats showed no change in general condition or skin appearance. No abnormalities were seen in the organs.

After ingestion of 45 g of Weedol (2.5% paraquat), a person was admitted to the hospital. The gastric aspirate contained 0.215g paraquat/litre, and the urine 0.148 g/l at the time of admission. Later the amounts in urine and serum were:

	admission	2-4 hours later	16-24 h	15 days
urine	0.148 g/l	5.1 mg/l	0.95 mg/l	D
serum		0.4 mg/l	ND	ND

D=detected in small amounts
ND=not detected (from EHC 39)

5. Irritation

5.1 Studies

SKIN IRRITATION OF PARAQUAT: DRAIZE`S TEST IN RABBITS
Single doses of 0.5 ml Gramoxone (20% paraquat) were applied to intact and abraded skin for 24 hours. Draize`s scale was used. Because of adverse effects (pain and deaths) a second study was carried out using a 25% v/v solution of Gramoxone in water. The formulation was a moderate skin irritant, PII=3. (1979).

Rabbits developed ulceration of the tongue if they were allowed to lick the washed skin site that had been exposed to paraquat (Hayes).

EYE IRRITATION OF PARAQUAT: IN RABBITS
JF6924 (200 g paraquat/l) was classified as a moderate irritant to rabbit eyes after instillation of 0.5 ml. Initial pain was followed by opacity of the cornea among other things. At the end of the 9-day observation period, the eyes still showed some redness of the conjunctiva with some discharge. (1979).

5.2 Experiences in humans

Paraquat has a delayed effect on the skin. Skin, nail and eye lesions were found in subjects with prolonged occupational exposure to paraquat (probably ~Gramoxone). The use of protective clothing and gloves is effective in preventing skin lesions.

5.3 Conclusions

Paraquat is classified as an irritant of the skin, eyes and mucous membranes.

6. Sensitization

6.1 Studies in animals

PARAQUAT: SKIN SENSITIZATION IN EAR/FLANK IN GUINEA PIGS
0.1 ml of a 10% solution of Gramoxone (200 g paraquat/l) was applied to the outer surface of the ears of female guinea pigs for 3 consecutive days. Four days later challenge was done by applying 10%, 1% and 0.1% (w/v) solution of Gramoxone in DMF to the shaved flank skin. 24 hours after the challenge, the evaluation was done. Traces of a reaction was seen in the animals in the top dose group, but also in animals which had only received the challenge treatment. This is therefore considered to be an irritation response. (1979).

6.2 Conclusions

Preeglone is not classified as a sensitizer.

7. Neurotoxicity

7.1 Studies

No special studies have been submitted. Some general signs of neurotoxicity were observed in studies of acute toxicity.

7.2 Conclusions

Paraquat presumably has only weak neurotoxic potential.

8. Subacute and subchronic toxicity

8.1 Paraquat

13 WEEKS ADMINISTRATION OF PARAQUAT IN RATS

Groups of 20 male and 20 female Fischer-CDF (F344) CRJ-rats received diets containing 0, 10, 30, 100 and 300 ppm paraquat (-dichloride, AT-5) for 13 weeks. This corresponds to 0, 7, 22, 72 and 217 ppm paraquat ion. The highest dose caused remarkable depression in body weight gain (appr. 15%) and lower food intake and food efficiency. No animals died, nor were any signs of toxicity observed. On day 91 hematological and blood biochemical examinations were carried out on at least 10 animals of each sex from each group. On day 92 urinalysis was made in the remaining animals. Nothing abnormal was registered in the urinalysis, and no abnormal hematological or biochemical data were related to the administration of the test compound.

At the histopathological examination alveolar epithelial hypertrophy was observed in 6 of 20 male rats exposed to 300 ppm. Increased brown pigmentation was noted in the spleen in females.

NOEL was 100 ppm, equivalent to 6.57 mg paraquat dichloride/kg bw/day in males and 7.10 in females. (Inst. Env. Tox., 1980)

13 WEEKS ADMINISTRATION OF PARAQUAT IN MICE

Groups of 20 male and 20 female mice (ICR-CRJ) received 0, 7.2, 22, 72 and 217 ppm paraquat ion for 13 weeks. Lung damages occurred. NOEL was 72 ppm, i.e. 12 mg/kg bw in lames and 14 in females. (Publ, 1980, from FAO 78/2).

THREE WEEKS INHALATION STUDY IN RATS

Groups of 36 Sprague Dawley rats (CD) of each sex were exposed to an aqeous aerosol of paraquat, at these concentrations; 0, 0.01, 0.10 and 1.0 µg paraquat ion/l. The highest dose had to be replaced with 0.50 µg because almost all the animals died within 72 hours of the first exposure. None of the animals in the new highest dose group (16 males + 16 females) died. The whole body was exposed in a $6m^3$ inhalation chamber, six hours a day, 5 days a week for 3 weeks.

The exposure reduced body weight in all groups, and caused slight nasal staining in some animals. No compound related abnormalities were detected at the macroscopic examination. The microscopic examinations revealed the following treatment-related changes in the respiratory system:

Larynx: Ulceration, necrosis and acute inflammatory cell infiltration with squamous keratinising metaplasia and moderate/marked hyperplasia of adjacent epithelia was seen in animals exposed to 0.1µg/l and up. Animals examined after two weeks recovery had no ulceration or necrosis, but

still epithelial squamous metaplasia and/or hyperplasia in almost all rats from 0.1µg/l. Some regeneration of cuboidal cells were noted.

Lungs: Aggregation of foamy macrophages with traces of mucus and debris were present in the lumina of bronchioles and occasionally in adjacent alveoli in all 16 rats in the highest dose group. The epithelium lining the lower bronchioles was hypertrophic with loss of ciliated and Clara cell characteristics in most rats. In 8/16 rats some areas of thickened alveolar walls were observed; the thickening appeared in most instances to be due to inflammatory cell infiltration and a slight increase in collagen and reticular fibres. After a two weeks recovery period the other 16 animals in this dose group were examined. The changes were still present with no obvious regression. In addition, disruption of bronchiolar areas of peribronchiolar lymphoid aggregations, was noted. No histopathological changes were found in lungs from rats exposed to doses below 0.5µg/l. (Huntingdon, 1979).

THREE WEEKS INHALATION STUDY IN RATS - REPEAT STUDY
Groups of 36 male and 32 female Sprague Dawley rats (CD) were exposed to an aqeous aerosol of paraquat, at these concentrations: 0, 0.01µg and 0.10µg paraquat ion/litre air. The whole body was exposed in a 6 m^3 inhalation chamber, six hours a day, five days a week for three weeks. Some animals were killed during the study, for interim investigations macroscopically and histopathologically..

There were no treatment related effects on body weight or food consumption, and no signs of paraquat intoxication were observed. Exposure at an aerosol concentration of 0.1µg paraquat ion/litre air produced histopathological changes in the larynx, while exposure at 0.01µg/l did not. In animals examined three days after the first exposure at 0.10µg/l there was squamos metaplasia and/or hyperplasia predominantly in the ventro-lateral aspect at the base of the epiglottis in all 8 examined rats. There were no changes in the pharynx at either concentration. Remaining animals were examined macroscopically only. No treatment related abnormalities were seen.

(Huntingdon, 1979)

13 WEEKS ADMINISTRATION OF PARAQUAT IN BEAGLES
Four groups of beagle dogs received 0, 7, 20, 60 and 120 ppm paraquat in the diet for 13 weeks. Each group consisted of 3 males and 3 females. The study does not follow the OECD-guidelines sufficiently, since the dosegroups are one animal short. Two dogs of each sex were killed in extremis from the 120 ppm group between days 16 and 23. All four dogs had marked dyspnoea, body weight loss and made increased respiratory sounds. No other exposure related clinical signs of toxicity were seen in the remaining dogs. The treatment of paraquat markedly increased lung weight (twofold). Distinct gross and histological pulmonary lesions were seen in dogs in the 60 and 120 ppm group.
There were no distinct changes in the hematological, clinical chemical or urinary parameters examined. NOEL was 20 ppm, i.e. 0.55 mg/kg/day in males and 0.71 mg/kg/day in females. (Hazleton, 1981).

8.2 Formulations

No studies submitted.

8.3 Conclusions

217 ppm paraquat ion in rodents` diet for 13 weeks, 0.1µg paraquat ion/l air to rats for three weeks and 60 ppm paraquat ion in beagle dogs` diet for 13 weeks caused lung damage, i.a. hyperplastic alveolar epithelial hypertrophy.

9. Chronic toxicity and carcinogenicity

9.1 Studies

113 - 122 WEEKS ADMINISTRATION OF PARAQUAT IN RATS

Rats of the strain Fischer 344 were fed paraquat in the diet for at least 113 weeks in males and 122 weeks in females. Five groups of rats, including two control groups, received 0, 0, 25, 75 and 150 ppm paraquat ion in the diet for more than two years, which corresponds to about 0.8-2.9 mg/kg/day in the 25 ppm-group, to 4.8-16.8 mg/kg/day in the 150 ppm-group. Each group consisted of 70 males and 70 females, from two batches. After one year 10 animals per sex and group were sacrificed for histopathological investigation. An additional 5 males and 5 females in each group were sacrificed for investigation of tissues concentrations of paraquat at the same time.

Body weight gain and food intake were reduced. After one year opacity of the eyes (because of lenticular cataract) was seen in animals in all treated groups. Paraquat residues were found in plasma and kidneys after 52 weeks in all treated groups. In males and females from the two highest dose groups, residues of paraquat were found in skin and lungs. Females in the 150 ppm group had paraquat in the liver. In lungs from animals of both sexes in the two top groups the microscopic examination showed proliferative lesions of the alveolar epithelium. Sections of lung were examined microscopically by two professional pathologists. One of them concluded that there was a significant trend between increasing dosage of paraquat and the incidence of pulmonary adenoma, while the other one said there was no association between paraquat administration and the incidence of adenomas and carcinomas. The exposure did not cause an oncogenic effect. The mortality was unaffected by the treatment, and there was no effect on hematology, blood chemistry and urinalysis. NOEL was 25 ppm. (Life Sci. Res., 1983).

104 WEEKS ADMINISTRATION OF PARAQUAT IN RATS (Fisher)

Carcinogenicity was investigated in rats. Groups consisted of 80 males and 80 females, which were fed diets containing 0, 7.2, 22, 72 and 217 ppm paraquat ion for two years. Mortality increased in female rats in the 217 ppm-group between week 66 and 74. In males and females at this dose there was reduction in body weight gain and food consumption. No, or minor effects to urinalysis and hematology was seen due to the exposure. Histological examination of the lung at termination revealed a marked, treatment related increase in the incidence of proliferation of interalveolar septum cells and of hyperplasia of alveolar epithelium in animals given 217 ppm. The effect was also seen in male rats in the 72 ppm-group. 217 ppm paraquat speeded up the incidence of age related cataract in males and females killed or found dead after week 79. NOEL was 22 ppm in males, i.e. 0.77 mg/kg bw/day and 72 ppm in females, i.e. 3.12 mg/kg/day. (Yoshida et al., 1982, from FAO 78/2).

LIFETIME FEEDING STUDY OF PARAQUAT IN THE MOUSE

Groups of 60 male and 60 female mice (Ald.Pk.) were fed diets containing 0, 0, 12.5, 37.5 and 100/125 ppm paraquat for up to 99 weeks. 100 ppm was increased to 125 ppm at week 36, due to the absence of adverse effects. Further groups of 10 animals per sex were fed the same dose levels

as above for 52 weeks for the measurement of paraquat concentration in organs. The concentration of paraquat in urine, plasma and tissue were doserelated. Paraquat was not oncogenic in this study. Of the non-neoplastic findings mild degeneration in the kidneys and fatty vacuolation was predominating, and occurred in the two groups with highest dosage. Two males who received 100/125 ppm developed focal pneumonitis/alveolitis, a typical paraquat-induced injure. Mortality was 10-20% in females and 16% in males after one year, and 65-85% in females and 25-80% in males after 98 and 99 weeks, respectively. NOEL was 12.5 ppm, i.e. (ICI, 1981).

1 YEAR PARAQUAT FEEDING STUDY IN DOGS

Four groups of beagle dogs, each containing six males and six females, received paraquat in the diet at levels of 0, 15, 30 and 50 ppm for one year. The incidence of chronic pneumonitis in dogs dosed with 30 and 50 ppm paraquat, increased (comprising interstitial fibrosis, alveolar epithelialisation and mononuclear cell infiltration). The occurrence of respiratory dysfunction and increased lung weight increased in animals receiving 50 ppm or more. Ophtalmoscopy revealed no treatment-related changes. Paraquat was detected in urine, kidneys and lungs. NOEL was 15 ppm paraquat, i.e. 0.45 mg/kg/day in males and 0.48 mg/kg/day in females. (ICI, 1983).

9.2 Chronic toxicity

Exposure to less than 3 mg/kg bw/day for one year in rats caused cataract in the lens. Lung damage was seen after administration of 217 ppm paraquat ion in the feed for 104 weeks in rats, consisting of epithelial hyperplasia. 125 ppm paraquat ion for 99 weeks in mice, and 30 ppm for one year in dogs resulted in chronic pneumonitis.

9.3 Carcinogenicity

Increased incidence of pulmonary adenoma was possibly observed in rats, but two professional pathologists did not agree on the results. There was no oncogenic effect of exposure to paraquat.

10. Genotoxicity

10.1 In vitro studies

Results from in vitro tests on 110 herbicides were published in 1972. Paraquat did not induce mutations in tests with Salmonella t. or various bacteriophages.
Paraquat dichloride did not induce mutagenicity in Ames test using two strains of Bacillus subtilis, S. typhimurium or E. coli. (Inst. Env. Tox., 1978).

In a publication from 1979 both paraquat and diquat were tested in tests with different genetic endpoints. They were weakly positive in forward mutation tests in procaryotic *(Salmonella typhimurium)* and eucaryotic microorganisms *(Aspergillus nidulans)*, and they induced unspecific genetic damage as lethal recessives in A. nidulans. Both paraquat and diquat induced clearly detectable unscheduled DNA synthesis (UDS) in human epithelial-like cells (EUE), in the range of 20 - 2000 and 20 - 1000 µg/ml respectively. Thus these herbicides seemed to have a weak mutagenic potential. Paraquat and diquat were negative in Ames test (reverse mutation assay).

In another publication from 1979 (same authors) both paraquat and diquat induce 8-azaguanine (8-AG) resistant mutants of S. typhimurium, but are not mutagenic in the Ames test (that tests for histidine-mutants). The concentrations for paraquat and diquat were 0.1 - 2.5 and 0.1 - 1.0 µg/plate, respectively. The report does not take into account bacterial mortality.

In 1982 Levin et al. (among them Bruce Ames) reported that a new Salmonella strain - TA 102 - had been tested. It has AT at the site of mutation instead of GC, and can be used to test for oxidative mutagens. Paraquat and diquat were not detected as mutagens, though they were thought to be active through formation superoxide radicals.

In another publication from 1982 the authors show that paraquat is mutagenic only when free electrons and oxygen is available, and that cells with more superoxide dismutase (SOD) are more resistant to both the toxicity and mutagenicity of paraquat, because they can handle the production of superoxide radicals.

Cytogenetic test in human cells.
In 1985 ICI tested paraquat for the ability to induce structural aberrations in human lymphocytes from two donors, in vitro. Incubation was done with and without auxiliary metabolic activation (S9-mix), at cytotoxic levels of paraquat (125-3500µg/ml). Statistical significant increase in chromosomal damage was observed at the highest dose level tested. This level induced marked cytotoxicity. There also was a tendency to an increase at lower levels. Paraquat thus showed clastogenic effect to human lymphocytes in vitro, at cytotoxic levels.
Test for gene mutations in mouse lymphoma cells
Dose related cytotoxicity arose when cultured, L5178Y-cells were treated with 31.3 - 1000 µg paraquat dichloride/ml for two hours, in vitro. A mutagenic effect seemed to occur after treatment with S9-mix, but the results were inconsistent. Therefore, the author concludes that paraquat did not induce forward mutation. (ICI, 1985).
UDS in rat hepatocytes (Alpk:AP).
Hepatocyte preparations were made after liver perfusion. Technical paraquat dichloride was tested at the levels of 10^{-2} - 10^{-9} M; the cells were incubated with the testsubstance for 19 hours. Afterwards the supernatant medium was removed, the cells washed and incubated overnight (appr. 18 hours). Diethylnitrosamine was the positive control. The exposure did not induce unscheduled DNA synthesis in rat hepatocytes. (ICI, 1985).
Sister chromatid Exchange (SCE) study in chinese hamster lung fibroblasts
The effect of paraquat dichloride was tested on the frequency of SCE in lung fibroblasts from chinese hamster, with and without metabolic activation with S9-mix. The highest tested dose levels caused 50-80% reduction in the mitotic index. Test concentrations of paraquat dichloride in the SCE-study were 1.2 - 124 µg/ml. The cells were incubated with paraquat for three hours at 37°C. This induced increased levels of SCE formation. The effect was most apparent in the absence of auxiliary metabolism (S9-mix). This could be due to protein-compound binding to the S9-mix, since no metabolism of paraquat is expected to have happened. (ICI, 1985).

ICI tested the mutagenicity of the *paraquat metabolite* N-methyl isonicotinic acid metho-sulphate in Ames test using 5 Salmonella strains and E. coli WP2 uvrA pKM101. The Salmonella strains used were: TA1535, TA1537, TA1538, TA98 and TA100. The study was done according to OECD-guidelines, with and without metabolic activating S9-mix. The metabolite did not induce mutagenicity. (1986).

10.2 In vivo studies

CYTOGENETIC STUDIES

Rat bone marrow

Groups of 24 male and 24 female rats (Alpk:AP) received 0, 15, 75 or 150 mg paraquat ion*/kg body weight in water, by gavage in a single dose. 150 mg was the maximum tolerated dose, and it caused reduction in mitosis. This showed that the test substance reached the target organ (the bone marrow). Chromosome preparations were made from 8 male and 8 female rats after 12, 24 and 48 hours, to examine for structural changes. There was no clastogenic effect of paraquat ion in the rat bone marrow test system. (ICI, 1978). The results were the same in another Hungarian, summary report from 1978.

Micronucleus test

Mice of the strain C57BL/6J/Alpk received single oral doses of technical paraquat dichloride in the order of 50 - 80% of LD50 (calculated over 7 days). As the LD50 was 105 mg/kg, the administered doses were 51.75 and 82.8 mg/kg. The treatment did not induce an increase in polychromatic erythrocytes containing micronuclei. (ICI, 1985).

LIVER SPECIFIC ASSAYS

UDS in rat hepatocytes (Alpk:AP).

Technical paraquat dichloride, containing 33.07% paraquat ion, was given to groups of 10 rats by gavage in single doses; 0, 45, 75 and 120 mg par. dichloride/kg bw. The animals were sacrificed after 4 or 12 hours. Hepatocytes preparations were made after liver perfusion. 6BT was the positive control. The exposure did not induce unscheduled DNA synthesis in rat hepatocytes, examined on slides. (ICI, 1987).

MAMMALIAN GERM CELL STUDIES

Dominant Lethal Test with paraquat and diquat.

The test was not carried out according to the OECD-guideline; there was only one dosegroup, no positive control and to few female mice participating.

Groups of five male mice were exposed to 66 mmole paraquat/kg bw or 76 mmole diquat/kg bw intraperitonale. They were caged with three untreated females within two hours after treatment, and got a new group of females every 7 days for 8 weeks (the duration of one spermatogenic cycle). The females were killed 15 days after the first day of caging. No mutagenic effects were detected, but an antifertility effect; the pregnancy rates were significantly reduced after treatment of the males with both paraquat and diquat. (Publ., 1974)

HOST MEDIATED ASSAY

Paraquat dichloride did not induce mutations in Salmonella t. injected in mouse tissues after oral administration of 2X10 or 2X40 mg/kg bw. (Inst. Env. Tox., 1978).

*from techn. paraquat dichloride with 33.07% paraquat ion, w/w.

DROSOPHILA ASSAYS

Drosophila wing spot test

The wing spot tests are assays for somatic mutation and recombination using the induction of mosaic spots in the wings.

Third-instar larvae of Drosophila melangoster, trans-heterozygous for two recessive mutations of wing trichomes; multiple wings hairs (mwh) and flare (flr^3), were fed paraquat chronically. The feeding ended with pupation of the surviving larvae. The genotoxic effects were determined from the appearance of clones of cells with mwh, flr^3 or mwh-flr^3 phenotypes. Paraquat induced significant increases in both small and total spots at three of the four concentrations tested, without indication of a direct dose-effect relationship. (Publ., 1992).

10.3 Conclusions of in vitro tests

Paraquat was clearly mutagenic in a UDS-test in human cells (also diquat), in absence of cytotoxicity. Paraquat was not mutagenic in UDS-test in rat hepatocytes or in the Ames test. Paraquat seemed to induce forward mutation at cytotoxic levels.

10.4 Conclusions of in vivo tests

Of all the tests; cytogenetic, liverspecific, with mammalian germ cells, host mediated and Drosophila assay, only the Drosophila wing spot test indicated a mutagenic effect of paraquat.

11. Teratogenicity

11.1 Studies

In a study from 1966, ICI reports that no teratogenic effect was seen after administration of paraquat to rabbits of three different stocks during the gestation period. The rabbits were dosed:
1) Intravenous with 8 X 2.4 mg/kg/day, and then 1.2 mg/kg/day, or
2) Intravenous with 10 X 1,2 mg/kg/day, and then 12 mg/day in the drinking water, or
3) 30 ppm in the diet through the gestation.
The report from the study is of terribly low quality, not specifying the investigations carried out, or the statistics employed. One should therefore not attach much importance to it.

Paraquat caused a marked reduction of pregnancy rates in females mated to males with sperm that had been treated in the postmeiotic late spermatid stage (from Hayes).

For this evaluation ICI has supplied us with several reviews of the toxicity of paraquat, including a paper on paraquat teratology. Maternal toxicity has been seen in rodents, but only minimal embryotoxic effects. The concentration of paraquat in embryos/fetuses is low. This reflects the fact that this compound does not cross the placental barrier easily.

11.2 Conclusion

Paraquat presumably has no teratogenic potential, and is only slightly embryotoxic.

12. Effects on reproduction

12.1 Studies

THREE GENERATIONS IN RATS
Wistar-derived rats of the Ald.pk.-strain were fed test diets throughout the study. The diets contained 0, 25, 75 and 150 ppm paraquat. There were 15 males and 30 females in each group. Concentration of paraquat in urine was doserelated. The layout of the study is shown in enclosure no. 5. Inhibition in body weight gain was not strictly dosage related, but some indications was seen, especially in the last generation. The treatment had no adverse effect on the reproduction parameters. The only significant adverse effects of the paraquat exposure in organs were found in the lungs of several animals; Some of the females in the 150 ppm-group died from severe, acute or subacute lung damage. There was a dose related increase in the incidence and severity of focal alveolar histiocytis (disease of the lung that causes fibrotic tissue breakdown) in the lungs of

parents receiving the two highest doses. Mild perivascular inflammation in the lungs was seen in the first generation of pups in the 150 ppm-group. The lung injuries were typical of paraquat induced changes. NOEL (in any group) was 25 ppm, i.e. 2.9 mg/kg/day in females and 2.1 mg/kg/day in males. (ICI, 1982).

Two additional studies are summarized in FAO 78/2 from 1986:

- Three generations in rats were exposed to 0, 30 and 100 ppm paraquat ion in the diet. The only positive finding was a slightly increased incidence of renal hydropic degeneration in 3-4 week-old offspring in the 100 ppm-group. (Fletcher et al., 1972).

- Three generations in rats were exposed to 0, 72, 145 and 290 ppm paraquat ion in the diet. Asthmatoid wheesing and increased mortality was observed in the first parental generation after exposure to 290 ppm. In the second generation lung damage, bw reduction and increased mortality was seen in the 290 ppm-group. White spots in the lungs were seen in males and females exposed to 290 ppm in all generations. In a sub-group teratology study no teratogenic effect was seen. (Suzuki et al., 1983).

12.2 Conclusion

Lung damages typically induced by paraquat were seen in rats exposed to doses from 75 ppm in the diet. Slight renal paraquat-induced toxicity was seen in one of the three rat studies.

13. Toxicity of metabolites and degradation products, residues in mammals and hens`eggs

13.1 Toxicity

The acute and subacute toxicity of the paraquat metabolite N-methyl isonicotinic acid metho-sulphate was tested by ICI in 1966. This is a product of the photochemical degradation of paraquat. As the report is of poor quality, too much importance should not be attached to it. It looks like, however, that the LD50 in rats is more than 4.0 g/kg body weight after oral administration, and about 4.0 g/kg bw after intraperitoneal injection. The toxicity after repeated administration was also low, and the metabolite produced weak skin irritation. It was not tested for eye irritation because it is assumed to be a severe eye irritant.

There is another report from 1966 of a study of 90 days feeding of the same metabolite at dietary levels og 0, 5,000, 20,000 and 40,000 ppm. This report seems to be of a higher quality than the one mentioned above. There were 25 animals of each sex in each group. Only the highest concentration had any effect on the rats (Wistar). In this group growth was slightly retarded and males showed a microscopic abnormality confined to the testis and epididymis. (ICI, 1966).

A 90 days feeding study was also carried out exposing beagle dogs to the metabolite. There were four animals of each sex in each group. Dose levels were 0, 0.125 and 0.5 g/kg bw/day, mixed with the diet. Body weight gain was not influenced by the treatment. No changes were seen in haematology, blood chemistry, liver function, urinalysis or pathology. (ICI, 1966).

13.2 Residues in mammals

Species	dose and exposure	14C-residues in milk	in kidney	in liver	other	year
cattle	½LD50 single PO	<0.1 ppm				1965
pigs	50µg/g, 7 days diet		0.38 ppm	0.10 ppm		1976
pigs	"		0.46 ppm		75.3% in urine/ fec.	1977 ?
calves	3-7 days grazing on Gramoxone treated pasture		0.16 ppm		73 ppm in stomach tissue	1969
cattle	½LD50/day for weeks				No signs of toxicity	1968
horses	"				Signs of tox. in the mouth	"
cattle	single	<0.02%			<5% in urine	1966
cow	3 PO 8mg/kg/day	0.004-0.01 ppm			0.1% in urine	1971
cow	25-170ppm in grass	<0.001 ppm	0.2-0.31 ppm	<0.01 ppm		1971
cattle	5ppm,21 days in diet	ND	ND	ND		1966
goats	100 ppm, 7 days in diet	0.009 ppm	0.74 ppm	0.56 ppm	2.4% in urine	1976
sheep	PO				4% in urine	1972
"	SC				80% in urine	"
pigs	150 ppm, 30 days in diet		0.4 ppm		0.12 ppm in lung	1975
rabbits	272 mg/kg/day in treated lucerne				No toxic observatio.	1979

ND=not detected

As the table shows paraquat is poorly absorbed from the GI-tract. Because of this it is mainly excreted in the feces rapidly. After subcutaneous administration it is excreted in the urine. Residues in milk and organs are small, and the greatest amounts is generally found in the kidneys.

The residues-results are independent of which part of the paraquat molecule that is radiolabelled with ^{14}C, ring- or methyl-labelling. This indicates that the molecule is not metabolized. In some of this studies the quite seldom metabolites were identified. Enclosure no. 6 shows their structure.

13.3 Metabolism and residues in hens and eggs

Earlier work has shown that 0.1 ppm paraquat injected into eggs reduced hatching. In this study egg laying chickens had drinking water containing 0 or 40 ppm paraquat dichloride for 14 days. Recovery was also 14 days. There was a slight fall in egg production and a slight increase in the percent of abnormal eggs during the paraquat treatment. The amount of paraquat in the eggs rose to 0.1 ppm. All effects were reversible and declined when the exposure stopped. (ICI, 1967).

When one hen was fed a single dose of ^{14}C-paraquat equivalent to 60 ppm in the feed, 101% av the radioactivity was recovered in feces after three days.
Four hens were given 60 ppm paraquat in the feed, and the feed consisted of feces from ruminants. Two hens had diet mixed with paraquat two weeks before the exposure started. The other two`s diet was mixed with paraquat immediately before feeding. The hens were exposed for 18-20 days. The residues were significantly lower where paraquat was bound to the feed, i.e. mixed earlier. The yolk contained 0.03 - 0.04 ppm ion equivalents. In albumin the residues were small and approx. 0.0005 ppm. Maximum residue in the whole egg was 0.01 ppm, virtually all residues were paraquat. Residues in tissues from the birds were extremely low and paraquat did not accumulate. (ICI, 1974).

In another study chickens were administered 0, 2.5, 5, 10 and 50 ppm paraquat dichloride in the feed for 30 days. Groupsize was 18. Chickens were sacrificed on day 21, 30 or 33, the last group after three days on control diet. Eggs were collected on days 1, 5, 10, 21, 25, 30 and 33. No paraquat was detected in the eggs from hens who had received the two lowest doses. 10 ppm in the feed gave maximum 0.01 ppm in the eggs (day 5), and 50 ppm gave <0.01 - 0.05 ppm. Residues of paraquat were detectable in the gizzard at all levels. The gizzard was washed free of feed prior to the analysis, but still contained 0.02 - 0.16 ppm. No paraquat was detected in heart and fat, and the highest dose gave 0.01 - 0.03 ppm in skin, liver and muscle. All residue levels declined during the recovery period. (Chevron, 1974).

13.4 Conclusion

The photoproduct N-methyl isonicotinic acid metho-sulphate induced little toxicity in rats and dogs. Paraquat is poorly absorbed and metabolized in mammals. Residues were mainly found in kidneys and liver. Only small residues were found in milk and eggs.

14. Human studies and occupational exposure

Paraquat intoxication has frequently been studied in accidents and suicidal attempts (most of them "successes"), usually after oral or cutaneous exposure to the formulation "Gramoxone". Prolonged skin contact with Gramoxone can produce a chemical burning, usually severe. Following ingestion, ulceration of the mouth and pharynx is common. Humans die from renal and respiratory insufficiency, after up to 26 days after the ingestion. The smallest lethal oral dose of Gramoxone known in humans contains ~16.7 mg paraquat/kg bw. Gramoxone (20% paraquat) is not on the Norwegian market today.

Studies in the field indicate that exposed skin is the most likely entrance route during normal use of paraquat, pointing out the importance of protective clothing included. A major source of

contamination in fields comes from walking through recently sprayed vegetation, but paraquat is not allowed to be used in fields in Norway.

The permeability of paraquat (a charged moiety) through human skin is extremely slow, compared to many other pesticides. This is also seen in vitro, see page . The lethal dose of paraquat is maximum 3 ml (3/4 of a teaspoon Gramoxone, 20% w/v). The importance of correct storage of any paraquat formulation cannot be stressed enough, especially when considering the fact that death from paraquat poisoning is both slow and painful. Enclosure no.7 form a true picture of this.

When evaluating the risk connected to the continued approval of Preeglone, the concentration of paraquat must be considered. In Preeglone the concentration of paraquat is 2.5% (w/v), and the recommended dilution is 0.06%. Deaths after dermal exposure has been registered with 0.5% dilutions.

Paraquat should not be spread with mist sprayers, because this produces approx. thousand times higher concentration of paraquat in inspired air during application. This has been tested with a 0.5% dilution of Gramoxone. (Publ., 1975) Preeglone is formulated as wettable powder.

Discolouration, deformity and even loss of nails occurred in 55 out of 296 spray operators on sugar estates in Trinidad. This was due to leakage of the knapsack sprayer of diluted Gramoxone. (Publ., 1971).

15. Summary & conclusion

The application for approval of Preeglone is supplied with studies of generally high quality conserning the active ingredient. No studies of Preeglone tested for irritation and sensitization properties have been submitted.

Paraquat participates in cyclic reduction-oxidation reactions in biological systems, see enclosure no. 8. The compound readily undergos a single electron reduction in tissues, forming a free radical. In an aerobic environment, the free radical is immediately oxidized by molecular oxygen, generating the superoxide anion radical. The reoxidized paraquat is capable of accepting another electron and continuing the electron transfer reactions in a catalytic manner.

The toxic mechanism in animals is basically similar to the herbicidal activity. No specific treatment for paraquat poisoning is known. Many kinds of treatment have been tried, e.g. administration of absorbents, evacuation of the GI-tract, hemodialysis and lung transplantation. Induced vomiting and absorption treatments with clays like Bentonite and Fuller`s Earth seem to have the best effect.

Paraquat is generally poorly absorbed from the gut and through the skin, and is metabolized only to a small degree. Via energy dependent processes the compound is accumulated in the lungs of mammals where it triggers the specific lung toxicity, that is so different from diquat intoxication. Paraquat is classified as an irritant. It has a very weak mutagenic potential, and does not seem to be neither teratogenic nor carcinogenic.

Excess exposure to paraquat has been the cause of death in numerous suicides and accidents, with the use of strong concentrated formulations, e.g. Gramoxone (20%). Preeglone contains 2.5%

paraquat and 2.5% diquat and is in, all probability, unlikely to give rise to serious health problems when properly used.

ADI in humans is 0-0.004 mg/kg bw as ion, corresponding to 0-0.006 mg/kg bw of paraquat dichloride in the diet.

Preeglone is toxic and belong in Class B. It is classified as an irritant of the skin, eyes and mucous membranes.

8 enclosures

A: Treeglone
Enclosure # 1

TOXICOLOGY OF ADDITIVES

PP796 (Guanazole) Emetic

Acute oral LD50 to rats: 150-155 mg/kg
Acute oral LD50 to mice: 300-316 mg/kg

Acute intravenous LD50 to rats: 50-75 mg/kg
Acute intravenous LD50 to mice: >150 mg/kg

90 day tests in rats and dogs did not generate any significant toxic effects.

PP796 is neither teratogenic in the rabbit nor carcinogenic in the mouse.

It is a potent inhibitor of gastric emptying in non-vomiting species such as rats and mice, and in vomiting species such as monkeys.

NONYL PHENOL ETHYLENE OXIDE CONDENSATE

In the Ames test, this gave a positive response in the Salmonella tester strains TA1535 and TA98 and a negative response in the strains TA1538 and TA100. These results along with a knowledge of the chemical structure indicate that nonyl phenol ethylene oxide condensate is not carcinogenic.

The acute oral LD50 to the rat is 4.9 mg/kg. Undiluted the material is a slight-moderate irritant to rat skin and a moderate irritant to rabbit skin and eyes. A 0.5% aqueous solution is practically non-irritant to rabbit skin and eye.

The product is not a sensitiser to guinea pig skin.

ALKYL AMINE ETHOXYLATE

Acute oral LD50 to the male rat is 1850 mg/kg.
Acute oral LD50 to the female rat is 1200 mg/kg.

The material is a severe irritant to rat skin and a very severe irritant to the rabbit eye.

POLYSILOXANE

Acute oral LD50 to male and female rats is >5000 mg/kg.

The material is irritant to rat skin and a mild irritant to rabbit eye.

B3 INFORMATION ON THE ACTIVE INGREDIENT IN TECHNICAL a.i.

3.1	Purity	In % (w/w) Minimum purity: 94.4% Not less than 30% w/v paraquat ion (equivalent to 41.43% u/v paraquat dichloride)
3.2	Chemical name and quantity of impurities	Optical isomers, synthesis by-products, metabolites, etc in % (w/w) with unambiguous chemical name. IUPAC or CAS nomenclature. Method of analysis and accuracy must be stated.

Identity	Maximum Content (as % paraquat ion)
1-methyl-4,4'bipyridinium ion	<1% w/w
1-methyl-2,4'-bipyridinium ion	<0.25% w/w
1,1'dimethyl-2,4'bipyridinium ion	<0.25% w/w
Monopyridone	<0.5% w/w
Sodium chloride	<1% w/w
Methanol	<1% w/w
Digylone	<0.5% w/w
Sulphated ash	<2% w/w
Water	<55% w/w

These impurities may all be identified by a range of analytical methods using gas-liquid chromatography/mass spectrometry.

Paraquat enclosure 3

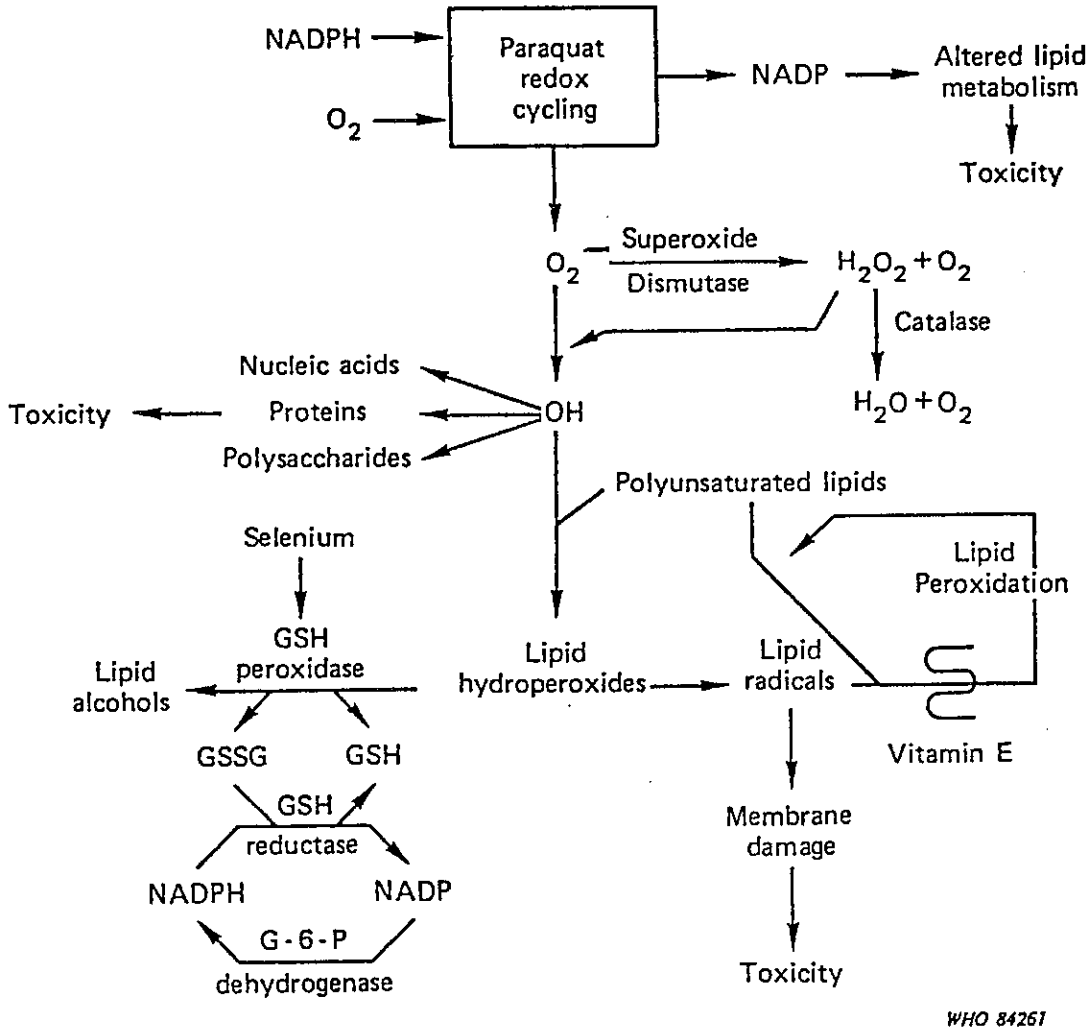


Fig. 6. Proposed biochemical mechanism of paraquat toxicity (Bus & Gibson, 1982).

Paraquat

enclosure 4

Table 9. Paraquat distribution in tissues

Route of entry	Dose	Species	Time after treatment	Tissue	Concentration
1. Intrabronchial	10 ng	rat	60 min	plasma	0.0092 µg/litre
				lung	5.2 ng
				kidney	0.052 ng
				liver	-
				heart	-
				brain	-
2. Intravenous	20 mg/kg	rat	24 h	plasma	0.7 mg/litre
				lung	8.0 mg/kg
				kidney	1.45 mg/kg
				liver	0.48 µg/g
				heart	0.75 mg/kg
				brain	-
3. Intravenous	20 mg/kg	rat	24 h	plasma	ND
				lung	11.36 µm/kg
				kidney	1.93 µmol/kg
				liver	0.90 µmol/kg
				heart	1.13 µmol/kg
				brain	0.87 µmol/kg
	20 mg/kg	rabbit	24 h	plasma	0.28 µmol/litre
				lung	7.9 nm/g
				kidney	5.25 µmol/kg
				liver	1.59 µmol/kg
				heart	1.52 µmol/kg
				brain	0.49 µmol/kg
4. Intraperitoneal	15 mg/kg	rat	24 h	plasma	0.32 µmol/litre
				lung	26.28 µm/kg
				kidney	10.4 µmol/kg
				liver	5.04 µmol/kg
				heart	4.59 nmol/g
				brain	1.22 µmol/kg
5. Oral	126 mg/kg	rat	16 h	plasma	0.90 mg/litre
				lung	5.0 mg/kg
				kidney	7.00 mg/kg
				liver	2.1 mg/kg
				heart	2.7 mg/kg
				brain	-
	22 mg/kg	guinea-pig	16 h	plasma	0.03 mg/litre
				lung	1.29 mg/kg
				kidney	1.99 mg/kg
				liver	0.08 mg/kg
				heart	0.31 mg/kg
				brain	-

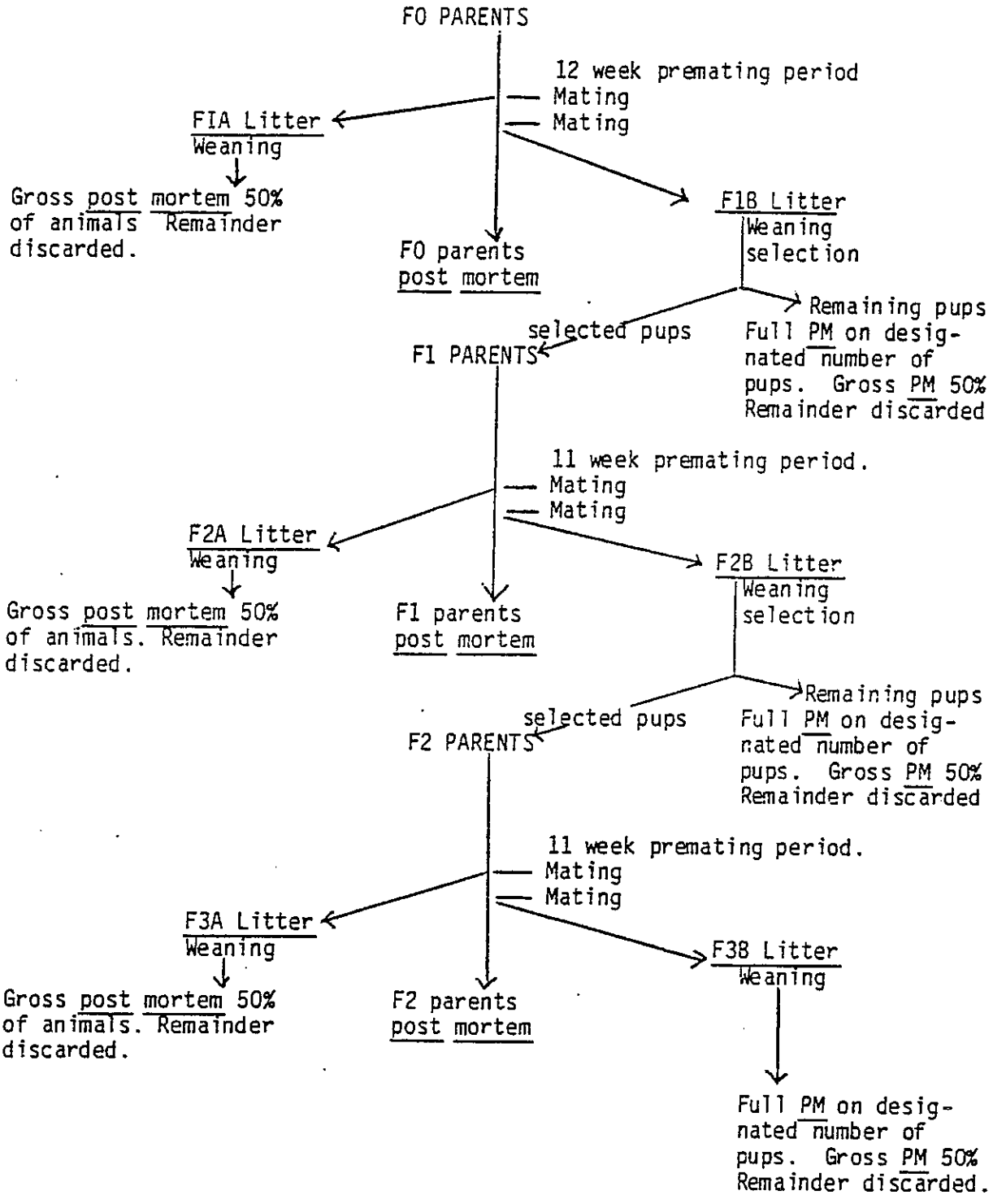
1. From: Wyatt et al. (1981).
2. From: Sharp et al. (1972).
3. From: Ilett et al. (1974).
4. From: Maling et al. (1978).
5. From: Murray & Gibson (1974).

(EHC 39)

PARAQUAT: MULTIGENERATION REPRODUCTION
STUDY IN RATS - THREE GENERATIONS

APPENDIX 8

SEQUENCE OF EVENTS IN A MULTI-GENERATION REPRODUCTION STUDY

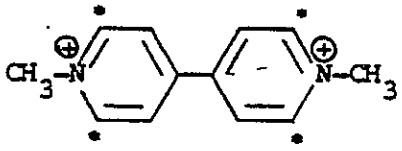


TERMINATION

Paraquat
Enclosure 6

Pigs' liver ds.

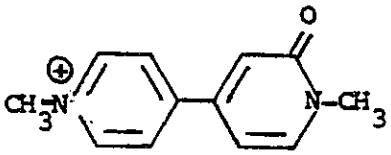
liver goat.



PARAQUAT ION
(*denotes the position of the ^{14}C-label)

50%

0.6%

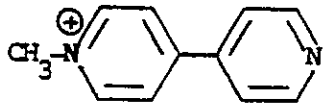


Compound I
(4-(1,2-dihydro-1-methyl-2-oxo-4-pyridyl)-1-methyl pyridinium ion)

<50%

7%

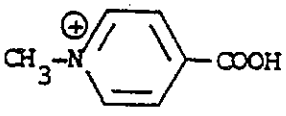
4%



Compound II
(1-methyl-4-[4'-pyridyl] pyridinium ion)

2-3%

5%



Compound III
(N-methyl-isonicotinic acid)

<1%?

Metabolites in mammals

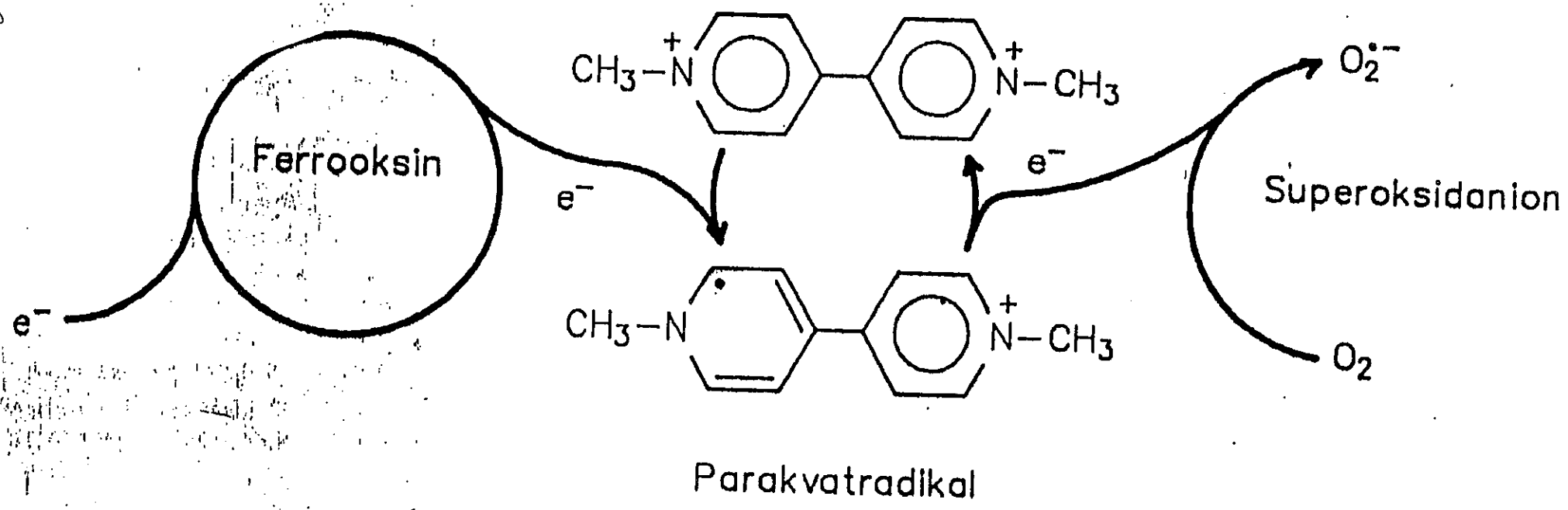
from Handbook of Pesticide Toxicology, 1991:

Paraquat

Enclosure # 7

Most of the features of poisoning by paraquat are illustrated by a case reported by Almog and Tal (1967) involving suicide by subcutaneous injection of the compound. The dosage was said to be 1 ml of 20% paraquat dimethanosulfate. The patient, a 30-year-old male with a history of schizophrenia, reported to the hospital a few hours after the injection because he had already vomited and passed loose bloody stools. Obviously, the action of paraquat on the gastrointestinal tract does not depend exclusively on the presence of unabsorbed poison in the lumen. The admission physical examination was normal and the patient felt well for the first 2 days. Two days after admission there was right facial paralysis, absence of abdominal reflexes on the right, and a positive Oppenheim's sign on the left. All of these signs disappeared by the fifth day. However, on the third day after admission, the patient complained of anorexia and chest pain, and his temperature rose to 39°C. He was not dyspneic, but X-ray examination showed a slight infiltration of the right lung base. After 5 days he again improved and had neither pain nor fever, but his radiological changes persisted. Jaundice appeared on the eighth day; the liver was felt 6 cm below the rib margin, and the area was tender. These findings in turn disappeared by day 11, and the patient felt well for the next 3 days. On day 14 he developed dyspnea and tachycardia. X-ray examination showed areas of opacity in both lungs and a shift of the mediastinum to the left. He became oxygen dependent, grew steadily worse, and died of severe respiratory difficulty on day 18.

Paraquat
Enclosure # 8



Figuren viser hvordan parakvat bidrar til å danne det giftige superoksid-anionet gjennom en syklisk prosess

FAREKLASSE B

PREEGLONE®

Parakvat + dikvat vannløselig granul ugrasmiddel

Til nedsviing av grasarter og to-frøblada ugras under frukttrær, jordbær og andre bærvekster, under prydtrær og -busker, i veksthus, på kompost- og jordhauger, grusganger, garasjeplasser, tennisbaner og langs gjerder.

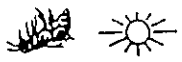
Sammensetning :

Parakvat (som parakvat-diklorid)	35 g/kg
(Tilsvarer 25 g/kg parakvat-ion)	
Dikvat (som dikvat-dibromid)	47 g/kg
(Tilsvarer 25 g/kg dikvat-ion)	
Fyllstoffer	918 g/kg

ADVARSEL

Farlig ved svelging og innånding
OPPBEVARES INNELÅST OG UTILGJENGELIG FOR BARN
Irriterer huden og øynene
Bruk egnet verneutstyr
Uskadeliggjør tomemballasjen (Se forsiktighetsreglene)

FARLIG FOR BIER



Forbudt å bruke på eller over blomstrende vegetasjon om dagen

Tilvirker : Zeneca, England

Importør : PK **as Plantevern-Kjemi** Huggenes Gård, 1580 Rygge

Fabr.nr.:

Prod.år :

STIL :

® Varemerke - Zeneca Limited, England

Nettoinnhold : 1 kg *e*

FAREKLASSE B

Det er forbudt å bruke Preeglone i strid med godkjent bruksområde eller å overskride den tillatte maksimale dosering/konsentrasjon.

BRUKS- OG VIRKEOMRÅDE

Preeglone er tillatt brukt til nedsviing av grasarter og to-frøblada ugras under frukttrær og bærvekster, under prydtrær og -busker, i veksthus, på kompost- og jordhauger, grusganger, garasjeplasser, tennisbaner og langs gjerder. Preeglone brukes også mellom radene i jordbær for å svi ned utløpere.

VIRKEMÅTE

Preeglone virker hurtig og svir ned alle grønne plantedeler som får væsken på seg. Preeglone virker ikke på brun bark og kan derfor brukes inntil trær og busker.
Preeglone mister sin virkning i kontakt med jord og kan derfor ikke tas opp og skade røttene til kulturplanter i nærheten og virker av samme grunn bare på ugras som har spirt.
Jord fra kompost- og jordhauger kan brukes når ugraset er nedvisnet.
Preeglone avgir ingen skadelige gasser og kan derfor brukes i ganger og under bord i veksthus.

BRUKSRETTLEDNING

Sprøytetid : Sprøyt på oppspirt ugras. Der en vil holde ugraset borte hele sommeren, må sprøytingen gjentas etter behov.

FAREKLASSE B

Preparatmengde : 1,2 kg pr. dekar i 50 liter vann pr. dekar.
Tillaging av sprøytevæske : Rør Preeglone ut i litt vann til alt granulat er løst opp. Fyll noe vann på sprøytetanken før det oppløste granulatet tilsettes. Etterfyll sprøytetanken til ønsket væskemengde.
Sprøyting : Sprøytevæsken må ikke komme på kulturplanter eller plenkanter. Ved sprøyting mellom radene eller plantene må en bruke skjerm for å unngå at sprøytevæske kommer på kulturen. **Bruk ikke tåkesprøyte.**

LAGRING

Lagres tørt i godt lukket originalemballasje.

FORSIKTIGHETSREGLER

Vernehansker, overtrekksklær, vernebriller og halvmaske med kombinasjonsfilter for støv og gass. (P2,A1) bør brukes ved tillaging av sprøytevæske og ved sprøyting. Unngå sprut i øynene, på hud og klær. Hud som har vært i kontakt med preparatet vaskes godt med rikelig vann og såpe. Stenk i øynene må skylles grundig vekk med vann.
Preparatet må ikke brukes i den delen av døgnet som bier flyr, i tida fra kl. 03.00 til kl. 22.00 normaltid. Hvis temperaturen ikke overskrider 10°C, kan preparatet brukes i tida fra kl. 21.00 til kl. 05.00 normaltid.
Skyll sprøyte og annet spredeutstyr med vann, deretter rengjøres med egnet rengjøringsmiddel, f.eks. PK Sprøytevask. Unngå forurensning av vannkilder. Grundig rengjort tomemballasje kan deponeres på offentlig fyllplass eller brennes.