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Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade

Chemical Review Committee
Eighteenth meeting
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Item 5 (c) (ix) of the provisional agenda*

Technical work: review of notifications of final regulatory action: paraquat

Paraquat: supporting documentation provided by Malaysia

Note by the Secretariat

As is mentioned in the note by the Secretariat on paraquat: notifications of final regulatory action (UNEP/FAO/RC/CRC.18/13), the annex to the present note sets out documentation provided by Malaysia to support its notification of final regulatory action for paraquat in the pesticide category. The present note, including its annex, has not been formally edited.

* UNEP/FAO/RC/CRC.18/1.

Annex

Paraquat: supporting documentation provided by Malaysia

List of documents:

1. Focused summary report of the review process of registration of Paraquat that leads to the banning.
2. Official circular JP/KRP/207/12/656/2 Vol.6 (54), 16 May 2014 (Malay and translation in English).
3. FAO/WHO Evaluation report on Paraquat dichloride 2003, http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Specs/Paraquat08.pdf.
4. Review report for the active substance Paraquat, SANCO/10382/2002 –final, Directorate E – Food Safety: plant health, animal health and welfare, international questions E1 - Plant health (EC), October 2003.
5. World Health Organization & International Programme on Chemical Safety. (1991). Paraquat : health and safety guide. World Health Organization. https://apps.who.int/iris/handle/10665/41647.
6. Pesticide residues in food, 2003. Joint FAO/WHO Meeting on Pesticide Residues PARAQUAT.
7. US EPA, Re-registration eligibility decision (RED), 1997. Paraquat dichloride RED facts. Ministerial Agreement No. 0112.-published in the Official Registry No. 64, November 12, 1992. Art.1 (Spanish).

DRAFT

FOCUSED SUMMARY REPORT OF THE REVIEW PROCESS OF REGISTRATION OF PARAQUAT THAT LEADS TO THE BANNING

A. INTRODUCTION

During the review period conducted from 2002 to 2013, the Ministry of Agriculture and Agro-based Industry through the Department of Agriculture and the Pesticides Board had reviewed and scrutinized many research information and publications related to paraquat from within and outside the country. In addition, the Agriculture Department in collaboration with relevant government agencies had also conducted studies on the effectiveness of alternative pesticides to paraquat. The Agriculture Department and Board had also held a series of consultations with stakeholders such as the paraquat pesticide industry, and alternative pesticides, plantation sector, consumer unions, Non-Governmental Organizations (NGOs), academia, public and many more.

B. REVIEW PROCESS

The following were the topic covered in the paraquat registration review conducted:

1. Facts about paraquat
2. Status of paraquat registration in Malaysia
3. International status
4. Assessment of paraquat poisoning cases in Malaysia
5. Evaluation of cases of poisoning and suicide caused by paraquat at the international level
6. Status of paraquat under the Rotterdam Convention
7. Evaluation of alternative pesticides to paraquat
8. Verification of the effectiveness of paraquat and alternative pesticides and demonstration
9. Impact assessment on the agriculture sector
10. Evaluation of the study by CABI/RSPO
11. Evaluation of paraquat study by malaysian palm oil board (MPOB)
12. Evaluation of the opinions of all stakeholders on paraquat

The following were the summary findings of the paraquat registration review process:

1. Facts about paraquat

i. Chemical and Physical Properties

- Paraquat is a type of contact herbicide and non-selective from the bipyridylium group.
- Paraquat salt is white while technical paraquat is yellow. Paraquat resembles a crystalline form and it has no odor.

- Paraquat has the property of being insoluble in organic solvents but slightly soluble in alcohol. Paraquat has no explosive and flammable features. However, paraquat can corrode metals.

ii. Toxicology

- Studies on animals show that paraquat is an acutely toxic pesticide (short period after exposure), with an oral LD50 value of 110-150 mg / kg (in rats). The value of LD50 through the skin is 236-325 mg / kg which indicates that it is quite toxic through the skin.
- Studies on animals show that paraquat will not cause cancer, mutagenic, and effects on the reproductive system of animals
- Effects on humans indicate that spillage of concentrated poisons on the eyes can cause serious irritating effects. Exposure to the skin in turn can cause irritating effects and if this exposure is for a long period of time or chronic, the skin can occur. One of the long - term effects of exposure to paraquat over a long period of time is problems to the nails where the nails will come off or pull out. This situation is common among workers who carry out paraquat spray work on farms, if users do not practice safe use and spraying.
- If ingested, paraquat causes 'burning of the mouth and throat' and is followed by abdominal pain, vomiting, dizziness, fainting and death. Other medium-term effects are shortness of breath, thirst, increased blood pressure, kidney, lung and problems to the liver.
- If inhaled spray mist during use on the farm can cause nasal bleeding.
- Like most other pesticides, paraquat does not has an antidote. This enhances the risk of paraquat which is already highly toxic acutely, where in most cases victims cannot be saved and therefore will die, in case of ingestion.
- According to the WHO Pesticides Classification By Hazard system, technical paraquat is categorized as a 'moderately toxic' or Class II pesticide. According to the Pesticide Board's classification system, all paraquat products are classified as 'highly toxic' or Class Ib. The Pesticide Board classified paraquat under Class Ib instead of Class II (of WHO classification) because after taken into consideration that under local conditions paraquat cannot be used safely due to hot and humid weather making wearing full protective gears not always practical. In addition, pesticide poisoning cases reported yearly indicates that paraquat is the number one pesticide associated with poisoning incidences either due to suicide, accidental and occupational poisoning.
- As a legal requirement under the Pesticide Act 1974, all paraquat products must contain stanching agent and emetic as approved by the Board.

iii. Eco-toxicology

- Studies on birds show paraquat is quite toxic to some species of birds. Acute studies show that, the LD50 value is 981 mg/kg in bobwhite quail and 970 mg/kg in Japanese quail.
- Studies of the effects of toxicity on aquatic organisms show that paraquat is also harmful to most species of aquatic organisms such as rainbow trout, bluegill, and channel catfish. The 90 -hour LC50 value for rainbow trout was 32 mg/L while for brown trout it was 13 mg/L. The LC50 value for aquatic invertebrates is between 1.2 to 4.0 mg/L.

- Other studies show that paraquat has no toxic effects to honey bees.
- Ecological impact risk assessment indicates that paraquat exposure to birds, mammals and other living things may occur as a result of spraying while paraquat is used on the farm. An assessment conducted by the United States Environmental Protection Agency (USEPA), found that in normal use paraquat may have short-term effects on the above animals. Nevertheless, this effect is an effect in a short time after spraying only. This hazardous effect will diminish when the spray becomes dry and when paraquat particles are bound to the soil particles. USEPA therefore concludes that paraquat will not present significant toxic effects to birds or mammals in normal use.

iv. Environmental Fate

- Decomposition studies in soil show that paraquat is persistent, or not easily decomposed in soil. According to one study, the half-life of paraquat in the soil can reach up to 1000 days, i.e. it is able to survive in the soil for up to a long period of time. In another study, the half-life of paraquat was reported to be up to 16 months (under oxygenated conditions).
- Another property of paraquat in soil is the ability of paraquat to bind to clay particles and organic matter. This condition will make the paraquat inactive, therefore will not pose a danger to plants, earthworms and other soil microbial organisms. However, residual paraquat residues bound to soil particles can stay in the soil for a long time, and can be transported to other places through run-offs along with soil sediments. However, due to the ability of paraquat to bind to soil particles and organic matter, it is unlikely to contaminate groundwater. According to a monitoring conducted, out of 721 groundwater samples analyzed in the United States, only one sample was contaminated with paraquat at a level of 20 mg/L.
- Studies of decomposition in water show that paraquat will bind to sediments that float and settle in the aquatic environment. Studies show that the half-life of paraquat in running water in the laboratory is about 13.1 hours. In another study, paraquat dichloride was stable for up to 30 days. In the third study, the half-life of paraquat was 23 weeks.

v. Residue

- Residual paraquat waste in agricultural commodities is not expected to be problematic because paraquat is not sprayed on crops, instead it is sprayed to kill weeds.
- Through the monitoring of pesticide residues conducted by the Department of Agriculture of Malaysia, paraquat was never found in the agricultural commodities analyzed.
- The assessment conducted by the Joint FAO/WHO Meeting on Pesticide Residue (JMPR) has concluded that exposure to paraquat through the intake of residual waste in agricultural commodities is unlikely to affect public health either in the short or long term.

2. Current status of paraquat registration in Malaysia

As of 30 September 2011, there were 42 products containing paraquat have been registered by Pesticide Board. Of these, 28 were ready -to -use products at a concentration of 13% w/w, while another 14 were products for manufacturing purposes only, at a concentration of 42%. The number of registrar companies involved in paraquat registration is 29.

All the registered paraquat products have approved recommendations on oil palm, coconut, rubber, paddy, cocoa, bananas, fruits and vegetables.

3. International status

At the time of review process, paraquat was still registered and used in more than 100 countries. However, some European countries have long banned it such as Sweden (1984), Finland (1986), Switzerland (1989), Denmark (1994), Norway (1991), Austria (1992), Slovenia (1997). and Norway (1993). Reasons for the ban in these countries include the toxic nature of the pesticide as well as its impact on the environment, which they consider to be negative.

The European Union (EU) began banning paraquat in July 2007 for reasons of danger to human health. This means that the use of paraquat was not allowed in 27 EU countries.

In the Asian region, paraquat was banned in 3 countries namely Cambodia (2003), Kuwait and Qatar. For Kuwait and Qatar, the real reason why paraquat was banned in those countries was not clear while for Cambodia, the ban was based on the toxic nature of the pesticide.

For some countries that allow the use of paraquat, some restricted use is imposed to ensure that paraquat is used in a safe manner to avoid negative effects on the health of consumers, non - target organisms and the environment. For example in the USA, the use of paraquat is still allowed but its use must comply with some very strict conditions.

Apart from the USA, countries such as Indonesia, Hungary, Saudi Arabia, South Korea, Chile, Togo and Germany have also imposed conditional use/sale controls which are categorized as ‘restricted pesticides’.

4. Assessment of paraquat poisoning cases in Malaysia

Information related to cases of poisoning caused by chemicals including pesticides in Malaysia is based on information from the Ministry of Health through cases of poisoning referred to government clinics/hospitals only. This means the actual cases of poisoning reported is far greater than this if cases referred to private clinics/hospitals and unreported cases are taken into account.

Based on the information obtained, it was found that a total of 2,426 cases of poisoning have been reported in Malaysia over 12 years from 1997 to 2009. There were approximately 8 types of pesticides that were often involved in reported cases of poisoning as shown in the Table below.

Pesticides/Pesticide Groups	Number of poisoning cases (1997-2009)
1. Paraquat	1082
2. Organophosphates	511
3. Glyphosate	161
4. Carbamates	47
5. Organochlorines	26
6. Pyrethroids	22
7. Thiocarbamates	9
8. Nitrophenols	3
9. Unknown	565
TOTAL	**2,426**

As shown in the Table above, the highest pesticide involved in poisoning cases is paraquat which is 45% (1,082 cases of poisoning) involving at least 272 deaths. This was followed by pesticides of the organophosphates group of 511 cases of poisoning (21%) and glyphosate of 161 cases (6%), however cases of pesticides other than paraquat mostly did not involve death. Cases of pesticides involving groups of carbamates, organochlorines, pyrethroids, thiocarbamates and nitrophenols are low.

Analysis of poisoning data shows that the cause of paraquat poisoning is suicide (suicidal) and followed by accidental drinking and occupational poisoning.

5. Evaluation of cases of poisoning and suicide caused by paraquat at the international level

At the request of the German National Pesticides Authority a few years ago, Syngenta Company conducted a study on poisoning and suicide involving paraquat worldwide until 2003. This report has been made one of the documents published by the International Center For Pesticides And Health Risk Prevention (ICPS) and published in February 2005.

The results of this study indicate that there are many reports that have been published by various countries on the effects of acute poisoning caused by paraquat. However, due to the quality of the referenced report was not complete, the conclusions made in the report by Syngenta stated that the cause of the poisoning occurred could not be determined accurately. What can be seen, the cases that end in death are mostly due to intentional drinking (suicidal intent), although there were also cases of accidental drinking.

Poisoning due to exposure through the skin is quite frequently reported and is mostly due to not wearing appropriate protective clothing and unsafe working methods such as inhaling spray mist or using leaky spray equipment. Among the effects reported was damage to nails and skin as a result of repeated exposure.

The study also recommends that several measures be taken to prevent poisoning from occurring, such as specific preventive measures and training to users.

The recommendations stated in this report need to be examined if they are to be practiced in developing countries such as Malaysia, as they may not be fully complied with due to different circumstances compared to developed countries except with strict and effective implementation of enforcement.

6. Status of paraquat under the Rotterdam Convention

At the international agreement level, at the Chemical Review Committee (CRC) meeting in March 2011, a proposal was made under the Rotterdam Convention that paraquat at a concentration of 200g/liter be specially controlled under this Convention by listing it in Annex III of the Convention, referred to as 'Severely Hazardous Pesticide Formulation'. This is based on evidence showing that paraquat has caused many poisonings and deaths, especially on the African continent. With this listing, the export and import activities of paraquat will be regulated under this Convention to ensure human health and the environment are always taken care of. The proposed listing will be taken to the 'Conference of the Parties' (COP) of the Rotterdam Convention for approval, after all documents related to this listing were prepared by the Rotterdam Convention Secretariat.

7. Evaluation of alternatives to paraquat

In general, at present there are many alternative pesticides that can be used to replace paraquat in all conditions in Malaysia, where the alternatives are already being registered for use in the country. Among the alternative pesticides often used to replace paraquat are glyphosate isopropylamine, glufosinate ammonium, sodium chlorate, metsulfuron methyl, bensulfuron methyl, tryclorpyr, 2,4-D, diuron and fluroxypyr.

It should be noted here that there are farms and big plantations in the country which had long stopped using paraquat and had replaced it with alternative herbicides. This action was taken more than 10 years ago (from the date of the review) and it was reported that the replacement of paraquat with other herbicides did not affect the income of these plantation groups in fact they were still making a profit. The members of Pesticide Board themselves have visited one of the plantations and saw for themselves the situation and were able to hear for themselves the explanation by the farm management about their efforts in alternative weed management practices without paraquat, which was greatly appreciated by the members.

8. Verification of the effectiveness of paraquat and alternative pesticides and demonstration

In assisting the Pesticide Board to make decisions on paraquat, the Department of Agriculture Malaysia has conducted an alternative efficacy study to control weeds in the recommended crop areas. The Alternative to Paraquat Study Committee was formed comprised of members from Malaysia Agricultural Research and Development Institute (MARDI), Cocoa Board, Malaysian Rubber Board, MPOB and the Department of Agriculture. Studies have been conducted for

mango, starfruit, cocoa, rubber, oil palm and vegetables. In this study paraquat herbicides, glufosinate and glyphosate were used for comparative purposes in terms of effectiveness, cost, phytotoxic effects. The study was conducted for the period from 19 May 2010 to March 2011.

The results of the above study were presented at the Pesticide Board in 2011. The findings of the study have summarized the following:

- All three herbicides were effective in controlling weeds on all crops tested.
- All crops tested did not show phytotoxic effects to the three herbicides if used according to the instructions on the label.
- Although all pesticides can control weeds, the control period varies according to the pesticides where the longest control was with glyphosate and followed by ammonium glufosinate.
- After taking into account all the costs involved (pesticides, equipment, manpower, transportation, water and spray frequency) it was concluded that the cost of using glyphosate was the lowest (RM273/ha/year @ USD65/ha/year) and followed by paraquat (RM378/ha/year @ USD90/ha/year) and glufosinate (RM426/ha/year @ USD100/ha/year)

The results of the verification study conducted on the alternative poisons were disseminated to consumers through demonstration plots. Apart from that, the Department of Agriculture has organized a series of briefings to consumers to disseminate information on alternative pesticides that can be used in weed control to replace paraquat.

It is clear from the verification and demonstration study that there are cost effective alternative herbicides to control weeds under all crop conditions in place of paraquat, thus support the argument that the banning of paraquat will not result in negative implication to farms and plantations industry in Malaysia.

9. Impact assessment on the agriculture sector

Based on a study entitled, 'The Economic And Social Impact of A Paraquat Prohibition In Malaysia: A Position Paper' conducted by Intercedent Asia (Asian Consultation & Research) sponsored by Syngenta Malaysia in 2003, the following findings, assumptions and allegations have been formulated with respect to the ban on paraquat:

- Affect the productivity of oil palm, rubber and fruit plantations with an area of about 4.2 million ha if paraquat is not used.

- Increases the effects of soil erosion if paraquat is not used

- Reduction in crop yield up to RM1.16 million per year due to soil erosion

- The cost of weed control will increase to RM1.57 million per year due to weed succession, re-spraying and replacement with more expensive pesticides

- 3-7% annual income decline among rubber, oil palm and fruit smallholders
- The competitiveness of Malaysian palm oil prices is declining compared to competitors from other countries
- Increased incidence of illegal use of paraquat

However, it should be noted that this study was conducted at the request and funding of the industry which may be biased.

10. Evaluation of the study conducted by CABI/RSPO

The Commonwealth Agricultural Bureau International (CABI) conducted a study on the use of pesticides in the oil palm plantation sector in Malaysia on behalf of The Roundtable On Sustainable Oil Palm (RSPO). The purpose of the study was to identify issues related to the use of pesticides in oil palm plantations in Malaysia and to ensure that these issues are given due attention in the RSPO guidelines. One of findings of the study was that paraquat has been identified by the Roundtable on Sustainable Palm Oil (RSPO) as one of the pesticides that cannot be used in oil palm cultivation as it is not consistence with sustainable palm oil cultivation and production.

11. Evaluation of paraquat study by Malaysian Palm Oil Board (MPOB)

The Malaysian Palm Oil Board (MPOB) in collaboration with Universiti Sains Malaysia (USM), Universiti Putra Malaysia (UPM) and several other parties conducted a study on the implication of paraquat banning in Malaysia.

The above study was completed and a report on was received by the Pesticide Board's Secretariat in January 2008. The Technical Committee of the Pesticide Board held a special meeting on 29 January 2008 with MPOB and all researchers involved to review the findings of the above study.

Based on the MPOB report entitled "Paraquat: Impact Of Application In The Malaysian Agriculture Sector", it is clear that the purpose of MPOB conducting this study is to support the efforts of the industry so that paraquat is not banned from use in Malaysia.

The following is a summary of the study and the Pesticide Board's Secretariat comments on the study:

- A total of 15 research papers covering several aspects such as efficacy, health, socio-economics, residues, toxicology and eco-toxicology were reviewed. Agencies and statutory bodies such as Universiti Sains Malaysia, Universiti Putra Malaysia, MARDI, Malaysian Cocoa Board as well as Syarikat Pasaran Informasi (M) Sdn. Bhd. and Chia Meng Yan & Sons Sdn. Bhd. directly involved in carrying out this study.

- The findings of the study are observations that tend and lead to the objective that the use of paraquat should be continued in the agricultural sector, and do not describe or meet a level of scientific research related to the issue of paraquat as a whole.

- All herbicides whether paraquat, glufosinate or glyphosate are effective in controlling weeds. Paraquat, as is well known, is quick to cause of scotching and browning effects , but the 'recovery/regrowth' period of weeds is also relatively fast compared to the longer "regrowth" period if glufosinate and glyphosate are used.

- In the OEL (Operator Exposure Level) study, the findings support the argument that the risk of paraquat exposure to consumers under local conditions is unacceptably high and it was recommended that the use of complete Personal Protective Equipment (PPE) (long sleeves, long pants, face masks, gloves, boots and hats) when handling paraquat products. However, the use of complete PPE is not always practical under hot and humid like Malaysia.

- There are some users who experience signs of paraquat poisoning especially when not using PPE. In addition, it was also found that the type of nozzle used during spraying can influence the exposure to the user.

- There was detection of paraquat at low levels in urine and blood analysis studies in samples taken from several operators who frequently sprayed paraquat.

- The LD50 study conducted clearly shows that paraquat should indeed be classified in the toxicity category of Class Ib pesticide.

12. Evaluation of the opinions of relevant stakeholders on paraquat

The Board Secretariat held two discussions to gather information on alternative pesticides and paraquat from pesticide manufacturing companies and NGOs. The purpose of the discussion was to get their views on paraquat in helping the Board make a decision on the future of paraquat in Malaysia and if the decision made will be agreed by all parties. The discussion in question was held on 12 June and 26 June 2008 and during the session several papers were presented by the invited parties as follows:

- The use of paraquat in dealing with weeds in the agricultural sector. The paper was presented by Syngenta Crop Protection Sdn. Bhd.
- The use of glyphosate in dealing with weed problems in the agricultural sector by Monsanto (Malaysia) Sdn. Bhd.
- The use of ammonium glufosinate in dealing with weed problems in the agricultural sector by Bayer Co. (Malaysia) Sdn. Bhd.
- The use of triclopyr in the pineapple industry by Zeenex Agroscience Sdn. Bhd.
- Effects of pesticide use on humans and the environment paper presented by PANAP, Tenaganita and CAP.

The following were the outcomes of the discussion:

- As expected, the results of the above presentations and discussion showed that every company has its own arguments to defend their products and sometimes they claim that their product is the best when compared to other products.

- On behalf of NGOs, PANAP still maintains that the use of pesticides in agriculture is not in line with the concept of sustainable agriculture because it endangers humans and the environment. With regard to paraquat, they argued that paraquat should be banned because it is not only not in line with the concept of sustainable agriculture but paraquat is known to be a pesticide that is very dangerous to the health of consumers.

- Therefore, the original purpose of the meeting to obtain consensus from all stakeholders in determining a decision that was agreed upon by all to determine the future of paraquat has not been achieved.

C. SUMMARY DECISIONS ON THE FUTURE REGISTRATION OF PARAQUAT

Based on the above review process, the Pesticide Board of Malaysia with the consent from the Cabinet took the decision to phase-out the use of paraquat in stages with the effective date of total banning starts from 1st January 2020. The followings were the basis for the decision:

- The continued registration of paraquat in the country would contribute to the high incident of pesticide poisonings as paraquat has been constantly reported to be the number one pesticide associated with poisonings
- The banning of paraquat is consistence with the principle of precautionary measures, as paraquat has been shown cannot be applied and used safely without complete PPE to prevent exposure under the hot and humid conditions, which is not always feasible in country like Malaysia.
- Currently there are already several herbicides, other than paraquat, that are registered by the Pesticide Board for weed control in all crops situation. These alternative pesticides are comparable to paraquat in terms of efficacy and cost.
- Cost-effectiveness studies showed that glyphosate is the cheapest herbicide followed by paraquat and glufosinate.
- Paraquat is a very highly hazardous to humans and is in the Class Ib (Highly Poisonous) and it has no antidote for treating cases of poisoning.
- Internationally, paraquat (200g/l) will be regulated under the Rotterdam Convention due to reports of frequent cases of poisoning on the African continent.
- Paraquat has been identified by the Roundtable on Sustainable Palm Oil (RSPO) as one of the pesticides that cannot be used in oil palm cultivation as it is not consistence with sustainable palm oil cultivation and production.
- Final analysis shows that risk of paraquat outweighs the benefit.

D. CONCLUSION

Following the above decisions, a circular letter, JP/KRP/207/12/656/2 Jld.VI (54) dated 16 May 2014 was issued out to all concerned parties detailing the phase-out strategies and plans.

E. REFERENCES

1. Statistic on pesticides poisoning cases published by the Ministry of Health, Malaysia
2. Paraquat and Diquat (EHC 39, 1984) http://www.inchem.org/documents/ehc/ehc/ehc39.htm)
3. Paraquat (http://www.inchem.org/documents/pims/chemical/pim399.htm)
4. Paraquat-Extoxnet (http://extoxnet.orst.edu/pips/paraquat.htm)
5. World Compendium – The Pesticides Manual, British Crop Protection Council
6. Final Report to the World Bank on Paraquat and Possible Alternatives, March 1994
7. 'The Economic And Social Impact of A Paraquat Prohibition In Malaysia: A Position Paper' conducted by Intercedent Asia (Asian Consultation & Research) sponsored by Syngenta Malaysia, 2003
8. The WHO Recommended Classification by Hazard
9. Joint FAO/WHO Meeting on Pesticide Residue (JMPR)
10. "Paraquat: Impact Of Application In The Malaysian Agriculture Sector" by Malaysian Palm Oil Board (MPOB), 2008
11. Report on The Roundtable On Sustainable Oil Palm (RSPO) by The Commonwealth Agricultural Bureau International (CABI)
12. Unpublished information and reports

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F. Initiatives Prior Total Banning

Pesticides Board initiated the following regulatory and non-regulatory measures to reduce risks associated with paraquat prior total banning in 2020. These measures include:

1. Paraquat were continued strictly controlled under Highly Toxic Pesticides Regulations, 1996. The rerulations were to deal with the enforcement of safety measures application of certain toxic pesticides including paraquat

2. Conditional registration of paraquat were imposed meaning that only certain criteria were allowed. These include:

- New company is not allowed to apply for new registration.
- Use is limited to only four types of plants – immature oil palm trees, rubber trees, hill padi fields and pineapple stumps.
- Prohibiting advertisement for all uses
- Limiting the size container to 20L only
- Allowed only paraquat concentration 13% w/w for finished product.
- Limiting the sale from registrant, manufacturer and certain authorized Area Farmer Organisation
- Imposed quota of import for company to bring paraquat into the country

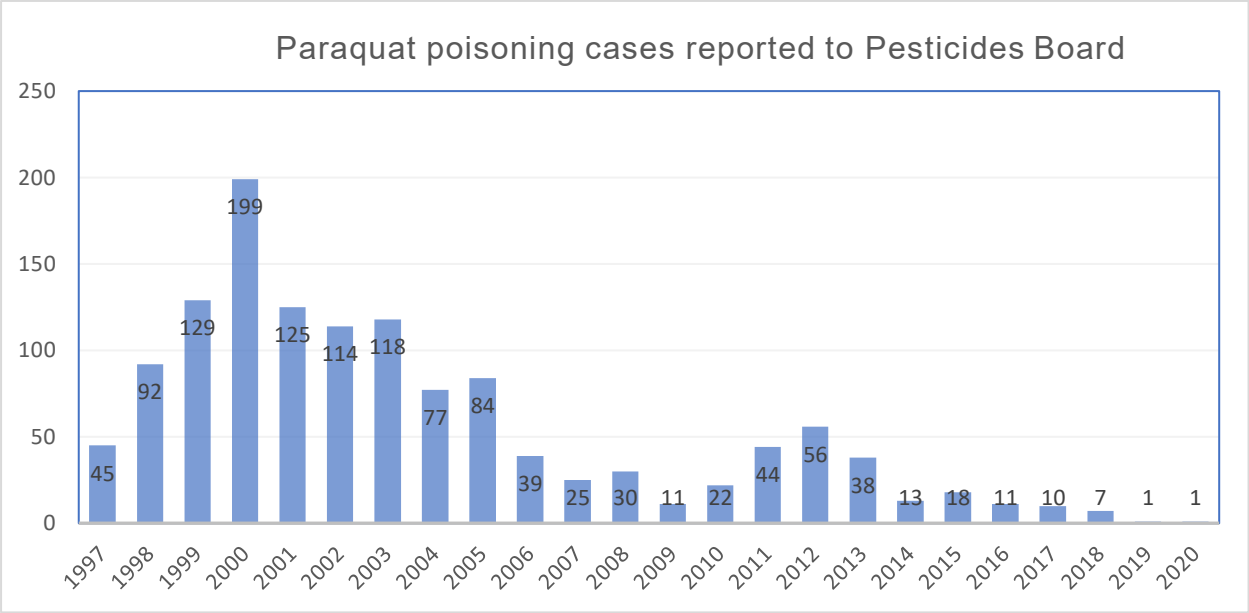
3. Encouraged the registration of new pesticides which posed a lesser risk.

4. Implement an aggressive public outreach campaign on using alternatives of paraquatand promoting more sustainable management of agriculture.

Registered Herbicides Alternatives to Paraquat in Malaysia

1. Glyphosate isopropylammonium
2. Glufosinate ammonium
3. Metsulfuron methyl
4. 2,4-d-dimethylammonium
5. Msm diuron
6. Imazapyr-isopropylammonium
7. Fluroxypyr-meptyl
8. Ametryn
9. Imazathapyr
10. Flumioxazin
11. Aminopyralid potassium + triclopyr butoxyl
12. Sulfentrazone
14. Triclopyr
15. Fluazifop-butil
16. Florpyrauxifen-benzy
17. Pyrazosulfuron-ethyl

Paraquat Poisoning cases reported to Pesticides Board



Although the number of reported cases of poisoning is declining, nonetheless it is believed there are still cases of pesticide poisoning that do not reported.

In addition, the Ministry of Health and the Pesticides Board need to increase collaboration to organize partnership sessions information as well as awareness training to officers from both the agencies as well as the public responsibility for safety and health of workers using the pesticides.

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Ruj. Kami : JP/KRP/207/12/656/2
(Our Ref.) Jld.VI (54)

Tarikh : 16 Mei 2014
(Date)

KEPADA YANG BERKENAAN

Tuan/Puan,

AKTA RACUN MAKHLUK PEROSAK 1974
KEPUTUSAN MENGENAI PENDAFTARAN DAN PENGGUNAAN PARAQUAT DI MALAYSIA

Perkara yang tersebut di atas adalah dirujuk.

2. Seperti yang tuan/puan sedia maklum bahawa Jemaah Menteri pada tahun 2002, telah memutuskan agar paraquat diharamkan penggunaannya di Malaysia kerana sifatnya yang sangat toksik yang telah banyak menyebabkan keracunan dan kematian kepada pengguna. Walaubagaimanapun, setelah diambil kira rayuan daripada pihak industri racun perosak dan beberapa sektor perladangan, Y.B. Menteri Pertanian dan Industri Asas Tani telah memutuskan agar tarikh mula kuatkuasa pengharaman paraquat ditangguhkan bagi membolehkan Kementerian Pertanian dan Industri Asas Tani melalui Jabatan Pertanian dan Lembaga Racun Makhluk Perosak menjalankan kajian semula yang lebih terperinci dari berbagai aspek sebelum satu keputusan muktamad mengenai paraquat dibuat.

3. Dalam tempoh penangguhan pengharaman tersebut, syarat-syarat pendaftaran, penggunaan, penjualan paraquat telah diperketatkan bagi mengurangkan kesan bahaya kepada kesihatan pengguna seperti berikut:-

i. Paraquat dikawal di bawah Peraturan-Peraturan Racun Makhluk Perosak (Racun Makhluk Perosak Amat Berbisa) 1996.

(Sila nyatakan rujukan kami apabila menjawap surat ini)

ii. Hanya paraquat dengan kepekatan rendah sahaja (13%w/w *paraquat dichloride*) boleh didaftarkan dan digunakan. Setiap syarikat pendaftar hanya dibenarkan mendaftar satu jenama produk paraquat sahaja pada kepekatan 13%w/w *paraquat dichloride* dan satu bahan teknikal paraquat pada kepekatan minima 42%w/w.

iii. Pendaftaran produk pracampuran paraquat dengan perawis aktif lain tidak dibenarkan.

iv. Semua keluaran paraquat dimestikan memasukkan ke dalam produk mereka bahan pembusuk (*stenching agent*), pewarna (*colouring agent*) dan bahan pemuntah (*emetic*) yang telah diluluskan oleh Lembaga.

v. Iklan bagi mempromosi penggunaan paraquat tidak lagi dibenarkan.

4. Dalam tempoh kajian semula yang dijalankan dari tahun 2002 hingga 2013, Kementerian Pertanian dan Industri Asas Tani melalui Jabatan Pertanian dan Lembaga Racun Makhluk Perosak telah mengkaji dan meneliti banyak maklumat kajian dan penerbitan berkaitan paraquat dari dalam dan luar negara. Disamping itu, Jabatan Pertanian dengan kerjasama agensi-agensi kerajaan yang berkaitan telah juga menjalankan kajian keberkesanan racun alternatif kepada paraquat. Jabatan Pertanian dan Lembaga juga telah mengadakan beberapa siri konsultasi dengan semua *stakeholder* yang berkepentingan seperti industri racun perosak paraquat, dan racun alternatif, sektor perladangan, kesatuan pengguna, *Non Governmental Organizations* (NGOs), akademia, orang ramai dan lain-lain lagi.

5. Berdasarkan kepada kajian semula yang dijalankan seperti di atas, dan dengan mengambil kira perkembangan mutakhir mengenai kawalan dan pengurusan bahan kimia berbahaya seperti racun perosak secara lestari (yang mengambil kira kepentingan keselamatan makanan, pengguna dan alam sekitar) di peringkat serantau dan antarabangsa, serta trend masa hadapan yang menjurus kearah pengeluaran komoditi pertanian yang selari dengan konsep amalan pertanian baik, maka Lembaga Racun Makhluk Perosak dengan persetujuan Jemaah Menteri telah membuat keputusan agar paraquat diharamkan penggunaannya di Malaysia mulai 1 Januari 2020. Walaubagaimanapun, sehingga tarikh tersebut , pendaftaran dan penggunaan paraquat akan terus dibenarkan, tetapi tertakluk kepada syarat-syarat tambahan seperti di bawah:-

i. Bilangan produk dan syarikat pendaftar paraquat dihadkan kepada bilangan produk dan syarikat yang sedia ada sahaja.

ii. Berkuatkuasa serta merta pertimbangan bagi semua permohonan pendaftaran baru yang sedang diproses akan dihentikan dan tiada permohonan baru diterima.

iii. Produk paraquat berdaftar sedia ada boleh didaftar semula tetapi tarikh sah laku pendaftaran telah ditetapkan supaya tamat pada 1 Januari 2019. Keputusan ini diambil bagi membolehkan semua keluaran paraquat yang berada di pasaran dihabiskan penjualan dan penggunaannya menjelang 2020. Bagi mengelakkan pengimportan dan pengilangan paraquat secara berlebihan sebelum tempoh pendaftaran tamat, Lembaga mungkin akan mengenakan kawalan kuantiti yang diimport dan dikilang, jika perlu.

iv. Paraquat akan dihadkan penggunaannya kepada kawalan rumpai dalam tanaman sawit di bawah umur 2 tahun, tanaman getah, padi bukit dan untuk membunuh tunggul nanas sahaja. Saiz bungkusan (*pack size*) produk paraquat yang dibenarkan akan dihadkan kepada saiz 20 liter sahaja dan bagi gred teknikal untuk tujuan perkilangan 200 liter sahaja. Bagi maksud ini semua syarikat pendaftar dikehendaki mengemukakan draf label secepat mungkin untuk pengesahan Lembaga sebelum 1 Januari 2015, dan selepas tarikh tersebut semua label lama akan dibatalkan.

v. Berkuatkuasa mulai 1 Jun 2015, paraquat hanya boleh dijual oleh dan dibeli dari pendaftar, pengilang dan Pertubuhan Peladang Kawasan. Bermula daripada tarikh yang sama juga, syarat-syarat baru bagi Lesen Menjual/Lesen Menyimpan Untuk Jualan Racun Makhluk Perosak bagi premis-premis lain akan diketatkan di mana paraquat tidak lagi boleh dijual. Satu pekeliling yang berasingan akan dikeluarkan kepada semua premis berlesen yang terlibat bagi memaklumkan perkara ini.

vi. Berkuatkuasa mulai 1 Jun 2015, pembelian paraquat hanya boleh dibuat selepas pengesahan butir-butir permohonan telah dibuat oleh Pegawai Pelesenan di bawah Akta Racun Makhluk Perosak 1974 dan surat kebenaran dikeluarkan untuk pembelian, penggunaan dan tambah stok.

vii. Syarikat-syarikat yang mendaftar paraquat perlu melaksanakan program *Stewardship* dan melaporkan cadangan program serta laporan tahunan kepada Lembaga. Kegagalan syarikat untuk melapor dan melaksana program tersebut boleh mengakibatkan pendaftaran paraquat milik syarikat berkenaan ditarik balik.

Sekian harap maklum.

'ANDA KAMI UTAMAKAN'

'BERKHIDMAT UNTUK NEGARA'

Saya yang menurut perintah,

(HALIMI MAHMUD)
Setiausaha,
Lembaga Racun Makhluk Perosak

s.k.

1. Ketua Pengarah Pertanian (Merangkap Pengerusi Lembaga Racun Makhluk Perosak)
2. Timbalan Ketua Pengarah Pertanian (Operasi) (Merangkap Pengerusi Jawatankuasa Teknikal Lembaga Racun Makhluk Perosak)
3. Ahli-Ahli Lembaga Racun Makhluk Perosak
4. Jawatankuasa Teknikal Lembaga Racun Makhluk Perosak
5. Pengarah Bahagian / Pengarah Pertanian Negeri
6. Pegawai Pelesenan Negeri
7. Malaysian CropLife & Public Health Association (MCPA)

Our Ref.: JP/KRP/207/12/656/2 Jld.VI (54)
Date : 16 May 2014

TO WHOM IT MAY CONCERN,

Sir/Madam,

PESTICIDES ACT 1974
DECISION ON REGISTRATION AND USE OF PARAQUAT IN MALAYSIA

The above matters are referred to.

2. As you are aware, the Cabinet in 2002, decided that paraquat should be banned in Malaysia due to its highly toxic nature which has caused may poisoning and death to consumers. However, after taking into account appeals from the pesticide industry and some plantation sectors, Y.B. The Minister of Agriculture and Agro-based Industry has decided to postpone the effective date of paraquat ban to allow the Ministry of Agriculture and Agro-based Industry through the Department of Agriculture and the Pesticides Board to conduct a more detailed review from various parties before a final decision on paraquat is made.

3. During the period of suspension of the ban, the conditions for registration, use, sale of paraquat have been tightened to reduce the harmful effects on the health of consumers as follows:-

i. Paraquat is regulated under the Pesticides (Highly Poisonous Pesticides) Regulations 1996.
ii. Only low-concentration paraquat (13%w/w *paraquat dichloride*) can be registered and used. Each registrar company is only allowed to register one brand of paraquat product at a concentration of 13% w/w *paraquat dichloride* and one technical ingredient of paraquat at a minimum concentration of 42% w/w.
iii. Registration of paraquat premixed products with other active ingredients is not permitted.
iv. All paraquat products must include in their products stenching agents, coloring agents and emetics that have been approved by the Board.
v. Advertisements to promote the use of paraquat are no longer permitted.

4. During the review period conducted from 2002 to 2013, the Ministry of Agriculture and Agro-based Industry through the Department of Agriculture and the Pesticides Board have reviewed and scrutinized many research information and publications related to paraquat from within and outside the country. In addition, the Agriculture Department in collaboration with relevant government agencies has also conducted studies on the effectiveness of alternative pesticides to paraquat. The Agriculture Department and Board have also held a series of consultations with also stakeholders such as the paraquat pesticide industry, and alternative pesticides, plantation sector, consumer unions, Non-Governmental Organizations (NGOs), academia, public and many more.

5. Based on the review conducted as above, and taking into account the latest developments on the control and management of hazardous chemicals such as pesticides in a sustainable manner (taking into account the importance of food safety, consumer and environment) at the regional and international levels, as well as time trends the Pesticides Board with the consent of the cabinet has decided to ban paraquat in Malaysia from January 1, 2020. However, until that date, registration and use of paraquat will continue to be allowed, but subject to additional conditions as below:-

i. The number of paraquat registered products and companies is limited to the number of existing products and companies only.
ii. Effective immediately consideration of all new registration applications being processed will be discontinued and no new applications will be received.
iii. Existing registered paraquat products can be re-registered but the validity date of registration has been set to expire on 1 January 2019. This decision was taken to enable all paraquat products on the market to be sold and used by 2020. To avoid excessive importation and manufacturing of paraquat before the registration period expires, the Board may impose controls on the quantity imported and manufactured, if necessary.
iv. Paraquat will be restricted to weed control in oil palm crops under years of age, rubber crops, hill paddy and to kill pineapple stumps only. The pack size of paraquat products allowed will be limited to 20 liters only and for technical grade for manufacturing purposes only 200 liters. For this purpose, all registrar companies are required to submit draft labels as soon as possible for Board approval before 1 January 2015, and after that date, all old labels will be cancelled.
v. Effective June 1, 2015, paraquat can only be sold by and purchased from registrars, manufacturers and area farmer's organizations. Starting from the same date, the new conditions for selling licenses/storage licenses for the sale of pesticides for other premises will be tightened where paraquat can no longer be sold. A separate circular will be issued to all licensed premises involved to inform this.
vi. Effective June 1, 2015, the purchase of paraquat can only be made after confirmation of the details of the application has been made by the Licensing Officer under the Pesticides Act 1974 and a letter of permission is issued for purchase, use and stock replenishment.
vii. Companies that register paraquat are required to implement a Stewardship program and report program proposals as well as annual reports to the Board. The company's failure to report and implement the program may result in the company's registration of paraquat being revoked.

Thank you.

Our Ref.: JP/KRP/207/12/656/2 Jld.VI (54)

‘ANDA KAMI UTAMAKAN’

‘BERKHIDMAT UNTUK NEGARA’

Your sincerely,

(HALIMI MAHMUD)

Secretary of the Pesticide Board.

_Cc:

1. Director General of Agriculture (Cum Chairman of the Pesticide Board)
2. Deputy Director General of Agriculture (Operations) (Cum Chairman of the Technical Committee of the Pesticide Board)
3. Members of the Pesticide Board
4. Technical Committee of the Pesticide Board
5. Division Director/State Agriculture Director
6. State Licensing Officer
7. Malaysian CropLife & Public Health Association (MCPA)

FAO SPECIFICATIONS AND EVALUATIONS FOR AGRICULTURAL PESTICIDES

PARAQUAT DICHLORIDE[1]

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

FOOD AND AGRICULTURE ORGANIZATION of THE UNITED NATIONS

[1] Paraquat is the ISO common name for the 1,1'-dimethyl-4,4'-bipyridyldinium dication.

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PARAQUAT DICHLORIDE

Disclaimer[1]

FAO specifications are developed with the basic objective of promoting, as far as practicable, the manufacture, distribution and use of pesticides that meet basic quality requirements.

Compliance with the specifications does not constitute an endorsement or warranty of the fitness of a particular pesticide for a particular purpose, including its suitability for the control of any given pest, or its suitability for use in a particular area. Owing to the complexity of the problems involved, the suitability of pesticides for a particular purpose and the content of the labelling instructions must be decided at the national or provincial level.

Furthermore, pesticides which are manufactured to comply with these specifications are not exempted from any safety regulation or other legal or administrative provision applicable to their manufacture, sale, transportation, storage, handling, preparation and/or use.

FAO disclaims any and all liability for any injury, death, loss, damage or other prejudice of any kind that may be arise as a result of, or in connection with, the manufacture, sale, transportation, storage, handling, preparation and/or use of pesticides which are found, or are claimed, to have been manufactured to comply with these specifications.

Additionally, FAO wishes to alert users to the fact that improper storage, handling, preparation and/or use of pesticides can result in either a lowering or complete loss of safety and/or efficacy.

FAO is not responsible, and does not accept any liability, for the testing of pesticides for compliance with the specifications, nor for any methods recommended and/or used for testing compliance. As a result, FAO does not in any way warrant or represent that any pesticide claimed to comply with a FAO specification actually does so.

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[1] This disclaimer applies to all specifications published by FAO.

INTRODUCTION

FAO establishes and publishes specifications* for technical material and related formulations of agricultural pesticides, with the objective that these specifications may be used to provide an international point of reference against which products can be judged either for regulatory purposes or in commercial dealings.

From 1999, the development of FAO specifications has followed the **New Procedure**, subsequently described in the 1st edition of "Manual for Development and Use of FAO and WHO Specifications for Pesticides" (2002) and amended with the supplement of this manual (2006), which is available only on the internet through the FAO and WHO web sites. This **New Procedure** follows a formal and transparent evaluation process. It describes the minimum data package, the procedure and evaluation applied by FAO and the Experts of the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS). [Note: prior to 2002, the Experts were of the FAO Panel of Experts on Pesticide Specifications, Registration Requirements, Application Standards and Prior Informed Consent, which now forms part of the JMPS, rather than the JMPS.]

FAO Specifications now only apply to products for which the technical materials have been evaluated. Consequently from the year 2000 onwards the publication of FAO specifications under the **New Procedure** has changed. Every specification consists now of two parts, namely the specifications and the evaluation report(s):

Part One: **The Specification** of the technical material and the related formulations of the pesticide in accordance with chapters 4 to 9 of the "Manual on development and use of FAO and WHO specifications for pesticides".

Part Two: **The Evaluation Report(s)** of the pesticide, reflecting the evaluation of the data package carried out by FAO and the JMPS. The data are provided by the manufacturer(s) according to the requirements of chapter 3 of the "FAO/WHO Manual on Pesticide Specifications" and supported by other information sources. The Evaluation Report includes the name(s) of the manufacturer(s) whose technical material has been evaluated. Evaluation reports on specifications developed subsequently to the original set of specifications are added in a chronological order to this report.

FAO specifications developed under the **New Procedure** do not necessarily apply to nominally similar products of other manufacturer(s), nor to those where the active ingredient is produced by other routes of manufacture. FAO has the possibility to extend the scope of the specifications to similar products but only when the JMPS has been satisfied that the additional products are equivalent to that which formed the basis of the reference specification.

Specifications bear the date (month and year) of publication of the current version. Dates of publication of the earlier versions, if any, are identified in a footnote. Evaluations bear the date (year) of the meeting at which the recommendations were made by the JMPS.

* NOTE: publications are available on the internet at http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/en/

PART ONE

SPECIFICATIONS

PARAQUAT DICHLORIDE

PARAQUAT DICHLORIDE

INFORMATION

Common name (dication):

paraquat (E-ISO, (m)F-ISO, BSI, ANSI, WSSA, JMAF)

Synonyms:

methyl viologen

Chemical names:

dication -
IUPAC, 1,1'-dimethyl-4,4'-bipyridinium [1]
CA, 1,1'-dimethyl-4,4'-bipyridinium

dichloride -
IUPAC, 1,1'-dimethyl-4,4'-bipyridinium dichloride [1]
CA, 1,1'-dimethyl-4,4'-bipyridinium dichloride

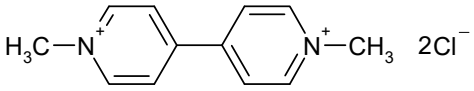
CAS No:

1910-42-5 (dichloride); 4685-14-7 (dication)

CIPAC No:

56 (dication); 56.302 (dichloride)

Structural formula (dichloride):



Molecular formula:

$C_{12}H_{14}Cl_2N_2$ (dichloride); $C_{12}H_{14}N_2$ (dication)

Relative molecular mass:

257.2 (dichloride); 186.3 (dication)

Identity tests (CIPAC G 56/SL/M-):
HPLC retention time; UV spectrum; addition of alkaline sodium dithionite to a dilute solution, where a blue colour indicates the presence of paraquat. The presence of the dichloride salt is tested with silver nitrate solution or, in the presence or absence of diquat dibromide, by capillary electrophoresis.

[1] The IUPAC name for the bipyridinium moiety is alternatively expressed as “bipyridinediium” or “bipyridilium”.

PARAQUAT DICHLORIDE TECHNICAL CONCENTRATE (Note 1)

FAO Specification 56.302/TK (2003*)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose name is listed in the evaluation report (*56.302/2003*). It should be applicable to TK produced by this manufacturer but it is not an endorsement of those products, nor a guarantee that they comply with the specifications. The specification may not be appropriate for TK produced by other manufacturers. The evaluation report (*56.302/2003*), as PART TWO, forms an integral part of this publication.*

1 Description

The material shall consist of paraquat dichloride, together with related manufacturing impurities, in the form of an aqueous solution , free from visible extraneous matter, and must contain an effective emetic (Note 2). The material may also include colorants and olefactory alerting agents.

2 Active ingredient

2.1 **Identity tests** (56/SL/M/2, CIPAC Handbook G, p.128, 1995)

The active ingredient (paraquat and chloride, Note 3) shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Paraquat dichloride content** (56/SL/M/3, CIPAC Handbook E, p.167, 1993)

The paraquat dichloride content (Note 4) shall be declared (not less than 500 g/l at 20 ± 2ºC, Note 5) and, when determined, the average measured content shall not differ from that declared by more than ± 25 g/l.

3 Relevant impurities

3.1 **Free 4,4'-bipyridyl** (56/13/M/7.4, CIPAC Handbook 1A, p.1317, 1980)

Maximum: 1.0 g/kg (1000 ppm).

3.2 **Total terpyridines** (Note 6)

Maximum: 0.001 g/kg (1.0 ppm).

4 Physical properties

4.1 **pH range** (MT 75.3, CIPAC Handbook J, p. 131, 2000) (Note 1)

pH range: 2.0 to 6.0.

Note 1 The product must not be allowed to come into direct contact with metal. Containers may be manufactured from suitable polymeric materials or metal and must comply with pertinent national and international transport and safety regulations. If metal is used, containers must be lined with suitable polymeric material, or the internal surfaces treated to prevent corrosion of the container and/or deterioration of the contents.

Note 2 An effective emetic, having the following characteristics, must be incorporated into the TK.

— It must be rapidly absorbed (more rapidly than paraquat) and be quick acting. Emesis must occur in about half an hour in at least 50% of cases.
— It must be an effective (strong) stimulant of the emetic centre of the brain, to produce effective emesis. The emetic effect should have a limited 'action period', of about two to three hours, to allow effective treatment of poisoning.
— It must act centrally on the emetic centre in the brain.
— It must not be a gastric irritant because, as paraquat is itself an irritant, this could potentiate the toxicity of paraquat.
— It must be toxicologically acceptable. It must have a short half-life in the body (to comply with the need for a limited action period).
- It must be compatible with, and stable in, the paraquat formulation and not affect the herbicidal efficacy or occupational use of the product.

To date, the only compound found to meet these requirements is 2-amino-4,5-dihydro-6-methyl-4-propyl-*s*-triazole-(1,5*a*)pyrimidin-5-one (PP796). PP796 must be present in the TK at not less than 0.8 g/l.

The method for determination of PP796 content can be downloaded here:

Note 3 Chloride in paraquat dichloride TK may be identified by means of the white precipitate produced on reaction of a solution of the TK with silver nitrate solution. Alternatively or in addition, the method for identification of chloride in mixed formulations of diquat dibromide and paraquat dichloride may be used. This method can be downloaded here:

Note 4 To obtain the paraquat dichloride content, multiply the paraquat ion content (as determined by CIPAC method 56/SL/M/3) by 1.38.

Note 5 The lower limit of 500 g/l corresponds nominally to 442 g/kg and thus the tolerance of ± 25 g/l corresponds to ± 5% on a g/kg basis. If, in a particular case, the declared concentration exceeds 566 g/l (>500 g/kg), the tolerance shall be ± 25 g/kg, not ± 25 g/l (± 22 g/kg). If the buyer requires specification of both g/l at 20°C and g/kg, then in case of dispute the analytical results shall be calculated as g/kg.

Note 6 The method for determination of total terpyridines in technical and formulated paraquat dichloride is available from CIPAC at http://www.cipac.org/lnpub.htm.

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* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/en/ .

PARAQUAT DICHLORIDE SOLUBLE CONCENTRATE (Notes 1, 2 and 3)

FAO specification 56.302/SL (February 2008*)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose names is listed in the evaluation report (*56.302/2003*). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only TK from the evaluated source. The specification is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use TK from other sources. The evaluation report (*56.302/2003*), as PART TWO, forms an integral part of this publication.*

1 Description

The material shall consist of technical paraquat dichloride, complying with the requirements of FAO specification 56.302/TK (2003), in the form of an aqueous solution (Notes 1 and 3), together with any other necessary formulants, and must contain an effective emetic (Note 2). The material may also include colorants, olefactory alerting agents and thickeners. It shall contain not more than a trace of suspended matter, immiscible solvents and sediment.

2 Active ingredient

2.1 **Identity tests** (56/SL/M/2, CIPAC Handbook G, p.128, 1995)

The active ingredient (paraquat and chloride components, Note 4) shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Paraquat dichloride content** (56/SL, CIPAC Handbook E, p.167, 1993, Note 2)

The paraquat dichloride content (Note 5) shall be declared (g/kg and/or g/l at 20 ± 2ºC, Note 6) and, when determined, the average content measured shall not differ from that declared by more than the following tolerances.

Declared content, g/kg or g/l at 20 ± 2ºC	Permitted tolerance
25 up to 100	± 10% of the declared content
Above 100 up to 250	± 6% of the declared content
Above 250 up to 500	± 5% of the declared content
Note: the upper limit is included in each range.	

3 Relevant impurities

3.1 **Free 4,4'-bipyridyl** (56/13/M/7.4, CIPAC 1A, p.1317, 1980)

Maximum: 1 g/kg (1000 ppm).

* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/en/

3.2 **Total terpyridines** (Note 7)

Maximum: 0.001 g/kg (1.0 ppm).

4 Physical properties

4.1 **pH range** (MT 75.3, CIPAC Handbook J, p. 131, 2000)

pH range: 4.0 to 8.0.

4.2 **Solution stability** (MT 41, CIPAC Handbook F, p. 131, 1995)

The formulation, after the stability test at 54°C (see 5.2) and following dilution (Note 8) with CIPAC standard water D and standing at 30 ± 2°C for 18 h, shall give a clear or opalescent solution, free from more than a trace of sediment and visible solid particles. Any visible sediment or particles produced shall pass through a 45 μm test sieve (Note 9).

4.3 **Persistent foam** (MT 47.2, CIPAC Handbook F, p. 152, 1995) (Note 10)

Maximum: 60 ml after one minute.

5 Storage stability

5.1 **Stability at 0°C** (MT 39.3, CIPAC Handbook J, p. 126, 2000)

After storage at 0 ± 2ºC for 7 days, the volume of solid and/or liquid which separates shall not be more than 0.3 ml.

5.2 **Stability at elevated temperature** (MT 46.3, CIPAC Handbook J, p.128, 2000)

After storage at 54 ± 2ºC for 14 days, the determined average active ingredient content must not be lower than 97%, relative to the determined average content found before storage (Note 11), and the product shall continue to comply with the clause for:

- pH range (4.1).

Note 1 An effective emetic, having the following characteristics, must be incorporated into the SL.

- It must be rapidly absorbed (more rapidly than paraquat) and be quick acting. Emesis must occur in about half an hour in at least 50% of cases.
- It must be an effective (strong) stimulant of the emetic centre of the brain, to produce effective emesis. The emetic effect should have a limited 'action period', of about two to three hours, to allow effective treatment of poisoning.
- It must act centrally on the emetic centre in the brain.
- It must not be a gastric irritant because, as paraquat is itself an irritant, this could potentiate the toxicity of paraquat.
- It must be toxicologically acceptable. It must have a short half-life in the body (to comply with the need for a limited action period).
- It must be compatible with, and stable in, the paraquat formulation and not affect the herbicidal efficacy or occupational use of the product.

To date, the only compound found to meet these requirements is 2-amino-4,5-dihydro-6-methyl-4-propyl-*s*-triazole-(1,5*a*)pyrimidin-5-one (PP796). PP796 must be present in the SL at not less than 0.23% of the paraquat ion content.

The method for determination of PP796 content can be downloaded here:

Note 2 FAO specifications 55/SL and 56/SL are applied to mixed SL formulations, containing both paraquat and diquat. Emetic is added to all formulations containing paraquat and the extra precautions required for handling solutions of paraquat must be observed when handling the mixed formulation. If the SL contains both diquat and paraquat, CIPAC method 55+56/SL/M/3 (CIPAC Handbook E, p.75, 1993) should be used for determination of active ingredient content.

Note 3 The product must not be allowed to come into direct contact with metal. Containers may be manufactured from suitable polymeric materials or metal and must comply with pertinent national and international transport and safety regulations. If metal is used, containers must be lined with suitable polymeric material, or the internal surfaces treated to prevent corrosion of the container and/or deterioration of the contents.

Note 4 Chloride in paraquat dichloride SL may be identified by means of the white precipitate produced on reaction with silver nitrate solution. Alternatively or in addition, the method for identification of bromide and chloride in mixed formulations of diquat dibromide and paraquat dichloride may be used. This method can be downloaded here:

Note 5 To obtain the paraquat dichloride content, multiply the paraquat ion content (as determined by CIPAC method 55/SL/M/3) by 1.38.

Note 6 If the buyer requires specification of both g/l at 20°C and g/kg, then in case of dispute the analytical results shall be calculated as g/kg.

Note 7 The method for determination of total terpyridines in technical and formulated paraquat dichloride is available from CIPAC at http://www.cipac.org/lnpub.htm.

Note 8 The concentration for the test should not be higher than the highest concentration recommended for use.

Note 9 Some formulations containing additional wetter may show signs of layering and produce a trace of oily precipitate under the test conditions defined in MT 41. This is acceptable and does not affect biological efficacy or spray characteristics at normal spray dilution.

Note 10 The mass of sample used in the test should correspond to the highest concentration recommended for use.

Note 11 Samples of the product taken before and after the storage stability test should be analyzed concurrently after the test to reduce the analytical error.

PARAQUAT DICHLORIDE WATER SOLUBLE GRANULES (Note 1)

FAO Specification 56.302/SG (February 2008*)

*This specification, which is PART ONE of this publication, is based on an evaluation of data submitted by the manufacturer whose names is listed in the evaluation report (*56.302/2003*). It should be applicable to relevant products of this manufacturer, and those of any other formulators who use only TK from the evaluated source. The specification is not an endorsement of those products, nor a guarantee that they comply with the specification. The specification may not be appropriate for the products of other manufacturers who use TK from other sources. The evaluation report (*56.302/2003*), as PART TWO, forms an integral part of this publication.*

1 Description

The material shall consist of granules containing technical paraquat dichloride complying with the requirements of the FAO specification 56.302/TK (2003) and suitable carriers, if required, and it must contain an effective emetic (Note 2). The material may also contain colorants and olefactory alerting agents. It shall be homogeneous, free from visible extraneous matter and/or hard lumps, free flowing, and nearly dust-free. Insoluble carriers and formulants shall not interfere with compliance with clause 4.2.

2 Active ingredient

2.1 **Identity tests** (56/SL/M/2, CIPAC Handbook G, p.128, 1995)

The active ingredient (paraquat and chloride components, Note 3) shall comply with an identity test and, where the identity remains in doubt, shall comply with at least one additional test.

2.2 **Paraquat dichloride content** (55+56/SG/M/4, CIPAC Handbook E, p.78, 1993)

The paraquat dichloride content (Note 4) shall be declared (g/kg) and, when determined, the content measured shall not differ from that declared by more than the following:

Declared content, g/kg	Permitted tolerance
25 up to 100	± 10% of the declared content
Above 100 up to 250	± 6% of the declared content
Note: the upper limit is included in each range.	

3 Relevant impurities

3.1 **Free 4,4'-bipyridyl** (56/13/M/7.4, CIPAC Handbook 1A, p.1317, 1980)

Maximum: 1.0 g/kg (1000 ppm).

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* Specifications may be revised and/or additional evaluations may be undertaken. Ensure the use of current versions by checking at: http://www.fao.org/agriculture/crops/core-themes/theme/pests/jmps/en/ .

3.2 **Total terpyridines** (Note 5)

Maximum: 0.001 g/kg (1.0 ppm).

4 Physical properties

4.1 **pH range** (MT 75.3, CIPAC Handbook J, p. 131, 2000) (Note 1)

pH range of a 1% w/v dispersion: 6.0 to 8.0.

4.2 **Degree of dissolution and solution stability** (MT 179, CIPAC Handbook H, p.307, 1998)

Residue of formulation retained on a 75 µm test sieve after dissolution in CIPAC Standard Water D at 30 ± 2°C.

Maximum: 2% after 5 minutes.

Maximum: 2% after 18 hours.

4.3 **Persistent foam** (MT 47.2, CIPAC Handbook F, p. 152, 1995) (Note 6)

Maximum: 30 ml after 1 minute.

4.4 **Dustiness** (MT 171, CIPAC Handbook F, p.425, 1995) (Note 7)

Nearly dust-free, with a maximum of 1 mg (0.0033% by weight) dust collected by the gravimetric method.

4.5 **Flowability** (MT 172, CIPAC Handbook F, p.430, 1995)

At least 98% of the formulation shall pass through a 5 mm test sieve after 20 drops of the sieve.

4.6 **Attrition resistance** (MT 178.2, CIPAC Handbook K, p.140, 2003)

Minimum 99.5% attrition resistance.

5 Storage stability

5.1 **Stability at elevated temperatures** (MT 46.3, CIPAC Handbook J, p.128, 2000)

After storage at 54 ± 2°C for 14 days the determined average active ingredient content shall not be lower than 97% relative to the determined average content found before storage (Note 8) and the formulation shall continue to comply with the clauses for:

- pH range (4.1),
- degree of dissolution and solution stability (4.2),
- dustiness (4.4),
- flowability (4.5),
- attrition resistance (4.6).

Note 1 Containers may be manufactured from suitable polymeric materials or metal, and must comply with pertinent national and international transport and safety requirements. Where metal is used containers shall be lined with suitable polymeric material, or the internal surfaces treated to prevent corrosion of the container and/or deterioration of the contents. The product must not be allowed to come into direct contact with metal.

Note 2 An effective emetic, having the following characteristics, must be incorporated into the SG.

- It must be rapidly absorbed (more rapidly than paraquat) and be quick acting. Emesis must occur in about half an hour in at least 50% of cases.
- It must be an effective (strong) stimulant of the emetic centre of the brain, to produce effective emesis. The emetic effect should have a limited 'action period', of about two to three hours, to allow effective treatment of poisoning.
- It must act centrally on the emetic centre in the brain.
- It must not be a gastric irritant because, as paraquat is itself an irritant, this could potentiate the toxicity of paraquat.
- It must be toxicologically acceptable. It must have a short half-life in the body (to comply with the need for a limited action period).
- It must be compatible with, and stable in, the paraquat formulation and not affect the herbicidal efficacy or occupational use of the product.

To date, the only compound found to meet these requirements is 2-amino-4,5-dihydro-6-methyl-4-propyl-*s*-triazole-(1,5*a*)pyrimidin-5-one (PP796). PP796 must be present in the SG at not less than 0.23% of the paraquat ion content. The method for determination of PP796 content can be downloaded here:

Note 3 Chloride in paraquat dichloride SG may be identified by means of the white precipitate produced on reaction of a solution of the SG with silver nitrate solution. Alternatively or in addition, the method for identification of chloride in mixed formulations of diquat dibromide and paraquat dichloride may be used. This method can be downloaded here:

Note 4 To obtain the paraquat dichloride content, multiply the paraquat ion content (as determined by CIPAC method 55+56/SG/M/4) by 1.38.

Note 5 The method for determination of total terpyridines in technical and formulated paraquat dichloride is available from CIPAC at http://www.cipac.org/lnpub.htm.

Note 6 The mass of sample to be used in the test should correspond to the highest concentration recommended for use by the supplier. The test is to be conducted in CIPAC standard water D.

Note 7 The optical method, MT 171, would not give reliable values for dust at levels around the specified limit and should therefore not be used.

Note 8 Samples of the formulation taken before and after the storage stability test should be analyzed concurrently after the test in order to reduce the analytical error.

PART TWO

EVALUATION REPORTS

PARAQUAT

PARAQUAT

FAO EVALUATION REPORT 56.302/2003

Explanation

The data for paraquat dichloride were evaluated in support of a review of existing FAO specifications (AGP:CP/344, Rome,1996).

Paraquat dichloride is not under patent.

Paraquat was reviewed by the World Health Organization (WHO) and the United Nations Environment Programme (UNEP) in 1983, resulting in the publication of Environmental Health Criteria 39 (WHO, 1984), and by the International Programme on Chemical Safety (IPCS, 1991), resulting in IPCS Health & Safety Guide No 51. Paraquat was reviewed by the FAO/WHO Joint Meeting on Pesticide Residues (JMPR) in 1986 and was scheduled for periodic re-evaluation in 2003. It has been evaluated by US EPA (USEPA, 1996) and is currently under evaluation by the European Commission.

The draft specification and the supporting data were provided by Syngenta Crop Protection AG, in 2002.

Uses

Paraquat dichloride is a non-selective contact herbicide, which is absorbed by foliage, with some translocation in the xylem. It is used in broad-spectrum control of broad-leaved weeds and grasses, in a wide range of agricultural applications, for general weed control on non-crop land and also for pasture restoration.

Identity

Common name (dication):

paraquat (E-ISO, (m)F-ISO, BSI, ANSI, WSSA, JMAF)

Synonyms:

methyl viologen

Chemical names:

dication -
IUPAC, 1,1'-dimethyl-4,4'-bipyridinium [1]
CA, 1,1'-dimethyl-4,4'-bipyridinium

dichloride -
IUPAC, 1,1'-dimethyl-4,4'-bipyridinium dichloride [1]
CA, 1,1'-dimethyl-4,4'-bipyridinium dichloride

CAS No:

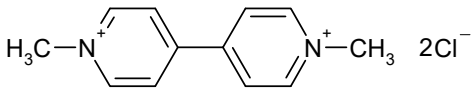
1910-42-5 (dichloride); 4685-14-7 (dication)

CIPAC No:

56 (dication); 56.302 (dichloride)

[1] The IUPAC name for the bipyridinium moiety is alternatively expressed as “bipyridinediium” or “bipyridilium”.

Structural formula (dichloride):



Molecular formula:

$C_{12}H_{14}Cl_2N_2$ (dichloride); $C_{12}H_{14}N_2$ (dication)

Relative molecular mass:

257.2 (dichloride); 186.3 (dication)

Identity tests (CIPAC G 56/SL/M-):

HPLC retention time; UV spectrum; addition of alkaline sodium dithionite to a dilute solution, where a blue colour indicates the presence of paraquat. The presence of the dichloride salt is tested with silver nitrate solution or, in the presence or absence of diquat dibromide, by capillary electrophoresis.

Physicochemical properties

Table 1. Physicochemical properties of pure paraquat dichloride

Parameter	Value(s) and conditions	Purity %	Method reference
Vapour pressure	<<1x10-8kPa at 25ºC (extrapolated)	99.5	OECD 104
Melting point, boiling point and/or temperature of decomposition	Melting point: >400ºC Boiling point: not applicable Decomposition temperature: 340ºC	99.5	OECD 102
Solubility in water	620g/l at 20 °C across pH range	99.5	OECD 105 (flask method)
Octanol/water partition coefficient	log P_{ow} = -4.5 at 20ºC	99.5	OECD 107 (flask method)
Hydrolysis characteristics	Paraquat dichloride is hydrolytically stable under acidic, neutral and alkaline conditions, no significant decrease in concentration having been recorded at pH 5, 7 and 9 after 30days at 25ºC and 40ºC.	Not stated	Analysis of sterile aqueous buffer solutions containing known amounts of paraquat dichloride before and after storage.
Photolysis characteristics	The environmental half-life of paraquat dichloride in water under mid-European conditions was calculated to be between 2 and 820 years, depending upon seasonal sunlight and depth of water.	99.7	Measurement of molar extinction coefficients and quantum yield, then these data used in the Frank and Klöpffer model to obtain an estimate of half-life.
Dissociation characteristics	In aqueous solution the paraquat dichloride is completely dissociated.	Not applicable	-

Table 2. Chemical composition and properties of paraquat dichloride (TK)

Manufacturing process, maximum limits for impurities ≥ 1 g/kg, 5 batch analysis data	Confidential information supplied and held on file by FAO. Mass balances were 98.1-99.3% and percentages of unknowns were 1.9-0.7%.
Declared minimum paraquat dichloride content	500 g/l (442 g/kg).
Relevant impurities ≥ 1 g/kg and maximum limits for them	4,4 bipyridyl, 1 g/kg (1000 ppm).
Relevant impurities < 1 g/kg and maximum limits for them	Total terpyridines 0.001 g/kg (1.0 ppm)
Stabilisers or other additives and maximum limits for them	An effective emetic (reference to effective emetic criteria) – see below. PP796, 2-amino-4,5-dihydro-6-methyl-4-propyl-s-triazole-[1,5-a]pyrimidin-5-one is the only emetic known to meet these effective emetic criteria. If PP796 is the effective emetic employed, it must be present at a minimum level of 0.23% by weight of the paraquat ion content[0.17% on a paraquat dichloride basis]
Melting or boiling temperature range	340°C, at which decomposition occurs

Criteria for effective emesis.

- The emetic must be rapidly absorbed (more rapidly than paraquat) and be quick acting. Emesis must occur in about half an hour in at least 50% of cases.
- The emetic must be an effective (strong) stimulant of the emetic centre, to produce effective emesis. The emetic effect should have a limited “action period” of about two to three hours, to allow effective treatment of poisoning.
- The emetic must be act centrally on the emetic centre in the brain.
- The emetic must be not be a gastric irritant because, as paraquat is itself an irritant, this could potentiate the toxicity of paraquat.
- The emetic must be toxicologically acceptable. It must have a short half-life in the body (to comply with the need for a limited action period).
- The emetic must be compatible with, and stable in, the paraquat formulation and not affect the herbicidal efficacy or occupational use of the product.

Toxicological summaries

Notes. (i) The proposer confirmed that the toxicological and ecotoxicological data included in the summary below were derived from paraquat dichloride having impurity profiles similar to those referred to in the table above.
(ii) The conclusions expressed in the summary below are those of the proposer, unless otherwise specified.

Table 3. Toxicology profile of paraquat dichloride TK, based on acute toxicity, irritation and sensitization

Species	Test	Duration and conditions or guideline adopted	Result (paraquat dichloride technical / paraquat cation).
Rat, Alpk:ApfSD, male	oral	OECD 401, 14 day observation	MLD = 344 [246 – 457] mg paraquat dichloride technical/kg bw, equivalent to 113.5 mg/kg bw expressed as paraquat cation.
Rat, Alpk:ApfSD, female	oral	OECD 401, 14 day observation	MLD = 283 [182 – 469] mg paraquat dichloride technical/kg bw, equivalent to 93.4 mg/kg bw expressed as paraquat cation.

Table 3. Toxicology profile of paraquat dichloride TK, based on acute toxicity, irritation and sensitization

Species	Test	Duration and conditions or guideline adopted	Result (paraquat dichloride technical / paraquat cation).
Rat, Alpk:ApfSD, male and female	dermal	OECD 402, 24 hour, occluded, 14 day observation	MLD = >2000 mg paraquat dichloride technical/kg bw equivalent to >660 mg/kg bw expressed as paraquat cation.
Rat, Alpk:Ap, male and female	inhalation	OECD 403, 4 hour nose only*, 14 day observation	LC_{50} = 0.83 – 1.93 mg/m^3 expressed as paraquat cation.
Rabbit, New Zealand White, female	skin irritation	OECD 404, 4 hour, occluded, 34 day, observation	Slight but persistent skin irritant.
Rabbit, New Zealand White, female	eye irritation	OECD 405, 28 day observation	Persistent, moderate to severe irritant to the rabbit eye [Class 5 on a 1-8 scale].
Guinea pigs, Dunkin Hartley, female	skin sensitization	OECD 406, Magnusson and Kligman maximization test, 24 hour, occluded, 48 hour observation	Negative, not a skin sensitizer.

* Paraquat dichloride is non-volatile and formulations containing paraquat are not applied through equipment which will generate a significant proportion (>1% w/w) of spray droplets of diameter less than 50 µm. Therefore, respirable vapour or droplets of paraquat dichloride will not be produced in practice and these toxicity data are not relevant to assessment of human risks.

Table 4. Toxicology profile of paraquat TK, based on repeated administration (sub-acute to chronic)

Species	Test	Duration and conditions or guideline adopted	Result
Rabbit, New Zealand White, male and female	Short-term dermal toxicity	21-day dermal toxicity	NOEL = 1.57 mg paraquat dichloride/kg bw/day equivalent to 1.15 mg/kg bw/day, expressed as paraquat cation. LOEL = 3.61 mg paraquat dichloride /kg bw/day, equivalent to 2.6 mg/kg bw/day, expressed as paraquat ion.
Mouse, ICR-CRJ SPF, male and female	Short-term toxicity	13-week dietary	NOEL = 100 ppm, equivalent to approximately 12 and 14 mg/kg bw/day, expressed as paraquat ion in males and females, respectively. LOEL = 300 ppm, equivalent to approximately 36 and 42 mg/kg bw/day, expressed as paraquat ion in males and females, respectively.
Rat, Fischer CDF (F344), male and female	Short-term toxicity	13-week dietary	NOEL = 100 ppm, equivalent to approximately 6 and 7 mg/kg bw/day, expressed as paraquat ion in males and females, respectively. LOEL = 300 ppm, equivalent to approximately 20 and 21 mg/kg bw/day, expressed as paraquat ion in males and females, respectively.

Table 4. Toxicology profile of paraquat TK, based on repeated administration (sub-acute to chronic)

Species	Test	Duration and conditions or guideline adopted	Result
Dog, Beagle, male and female	Short-term toxicity	13-week dietary	NOEL = 20 ppm, equivalent to approximately 0.6 and 0.7 mg/kg bw/day, expressed as paraquat ion in males and females, respectively. LOEL = 60 ppm, equivalent to approximately 2 mg/kg bw/day, expressed as paraquat ion in males and females.
Dog, Beagle, male and female	Short-term toxicity	1-year dietary	NOEL = 15 ppm, equivalent to approximately 0.45 and 0.48 mg/kg bw/day, expressed as paraquat ion in males and females, respectively. LOEL = 30 ppm, equivalent to approximately 0.9 and 1.0 mg/kg bw/day, expressed as paraquat ion in males and females, respectively.
Mouse, Alpk Swiss-derived, male and female	Carcinogenicity	99-week dietary	Not tumorigenic. NOAEL = 12.5 ppm, equivalent to approximately 1.5 mg/kg bw/day, expressed as paraquat ion in males. NOEL = 37.5 ppm, equivalent to approximately 4.3 mg/kg bw/day, expressed as paraquat ion in females.
Rat, Fischer 344, male and female	Chronic toxicity / carcinogenicity	113-117 weeks for males and 122-124 weeks for females	Not carcinogenic. NOEL = 25 ppm, equivalent to approximately 1.25 mg/kg bw/day, expressed as paraquat ion. LOEL = 75 ppm, equivalent to approximately 3.75 mg/kg bw/day, expressed as paraquat ion.
Rat, Alpk:APfSD, male and female	Reproductive toxicity	3-generation, 2 litters per generation	No effect on reproductive parameters. NOEL for toxicity = 25 ppm, equivalent to approximately 2.3 mg/kg bw/day, expressed as paraquat ion. NOEL for reproductive effects = >150 ppm, equivalent to approximately 13 mg/kg bw/day, expressed as paraquat ion.
Mice, Crl:CD1 (ICR) BR, female	Developmental toxicity	Gavage	NOEL for both maternal and developmental toxicity = 15 mg/kg bw/day expressed as paraquat ion.
Mice, Alpk SPF, female	Developmental toxicity	Gavage	Not teratogenic. No significant influence on embryonic or foetal development. NOEL for developmental toxicity = >10 mg/kg bw/day expressed as paraquat ion.
Rat, Alpk:SPF, female	Developmental toxicity	Gavage	Not teratogenic. NOEL for maternal and developmental toxicity > 1mg/kg bw/day expressed as paraquat ion.
Rat, Alpk:APfSD	Developmental toxicity	Gavage	Not teratogenic. NOAEL for maternal and developmental toxicity = 3 mg/kg bw/day expressed as paraquat ion.

Table 5. Mutagenicity profile of paraquat dichloride TK, based on *in vitro* and *in vivo* tests

Species	Test	Conditions	Result
Mouse, lymphocytes (L5178Y)	OECD 476, L5178Y mouse lymphoma assay (*in vitro*)	Doses of 23 – 361 µg/ml	Negative
Human lymphocytes	OECD 473, Cytogenetic study (*in vitro*)	Dosed at 90, 903 and 1807 µg/ml	Positive
Chinese hamster lung fibroblasts	OECD 479, Sister chromatid exchange assay (*in vitro*)	Dosed at 0.9, 1.8, 9, 18, 90 and 177 µg/ml	Positive
Rat hepatocytes	OECD 482, DNA damage and repair/unscheduled DNA synthesis (*in vitro*)	Dosed at 0.19 ng/ml to 1.86 mg/ml	Negative
Rat somatic cells	Rat cytogenetic assay (*in vivo*)	Male and female Wistar rats given a single oral dose at 15, 75 and 150 mg/kg	Negative
Mouse somatic cells	OECD 474, Micronucleus test (*in vivo*)	Male and female C57BL/6J/Alpk mice given a single oral dose at 52 and 83 mg/kg	Negative
Rat somatic cells	UDS assay (*in vivo*)	Single oral dose at 42 to 120 mg/kg	Negative
Mouse germ cells	Dominant lethal (*in vivo*)	Male CD1 mice dosed orally at 0, 0.04, 0.4 and 4.0 mg/kg for 5 days.	Negative

Table 6. Ecotoxicology profile of paraquat dichloride TK.

Species	Test	Duration and conditions	Result
Daphnia magna, (water flea)	Acute toxicity	EEC Method C2, Static system, 20-21°C, 48-hour observation	24 and 48 hour EC_{50} = 11.8 and 4.4 mg/l, expressed as paraquat ion, respectively. 48 hour NOEC = 2.2 mg/l expressed as paraquat ion.
Daphnia magna, (water flea)	Chronic toxicity	21-day exposure, based on OECD Guideline 202, modified by individually separating the Daphnia static system, growth and reproduction monitored	NOEC = 0.12 mg/l expressed as paraquat ion.
Oncorhynchus mykiss, (rainbow trout)	Acute toxicity	EEC Method C1, static system at 15°C	24, 48, 72 and 96 hour LC_{50} = 33, 22, 22 and 19 mg/l, expressed as paraquat ion, respectively. 96 hour NOEC = <0.3 mg/l, expressed as paraquat ion
Cyprinus carpio, (mirror carp)	Acute toxicity	EEC Method C1, static system at 22°C	24, 48, 72 and 96 hour LC_{50} = >112, >112, >112 and 98 mg/l expressed as paraquat ion, respectively. 96 hour NOEC = 60 mg/l expressed as paraquat ion.

Table 6. Ecotoxicology profile of paraquat dichloride TK.

Species	Test	Duration and conditions	Result
Oncorhynchus mykiss, (rainbow trout)	Chronic toxicity	21-day fish juvenile growth test, based upon OECD Method 204, with the exposure period extended to 21 days. Broadly in agreement with the draft OECD guideline 'Fish, juvenile growth test - 28 days', except that the exposure was for 21 days. Flow through system at 15°C	NOEC = 8.5 mg/l expressed as paraquat ion.
Selenastrum capricornutum, (green alga)	Effect on growth	Based on OECD Guideline 201 but with an extension of the exposure period to 96 hours. Static system at 24°C, biomass and growth rate observed	EbC_{50} = 0.075 mg/l expressed as paraquat ion. ErC_{50} = 0.20 mg/l expressed as paraquat ion. NOEC = 0.016 mg/l expressed as paraquat ion.
Eisenia foetida, (earthworm)	Acute toxicity	Laboratory study in artificial soil	LC_{50} = >1000 mg/kg dry soil, expressed as paraquat ion
Apis mellifera (honey bee)	Acute oral toxicity	Based on UK data requirements for approval under the Control of Pesticides Regulations, Working Document D3 (revised 1979). Consistent with EPPO guideline 170. Controlled environment at 22°C	24, 48, 72, 96 and 120 hour LD_{50} = 154, 50.9, 26.3, 19.5 and 11.2 µg/bee, expressed as paraquat ion, respectively.
Apis mellifera (honey bee)	Acute contact toxicity	Based on UK data requirements for approval under the Control of Pesticides Regulations, Working Document D3 (revised 1979). Consistent with EPPO guideline 170. Controlled environment at 22°C	72, 96 and 120 hour LD_{50} = 108, 89.1 and 50.9 µg/bee, expressed as paraquat ion, respectively.
Colinus virginianus, (bobwhite quail)	Acute toxicity	Oral intubation in distilled water, 14 day observation	LD_{50} = 127 mg/kg bw expressed as paraquat ion. LLD = 115 mg/kg bw expressed as paraquat ion. NOEL = 72 mg/kg bw expressed as paraquat ion.
Anas platyrhynchos, (mallard duck)	Acute toxicity	Oral intubation in propylene glycol, 14 day observation	LD_{50} = 144 mg/kg bw expressed as paraquat ion.
Colinus virginianus, (bobwhite quail)	Short-term toxicity	5 days treatment, 3 days observation	LC_{50} = 711 mg/kg diet expressed as paraquat ion.
Anas platyrhynchos, (mallard duck)	Short-term toxicity	5 days treatment, 3 days observation	LC_{50} = 2932 mg/kg diet expressed as paraquat ion.
Coturnix japonica, (Japanese quail)	Short-term toxicity	5 days treatment, 3 days observation	LC_{50} = 703 mg/kg diet expressed as paraquat ion

Table 6. Ecotoxicology profile of paraquat dichloride TK.

Species	Test	Duration and conditions	Result
Colinus virginianus, (bobwhite quail)	Reproductive toxicity	18 week dietary treatment. Egg laying and collection started after 10 weeks on treated diet and lasted for 8 weeks.	NOEC for toxicity and reproduction = 100 mg/kg diet expressed as paraquat ion.
Anas platyrhynchos, (mallard duck)	Reproductive toxicity	18 week dietary treatment. Egg laying and collection started after 10 weeks on treated diet and lasted for 8 weeks.	NOEC for toxicity = 100 mg/kg diet expressed as paraquat ion. NOEC for reproduction = 30 mg/kg diet expressed as paraquat ion.

Paraquat dichloride was evaluated by WHO (WHO, 1984), by IPCS (IPCS, 1991) and by the FAO/WHO JMPR in 1986 (by which it is subject to a periodic re-evaluation in 2003). The IPCS (1991) review concluded that residue levels of paraquat in food and drinking-water, resulting from its normal use, are unlikely to pose a health hazard for the general population.

The WHO/PCS hazard classification (WHO 2002) of paraquat dichloride is: moderately hazardous, class II.

The US EPA concluded, from acute toxicity studies on laboratory animals, that paraquat is highly toxic by the inhalation route and was placed in Toxicity Category I (the highest of four levels) for acute inhalation effects. However, the EPA established that the large droplets arising in agricultural practice (400 to 800 µm) are well beyond the respirable range and therefore inhalation toxicity is not a toxicological endpoint of concern. Paraquat is moderately toxic (Category II) by the oral route and slightly toxic (Category III) by the dermal route. Paraquat will cause moderate to severe eye irritation and minimal dermal irritation and has been placed in Toxicity Categories II and IV for these effects (USEPA, 1997). Paraquat was classified as a “Group E” chemical, i.e. one showing evidence of non-carcinogenicity to humans. The no observed effect levels (NOEL) for maternal toxicity are equal to, or more conservative (protective) than, the NOEL based on developmental toxicity. There is no evidence that paraquat is associated with reproductive effects. Paraquat also shows no evidence of causing mutagenicity. The US EPA has determined that there is a reasonable certainty that no harm will result to infants and children or to the general population from aggregate exposure to paraquat dichloride residues. The EPA does not believe that the effects produced by paraquat would be cumulative with those of other, structurally related, compounds.

Formulations

The main formulation types available are SL and SG.

The SL formulations are registered and sold in many countries throughout the world. SG formulations are registered in Europe and sold mainly in the UK.

Methods of analysis and testing

Analytical methods for the active ingredient (including identity tests) were published in CIPAC Handbook E, pp. 75 and 167, and utilise a colorimetric procedure based on

the blue free-radical ion produced by paraquat. The method(s) for determination of impurities are based on GC-FID, GC-MS and CE.

Relevant impurity, 4,4'-bipyridyl, is determined by GC-FID (CIPAC 56/13) the group of relevant impurities, the terpyridines, are determined by GC-MS.

The methods for the terpyridines and the emetic have been peer evaluated for the TK but peer validation for the analysis of formulations is still to be finalized[1][2].

Test methods for determination of physico-chemical properties of the technical active ingredient were essentially OECD methods, with CIPAC procedures being used for formulation assessment (as indicated in the specifications).

Physical properties

The physical properties, the methods for testing them and the limits proposed for the SL and SG formulations, comply with the requirements of the FAO Manual (5th edition).

Containers and packaging

Detailed requirements for containers are given in the specifications, as a note, but it is important to prevent paraquat dichloride from coming into contact with metals.

Expression of the active ingredient

The active ingredient is expressed as paraquat dichloride.

Appraisal

Data submitted were in accordance with the FAO/WHO Manual (2002, 1st edition) and supported the proposed specifications.

Paraquat dichloride specifications were previously developed under the old FAO procedure in 1994 (TK and SL) and published by FAO. Revised FAO specifications (TK and SL) and an additional specification (SG) for paraquat dichloride were proposed under the new procedure by Syngenta Crop Protection AG.

Paraquat dichloride is no longer under patent.

Paraquat dichloride is a non-selective contact herbicide, highly soluble and stable in water (pH 5-9), only very slowly subject to photolysis and essentially non-volatile. It very readily, and essentially irreversibly, binds to soils and sediments.

The proposer provided the meeting with commercially confidential information on the two manufacturing processes (a third manufacturing process was no longer in use) for paraquat dichloride and concomitant impurities. Data for five batches from each of the two manufacturing processes were provided for the TK. Addition of water and an emetic (after reactions are complete) complete the TK manufacturing process. Other safening additives, such as warning colorants, stenching agents and

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[1] The method for determination of total terpyridines in technical and formulated paraquat dichloride was accepted by CIPAC in 2007 and is available at http://www.cipac.org/lnpub.htm.

[2] The method for determination of the emetic in technical and formulated paraquat was peer-validated in 2003 and is available from the Pesticide Management Group of the FAO Plant Protection Service or can be downloaded here..

thickeners (for liquid formulations) are also incorporated. Mass balances were good: 99.0-99.3% characterized one manufacturing process, while 98.1-99.0% characterized the second process.

The proposer identified two relevant impurities of manufacturing (4,4'-bipyridyl and total terpyridines), both of which are normally below 0.5 g/kg. Minimum levels were specified for the emetic additive, and maximum levels for the two proposed relevant impurities, in the draft specifications for paraquat dichloride TK, SL and SG. Data submitted to FAO for TK purity, impurities and emetic content were similar to those submitted for registration of paraquat dichloride in the UK. A difference between the two sets of data was that terpyridines were not included in the UK data, because the concentrations are well below 1 g/kg. Both the terpyridines and 4, 4' bipyridyl were below 1 g/kg in batch analysis data submitted to FAO, regardless of which of the two current manufacturing processes was employed. The proposer noted that terpyridines are highly toxic, whilst, in some respects, 4,4'-bipyridyl is rather more toxic than paraquat dichloride. WHO/PCS opinion was to accept these views. The proposed new limit of 1 g/kg for 4,4'-bipyridyl is below the level of the previous FAO Specification (56/TK/S/F-1994). The Meeting agreed that the two impurities should be considered as relevant.

The method of analysis for paraquat dichloride is based on a colorimetric procedure, in which the blue paraquat radical, formed upon addition of alkaline sodium dithionite, is measured (CIPAC Handbook E, pages 75-78 and 167-168). The presence of paraquat as the dichloride salt may be identified by a check for chloride, using silver nitrate solution.

Methods for impurities are based on GC-FID (4,4' bipyridyl, CIPAC Handbook E, p.168 and CIPAC Handbook 1A, p. 1245) or GC-MS (terpyridines). Determination of the content of emetic, PP796, is based on capillary GC. The methods for the emetic and terpyridines have under gone satisfactory peer validation for the TK but further validation is underway for analysis of the formulations[12].

The proposer stated that physiochemical properties of paraquat dichloride were essentially determined using OECD methods, with CIPAC procedures used for assessment of formulation characteristics, as indicated in the specifications.

Paraquat dichloride was evaluated by WHO IPCS (1983 and 1991) with a classification of moderately hazardous assigned. The acceptable daily intake estimated by the FAO/WHO JMPR is 0-0.004 mg/kg. The US EPA has assigned a Category II acute toxicity to paraquat dichloride, which indicates it is moderately toxic. However, once paraquat is ingested and absorbed in sufficient amount, poisoning is essentially irreversible, with death as the probable end-point. Thus, all paraquat products must contain an effective emetic, to reduce the risk of accidental or deliberate ingestion and absorption. Paraquat is of low dermal toxicity but the US EPA classified paraquat dichloride in its highest toxicity class, Category I, for inhalation hazard. Nonetheless, the agency noted that, because the spray droplets produced in normal agricultural uses are too large to be respirable, the inhalation risk

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[1] The method for determination of total terpyridines in technical and formulated paraquat dichloride was accepted by CIPAC in 2007 and is available at http://www.cipac.org/lnpub.htm.

[2] The method for determination of the emetic in technical and formulated paraquat was peer-validated in 2003 and is available from the Pesticide Management Group of the FAO Plant Protection Service or can be downloaded here.

is actually very low. Paraquat dichloride is moderately toxic to aquatic invertebrates, slightly toxic to fish, moderately toxic to avian species and relatively non-toxic to bees.

As a result of evaluation of paraquat under Directive 91/414/EEC, the European Commission is proposing to make a colorant, an effective emetic and a stenching (or other olfactory alerting) agent, mandatory requirements for paraquat formulations. The proposer recommended the revised specifications be amended to reflect these same standards. The Meeting accepted the requirements for a stenching agent and emetic in paraquat product descriptions. The Meeting also agreed that a note to the specifications should identify the only emetic currently known to be satisfactory and provide both a minimum concentration and a suitable analytical method for it. The Meeting agreed that the note on emetic content should allow for a possible alternative compound, by describing the characteristics required for an effective emetic.

Paraquat dichloride is not mutagenic and EPA placed it in Group E for chemicals showing evidence of being non-carcinogenic to humans. Further, the evidence available indicates that paraquat dichloride has no effect on reproduction parameters and is non-teratogenic.

Certain amendments were made to the draft specifications, as agreed between the Meeting and the proposer. Apart from the exceptional requirements identified in the appraisal, the specifications were in accordance with the normal requirements of the FAO/WHO Manual.

Recommendations

The Meeting recommended that the specification for paraquat dichloride TK, as amended, should be adopted by FAO. The Meeting recommended that the specifications for SL and SG, as amended should be adopted by FAO, subject to satisfactory completion of peer validation of the analytical method for terpyridines[1] and the emetic[2].

References

Text reference	Publication details
FAO/WHO 2006	Section 2.9, p. 16. Manual on development and use of FAO and WHO specifications for pesticides. March 2006 revision of the first edition. Available only on the internet at http://www.fao.org/ag/agp/agpp/pesticid/ and http://www.who.int/whopes/quality.
IPCS, 1991	Health and Safety Guide No. 51. Paraquat Health and Safety Guide. World Health Organization, Geneva. 1991.
US EPA, 1996	Reregistration Eligibility Decision (RED), Paraquat dichloride. List A Case 0262. United States Environmental Protection Agency, 1996.
USEPA, 1997	R.E.D. Facts. Paraquat dichloride (EPA-738-F-96-018). United States Environmental Protection Agency, 1997.

[1] The method for determination of total terpyridines in technical and formulated paraquat dichloride was accepted by CIPAC in 2007 and is available at http://www.cipac.org/lnpub.htm.

[2] The method for determination of the emetic in technical and formulated paraquat was peer-validated in 2003 and is available from the Pesticide Management Group of the FAO Plant Protection Service or can be downloaded here..

Text reference	Publication details
WHO, 1984	Environmental Health Criteria 39: Paraquat and diquat. World Health Organization, Geneva, 1984.
WHO, 2002	The WHO Recommended Classification of Pesticides by Hazard and Guidelines to Classification 2000-2002 (WHO/PCS/01.5). World Health Organisation, Geneva, 2002.

EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate E – Food Safety: plant health, animal health and welfare, international questions
E1 - Plant health

Paraquat

SANCO/10382/2002 -final

3 October 2003

Review report for the active substance **paraquat**

Finalised in the Standing Committee on the Food Chain and Animal Health at its meeting on 3 October 2003 in view of the inclusion of paraquat in Annex I of Directive 91/414/EEC

1. Procedure followed for the re-evaluation process

This review report has been established as a result of the re-evaluation of paraquat, made in the context of the work programme for review of existing active substances provided for in Article 8(2) of Directive 91/414/EEC concerning the placing of plant protection products on the market, with a view to the possible inclusion of this substance in Annex I to the Directive.

Commission Regulation (EEC) No 3600/92([1]) laying down the detailed rules for the implementation of the first stage of the programme of work referred to in Article 8(2) of Council Directive 91/414/EEC, as last amended by Regulation (EC) No 1972/99([2]), has laid down the detailed rules on the procedure according to which the re-evaluation has to be carried out. Paraquat is one of the 90 existing active substances covered by this Regulation.

In accordance with the provisions of Article 4 of Regulation (EEC) No 3600/92, United Phosphorus Ltd on 26 July 1993, Zeneca Agrochemicals (now Syngenta) on 27 July 1993, Barclay Chemicals Ltd on 27 July 1997, Aporta SA on 19 July 1993, Pilar Ibérica SL on 23 July 1993, Marubeni UK plc on 23 July 1993, Helm AG on 23 July 1993, Calliope SA on 21 July 1993, Industrias Afrasa on 27 July 1993, Grower on 29 July 1993, Agrolac SA on 26 July 1993 and B.V. Luxan on 21 July 1993 notified to the Commission of their wish to secure the inclusion of the active substance paraquat in Annex I to the Directive.
In accordance with the provisions of Article 5 of Regulation (EEC) No 3600/92, the Commission, by its Regulation (EEC) No 933/94([3]), as last amended by Regulation (EC) No 2230/95([4]), designated the United Kingdom as rapporteur Member State to carry out the assessment of paraquat on the basis of the dossiers submitted by the notifiers. In the same Regulation, the Commission specified furthermore the deadline for the notifiers with regard to the submission to the rapporteur Member States of the dossiers required under Article 6(2) of

[1] OJ No L 366, 15.12.1992, p.10.

[2] OJ No L 244, 16.09.1999, p.41.

[3] OJ No L 107, 28.04.1994, p.8.

[4] OJ No L 225, 22.09.1995, p.1.

Regulation (EEC) No 3600/92, as well as for other parties with regard to further technical and scientific information; for paraquat this deadline was 31 October 1995.

Zeneca Agrochemicals (now Syngenta), United Phosphorus Ltd, Barclay Chemicals Ltd and Marubeni UK plc submitted each a dossier to the rapporteur Member State. No dossiers were submitted by the other notifiers. Zeneca Agrochemicals (now Syngenta) was the main data submitter, with a dossier which did not contain substantial data gaps, taking into account the supported uses. United Phosphorus Ltd, Barclay Chemicals Ltd and Marubeni UK plc did not submit complete dossiers. Information has furthermore been submitted by third parties, European Federation of Agricultural Workers and the European Chemical Bureau.

In accordance with the provisions of Article 7(1) of Regulation (EEC) No 3600/92, the United Kingdom submitted on 31 October 1996 to the Commission the report of its examination, hereafter referred to as the draft assessment report, including, as required, a recommendation concerning the possible inclusion of paraquat in Annex I to the Directive. Moreover, in accordance with the same provisions, the Commission and the Member States received also the summary dossier on paraquat from Zeneca Agrochemicals (now Syngenta), on 26 February 1997.

In accordance with the provisions of Article 7(3) of Regulation (EEC) No 3600/92, the Commission forwarded for consultation the draft assessment report to all the Member States as well as to Zeneca Agrochemicals (now Syngenta) being the main data submitter, on 11 February 1996.

The Commission organised an intensive consultation of technical experts from a certain number of Member States, to review the draft assessment report and the comments received thereon (peer review), in particular on each of the following disciplines:

- identity and physical /chemical properties ;
- fate and behaviour in the environment ;
- ecotoxicology ;
- mammalian toxicology ;
- residues and analytical methods ;
- regulatory questions.

The meetings for this consultation were organised on behalf of the Commission by the Biologische Bundesanstalt für Land und Forstwirtschaft (BBA) in Braunschweig, Germany, from April to July 1997.

The report of the peer review (i.e. full report) was circulated, for further consultation, to Member States and the main data submitter on 30 July 1997 for comments and further clarification.

In accordance with the provisions of Article 7(3) of Regulation (EEC) No 3600/92, the dossier, the draft assessment report, the peer review report (i.e. full report) and the comments and clarifications on the remaining issues, received after the peer review were referred to the Standing Committee on the Food Chain and Animal Health, and specialised working groups of this Committee, for final examination, with participation of experts from the 15 Member States. This final examination took place from June 2000 to July 2003, and was finalised in the meeting of the Standing Committee on 3 October 2003.

The documents and information were also submitted to the Scientific Committee for Plants for a separate independent consultation. The Committee was asked to comment on the relevance for consumers and operators of the ocular and pulmonary changes, which were observed in the long-term rat study; on the risk for operators, taking into particular account potential inhalatory and dermal exposure; on potential long-term effects to soil dwelling organisms; and on the risks the intended uses might pose to reproducing birds and hares.

In its opinion[5], the Scientific Committee concluded that the systemic effects on the eye, observed in rats and not in other species, are not relevant to the risk assessment for operators and consumers. Furthermore the Scientific Committee expressed the opinion that pulmoray lesions are not expected to occur under the exposure conditions that can take place in occupational settings or for consumers, when paraquat is used as a plant protection product as recommended. Based on the field exposure studies, corroborated by information on health surveys on operators, the SCP voiced the opinion that when paraquat is used as a plant protection product as recommended under prescribed good working practices, its use does not pose any significant health risk for the operators.

The Committee also noted that uses at recommended field rates are unlikely to pose a significant risk to soil-dwelling organisms. However, a more detailed appraisal of the likely effects of paraquat on the rate of degradation of organic material in soil was requested in view of remaining uncertainty. This information was subsequently delivered and evaluated by the Rapporteur Member State.

Furthermore, the Scientific Committee concluded that available studies indicate a hazard to ground breeding birds but further information on realistic exposures is needed for a definitive assessment of the risk. This information was subsequently provided and the evaluation within the Standing Committee on the Food Chain and Animal Health concluded that there are several situations where exposure to ground nesting birds is negligible. However, there are also scenarios where exposure may occur. The evaluation within the Standing Committee on the Food Chain and Animal Health concluded that the risk would be acceptable, provided appropriate risk mitigation measures are applied. Finally, the Scientific Committee concluded that paraquat may be expected to cause lethal and sublethal effects for hares, but the available data are inadequate to estimate the proportion of hares affected. The views of the Scientific Committee were taken into consideration when drafting this Directive and the Review Report. The evaluation within the Standing Committee on the Food Chain and Animal Health concluded that the risk would be acceptable if appropriate risk mitigation measures are applied.

The present review report contains the conclusions of this final examination; given the importance of the draft assessment report, the peer review report (i.e. full report) and the comments and clarifications submitted after the peer review as basic information for the final examination process, these documents are considered respectively as background documents A, B and C to this review report and are part of it.

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5 Opinion of the Scientific Committee on Plants on specific questions from the Commission regarding the evaluation of paraquat in the context of Council Directive 91/414/EEC; SCP/PARAQ/002 adopted on 20 December 2001.

2. Purposes of this review report

This review report, including the background documents and appendices thereto, has been developed and finalised in support of the Directive 2003/112/EC[6] concerning the inclusion of paraquat in Annex I to Directive 91/414/EEC, and to assist the Member States in decisions on individual plant protection products containing paraquat they have to take in accordance with the provisions of that Directive, and in particular the provisions of article 4(1) and the uniform principles laid down in Annex VI.

This review report provides also for the evaluation required under Section A.2.(b) of the above mentioned uniform principles, as well as under several specific sections of part B of these principles. In these sections it is provided that Member States, in evaluating applications and granting authorisations, shall take into account the information concerning the active substance in Annex II of the directive, submitted for the purpose of inclusion of the active substance in Annex I, as well as the result of the evaluation of those data.

In accordance with the provisions of Article 7(6) of Regulation (EEC) No 3600/92, Member States will keep available or make available this review report for consultation by any interested parties or will make it available to them on their specific request. Moreover the Commission will send a copy of this review report (not including the background documents) to all operators having notified for this active substance under Article 4(1) of this Regulation.

The information in this review report is, at least partly, based on information which is confidential and/or protected under the provisions of Directive 91/414/EEC. It is therefore recommended that this review report would not be accepted to support any registration outside the context of Directive 91/414/EEC, e.g. in third countries, for which the applicant has not demonstrated to have regulatory access to the information on which this review report is based.

3. Overall conclusion in the context of Directive 91/414/EEC

The overall conclusion from the evaluation is that it may be expected that plant protection products containing paraquat will fulfil the safety requirements laid down in Article 5(1)(a) and (b) of Directive 91/414/EEC. This conclusion is however subject to compliance with the particular requirements in sections 4, 5, 6 and 7 of this report, as well as to the implementation of the provisions of Article 4(1) and the uniform principles laid down in Annex VI of Directive 91/414/EEC, for each paraquat containing plant protection product for which Member States will grant or review the authorisation.

Furthermore, these conclusions were reached within the framework of the uses which were proposed and supported by the main data submitter and mentioned in the list of uses supported by available data (attached as Appendix IV to this Review Report).

Extension of the use pattern beyond those described above will require an evaluation at Member State level in order to establish whether the proposed extensions of use can satisfy the requirements of Article 4(1) and of the uniform principles laid down in Annex VI of Directive 91/414/EEC.

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[6] OJ L 321, 6.12.2003, p. 32.

With particular regard to residues, the review has established that the residues arising from the proposed uses, consequent on application consistent with good plant protection practice, have no harmful effects on human or animal health. The Theoretical Maximum Daily Intake (TMDI; excluding water and products of animal origin) for a 60 kg adult is 17 % of the Acceptable Daily Intake (ADI), based on the FAO/WHO European Diet (August 1994). Additional intake from water and products of animal origin are not expected to give rise to intake problems. The results of acute dietary risk assessment show that acceptable uses can be demonstrated.

The review has identified several acceptable exposure scenarios for operators, workers and bystanders, which require however to be confirmed for each plant protection product in accordance with the relevant sections of the above mentioned uniform principles.

The review has also concluded that under the proposed and supported conditions of use there are no unacceptable effects on the environment, as provided for in Article 4 (1) (b) (iv) and (v) of Directive 91/414/EEC, provided that certain conditions are taken into account as detailed in section 6 of this report.

4. Identity and Physical/chemical properties

The main identity and the physical/chemical properties of paraquat are given in Appendix I.

The active substance shall comply with the FAO specification and there seem not to be reasons for deviating from that specification; the FAO specification is given in Appendix I of this report. Technical concentrates shall comply with the FAO specification and, in particular, shall contain an effective emetic. Liquid formulations shall contain an effective emetic, blue/green colourants and stenching or other olfactory alerting agent or agents. Other safeners, such as thickeners, may also be included.

The review has established that for the active substance notified by the main data submitter Syngenta, none of the manufacturing impurities considered are, on the basis of information currently available, of toxicological or environmental concern.
In accordance with the provisions of Article 13(5) of Directive 91/414/EEC, the United Kingdom is unable to determine, on the basis of the information currently available, that the substances notified by the other data submitters (United Phosphorus Ltd, Barclay Chemicals Ltd, Aporta SA, Pilar Ibérica SL, Marubeni UK plc, Helm AG, Calliope SA, Industrias Afrasa, Grower, Agrolac SA, and B.V. Luxan) do not, in the meaning of Article 13(2) and (5) of the Directive, differ significantly in degree of purity and nature of impurities from the composition registered in the dossier submitted by the main data submitter.

5. Endpoints and related information

In order to facilitate Member States, in granting or reviewing authorisations, to apply adequately the provisions of Article 4(1) of Directive 91/414/EEC and the uniform principles laid down in Annex VI of that Directive, the most important endpoints as identified during the re-evaluation process are set out under point 1 above. These endpoints are listed in Appendix II.

6. Particular conditions to be taken into account on short term basis by Member States in relation to the granting of authorisations of plant protection products containing paraquat

On the basis of the proposed and supported uses, the following particular issues have been identified as requiring particular and short term attention from all Member States, in the framework of any authorisations to be granted, varied or withdrawn, as appropriate:

- Member States must pay particular attention to the protection of operators, in particular for knapsack and handheld applications. Use restrictions and risk mitigation measures should be used where appropriate. The following specific measures should be implemented
  - the availability of the product should be limited to *bona fide* agriculturists, horticulturalists and professional users;
  - the maximum spray concentration must not exceed 2 g bipyridyl/litre for knapsack and hand held applications.

- For use scenarios where potential for exposure of eggs of ground nesting birds exists - use of paraquat may only be authorised when an appropriate risk assessment has demonstrated that there is no unacceptable impact and when the conditions of authorisation include, where appropriate, risk mitigation measures.

- For use scenarios where potential for exposure of hares exists - use of paraquat may only be authorised when an appropriate risk assessment has demonstrated that there is no unacceptable impact and when the conditions of authorisation include, where appropriate, risk mitigation measures. Risk mitigation measures may include:
  - no aerial spraying (to avoid over spraying);
  - to provide that a repellent, which it is effective against hares e.g. ammonium sulphate, is added to the plant protection product or the tank mix;
  - avoid spray patterns which would trap hares within the spray area e.g. spray from the centre of the field outwards;
  - avoid spraying the whole field with paraquat on the same day if there is no alternative forage adjacent to the sprayed field.

- Member States must pay particular attention to the protection of aquatic organisms. Conditions of authorization should include risk mitigation measures, where appropriate.

In addition to the above particular issues, Member States should also consider to limit knapsack and handheld use to trained/certified personnel where appropriate training and certification schemes are in operation at Member State level.

7. List of studies to be generated

No further studies were identified which were at this stage considered necessary in relation to the inclusion of paraquat in Annex I under the current inclusion conditions.

However the authorization holders of plant protection products containing paraquat should undertake to monitor and to report at the latest by 31 March each year until 2008 on incidences of operator health problems and impact on hares in one or more representative areas of use, which should be supplemented by sales data and a survey of use patterns, so that a realistic picture of the toxicological and ecological impact of paraquat can be obtained. This will allow a further evaluation, without delay and in line with scientific progress, of the properties and potentially related risks to humans and the environment.

Some uses however may require the generation or submission of additional studies or assessments to be submitted to the Member States to support authorisations for use under certain conditions.

8. Information on studies with claimed data protection

For information of any interested parties, Appendix III gives information about the studies for which the main data submitter has claimed data protection and which during the re-evaluation process were considered as essential with a view to annex I inclusion. This information is only given to facilitate the operation of the provisions of Article 13 of Directive 91/414/EEC in the Member States. It is based on the best information available to the Commission services at the time this review report was prepared; but it does not prejudice any rights or obligations of Member States or operators with regard to its uses in the implementation of the provisions of Article 13 of the Directive 91/414/EEC neither does it commit the Commission.

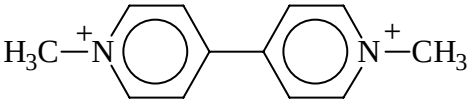
9. Updating of this review report

The technical information in this report may require to be updated from time to time in order to take account of technical and scientific developments as well as of the results of the examination of any information referred to the Commission in the framework of Articles 7, 10 or 11 of Directive 91/414/EEC. Such adaptations will be examined and finalised in the Standing Committee on the Food Chain and Animal Health, in connection with any amendment of the inclusion conditions for paraquat in Annex I of the Directive.

APPENDIX I

Identity, physical and chemical properties

PARAQUAT

Common name (ISO)	Paraquat
Chemical name (IUPAC)	1,1'-dimethyl-4,4'-bipyridinium
Chemical name (CA)	1,1'-dimethyl-4,4'-bipyridinium
CIPAC No	56 (paraquat)
CAS No	4685-14-7 (paraquat ion)
EEC No	225-141-7 (paraquat ion) 217-615-7 (paraquat dichloride)
FAO SPECIFICATION	The technical concentrate shall consist essentially of an aqueous solution of paraquat dichloride, together with related manufacturing impurities containing not more than a trace of suspended matter, immiscible solvents or sediment, and containing an effective emetic. Aqueous solutions of technical paraquat dichloride, should include wetting and safening agents which will include an effective emetic and blue/green colourants, and may include other safeners including stenching agents and thickeners. It shall contain not more than a trace of suspended matter, immiscible solvents and sediment. Technical concentrates may also include colourants. The paraquat dichloride content (Note 1) shall be declared (not less than 500 g/l at 20°C, Note 2) and, when determined, the content obtained shall not differ from that declared by more than ± 25g/kg. An effective emetic must be included at a specified level. The content shall be declared and, when determined, shall not differ from that declared by more than ± 15% (Note 3). Impurity: free 4,4¢-bipyridyl Maximum: 0.2% by weight of the paraquat dichloride content AGP: CP/344 Rome 1996 (56/SL/S/F & 56/TK/S/F)
Molecular formula	$C_{12}H_{14}N_2$
Molecular mass	186.3
Structural formula	
Melting point	Paraquat dichloride decomposes at approximately 340 °C.
Boiling point	Paraquat dichloride decomposes at approximately 340 °C.

Appearance	Hygroscopic solid Liquid (technical)
Relative density	1.5 g/cm^3 at 25 °C (purity 99.5 % w/w) 1.13 g/cm^3 at 25 °C (technical)
Vapour pressure	< 10^{-8} kPa at 25 °C (purity 99.5 % w/w) [Vapour pressure too low to be measured, therefore the value was estimated]
Henry's law constant	$4 \cdot 10^{-12}$ Pa·m^3·mol^{-1} (purity 99.5 % w/w)
Solubility in water	At 20 °C: pH 5.2: 618 g/l (purity 99.5 % w/w) pH 7.2: 620 g/l (purity 99.5 % w/w) pH 9.2: 620 g/l (purity 99.5 % w/w)
Solubility in organic solvents	At 20 °C: Methanol: 143 g/l (purity 99.5 % w/w) Acetone: <0.1 g/l (purity 99.5 % w/w) Dichloromethane: <0.1 g/l (purity 99.5 % w/w) Toluene: <0.1 g/l (purity 99.5 % w/w) Ethyl acetate: <0.1 g/l (purity 99.5 % w/w) Hexane: <0.1 g/l (purity 99.5 % w/w)
Partition co-efficient (log P_{OW})	-4.5 at 20 °C (purity 99.5 % w/w)
Hydrolytic stability (DT_{50})	Hydrolytically stable at pH 5, 7 and 9 after 30 days at 25 and 40°C
Dissociation constant	Paraquat ion does not dissociate.
Quantum yield of direct photo-transformation in water at ε >290 nm	6 hours
Flammability	Paraquat dichloride technical is an aqueous solution it does not evolve highly flammable gases and the determination of the flammability of paraquat dichloride as manufactured is therefore inappropriate.
Explosive properties	The chemical structure of paraquat does not include bond groupings which confer explosive properties
UV/VIS absorption (max.)	290 nm e M^{-1} cm^{-1}
Photostability in water (DT_{50})	Photolytically stable at pH 7 with no significant decrease in concentration having been recorded after the equivalent of 37 days of summer sunlight in Florida.

APPENDIX II

END POINTS AND RELATED INFORMATION

PARAQUAT

1 Toxicology and metabolism

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of absorption:	Rapid. Approximately 10 % absorption.
Distribution:	Extensive
Potential for accumulation:	Some potential in lungs
Rate and extent of excretion:	> 90 % in 72 h
Toxicologically significant compounds:	Parent compound
Metabolism in animals:	Minimal metabolism, representing < 1 % of recovery

Acute toxicity[7]

Rat LD_{50} oral:	93.4 - 113.5 mg/kg/bw paraquat ion
Rat LD_{50} dermal:	(in rabbit) > 660 mg/kg bw (paraquat ion) Other studies about 200 mg/kg bw (paraquat ion)
Rat LC_{50} inhalation:	0.6 - 1.4 mg/m^3
Skin irritation:	Slight but not classifiable in animal studies.
Eye irritation:	Irritant
Sensitization (test method used and result):	Negative in Magnusson & Kligman protocol

Short term toxicity

Target / critical effect:	Lungs - alveolar damage by oral route. Upper respiratory tract damage by inhalation.
Lowest relevant oral NOAEL / NOEL:	0.45 mg/kg bw/d, 1 year dog study
Lowest relevant dermal NOAEL / NOEL:	No studies available
Lowest relevant inhalation NOAEL / NOEL:	10µg/m^3, 3 week (15 exposure) rat study

Genotoxicity

Negative *in vivo.* Some *in vitro* positives.

[7] Expressed as paraquat ion.

Long term toxicity and carcinogenicity

Target / critical effect:	Eyes (cataract), kidney (tubule degeneration), lung and testes.
Lowest relevant NOAEL:	1.2 mg/kg bw/d (25 ppm) in chronic rat study
Carcinogenicity:	Not carcinogenic

Reproductive toxicity

Target / critical effect - Reproduction:	Lung lesions in parental animals. No specific effects on reproduction.
Lowest relevant reproductive NOAEL / NOEL:	2.5 mg/kg bw/d based on lung lesions in parents
Target / critical effect - Developmental toxicity:	Target / critical effect: Embryotoxic at maternally toxic doses.
Lowest relevant developmental NOAEL / NOEL:	3 mg/kg bw/d

Delayed neurotoxicity

No indication of neurotoxicity.

Other toxicological studies

None submitted.

Medical data

Published literature and company records report fatalities in cases of oral ingestion of concentrate i.e. not as a consequence of occupational exposure. Cases of skin irritation, nail discolouration and nosebleeds in manufacture and occupational use have been reported, related to inadequate working practices and poor hygiene.

Summary

	Value	Study	Safety factor
ADI:	0.004 mg/kg bw based on NOAEL	1 year dog study	100 fold factor
AOEL systemic (long term)	0.0004 mg/kg bw/d	on 1 y dog study corrected for 10 % oral absorption	100 factor
AOEL systemic (short term)	0.0005 mg/kg bw/d	on 90 day dog study corrected for 10 % oral absorption	100 factor
AOEL inhalation:	N/A, use systemic value	-	-
AOEL dermal:	N/A, use systemic value	-	-
ARfD (acute reference dose):	0.005 mg/kg bw/d	90 day dog study	100 factor

Dermal absorption

0.5 % based on overall weight of evidence.

2 Fate and behaviour in the environment

2.1 Fate and behaviour in soil

Route of degradation

Aerobic:

Mineralization after 100 days:	Due to strong adsorption to soil, the route of microbial degradation has only been demonstrated in pure cultures.
Non-extractable residues after 100 days:	Not relevant. See comment above
Major metabolites above 10 % of applied active substance: name and/or code % of applied rate (range and maximum)	Not relevant. See comment above

Supplemental studies

Anaerobic:	Relatively stable, withstands degradation.
Soil photolysis:	No significant degradation.
Remarks:	Standard requirements are not applicable due to strong adsorption to soil.

Rate of degradation

Laboratory studies

DT_{50}lab (20 °C, aerobic):	Not relevant. See comment above.
DT_{90}lab (20 °C, aerobic):	Not relevant. See comment above.
DT_{50}lab (10 °C, aerobic):	Not relevant. See comment above.
DT_{50}lab (20 °C, anaerobic):	Not relevant. See comment above.

Field studies

(country or region)

DT_{50f} from soil dissipation studies:	7 - 8 y (UK) and 10 - 20 y (USA)
DT_{90f} from soil dissipation studies:	DT_{90} values were never reached
Soil accumulation studies:	UK study with annual application, soil residues were 17 % of theoretical maximum after 20 y (3.5 times initial concentration). US study, 26 % of theoretical maximum after 20 y.

Soil residue studies:	Monitoring (220 sites) following extensive commercial use in northern and southern Europe gave residues between <0.2 and 15 mg/kg

Remarks

e.g. effect of soil pH on degradation rate	The strong adsorption of paraquat to soil precludes paraquat degradation in soil being studied effectively by standard guideline methods. The strong adsorption also greatly reduces the rate of formation of degradation products to amounts that would not be detectable using standard methods. Soil microbial studies fulfil the scientific intent of demonstrating the intrinsic degradability of paraquat.

Adsorption/desorption

K_f / K_{oc}:	K_{oc} values (220 soils in study) ranged from 8400 to 40 000 000 (very strong adsorption in all the soils tested).
K_d:	K_d values (224 soils in study) ranged from 480 to 400,000. Adsorption increased with clay content. No measurable correlation with % OC**.**
pH dependence:	Not relevant

Mobility

Laboratory studies:

Column leaching:	Not relevant as all studies indicate that paraquat is immobile.
Aged residue leaching:	Not relevant as all studies indicate that paraquat is immobile.

Field studies:

Lysimeter/Field leaching studies:	Not relevant as all studies indicate that paraquat is immobile.

Remarks:	Adsorption is correlated to clay content. The amount of paraquat deactivated by adsorption is determined by a wheat bioassay (SAC-WB). Most soils have a large excess of adsorption capacity relative to use rate. Exceeding SAC-WB values may be possible only in soils with very low SAC-WB values following repeated application at high rates.

2.2 Fate and behaviour in water

Abiotic degradation

Hydrolytic degradation:	Hydrolytically stable at pH 5, 7 and 9 after 30 d at 25 and 40 °C.
Major metabolites:	None
Photolytic degradation:	Photolytically stable at environmentally relevant wavelengths.
Major metabolites:	None

Biological degradation

Ready biological degradability:	Not studied since not relevant. Paraquat will not be used under conditions where sewage water or sludge contamination occurs.
Water/sediment study: DT_{50} water: DT_{90} water: DT_{50} whole system: DT_{90} whole system: Distribution in water / sediment systems (active substance) Distribution in water / sediment systems (metabolites)	Not studied since not relevant. In the unlikely event of paraquat entering an aquatic body at biologically significant concentrations, it will dissipate initially in a similar way to in soil, i.e. mainly by adsorption onto sediment, with an expected DT50 in the region of <24 h.
Accumulation in water and/or sediment:	Significant residues found in plant material and sediment, after complete dissipation from water. Not relevant for water, since any residues will rapidly dissipate to sediment. From soil studies, there is no evidence of desorption of paraquat back into the water phase.

Degradation in the saturated zone

Not studied since not relevant. Paraquat will Not be used under conditions where contamination of the saturated zone occurs.

Remarks:	None

2.3 Fate and behaviour in air

Volatility

Vapour pressure:	< 10^{-8} kPa at 25 °C
Henry's law constant:	< $4 \cdot 10^{-12}$ Pa·m^3·mol^{-1}

Photolytic degradation

Direct photolysis in air:	Not relevant, due to low vapour pressure.
Photochemical oxidative degradation in air	Not relevant, due to low vapour pressure.
DT_{50}:	
Volatilisation:	Not relevant, due to low vapour pressure.

Remarks:	None

3 Ecotoxicology

Terrestrial Vertebrates

Acute toxicity to mammals:	LD_{50} = 93.4 mg as/kg bw
Acute toxicity to birds:	LD_{50} = 35 mg as/kg bw
Dietary toxicity to birds:	LC_{50} = 698 ppm
Reproductive toxicity to birds:	NOEC 30 mg/kg diet
Short term oral toxicity to mammals:	NOEC of 100 ppm from 13 week rat study

Aquatic Organisms

Acute toxicity fish:	LC_{50} = 19 mg as/l (Rainbow trout, 96 h study)
Long term toxicity fish:	Continuous or repeated exposure not anticipated therefore study not submitted.
Bioaccumulation fish:	Log P_{ow} is -4.5 therefore no bioconcentration study submitted.
Acute toxicity invertebrate:	EC_{50} = 4.4 mg as/l (*Daphnia magna* - 48 h study)
Chronic toxicity invertebrate:	14 – 21 day NOEC = 0.12 mg as/l
Acute toxicity algae:	EC_{50} = 0.00023 mg as/l (*Navicula pelliculosa* 96h study)
Chronic toxicity sediment dwelling organism:	*Chironomus riparius*: 21 day NOEC in sediment = 100 mg as/kg;, 21 day water phase only NOEC = 0.367 mg as/l.
Acute toxicity aquatic plants: (for herbicides only)	EC_{50} = 0.037 mg as/l for *Lemna gibba* (14 day semi-static study)

Honeybees

Acute oral toxicity:	LD_{50} = 9.06 µg as/bee - 120 h study
Acute contact toxicity:	LD_{50} = 9.26 µg as/bee - 120 h study

Other arthropod species

Test species	% Effect
Pardosa sp.	Mortality: No effect on adults (1.0 g as/ha, SL formulation)
Aleochara bilineata	Mortality: No effect on adults (1.0 g as/ha, SL formulation)
Pterostichus melanarius	Mortality: No effect on adults (1.0 g as/ha, SL formulation)

Earthworms

Acute toxicity:	LC_{50} >1000 mg as/kg soil - 14 d study
Reproductive toxicity:	No adverse effects were observed on earthworm populations in a field study following an application of up to 720 kg as/ha in one year.

Soil micro-organisms

Nitrogen mineralization:	No adverse effects were observed after application up to 720 kg as/ha in one year.
Carbon mineralization:	No adverse effects were observed after application up to 720 kg as/ha in one year.

APPENDIX IIIA

PARAQUAT

List of studies for which the main submitter has claimed data protection and which during the re-evaluation process were considered as essential for the evaluation with a view to Annex I inclusion.

B.1 Identity, B.2 Physical and chemical properties, B.3 Data on application and further information, B.4 Proposals for classification and labelling, B.5 Methods of analysis

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports[8] on previous use in granting national authorizations
IIA 4.1	Baker H A J Duffin M R	1995	The determination of volatile (solvent type) impurities in technical material by capillary gas chromatography. Report No.: PAM 595/1 GLP status: Not applicable Unpublished.	
IIA 4.1	Duffin M R	1996	The determination of volatile paraquat associated impurities in technical material concentrate by capillary gas chromatography. Report No.: AMP10042-01B GLP status: Not applicable Unpublished.	
IIA 4.1	Navarro P C	1999	The determination of paraquat cation and associated impurities in technical material concentrate by capillary electrophoresis. Report No.: AMP10076-01B GLP status: Not applicable Unpublished.	
IIA 4.1	Navarro P C and Duffin M R	1999	Method validation: AMP10076-01B/VAL-01 The determination of paraquat cation and associated impurities in technical material concentrate by capillary electrophoresis. Report No.: AMP10076-01B/VAL-01 Not GLP Unpublished.	

[8] Entries are based on information received from the Notifier(s) and in certain cases Member States. Neither the Commission nor the Member States are responsible for the completeness or validity of this information received.

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports[8] on previous use in granting national authorizations
IIA 4.1	Thorndycraft MD	1994	The determination of paraquat in aqueous concentrates and formulated materials by spectrophotometry. PAM 179/2 GLP status: Not applicable Unpublished	
IIA 4.2.1	Anderson, L and Boseley, A D	1997	The determination of residues of paraquat and diquat in crops and soil - a High Performance Liquid Chromatographic Method. SOP RAM 272/02 GLP status: Not applicable Unpublished.	
IIA 4.2.1	Anderson L	1994a	The determination of residues of paraquat and diquat in crops: a second derivative spectrophotometric method. RAM 252/01 GLP status: Not applicable Unpublished	
IIA 4.2.1 4.2.2 4.2.3	Coombe N	1994a	Validation of Zeneca Agrochemicals standard operating procedures for the analysis of diquat and paraquat residues in crops, soil and water containing both compounds. CEM-322 GLP Unpublished	
IIA 4.2.1	Greenstreet C A	1997	Paraquat and diquat: Validation of Zeneca Agrochemicals SOP RAM 272/02 for Hops. Report No.: CEMR-730 GLP Unpublished.	
IIA 4.2.2	Anderson L	1994b	The determination of residues of paraquat and diquat in soils: a second derivative spectrophotometric method. RAM 253/01 GLP status: Not applicable Unpublished	
IIA 4.2.3 4.2.5.1	Anderson L	1994c	The determination of residues of paraquat and diquat in water, milk, oils and other liquids: a second derivative spectrophotometric method with confirmatory method for water residues by high performance liquid chromatography. RAM 254/01 GLP status: Not applicable Unpublished	

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports[8] on previous use in granting national authorizations
IIA 4.2.4	Anderson L	1994b	Paraquat and diquat: validation of model to determine residues in air. RJ1659B GLP Unpublished	
IIA 4.2.5.1	Anderson L	1994d	The determination of paraquat in animal products a high performance liquid chromatographic method. RAM 004/05 GLP Unpublished	
IIA 4.2.5.1	Coombe N	1994b	Paraquat : Animal tissue method validation - Zeneca Agrochemicals standard operating procedure. CEM-299 GLP Unpublished	
IIA 4.2.5.1	Green M	1994	Paraquat analysis in tissue extracts using the Enviroguard paraquat plate kit. WIU/009 Not GLP Unpublished	
IIA 4.2.5.1	Jones A	1994	Clean up and detection method for paraquat (HPLC) R009/94 Not GLP Unpublished	
IIA 4.2.5.2	Thomas D	1994a	The determination of paraquat in plasma, tissues and urine by radioimmunoassay. CT05-085 GLP Unpublished	
IIA 4.5.2.2	Thomas D Woollen BH	1994b	Rapid methods for the semi-quantitative determination of paraquat and diquat in urine. CTL/R/1191 GLP Unpublished	

B.6 Toxicology and metabolism

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
IIA 5.1	Lythgoe RE	1995a	Paraquat: excretion and tissue retention of a single oral dose (1 mg/kg) in the rat. CTL/P/4683 GLP Unpublished	

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
IIA 5.1	Lythgoe RE	1995b	Paraquat: excretion and tissue retention of a single oral dose (50 mg/kg) in the rat. CTL/P/4684 GLP Unpublished	
IIA 5.1	Lythgoe RE	1995c	Paraquat: excretion and tissue retention of a single oral dose (1 mg/kg) in the rat following repeat dosing. CTL/P/4685 GLP Unpublished	
IIA 5.1.2	Macpherson D	1995	Paraquat: biotransformation in the rat CTL/P/4806 GLP Unpublished	
IIA 5.2.1	Duerden L	1994c	Paraquat dichloride technical concentrate: acute oral toxicity to the rat. CTL/P/4424 3B.1/40 GLP Unpublished	
IIA 5.2.1 III A 10.3	Farnworth M., Foster J and Lock E	1993	The toxicity of paraquat to rabbits following oral administration. Report no CTL/R/1164 Not GLP Unpublished	
IIA 5.2.2	Duerden L	1994b	Paraquat dichloride technical concentrate: acute dermal toxicity to the rat. CTL/P/4412 3B.1/39 GLP Unpublished	
IIA 5.2.4	Duerden L	1994a	Paraquat dichloride technical concentrate: irritation to the rabbit. CTL/P/4411 GLP Unpublished	
IIA 5.2.5	Bugg L Duerden L	1994	Paraquat dichloride technical concentrate: eye irritation to the rabbit. CTL/P/4566 3B.1/42 GLP Unpublished	
IIA 5.2.6	Duerden L	1994d	Paraquat dichloride technical concentrate: sensitisation to the guinea pig. CTL/P/4460 GLP Unpublished	

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
IIA 5.5	Busey W M	1986	An independent pathology review of the lung slides from a rat chronic toxicity/carcinogenicity study with paraquat. Experimental Pathology Laboratories Inc C2.4/03 Not GLP Unpublished.	
IIA 5.5	Ishmael, J and Godley, M J	1983	Paraquat : lifetime feeding study in rats histopathological examination of the lungs. ICI Central Toxicology Laboratory Report No. CTL/P/738 Not GLP Unpublished.	
IIA 5.6.2	Hodge MCE	1992	Paraquat: developmental toxicity study in the rat. CTL/P/3864 4B.4/12 GLP Unpublished	
IIA 5.6.2	Palmer K	1992	Paraquat (technical): oral (gavage) mouse developmental toxicity study. ICL/19/92 CTL/C/2830 4B.4/11 GLP Unpublished	
IIA 5.9.6	Calderbank A	1992	Paraquat mortality statistics in UK for the period 1980 - 1991 ODM52 AC/RB GLP Unpublished	

B.7 Residue data

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
IIA 6.1.1	Grout SJ	1994b	Paraquat: Quantification and characterisation of radioactive residues in root and oilseed crop after dessicant treatment of foliage. RJ1683B GLP Unpublished	
IIA 6.1.1 6.1.2	Grout SJ	1994a	Paraquat: quantification and characterisation of radioactive residues in root and leafy crop after preplant soil treatment. RJ1595B GLP Unpublished	

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
IIA 6.1.2	Vickers JA Hurt AD Bewick DW	1990	Paraquat: Rotational crop study RJ0867B GLP Unpublished	
IIA 6.3.1	Anderson L Earl M	1993	Paraquat: Residues in olives from trials carried out in Spain during 1991/1992. RJ1292B GLP Unpublished	
IIA 6.3.1	Dick JP Taylor PS Bonfanti F	1995a	Paraquat: Residue levels in oranges from trials carried out in Italy during 1993. RJ1808B GLP Unpublished	
IIA 6.3.1	Dick JP Taylor PS Bonfanti F	1995b	Paraquat: Residue levels in olive fruit and oil from trials carried out in Italy during 1993. RJ1810B GLP Unpublished	
IIA 6.3.1	Earl M Anderson L	1992a	Paraquat: Residues in grapes from trials carried out in Germany during 1990. RJ1051B GLP Unpublished	
IIA 6.3.1	Earl M Anderson L	1992b	Paraquat: Residues in pome and stone fruits from trials carried out in Germany during 1990. RJ1053B GLP Unpublished	
IIA 6.3.1	Roper EM	1989a	Gramoxone Super: Residues of paraquat in fresh market and dried prunes. TMU3657B GLP Unpublished	
IIA 6.3.1	Roper EM	1989b	Paraquat: Magnitude of residues in fresh and dried figs. TMR0015B GLP Unpublished	
IIA 6.3.1	Roper EM	1989k	Paraquat: Magnitude of residues in olives and processing fractions. TMR0039B GLP Unpublished	
IIA 6.3.2	Roper EM	1989e	Paraquat: Magnitude of residues in whole tomatoes and processing fractions. TMR0024B GLP Unpublished	

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
IIA 6.3.2	Roper EM	1989i	Paraquat: Magnitude of residues in sugar beet processing fractions. TMR0036B GLP Unpublished	
IIA 6.3.2	Roper EM	1989c	Paraquat: Magnitude of residues in cucumbers, melons and summer squash. TMR0017B GLP Unpublished	
IIA 6.3.2	Roper EM	1989e	Paraquat: Magnitude of residues in whole tomatoes and processing fractions. TMR0024B GLP Unpublished	
IIA 6.3.2	Roper EM	1989h	Paraquat: Magnitude of residues in sugar beet tops and roots. TMR0031B GLP Unpublished	
IIA 6.3.5	Earl M Anderson L	1991	Paraquat: Residues in potatoes from trials carried out in Germany during 1990. RJ1040B GLP Unpublished	
IIA 6.3.6	Roper EM	1989j	Paraquat: Magnitude of residues in hops and processing fractions. TMR0038B GLP Unpublished	
IIA 6.3.7	Anderson L Lant M	1994	Paraquat and diquat: Residue levels in maize from trials carried out in Italy during 1993. RJ1731B GLP Unpublished	
IIA 6.3.7	Anderson L Lant MS Bonfanti F	1995	Paraquat and diquat: Residue levels in rice, grain and straw from trials carried out in Italy during 1993. RJ1728B GLP Unpublished	

B.8 Environmental fate and behaviour

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
IIA 7.1.1.1.1 7.1.1.2.1	Vickers JA Hurt AD Bewick DW	1989a	Paraquat: Degradation in Aerobic soil. RJ0788B 5B.1/62 GLP Unpublished	
IIA 7.1.1.1.2 7.1.1.1.1 7.1.1.2.1	Vickers JA Hurt AD Bewick DW	1989b	Paraquat: Degradation in Anaerobic soil. RJ0810B 5B.1/60 GLP Unpublished	
IIA 7.1.1.2.2	Dyson J S Chapman P	1995	Paraquat: Long-term, High-rate trial, Frensham, Fate of Soil Residues. RJ3430B Not GLP Unpublished	
IIA 7.1.1.2.2	Dyson JS Kirsch O Stevens JEB	1995a	Paraquat: Long-term soil trial at Goldsboro, USA, 1979-1991. 1. Trial description and crop measurements. TMJ3328B Not GLP Unpublished	
IIA 7.1.1.2.2	Dyson JS Chapman P Farmer K	1995b	Paraquat: Long-term soil trial at Goldsboro, USA, 1979-1991. 2. Fate of soil residues. TMJ3329B Not GLP Unpublished	
IIA 7.1.1.2.2	Dyson JS Chapman P	1995c	Paraquat: Long-term, High-rate trial, Frensham, UK, 1971-1991. Fate of soil residues. TMJ3430B Not GLP Unpublished	
IIA 7.1.1.2.2	Stevens JEB Bewick DW	1991	Paraquat: A survey of residues and deactivation capacities of soils in the United Kingdom. RJ0594B 5B.2/41 GLP Unpublished	
IIA 7.1.2	Dyson JS Ferguson RE Lane MCG	1994	Paraquat: Adsorption and desorption properties in temperate soils. TMJ3225B 5B.1/77 Not GLP Unpublished	
IIA 7.1.2	Lane MCG Bouwman JJ Bewick DW	1992	Paraquat: Long-term, High-rate trials in the Netherlands (1986-1991). Final report. RJ1186B 5B.2/46 GLP Unpublished	

B.9 Ecotoxicology

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
IIA 8.2.1	Tapp JF Sankey SA Caunter JE Stanley RD Adams DS	1990a	Paraquat: determination of acute toxicity to Rainbow trout (*Salmo gairdneri*). BL3801/B 5C.4/21 GLP Unpublished	
IIA 8.2.1	Tapp JF Sankey SA Caunter JE Stanley RD Penwell AJ	1990b	Paraquat: Determination of acute toxicity to Mirror carp (*Cyprinus carpio)* BL3800/B 5C.4/20 GLP Unpublished	
IIA 8.2.2.2	Tapp JF Sankey SA Caunter JE Stanley RD Penwell AJ	1990c	Paraquat: determination of the 21 day LC50 to Rainbow trout (*Salmo gairdneri).* BL3860/B 5C.4/22 GLP Unpublished	
IIA 8.2.4	Allison N Hamer MJ	1990	Paraquat: acute toxicity to first instar *Daphnia magna* of technical concentrate YF6219. RJ0851B 5C.6/6 GLP Unpublished	
IIA 8.2.5	Stewart KM Tapp JF Sankey SA Stanley RD	1991	Paraquat dichloride: chronic toxicity to *Daphnia magna.* BL4151/B 5C.6/9 GLP Unpublished	
IIA 8.2.6	Smyth DV Tapp JF Sankey SA Stanley RD	1990	Paraquat: determination of toxicity to the green alga *Selenastrum capricornutum.* BL3748/B GLP Unpublished	
IIA 8.2.6	Smyth D V, Sankey, S A and Cornish S K	1992	Paraquat dichloride: toxicity to the blue green alga *Anabaena flos-aquae.* Report No.: BL4579/B GLP Unpublished	
IIA 8.2.6	Smyth D V, Sankey, S A and Cornish S K	1992	Paraquat dichloride: toxicity to the fresh water diatom *Navicula pelliculosa.* Report No.: BL4464/B GLP Unpublished	
IIA 8.2.7	Hamer M J	1998	Paraquat: Sediment toxicity test with *Chironomus riparius* Report No.: RJ2649B GLP Unpublished	

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not	Reports on previous use in granting national authorizations
IIA 8.2.7	Hamer M J and Ashwell J A	1997	Paraquat: BBA sediment toxicity test with sediment dwelling *Chironomus riparius.* Report No.: RJ2392B GLP Unpublished.	
IIA 8.2.8	Hamer M J	2000	Paraquat: Risk to aquatic plants following use in the EU. Report No.: RAJ0034B Not GLP Unpublished.	
IIA 8.2.8	Smyth D V, Sankey, S A Cornish S K Penwell A J	1992	Paraquat dichloride: toxicity to the duckweed *Lemna gibba.* Report No.: BL4493/B GLP Unpublished.	
IIA 8.3	Grant R	2000	Non target arthropod risk assessment for Europe. Not GLP Report No.: RAJ0025B Unpublished.	
IIA 8.3.2 / IIIA 10.5.1	Austin H M	1999	Paraquat: A Tier I Laboratory Study to determine the LC_{50} of a 100g l^{-1} SL formulation to the parasitic wasp *Aphidius rhopalosiphi*. Ecotox Ltd Report No. ER-99-14 GLP Unpublished.	
IIA 8.3.2 / IIIA 10.5.1	Austin H M	1999	Paraquat: A Tier 2 Laboratory Study to determine the LC_{50} of a 100g l^{-1} SL formulation to the predatory mite *Typhlodromus pyri*. Ecotox Ltd Report No. ER-99-25. GLP Unpublished	
IIA 8.3.2 / IIIA 10.5.1	Austin H M and Elcock V L	1999	Paraquat: A Tier I Laboratory Study to determine the LC_{50} of a 100g l^{-1} SL formulation tot he predatory mite *Typhlodromus pyri*. Ecotox Ltd Report No. ER-99-12 GLP Unpublished.	
IIA 8.3.2	Gill, A and Austin, H M	1996	The effects of paraquat on the predatory mite *Typhlodromus pyri.* Ecotox Limited Report No. ER-96-06 GLP Unpublished.	

Annex point/ reference number	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No.** **GLP or GEP status (where relevant)** **Published or not**	**Reports on previous use in granting national authorizations**
IIA 8.3.2.1 10.3.2.1	Jackson D McMullin LC Canning L White JS	1991	Gramoxone 100: Investigation of the toxicity of the formulation (containing paraquat dichloride) to the Carabid beetle *P.melanariusI* and a Lycosid spider. RJ0928B GLP Unpublished	
IIA 8.3.2.1	Petto R	1993	Effects of Gramoxone 100 on *Aleochara bilineata* Gyll. (Coleoptera, Staphylinidae) in the laboratory. RCC 405000 5E.3(a)/2 GLP Unpublished	
IIA 8.3.2.2	Kendall DA Smith BD Chinn NE	1989	A field study of the effects of paraquat and glyphosate herbicides on the invertebrate fauna of arable farmland in SW England. RIC 1821 5E.3(b)/1 Not GLP Unpublished	
IIA 8.3.3.1	Edwards P J Coulson J M	1993	Paraquat: toxicity to the earthworm Eisenia foetida of a 200g litre^{-1} SL formulation . TMJ3067B Not GLP Unpublished	
IIA 8.3.5	Canning L White JS	1992a	Paraquat: a glasshouse study to evaluate the effects on vegetative vigour of a 300 g ai litre (2.5 lb ai US gal $^{-1}$) soluble concentrate formulation on terrestrial non-target plants. RJ1279B 6E./1 GLP Unpublished	
IIA 8.3.5	Canning L White JS	1992b	Paraquat: a glasshouse study to evaluate the effects on seedling emergence of a 300 g ai litre^{-1} (2.5 lb ai US gal $^{-1}$) formulation on terrestrial non-target plants. RJ1280B 6E./2 GLP Unpublished	

APPENDIX IIIB

PARAQUAT

List of studies which were submitted during the evaluation process and were not cited in the draft assessment report:

B.1 Identity, B.2 Physical and chemical properties, B.3 Data on application and further information, B.4 Proposals for classification and labelling, B.5 Methods of analysis

Annex point/ reference number	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No.** **GLP or GEP status (where relevant)** **Published or not**
IIIA 2.7.3	Shaunak , R	1996	Paraquat: Determination of the long-term storage stability and physico-chemical characteristics of a 200 g/l SL formulation. Report No. RY0102B GLP Unpublished.
IIA 4.1	Navarro P C	1999	The determination of paraquat cation and associated impurities in technical material concentrate by capillary electrophoresis. Report No.: AMP10076-01B GLP status: Not applicable Unpublished.
IIA 4.1	Baker H A J and Duffin M R	1995	The determination of volatile (solvent type) impurities in technical material by capillary gas chromatography. Report No.: PAM 595/1 GLP status: Not applicable Unpublished.
IIA 4.1	Duffin M R	1996	The determination of volatile paraquat associated impurities in technical material concentrate by capillary gas chromatography. Report No.: AMP10042-01B GLP status: Not applicable Unpublished.
IIA 4.1	Navarro P C and Duffin M R	1999	Method validation: AMP10076-01B/VAL-01 The determination of paraquat cation and associated impurities in technical material concentrate by capillary electrophoresis. Report No.: AMP10076-01B/VAL-01 GLP status: Not applicable Unpublished.

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA 4.2.1	Anderson, L and Boseley, A D	1997	The determination of residues of paraquat and diquat in crops and soil - a High Performance Liquid Chromatographic Method. SOP RAM 272/02 GLP status: Not applicable Unpublished.
IIA 4.2.1	Anderson, L	1996	The determination of paraquat in animal products - a High Performance Liquid Chromatographic Method. Report No.: SOP RAM 004/06 GLP status: Not applicable Unpublished.
IIA 4.2.1	Greenstreet C A	1997	Paraquat and diquat: Validation of Zeneca Agrochemicals SOP RAM 272/02 for Hops. Report No.: CEMR-730 GLP Unpublished.

B.6 Toxicology and metabolism

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA 5.3.3	Grimshaw, P *et al*	1979	Three week inhalation study in rats exposed to an aerosol of paraquat (Repeat Study). Huntingdon Research Centre Report No. ICI 279/79476 (CTL/C/810) Not GLP Unpublished.
IIA 5.3.3	Hardy, C J and Clark, G C	1980	Assessment of accumulation of paraquat in the lungs - 3 week inhalation study in rats (15 Exposures). Huntingdon Research Centre Report No. ICI 301/8037 (CTL/C/965) Not GLP Unpublished.
IIA 5.3.3	Hardy, C J *et al*	1979	Three week inhalation study in rats exposed to an aerosol of paraquat. Huntingdon Research Centre Report No. ICI 254/7949 (CTL/C/729) Not GLP Unpublished.

Annex point/ reference number	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No.** **GLP or GEP status (where relevant)** **Published or not**
IIA 5.3.3	Laird, W J D *et al*	1979	Paraquat concentrations in rat lungs following exposure to paraquat aerosols (Study No. ICI 254/7949). ICI Central Toxicology Laboratory Report No. CTL/P/460 Not GLP Unpublished.
IIA 5.5	Busey W M	1986	An independent pathology review of the lung slides from a rat chronic toxicity/carcinogenicty study with paraquat. Experimental Pathology Laboratories Inc C2.4/03 Not GLP Unpublished.
IIA 5.5	Ishmael, J and Godley, M J	1983	Paraquat : lifetime feeding study in rats histopathological examination of the lungs. ICI Central Toxicology Laboratory Report No. CTL/P/738 Not GLP Unpublished.
IIA 5.8.2	Smith, P and Heath, D	1974	The ultrastructure and time sequence of the early stages of paraquat lung in rats. Journal of Pathology, Volume 114, pp 117 – 184 Not GLP Published.
IIA 5.8.2	Rose, M S; Lock, E A; Smith, L L and Wyatt, I	1976	Paraquat accumulation. Tissue and species specificity. Biochemical Pharmacology, Volume 25, pp 419 – 423 Not GLP Published.
IIA 5.9	Clark, D.G., McElligot, T.F and Hurst, E.W	1966	The toxicity of paraquat. Brit .J.Indust.Med 23, 126-132. Not GLP Published.
IIA 5.9	Davies, D S; Hawksworth, G M and Bennett, P N	1977	Paraquat poisoning. Proceedings of the European Society of Toxicologists, Volume 18, pp 21 – 26 Not GLP Published.
IIIA 7.2.1.2	Findlay, M L, Chester G and Wiseman J M	1998	Worker exposure during mixing, loading and application of Gramoxone with knapsack sprayers. Report No.: WER004 GLP (part) Unpublished.
IIIA 7.2.1.2	Findlay M L and Hall M	1997	Diquat: worker exposure during mixing, loading and application of 'Reglone' with knapsack sprayers Report No. CTL/P/5379 GLP (part) Unpublished

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIIA 7.2.3.2	Iwata, T and Findlay, M L	1995	Worker exposure during re-entry into paraquat-treated cotton fields: biological monitoring in Georgia in 1994 (WRC-95-019) (WINO 18630). Zeneca Ag Products Western Research Center Report No. RR 95-010B GLP Unpublished.
IIIA 7.3	Feldman, K J and Maibach, H I	1974	Percutaneous penetration of some pesticides and herbicides in man. Toxicology and Applied Pharmacology, Volume 28, pp 126 – 132 Published.

B.7 Residue data

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not

No new information

B.8 Environmental fate and behaviour

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA 7.1.1.1	Ricketts D. C	1999	The microbial biodegradation of paraquat in soil. Pesticides Science 55: 566-614. Not GLP Published

B.9 Ecotoxicology

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIA 8.1	Blank	1968/ 69	The effect of Gramoxone on the hatchability of pheasant eggs. The Game Conservancy Annual Review pp 82-83. Not GLP Published
IIA 8.1	Edwards P J	1979	Status of common bird populations on an intensively managed farm where paraquat has been used extensively. ICI Plant Protection Division Report No:RJ0037B. Not GLP Unpublished.
IIA 8.1	Edwards, P.J., Newman, J.F., and Ward, R.J	1979	Paraquat: Effects of spraying eggs on hatchability and reproductive organs of Japanese Quail, *Coturnix coturnix japonica*. ICI Plant Protection Division Report No:RJ0044B. Not GLP Unpublished.
IIA 8.1	Hakin, B., and Chanter, D.O	1988	The measurement of residues of paraquat penetrating the egg shells of fertile mallard duck eggs. Huntingdon Research Centre Ltd Report No: ISN172/88. GLP Unpublished
IIA 8.1	Hakin, B., and Chanter, D.O	1989	The effect of paraquat on the hatchability of fertile mallard duck eggs. Huntingdon Research Centre Ltd Report No: ISN170/881711. GLP Unpublished
IIA 8.1	Newman JF and Edwards PJ	1980	Effect of spraying eggs on hatchibility and on the reproductive organs of the chicks of pheasant, *Phasianus colchicus* Not GLP Unpublished
IIA 8.1	Roberts, N.L., Hakin, B., and Chanter, D.O	1989	The effect of paraquat on the hatchability of fertile pheasant eggs. Huntingdon Research Centre Ltd Report No: ISN171/881712. GLP Unpublished
IIA 8.1.1	Johnson A J	1998	Acute oral LD50 to the mallard duck. Huntingdon Life Sciences Report number ISN 399/96360 GLP Unpublished.

Annex point/ reference number	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No.** **GLP or GEP status (where relevant)** **Published or not**
IIA 8.2.8 / IIIA 10.2	Hamer M J	2000	Paraquat: Risk to aquatic plants following use in the EU. Report No.: RAJ0034B Not GLP Unpublished.
IIA 8.2.6	Smyth D V, Sankey, S A and Cornish S K	1992	Paraquat dichloride: toxicity to the blue green alga *Anabaena flos-aquae.* Report No.: BL4579/B GLP Unpublished.
IIA 8.2.6	Smyth D V, Sankey, S A and Cornish S K	1992	Paraquat dichloride: toxicity to the fresh water diatom *Navicula pelliculosa.* Report No.: BL4464/B GLP Unpublished.
IIA 8.2.6	Smyth D V, Tapp J F, Sankey, S A and Stanley R D	1990	Paraquat dichloride: determination of toxicity to the green alga (*Selenastrum capricornutum*). BL3748/B GLP Unpublished.
IIA 8.2.7	Hamer M J	1998	Paraquat: sediment toxicity test with *Chironomus riparius* RJ2649B GLP Unpublished
IIA 8.2.7	Hamer M J Ashwell J A	1997	Paraquat: BBA toxicity test with sediment-dwelling Chironomus riparius. RJ2392B GLP Unpublished
IIA 8.2.8	Smyth D V, Sankey, S A Cornish S K Penwell A J	1992	Paraquat dichloride: toxicity to the duckweed *Lemna gibba.* Report No.: BL4493/B GLP Unpublished.
IIA 8.2.8 / IIIA 10.2	Van Dord, Hoogers B J and van Zon J C J	1974	Studies on the side-effects of herbicides used in the aquatic environment. Proc. EWRC 4th International Symposium on Aquatic Weeds. Wien. p173-179 Not GLP Published.
IIA 8.3 / IIIA 10.4/5	Grant R	2000	Non target arthropod risk assessment for Europe. Not GLP Report No.: RAJ0025B Unpublished.

Annex point/ reference number	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No.** **GLP or GEP status (where relevant)** **Published or not**
IIA 8.3.2 / IIIA 10.5.1	Austin H M	1999	Paraquat: A Tier I Laboratory Study to determine the LC_{50} of a 100g l^{-1} SL formulation to the parasitic wasp *Aphidius rhopalosiphi*. Ecotox Ltd Report No. ER-99-14 GLP Unpublished.
IIA 8.3.2 / IIIA 10.5.1	Austin H M	1999	Paraquat: A Tier 2 Laboratory Study to determine the LC_{50} of a 100g l^{-1} SL formulation to the predatory mite *Typhlodromus pyri*. Ecotox Ltd Report No. ER-99-25. GLP Unpublished.
IIA 8.3.2 / IIIA 10.5.1	Austin H M and Elcock V L	1999	Paraquat: A Tier 2 Laboratory Study to determine the LC_{50} of a 100g l^{-1} SL formulation to the parasitic wasp *Aphidius rhopalosiphi*. Ecotox Ltd Report No. ER-99-HMA 310 GLP Unpublished.
IIA 8.3.2 / IIIA 10.5.1	Austin H M and Elcock V L	1999	Paraquat: A Tier I Laboratory Study to determine the LC_{50} of a 100g l^{-1} SL formulation tot he predatory mite *Typhlodromus pyri*. Ecotox Ltd Report No. ER-99-12 GLP Unpublished.
IIA 8.3.2	Gill, A and Austin, H M	1996	The effects of paraquat on the predatory mite *Typhlodromus pyri.* Ecotox Limited Report No. ER-96-06 GLP Unpublished.
IIIA 10.1	Carter N, Muirhead L, and Greenwood C	1998	The use of minor crops by birds in the breeding season as measured by the Common Birds Census. British Trust for Ornithology Services Ltd Report. Not GLP Unpublished.
IIIA 10.1	Crocker D R, Prosser P, Tarrant K A, Irving P V, Watola G, Chandler-Morris S and Hart A D M	1998	Use of radio-telemetry to monitor bird's use of orchards. Central Science Laboratory, U.K. Ministry of Agriculture Fisheries and Food Report No EH18/02. Not GLP Unpublished.
IIIA 10.1	Edwards P J	1999	Risk assessment for the effect of long term exposure of birds to paraquat residues in their diet. Not GLP Unpublished.

Annex point/ reference number	Author(s)	Year	Title Source (where different from company) Company, Report No. GLP or GEP status (where relevant) Published or not
IIIA 10.1	Fletcher M R and Greig-Smith P W	1998	The use of direct observations in assessing pesticide hazard to birds. In BCPC Monograph No.40. Field Methods for the study of environmental effects of pesticides. Eds Greaves M P, Smith B D and Greig-Smith P W. Not GLP Published.
IIIA 10.1	Green R	1978	Factors affecting the diet of farmland skylarks, *Alauda arvensis.* Journal of Animal Ecology, 47, 9 13-928. Not GLP Published.
IIIA 10.1.2	Edwards, P J	1979	Status of common bird populations on an intensively managed farm where paraquat has been used extensively. ICI Plant Protection Division Report No. RJ0037B Not GLP Unpublished..
IIIA 10.2.1	Ibrahim E A	1990	The influence of the herbicide paraquat 'Gramoxone' on growth and metabolic activity of three chlorophytes. Water, Air and Soil Pollution 51 pp89-93 Not GLP Published.
IIIA 10.2.1	Cullimore D R	1975	The in vitro sensitivity of some species of Chlorophyceae to a selected range of herbicides. Weed Research 15 pp401-406 Not GLP Published.
IIIA 10.2.1	Krattky B A and Warren G F	1971	The use of three simple rapid bioassays on forty-two herbicides. Weed Research 11 pp257-262 Not GLP Published.
IIIA 10.3	Barnes, R.F.W., Tapper, S.C and Williams, J	1983	Use of pastures by brown hares. Journal of Applied Biology 20, 179-185. Not GLP Published.
IIIA 10.3	Bonino, N and Montenagro, A.	1997	Reproduction of the European hare in Patagonia, Argentina. Acta Thenologica 42 (1) 47-54. Not GLP Published.

Annex point/ reference number	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No.** **GLP or GEP status (where relevant)** **Published or not**
IIIA 10.3	Broekuizen, S and Maaskamp,F	1982	Movement, home range, and clustering in the European hare (*Lepus europaeus* Pallas) in The Netherlands. Z. Saugetierkunde 47, 22-32. Not GLP Published.
IIIA 10.3	Chapuis, J.L.	1990	Comparison of the diets of two sympatric lagomorphs, *Lepus europeus* (Pallas) and Oryctolagus cuniculus (L) in an agroecosystem of the Ile-de-France. Z.Saugetierkunde *55, 176-185.* Not GLP Published.
IIIA 10.3	Chassey, D and Duff, J.P	1990	European brown hare syndrome and associated virus particles in the UK. The Veterinary Record, June 23, 623-624. Not GLP Published.
IIIA 10.3	De Lavaur, E., Grolleau, G and Siou, G	1973	Intoxication experimentale de lievres par de la luzerne traitee au paraquat. Ann. Zool - Ecol. Anim. 5 (4) 609-622 Not GLP Published.
IIIA 10.3	Duff, J.P., D Chasey, D., Munro, R and Wooldndge, M	1994	European brown hare syndrome in England. The Veterinary Record, June *25,* 669-673. Not GLP Published.
IIIA 10.3	Duff, J.P., Whitwell, K and Chasey, D	1997	The emergence and epidemiology of European brown hare syndrome in the U.K. In: D, Chasey., Gaskell, R.M., Clarke, I.N. (Eds) Proc 1St Int. Symp. Calciviruses ESVV 176-181. Eds Not GLP Published.
IIIA 10.3	Edwards P J, Fletcher M R and Berny P	2000	Review of the factors affecting the decline of the European brown hare, *Lepus europeus* (Pallas, 1778) and the use of wildlife incident data to evaluate the significance of paraquat. Agriculture Ecosystems and Environment 79 pp95-103 Not GLP Published.
IIIA 10.3	Edwards, P J	1985	Investigation into the possible involvement of paraquat in hare deaths in the UK during Autumn 1984. ICI Plant Protection Division Report No. M4028A Not GLP Unpublished.

Annex point/ reference number	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No.** **GLP or GEP status (where relevant)** **Published or not**
IIIA 10.3/ IIA 5.2.1	Farnworth M., Foster J and Lock E	1993	The toxicity of paraquat to rabbits following oral administration. Report no CTL/R/1164 Not GLP Unpublished
IIIA 10.3	Fletcher, M.R and Grave, R.C., 1992	1992	Post-registration surveillance to detect wildlife problems arising from approved pesticides. Proceedings British Crop Protection Council: Pests and Diseases (2) 793-798. Not GLP Published.
IIIA 10.3	Fletcher, M.R., Hunter, K., Barnett, E.A. and Sharp E.A.	1997	Pesticide Poisoning of animals 1996: Investigations of suspected incidents in the United Kingdom. Report of the Environmental Panel of the Advisory Committee on Pesticides, MAFF, London. Not GLP Published.
IIIA 10.3	Flux, J.E.C	1997	Status of rabbits (*Oryctolagus cuniculus*) and hares (*Lepus europeus*) in New Zealand. Gibier Faune Sauvage, Game Wildl. 14 (3) 267-280. Not GLP Published.
IIIA 10.3	Frolich, K., Meyer, H.H.D.Pielowski, Z., Ronsholt, L., Seck-Lanzendorf, S.V and Stolte, M	1996	European brown hare syndrome in free-ranging hares in Poland. Journal of Wildlife Diseases, 32 (2) 280-285. Not GLP Published.
IIIA 10.3	Frylestam, B	1976	Effects of cattle - grazing and harvesting hay on density and distribution of an European hare population. Proceedings of a Symposium on Ecology and management of European hare populations, Warszawa. Not GLP Published.
IIIA 10.3	Gavier, D and Morner, T	1989	The European brown hare syndrome in Sweden. Proceedings 31. Internationalen Symposiums uber die Erkrakkungen der Zoo-und Wildtiere. Dortmund, Germany. 261-264. Not GLP Published.
IIIA 10.3	Gavier-Widen, D and Morner, T	1993	Descriptive epizootiological study of European brown hare syndrome in Sweden. Journal of Wildlife Diseases, 29 1) 15-20 Not GLP Published.

Annex point/ reference number	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No.** **GLP or GEP status (where relevant)** **Published or not**
IIIA 10.3	Goszczynski, J and Wasilewski, M	1992	Predation of foxes on a hare population in central Poland. Acta Theriologica 37 (4), 329-33 8. Not GLP Published
IIIA 10.3	Grolleau, G	1981	Les repuls, moyen pour eviter les intoxications chez les animaux-gigier et la faune vertebree en general. Phytiatrie-Phytopharmacie. 30 97-113. Not GLP Published.
IIIA 10.3	Hansen, K	1992	Reproduction in European hare in a Danish farmland. Acta Theriologica 37, (1-2) 27-40. Not GLP Published.
IIIA 10.3	Kaluzinski, J and Pielowski, Z	1976	The effect of technical operations on the hare population. Procedings of a Symposium on Ecology and management of European hare populations, Warszawa. Not GLP Published.
IIIA 10.3	Kovacs, C and Buza, C	1992	Home range size of the brown hare in Hungary. In: Bobek, B., Perzanowski, K., Regelin, W., (Eds). Global trends in wildlife management. Trans. 1 8 IUGB Congress, Krakow 1987. Swait Press, KrakowWarszawa. Not GLP Published.
IIIA 10.3	Lamarque, F., Barratt, J and Moutou, F	1996	Principle diagnoses for determining causes of mortality in the European hare (*Lepus europeus*) found dead in France between 1986 and 1994. Gibier Fauna Sauvage, Game Wildl. 13, 53-72. Not GLP Published.
IIIA 10.3	Marboutin, E and Peroux, R	1996	Trends and fluctuations in European hare hunting bags: The limits of multiple regression analysis. In: Botev, N., (Ed) Proceedings of the International Union of Game Biologists; XXII Congress, Bulgaria. 115-122. Not GLP Published.
IIIA 10.3	Marcato, P.S., Benazzi, C., Vecchi, G., Galeotti, M., Della Salda, L., Sarli, G and Lucidi, P	1991	Clinical and pathological features of viral haemorrhagic disease in rabbits and European brown hare syndrome. Rev. Sci. tech. Off . Epiz. 10 (2) 37 1-392. Not GLP Published

Annex point/ reference number	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No.** **GLP or GEP status (where relevant)** **Published or not**
IIIA 10.3	Mary, C and Trouvilliez, J	1995	(Eds). Special lievre d'Europe. Bulletin Mensuel, De L'Office National de la Chasse. No 204. Not GLP Published.
IIIA 10.3	McLaren, G.W., Hutchins, M.R and Hams, S	1997	Why are brown hares (*Lepus europeus*) rare in pastoral landscapes in Great Britain. Gibier Fauna Sauvage, Game Wildlife 14:3, 335-348. Not GLP Published.
IIIA 10.3	Milanov, Z.B	1996	Effect of mowing fodder plants on small game populations in central Bulgaria. Proceedings of the International Union of Game Biologists; XXII Congress: The Game and the Man, Sofia, Bulgaria, September 4-8. 1995. Pp 394-397. PENSOFT Publishers: Sofia, Bulgaria. ISBN *954-642-013-1* Not GLP Published.
IIIA 10.3	Pepin, D	1989	Variation in survival of brown hare (*Lepus europeus*) leverets from different farmland areas in Paris basin. J.Appl. Ecol 26:13-23. Not GLP Published.
IIIA 10.3	Pielowski, Z	1976	On the present state and perspectives of the European hare breeding in Poland. Proceedings of a Symposium on Ecology and management of European hare populations. Warszawa 1976. *25.* Not GLP Published.
IIIA 10.3	Pielowski, Z and Raczynski, J	1976	Ecological conditions and rational management of hare populations. Proceedings of a Symposium on Ecology and management of European hare populations. Warszawa 1976. 269-286. Not GLP Published.
IIIA 10.3	Reynolds, J.C and Tapper, S.C	1995	Predation by foxes *Vulpes vulpes* on brown hares *Lepus europeus* in central southern England, and its potential impact on annual population growth. Wildlife Biology 1 (3) 145-157. Not GLP Published.
IIIA 10.3	Sostaric, B., Lipej, Z., Fuchs, R and Paukovic, C	1991	Disappearance of free living hares in Croatia: European Brown Hare Syndrome. Veterinarski Ashiv 61, 133-150. Not GLP Published.

Annex point/ reference number	**Author(s)**	**Year**	**Title** **Source (where different from company)** **Company, Report No.** **GLP or GEP status (where relevant)** **Published or not**
IIIA 10.3	Strandgaard, H and Asferg, T	1980	The Danish Bag Record II. Fluctuations and trends in the Game bag record in the years 1941-1976 and the geographical distribution of the bag in 1976. Danish Review of Game Biology *11(5)* 32-33. Tapper, 5., 1987. The brown hare. Published by Shire Natural History. IBSN 0 85263 881 7. Not GLP Published.
IIIA 10.3	Tapper, S.C and Barnes, R.F.W	1986	Influence of farming practice on the ecology of the brown hare (*Lepus europeus*). Journal of Applied Ecology, 23, *39-52.* GLP Published.
IA 10.3	Tapper, S.C. and Parsons, N	1984	The changing status of the brown hare (*Lepus capensis*) in Britain. Mammal rev. 14:2, 57-70. Not GLP Published.
IIIA 10.4	Anon	1987-1989	Risk to honey bees: Results of nine semi-field tent studies conducted in Germany to assess the risk of paraquat to honeybees. Not GLP Submitted as Annex in Notifier's response to ECCO Full Report on paraquat. Unpublished.

APPENDIX IV

List of uses supported by available data

PARAQUAT

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hl min max	water l/ha min max	kg as/ha min max		
Citrus	Southern Europe		F	Non-selective weed control	SL	120-200	Between the plants		1-2			250-1500	0.264 1.100	NR	Total not to exceed 1.1 kg/ha
Tree nuts -Hazelnut	Southern Europe		F	Non-selective weed control	SL	132-200	Between the plants		1-2			1000-1500	0.528 1.000	NR	Total not to exceed 1.1 kg/ha
Pome fruit - Apple	Southern Europe			Non-selective weed control	SL	100-200	Between the plants		1-2			250-1500	0.300 1.100	NR	Total not to exceed 1.1 kg/ha
	Northern Europe		F	Non-selective weed control	SL	120-200	Between the plants		1			100-600	0.360 1.100	NR	
Grape	Southern Europe		F	Non-selective weed control	SL	120-200	Between the plants		1-2			250-1500	0.300 1.100	NR	Total not to exceed 1.1 kg/ha
			F	Sucker Control	SL	100	Plant bases	In Spring	1-2		0.100 0.140	200-400		NR	
	Northern Europe		F	Non-selective weed control	SL	100	Between the plants		1			250-1000	0.300 0.630	NR	
Strawberry	Northern Europe		F	Non-selective weed control	SL	120-200	Between the plants/runner control		1-2			100-1000	0.240 1.100	NR	Total not to exceed 1.1 kg/ha

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hl min max	water l/ha min max	kg as/ha min max		
Olives	Southern Europe		F	Non-selective weed control	SL	120-200	Between the plants		1-2			250-1500	0.198 1.100	3	Total not to exceed 1.1 kg/ha
Fruiting vegetables Tomatoes/ Cucumbers	Southern Europe		F, G	Non-selective weed control	SL	120-200	Between the plants		1			300-1000	0.360 0.600	7	
Vegetable crops - Beans	Southern Europe		F	Non-selective weed control	SL	120-200	Between the plants		1-2			250-1000	0.180 1.100	7	Total not to exceed 1.1 kg/ha
	Northern Europe			Non-selective weed control	SL	100-200	Between the plants		1			100-1000	0.360 1.100	7	
Potato	Southern Europe		F	Non-selective weed control	SL	120-200		Before or at emergence	1			250-1000	0.180 1.100	NR	
	Northern Europe		F	Non-selective weed control	SL	100-200		Before or at emergence	1			100-1000	0.240 1.100	NR	
Lucerne	Southern Europe		F	Non-selective weed control	SL	120-200		When crop dormant in winter, or immediately after cutting	1			200-1000	0.180 1.00	*	Only one application of 1.0 kg/ha Lucerne has a unique use pattern. Trials are ongoing to define the PHI.
	Northern Europe		F	Non-selective weed control	SL	100-200		When crop dormant in winter, or immediately after cutting	1			200-1000	0.180 0.600	*	Lucerne has a unique use pattern. Trials are ongoing to define the PHI.

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hl min max	water l/ha min max	kg as/ha min max		
Autumn stubbles	Northern Europe		F	Non-selective weed control	SL	100-200		Before cultivation sowing or pre-emergence including minimum tillage	1-2			100-1000	0.084 1.000	NR	
	Southern Europe		F	Non-selective weed control	SL	100-200		Before cultivation sowing or pre-emergence including minimum tillage	1			200-1500	0.300 1.000	NR	
Spring land preparation	Northern Europe		F	Non-selective weed control	SL	100-200		Before cultivation sowing or pre-emergence including minimum tillage	1			100-1000	0.240 1.100	NR	
	Southern Europe		F	Non-selective weed control	SL	100-200		Before cultivation sowing or pre-emergence including minimum tillage	1			300-1500	0.180 1.000	NR	

Crop and/ or situation (a)	Member State or Country	Product name	F G or I (b)	Pests or Group of pests controlled (c)	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks: (m)
					Type (d-f)	Conc. of as (i)	method kind (f-h)	growth stage & season (j)	number min max (k)	interval between applications (min)	kg as/hl min max	water l/ha min max	kg as/ha min max		
Forestry, Ornamentals	Northern Europe		F	Non-selective weed control	SL	120-200	Between the plants	Before or after emergence	1			100-1000	0.360 1.100	NR	
	Southern Europe		F	Non-selective weed control	SL	100		Before cultivation sowing or pre-emergence including minimum tillage	1			150-600	0.400 0.600	NR	
Non-crop land –	Northern Europe		F	Non-selective weed control	SL	100-200			1			100-500	0.360 1.100	NR	
	Southern Europe		F	Non-selective weed control	SL	100-200			1			300-1500	0.360 1.000	NR	

Remarks:

(a) For crops, the EU and Codex classifications (both) should be used; where relevant, the use situation should be described (*e.g.* fumigation of a structure)
(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
(c) *e.g.* biting and suckling insects, soil born insects, foliar fungi, weeds
(d) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(e) GCPF Codes - GIFAP Technical Monograph No 2, 1989
(f) All abbreviations used must be explained
(g) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, *e.g.* overall, broadcast, aerial spraying, row, individual plant, between the plants - type of equipment used must be indicated
(i) g/kg or g/l
(j) Growth stage at last treatment (BBCH Monograph, Growth Stages of Plants, 1997, Blackwell, ISBN 3-8263-3152-4), including where relevant, information on season at time of application
(k) The minimum and maximum number of application possible under practical conditions of use must be provided
(l) PHI - minimum pre-harvest interval
(m) Remarks may include: Extent of use/economic importance/restrictions

IPCS INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY
Health and Safety Guide No. 51

PARAQUAT
HEALTH AND SAFETY GUIDE

UNITED NATIONS ENVIRONMENT PROGRAMME

INTERNATIONAL LABOUR ORGANISATION

WORLD HEALTH ORGANIZATION

WORLD HEALTH ORGANIZATION, GENEVA 1991

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Paraquat and Diquat

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CONTENTS

INTRODUCTION

The Environmental Health Criteria (EHC) documents produced by the International Programme on Chemical Safety include an assessment of the effects on the environment and on human health of exposure to a chemical or combination of chemicals, or physical or biological agents. They also provide guidelines for setting exposure limits.

The purpose of a Health and Safety Guide is to facilitate the application of these guidelines in national chemical safety programmes. The first three sections of a Health and Safety Guide highlight the relevant technical information in the corresponding EHC. Section 4 includes advice on preventive and protective measures and emergency action; health workers should be thoroughly familiar with the medical information to ensure that they can act efficiently in an emergency. Within the Guide is a Summary of Chemical Safety Information which should be readily available, and should be clearly explained, to all who could come into contact with the chemical. The section on regulatory information has been extracted from the legal file of the International Register of Potentially Toxic Chemicals (IRPTC) and from other United Nations sources.

The target readership includes occupational health services, those in ministries, governmental agencies, industry, and trade unions who are involved in the safe use of chemicals and the avoidance of environmental health hazards, and those wanting more information on this topic. An attempt has been made to use only terms that will be familiar to the intended user. However, sections 1 and 2 inevitably contain some technical terms. A bibliography has been included for readers who require further background information.

Revision of the information in this Guide will take place in due course, and the eventual aim is to use standardized terminology. Comments on any difficulties encountered in using the Guide would be very helpful and should be addressed to:

The Manager
International Programme on Chemical Safety
Division of Environmental Health

World Health Organization
1211 Geneva 27
Switzerland

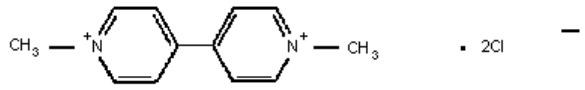
THE INFORMATION IN THIS GUIDE SHOULD BE CONSIDERED AS A STARTING POINT TO A COMPREHENSIVE HEALTH AND SAFETY PROGRAMME

1. PRODUCT IDENTITY AND USES

1.1 Identity

Common name	paraquat
Molecular formula:	$C_{12}H_{14}N_2Cl_2$ 1,1'-dimethyl-4,4'-bipyridyliumdichloride (paraquat dichloride)
	$C_{12}H_{14}N_2(CH_3SO_4)_2$ 1,1'-dimethyl-4,4'-bipyridylium dimethylsulfate sulfate (paraquat dimethylsulfate)

Chemical structure of 1,1'-dimethyl-4,4'-bipyridylium-dichloride:



CAS chemical name:	1,1'-dimethyl-4,4'-bipyridylium (9 Cl)
Trade names:	Gramoxone; Dextrone X; Esgram; and others
CAS registry number:	4685-14-7 (ion) 1910-42-5 (dichloride) 4032-26-2 (diiodide) 2074-50-2 (dimethylsulfate)
RTECS registry number:	DW1960000 (ion) DW2275000 (dichloride) DW2280000 (diiodide) DW2010000 (dimethylsulfate)
Relative molecular mass:	186.2 (ion)

1.2 Physical and Chemical Properties

Pure paraquat salts are white and the technical products, yellow. They are crystalline, odourless, hygroscopic powders.

Some of the physical properties of paraquat dichloride, the salt most used for herbicide formulations, are listed in the Summary of Chemical Safety Information (section 6).

Paraquat is slightly soluble in alcohol and practically insoluble in organic solvents.

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

1.3 Analytical Methods

Product analysis and determination of residues can be carried out colorimetrically after reduction; impurities can be determined by gas-liquid chromatography (GLC).

1.4 Uses

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

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

2. SUMMARY AND EVALUATION

2.1 Environmental Distribution and Transformation

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

(a) *Soil*

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

Paraquat is similarly strongly bound to humus and other organic material in soils containing little clay. However, in sandy soils with a low organic content, paraquat may be more readily released into soil water and be more bioavailable to organisms. While it is still unlikely to pose any hazard to the organisms in the soil, its bioavailability to higher animals feeding on soil biota may be increased.

(b) *Water*

When paraquat was applied as an aquatic herbicide, at a normal application rate of 1 mg/litre, the concentration was found to decrease to about one half of the initial level within 36 h and to below 0.01 mg/litre in less than 2 weeks. Phytotoxic damage to crops irrigated with treated water is unlikely to occur, if an interval of 10days is observed between treatment of the water and its use, because of the rapid decrease of paraquat residues in the water.

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

(c) *Air*

Paraquat is not volatile; thus, inhalation of paraquat vapour is not a problem. The amount of respirable airborne paraquat was found to be negligible under normal conditions of use.

The amount of paraquat present in airborne dust was found to range from 0.0004 to 0.001 mg/m^3. The paraquat was so strongly bound to the dust particles that it did not exert any toxicological effect on rats that were exposed via inhalation.

2.2 Kinetics and Metabolism

Although toxic amounts of paraquat may be absorbed after oral ingestion, the greater part of ingested paraquat is eliminated unchanged in the faeces. Paraquat is poorly absorbed through normal human skin, but the extent of absorption may increase significantly in cases of severe skin damage. The toxic effects of paraquat are largely the result of a metabolically catalysed, single-electron, reduction-oxidation reaction, resulting in depletion of cellular NADPH and the generation of potentially toxic forms of oxygen, such as the superoxide radical.

Absorbed paraquat is distributed via the bloodstream to practically all organs and tissues of the body, but storage is not prolonged in any tissue. The lung selectively accumulates paraquat from the plasma by an energy-dependent process. Consequently, this organ contains higher concentrations than other tissues. Since the removal of absorbed paraquat occurs mainly via the kidneys, an early onset of renal failure following uptake of toxic doses will have a marked effect on paraquat elimination and distribution, and on its accumulation in the lungs.

2.3 Effects on Experimental Animals

Paraquat induces a characteristic dose-related lung injury in the rat, mouse, dog, and monkey, but not in the rabbit, guinea-pig, or hamster.

Pulmonary toxicity is characterized by the initial development of pulmonary oedema and damage to the alveolar epithelium, which may progress to fibrosis. Exposure to high doses of paraquat may also cause less severe toxic effects in other organs, primarily the liver and kidney. Minor toxic effects have been noted in the nervous, cardiovascular, blood, adrenal, and male reproductive systems, but only at high doses. Toxic effects have not been reported at low doses of paraquat.

Paraquat has not been found to be teratogenic or carcinogenic in long-term studies on rats and mice. The results of in vitro mutagenicity studies were inconclusive, but generally suggested a weak potential activity; the results of *in vivo* studies were negative.

Concentrated solutions of paraquat have been found to irritate both the skin and the eyes.

The FAO/WHO (1986) determined no-observed-effect levels of paraquat dichloride of: 17 and 52 mg/kg diet, equivalent to 1.9 and 5.9 mg/kg body weight, per day, for male and female mice, respectively; 30 mg/kg diet, equivalent to 1.1 and 1.2 mg/kg body weight, per day, for male and female rats, respectively; and 20 mg/kg diet, equivalent to 0.62 and 0.66 mg/kg body weight, per day, for male and female dogs, respectively.

2.4 Effects on Human Beings

2.4.1 Occupational exposure

There are several studies on paraquat exposure during normal agricultural use. The main route of occupational exposure of agricultural workers is via the skin. The spray aerosol and dust particles are relatively large and are mostly deposited in the upper respiratory tract. Paraquat aerosol concentrations (total airborne) ranged up to 0.55 mg/m^3 in the work situation, depending on the method of spraying. Under normal conditions of use, the amount of respirable airborne paraquat was found to be insignificant.

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

2.4.2 Poisoning by paraquat

A large number of cases of poisoning have been reported, following the drinking of concentrated paraquat, overwhelmingly with suicidal intent. A few unusual cases, in which the liquid concentrate was used improperly to treat body lice, have also been reported.

The possibility of patient recovery clearly depends on the dose of paraquat taken and the time interval between ingestion and the commencement of emergency treatment. Speed is imperative, and it should be noted that emergency treatment can start before the patient arrives at hospital.

In less severe cases, without lung damage, recovery has always been complete.

(a) *Suicidal ingestion*

The majority of paraquat poisonings are due to swallowing liquid concentrates. The response to treatment is disappointing and the mortality rate is high. Ingestion of granular paraquat is less common and usually causes milder poisoning, though fatalities have occurred.

(b) *Accidental poisoning*

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

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

(c) *Occupational poisoning*

A number of cases of severe poisoning following inappropriate behaviour have occurred. Fatal poisoning through dermal soaking with insufficiently diluted paraquat, associated with severe skin lesions, has been reported. This may result from continuous contact with paraquat-soaked clothing, e.g., as a result of using a leaking sprayer.

Splashes of liquid concentrate may lead to severe ocular and skin damage. Spraying with inadequately diluted paraquat (e.g., with ultra-low-volume application) may result in similar problems.

Local skin effects (contact, irritative, or photoallergic dermatitis), delayed wound healing, and nail damage have been observed among formulation workers and among individuals handling the herbicide improperly. Blepharitis and epistaxis may result through the delayed irritative action of paraquat. Such incidents illustrate the need for strict personal hygiene and rigorous adherence to safe handling procedures (see section 4).

2.5 Effects on the Environment

The fact that paraquat is used as a herbicide indicates that it is toxic for aquatic and terrestrial vegetation.

On reaching the soil, paraquat becomes rapidly and strongly adsorbed on the clay minerals present. This process inactivates the herbicidal activity of the compound. Strongly-bound paraquat does not have any adverse effects on soil microfauna or soil microbial processes.

Paraquat residues disappear rapidly from water by adsorption on aquatic weeds and by strong adsorption on the bottom mud. The toxicity of paraquat for fish is low, and the compound is not cumulative. Normal applications of paraquat for aquatic weed control are not harmful for aquatic organisms. However, when applying paraquat to water containing heavy weed growth, care should be taken to treat only a part of the growth, since oxygen consumption by subsequent weed decay may result in a reduction in dissolved oxygen levels to an extent that may be dangerous for fish.

Treated water should not be used for overhead irrigation for 10 days following treatment.

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

Paraquat is not subject to bioconcentration and has not been found to accumulate in food chains.

3. CONCLUSIONS AND RECOMMENDATIONS

3.1 Conclusions

3.1.1 General population exposure

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

This likely lack of hazard with normal usage of dilute paraquat contrasts strongly with the potentially serious hazard that may result from handling concentrated paraquat.

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

The number of suicides by means of paraquat is of great concern, but the total number of such suicides is unknown. The reasons for suicide may be manifold and complex, and paraquat is only one among many means towards this goal. However, because of the prolonged and painful way of dying from paraquat poisoning, every effort should be made to diminish its attractiveness and availability for this purpose.

3.2.1 Occupational exposure

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

Spray concentrations should not exceed 5 g paraquat ion/litre, in order to avoid skin damage and absorption of the herbicide through the

skin. Hand-held, ultra-low-volume application should be discouraged.

3.1.3 Environment

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

3.2 Recommendations

3.2.1 General

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

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

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

National Registers of cases of poisoning should be maintained for all classes of chemicals, including paraquat. The information obtained should be made available to international bodies, such as the World Health Organization.

3.2.2 Prevention and treatment

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

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

4. HUMAN HEALTH HAZARDS, PREVENTION AND PROTECTION, EMERGENCY ACTION

4.1 Main Human Health Hazards, Prevention and Protection, First Aid

Paraquat is highly toxic and often fatal, if swallowed. Contact with liquid products can cause severe damage to the skin or eyes. Utmost care must be taken to avoid exposure during handling operations and application in the field. In applications where inhalation exposure to aerosols containing paraquat is likely, proper respiratory protective equipment should be used.

The human health hazards, together with preventive and protective measures and first-aid recommendations, are listed in the Summary of Chemical Safety Information (section 6).

4.1.1 Advice to physicians

The most important measures are the immediate neutralization of ingested paraquat by 15% Fuller's earth, bentonite, or activated charcoal, and urgent removal of the poison by vomiting or, when possible, gastric lavage. The urgency of these measures is such that, where transfer to hospital may involve a delay of an hour or more, the emergency treatment may need to be given by a paramedical person, e.g., a nurse or a medical assistant, without any delay. Furthermore, Fuller's earth should be given together with a strong purgative, such as magnesium sulfate or mannitol.

Admission to a hospital (preferably a specialized intensive care unit), either directly, or after emergency treatment elsewhere, is essential.

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

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

Care must be exercised in the administration of most of these

treatments, as the following serious complications may occur: perforation of the oesophagus during gastric intubation; serious blood chemistry disturbance, when severe diarrhoea is induced; fluid overload during forced diuresis.

In centres where facilities for analytical procedures are available, measurement of urinary, or, ideally, plasma levels of paraquat may give guidelines for the required intensity of treatment or likely prognosis. Determination of paraquat levels in stomach washings, serum, and urine is useful for the management of poisoning. The urinary levels decline rapidly during the 24 h following exposure and may remain low for some weeks.

Many other therapies including corticosteroids, immunosuppressive treatment, vitamins, beta-blocking and alkylating agents, alpha-tocopherol, superoxide dismutase and/or glutathione peroxides proved to be of no significant importance in human paraquat poisoning. The administration of oxygen should be avoided, unless vital for the patient's comfort.

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

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

In cases of skin and eye contamination, irrigation with water (preferably running water) should be commenced urgently and must be continued uninterrupted for at least 15 minutes (timed by the clock). Eye cases should always be taken for medical treatment. In cases of skin contamination by the concentrate, or extensive and/or prolonged contamination by the diluted material (particularly where signs of skin irritation are present), the patient must be assessed at hospital for systemic poisoning.

4.1.2 Health surveillance advice

Pre-employment and annual medical examinations should be made available to all persons who are regularly exposed to paraquat at potentially hazardous levels. Attention should be given to all normal parameters of overall health status, with particular attention to the state of the skin and of pulmonary function.

4.1.3 Personal protection and hygienic measures

Avoid all contact with skin, eyes, nose, and mouth, when handling concentrated paraquat. Wear PCV-, neoprene- or butyl-rubber gloves (preferably gauntlet form), neoprene apron, rubber boots, and face shield.

* Wear a face-shield when handling and applying the diluted formulation.

* Immediately remove heavily contaminated clothing and wash underlying skin.

* Wash clothes before re-use.

* Do not eat, drink, or smoke, when using paraquat.

* Wash splashes from skin or eyes immediately.

* Do not inhale spray.

* Wash hands and exposed skin, before meals and after work.

* Keep away from food, drink, and animal feed.

* Paraquat should not be sprayed with inadequate dilution, e.g., by hand-held, ultra-low-volume application.

* It should not be used by people suffering from dermatitis or by people with wounds, notably on the hands, until these have healed.

4.2 Explosion and Fire Hazards

Paraquat products are generally not flammable. If involved in a fire, control with dry powder or alcohol-resistant foam. Advise the fire service that protective clothing and self-contained breathing apparatus should be worn, to avoid skin contamination and the breathing of toxic fumes. Confine the use of water spray to the cooling of unaffected stock, thus avoiding the accumulation of polluted run-off from the site.

4.3 Storage

Store technical material and formulations away from heat, under lock and key, and out of reach of children, animals, and unauthorized personnel. Store in an area designated for pesticide storage, preferably without drains.

Store away from foodstuffs and animal feed.

4.4 Transport

Ensure that containers are sound and that labels are securely fixed and undamaged before dispatch. Comply with local transport regulations.

Do not load together with foodstuffs or animal feed.

Accident procedures:

Avoid exposure by the use of appropriate protective clothing, gloves, and goggles or masks. Keep spectators away from leaking or spilled product and prevent smoking, and the use of naked flames, in the immediate vicinity.

Extinguish fires with dry powder, carbon dioxide, alcohol-resistant foam, sand, or earth.

Prevent liquid from spreading to other cargo, vegetation, or waterways by containing it with the most readily available barrier material, e.g., earth or sand.

Absorb spilled liquid and cover contaminated areas with earth, lime, sand, or other absorbent material; sweep up and place in a secure container for subsequent safe disposal.

4.5 Spillage and Disposal

4.5.1 Spillage

Avoid exposure by the use of appropriate protective clothing and face-shield.

Empty any product remaining in damaged or leaking containers into a clean empty drum and label.

Absorb spillage with lime, damp sawdust, sand, or earth and dispose of safely (see below). If spillage is large, contain it by building a barrier of earth or sandbags.

Decontaminate empty, damaged, or leaking containers with a 10% sodium carbonate solution, added at the rate of at least 1 litre per 20-litre drum. Puncture or crush containers to prevent re-use.

4.5.2 Disposal

Waste containing paraquat should be burnt in a proper high temperature incinerator with effluent gas scrubbing.

Where no incinerator is available, contaminated absorbents or surplus products should be decomposed by hydrolysis at pH 12 or above. A 5% sodium hydroxide (caustic soda) solution or saturated (7-10%) sodium carbonate (washing soda) solution can be used. Before disposal of the resultant waste, the material must be analysed to ensure that the active ingredient has been degraded to a safe level.

Paraquat is rapidly inactivated by clay soil. If the above mentioned methods are not possible, it can be buried in an approved landfill.

Never pour untreated waste or surplus products into public sewers or where there is any danger of run-off or seepage into streams, water-courses, open waterways, ditches, fields with drainage systems, or the catchment areas of boreholes, wells, springs, or ponds.

5. HAZARDS FOR THE ENVIRONMENT AND THEIR PREVENTION

Paraquat is highly toxic for aquatic and terrestrial vegetation. Under normal conditions of use, the toxicity of paraquat for aquatic animal life is low, though resulting depletion of water-oxygen, because of weed decay, may pose a problem.

Do not contaminate ponds, waterways, or ditches with the product or used containers.

6. SUMMARY OF CHEMICAL SAFETY INFORMATION

This summary should be easily available to all health workers

concerned with, and users of, paraquat. It should be displayed at, or near, entrances to areas where there is potential exposure to paraquat, and on processing equipment and containers. The summary should be translated into the appropriate language(s). All persons potentially exposed to the chemical should also have the instructions in the summary clearly explained.

Space is available for insertion of the National Occupational Exposure Limit, the address and telephone number of the National Poison Control Centre, and for local trade names.

PARAQUAT

($C_{12}H_{14}N_2Cl_2$) 1,1'-dimethyl-4,4'-bipyridylium dichloride (paraquat dichloride)

CAS registry no. 1910-42-5

RTECS registry no. DW2275000

PHYSICAL PROPERTIES		OTHER CHARACTERISTICS
Physical state	crystalline powder	Total contact herbicide, used to control broad-leaved and grassy weeds; corrosive to metals, and incompatible with alkylarylsulfonate wetting agents; stable in acid or neutral solutions, but readily hydrolysed by alkali; slightly soluble in alcohol and practically insoluble in organic solvents
Colour	yellow	
Odour	odourless	
Relative molecular mass	186.2 (ion)	
Specific gravity (20°C)	1.240-1.260	
Melting point (°C)	175-180	
Boiling point (°C)	approximately 300 with decomposition	
Solubility in water (20°C)	700 g/litre	
pH of liquid formulation	6.5-7.5	
Vapour pressure	not measurable	

HAZARDS/SYMPTOMS	PREVENTION AND PROTECTION	FIRST AID
SKIN: Irritating to skin, may cause blisters	Proper application technique; proper skin protection, including impervious clothing and gloves	Remove contaminated clothing; wash skin with soap and water; wash clothes before re-use
EYES: Severe irritant	Wear face-shield; goggles	Flush immediately with clean water for at least 15 minutes; seek medical advice and observe for delayed effects
INHALATION: Irritant to respiratory system	Avoid inhalation of fine dust and mist; use proper respiratory protection	Fresh air
INGESTION: Unlikely occupational hazard	Do not eat, drink, or smoke during working hours; wash hands	
Accidental or deliberate ingestion may cause vomiting, abdominal discomfort, and soreness of mouth and throat; signs of liver and kidney damage may appear in 1-3 days; signs of lung damage may gradually develop after a few days; paraquat can kill		Obtain medical attention immediately; transport to hospital urgently; induce vomiting; do not delay

SPILLAGE	STORAGE	FIRE AND EXPLOSION
Absorb spillage with lime, damp sawdust, sand, or earth; sweep up, place in closed container, and dispose of safely; avoid contamination of personnel, ponds, and waterways	Store in locked, well-ventilated storeroom, away from foodstuffs and animal feed, children, and unauthorized personnel	Non-flammable and non-explosive

WASTE DISPOSAL		
Burn in high-temperature incinerator with effluent scrubbing;	National Occupational Exposure Limit:	UN No. 2781, 2782, 3015, 3016

alternatively treat with 5% caustic soda as a hydrolysing agent; comply comply with local regulations

National Poison Control Centre:

Local trade names:

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7. CURRENT REGULATIONS, GUIDELINES, AND STANDARDS

The information given in this section has been extracted from the International Register of Potentially Toxic Chemicals (IRPTC) legal file. A full reference to the original national document from which the information was extracted can be obtained from IRPTC. When no effective date appears in the IRPTC legal file, the year of the reference from which the data are taken is indicated by (r).

The reader should be aware that regulatory decisions about chemicals, taken in a certain country, can only be fully understood in the framework of the legislation of that country. The regulations and guidelines of all countries are subject to change and should always be verified with appropriate regulatory authorities before application.

7.1 Previous Evaluations by International Bodies

The FAO/WHO Joint Meeting on Pesticide Residues (JMPR) has reviewed residues and toxicity data on paraquat on several occasions (1970, 1972, 1976, 1978, 1981, 1982, 1985, and 1986). In 1986, it estimated the acceptable daily intake (ADI) for man to be 0-0.006 mg paraquat dichloride/kg body weight (or 0.004 mg paraquat ion/kg body weight).

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

The WHO/FAO (1979), in its series of "Data sheets on chemical pesticides", issued one on paraquat (No. 4). It classified technical paraquat as moderately hazardous in normal use (WHO, 1990).

7.2 Exposure Limit Values

Some exposure limit values are given in the table on pages 30-32.

7.3 Specific Restrictions

Paraquat is prohibited for use in, amongst other countries, Finland and Sweden.

In some other countries, e.g., the Federal Republic of Germany, Hungary, the United Kingdom, and the USA, the use of paraquat is only registered for certain specified applications or for use under certain specified conditions. For instance, in the United Kingdom and the USA, the use of the 20% liquid is restricted to bona fide, certified professionals. In the Federal Republic of Germany, paraquat may not be handled by adolescents or pregnant or nursing women.

EXPOSURE LIMIT VALUES

Medium	Specification	Country/ organization	Exposure limit description[a]	Value	Effective date
AIR	Work-place	Argentina	Maximum permissible concentration[b]		
			- Time-weighted average (TWA)	0.1 mg/m^3	1979
		Australia	Threshold limit value (TLV)[b]		
			- Time-weighted average (TWA) of respirable dust (provisional)	0.5 mg/m^3	1983
		Belgium	Tolerable limit value (TLV)		
			- Time-weighted average (TWA)	0.1 mg/m^3	1988
		Bulgaria	Maximum permissible concentration[b]		
			- Time-weighted average (TWA)	0.1 mg/m^3	1987
		Germany, Federal Republic of	Maximum work-site concentration (MAK)[b]		
			- Time-weighted average (TWA)	0.1 mg/m^3	1988
			- Short-term exposure level (STEL) (5min) (8 × per shift) (ceiling value)	0.2 mg/m^3	
		Hungary	Maximum permissible concentration		
			- Time-weighted average (TWA)	0.02 mg/m^3	1978

			- short-term exposure level (STEL) (30 min)	0.02 mg/m^3	
		Netherlands	Maximum permissible concentration - Time-weighted average (TWA)	0.1 mg/m^3	1986
		Switzerland	Maximum work-site concentration (MAK)[b] - Time-weighted average (TWA)	0.1 mg/m^3	1987

Medium	Specification	Country/ organization	Exposure limit description[a]	Value	Effective date
AIR	Work-place	United Kingdom	Recommended limit - 8-h Time-weighted average (TWA) (of respirable dust)	0.1 mg/m^3	1987
		USA (OSHA)	Permissible exposure limit (PEL)[b] - Time-weighted average (TWA) (respirable dust)	0.1 mg/m^3	1989
		USA (ACGIH)	Threshold limit value (TLV) - Time-weighted average (TWA) (respirable sizes)	0.1 mg/m^3	1987
FOOD	Intake from	FAO/WHO	Acceptable daily intake (ADI) (paraquat ion)	0-0.004 mg/kg body weight	1986
FOOD	General	FAO/WHO	Maximum residue limit (MRL) for specified products	0.01-10 mg/kg	1983
		European Community	Maximum levels in and on fruit and vegetables (expressed as paraquat cation)	0.05 mg/kg	1989

[a] TWA=time-weighted average over one working day (usually 8h).
[b] Skin absorption.

7.4 Labelling, Packaging, and Transport

The United Nations Committee of Experts on the Transportation of Dangerous Goods classifies paraquat in:

* Hazard Class 6.1: poisonous substance.

* Packing Group II: substances and preparations presenting a serious risk of poisoning, when the active ingredient is within the range of 40-100%.

* Packing Group III: substance presenting a relatively low risk of poisoning in transport, when the active ingredient is in the range of 8-40%.

The labels should be as follows:

Division 6.1
Poisonous (toxic) substances
Packing Groups: I and II
Symbol (skull and crossbones): black;
Background: white

Division 6.1
Poisonous (toxic) substances
Packing Group: III
The bottom half of the label should bear the inscriptions:
HARMFUL
Stow away from foodstuffs
Symbol (St Andrew's Cross over an ear of wheat): black; Background: white

The European Economic Community legislation requires labelling of paraquat as a dangerous substance using the symbol:

The label must read:

> *Toxic in contact with skin and if swallowed; irritating to eyes, respiratory system and skin.*

The European Economic Community legislation on the labelling of pesticide preparations classifies paraquat in Class 1A, for the purpose of determining the label for preparations containing paraquat and other active ingredients.

The chemical name must be stated on the label.

The FAO specifications for plant protection products containing paraquat specify the composition and purity of its formulations and the methods for checking this. They also specify the quality of the containers.

7.5 Waste Disposal

In the USA, paraquat is regarded as a hazardous waste and permits are required for its discharge from any point source into USA national waters. This requirement contains detailed instructions.

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See Also:
- Toxicological Abbreviations
- Paraquat (PIM 399)
- Paraquat (JMPR Evaluations 2003 Part II Toxicological)
- Paraquat (AGP:1970/M/12/1)
- Paraquat (WHO Pesticide Residues Series 2)
- Paraquat (Pesticide residues in food: 1976 evaluations)
- Paraquat (Pesticide residues in food: 1978 evaluations)
- Paraquat (Pesticide residues in food: 1981 evaluations)
- Paraquat (Pesticide residues in food: 1982 evaluations)
- Paraquat (Pesticide residues in food: 1986 evaluations Part II Toxicology)

Pesticide residues in food - 2003 - Joint FAO/WHO Meeting on Pesticide Residues

PARAQUAT

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Explanation

Paraquat is a bipyridilium herbicide that was evaluated by the JMPR in 1970, 1972, 1976, 1985 and 1986 (Annex 1, references *14, 18, 26, 47*), in order to establish an acceptable daily intake (ADI). A toxicological monograph was published after the 1970 JMPR and addenda to the monograph were published after the 1972, 1976 and 1982 Meetings. A toxicological monograph was published after the 1986 JMPR. At the JMPR in 1970, an ADI of 0-0.001 mg/kg bw, as paraquat dichloride, was established. The 1972 JMPR assigned an ADI of 0-0.002 mg/kg bw, while the 1982 JMPR reduced the ADI to 0-0.001 mg/kg bw. The 1986 JMPR established an ADI of 0-0.004 mg/kg bw as paraquat ion (equal to 0-0.006 mg/kg bw as the dichloride).

Paraquat was re-evaluated by the present Meeting within the periodic review programme of the Codex Committee on Pesticide Residues. A considerable amount of data has been generated since 1986 and was submitted for evaluation; these data include studies on the absorption, distribution, metabolism and excretion of paraquat and numerous studies of toxicity (acute, reproductive and developmental). Furthermore, a substantial number of papers in the open literature on, inter alia, the genotoxicity and neurotoxicity of paraquat have been reviewed. In all studies relevant to risk assessment, doses and intakes are expressed as paraquat ion.[1]

Evaluation for acceptable daily intake

1. Biochemical aspects

1.1 Absorption, distribution and excretion

Rats

In a study of the absorption, distribution and excretion of paraquat, a single oral dose of ^{14}C-labelled paraquat ion at 1 mg/kg bw was administered to five male and five female Alpk: ApfSD rats by gavage. Paraquat dichloride was used as the test material; the purity of the ^{14}C-labelled material was 100%, while that of the unlabelled material was >96%. The specific activity of the radiolabelled material was 4.0996 GBq/mmol and that of the dosing solution was 4.12 MBq/g. Urine was collected 6 h after dosing and urine and faeces were collected separately at 12, 24, 36, 48 and 72 h after dosing. The animals were killed after 3 days and selected organs and tissues were removed. The amount of radioactivity remaining in the blood, selected tissues and the carcasses was estimated. Excretion of the radiolabel was

rapid: in the first 24 h, in males 17.9% of the dose was excreted in the urine and 63.1% in the faeces. Equivalent figures for females were 11.6% and 74.1%. More than 90% of the radiolabel was eliminated in 72 h in both sexes. More radiolabel was excreted in the faeces of females than males. Only low concentrations of radiolabel were retained in the residual carcasses (0.64% and 0.54% of the administered dose in male and females respectively), the highest concentrations (0.01-0.02%) being found in the liver, lungs and kidneys (Lythgoe & Howard, 1995a).

In a second study of the absorption, distribution and excretion of paraquat, daily oral doses of paraquat (1 mg of paraquat ion/kg bw) were administered by gavage to eight male and eight female Alpk: ApfSD rats for 14 days. Paraquat dichloride was used as the test material; the purity of the ^{14}C-labelled material was 100%, while that of the unlabelled material was >96%. A single oral dose of ^{14}C-labelled paraquat ion at 1 mg/kg bw was subsequently administered by gavage. The specific activity of the radiolabelled material was 4.0996 GBq/mmol and that of the dosing solution was 4.12 MBq/g. Urine was collected 6 h after dosing and urine and faeces were collected separately at 12, 24, 36, 48 and 72 h after dosing. The animals were killed after 3 days and selected organs and tissues were removed. The amount of radioactivity remaining in the blood, selected tissues and the carcasses was estimated. Excretion of the radiolabel was rapid: in the first 24 h, in males, 18.8% of the dose was excreted in the urine and 68.3 % in the faeces. Equivalent figures for females were 10.3% and 70.7%. Of the radiolabel, 92.5% was eliminated within 72 h in the male rats and 93.9% in female rats. Tissue concentrations of radiolabel were generally lower in the females than in males. Only low concentrations of radiolabel were retained in the residual carcass (0.70% and 0.55% of the administered dose in males and females, respectively), the highest concentrations being found in the lungs, livers and kidneys (Lythgoe & Howard, 1995b).

In a third study of the absorption, distribution and excretion of paraquat, a single dose of ^{14}C-labelled paraquat (50 mg of paraquat ion/kg bw) was administered by gavage to five male and five female Alpk: ApfSD rats. The specific activity of the dosing solution was 79.83 kBq/g. Urine was collected 6 h after dosing and urine and faeces were collected separately at 12, 24, 36, 48 and 72 h after dosing. The animals were killed after 3 days and selected organs and tissues were removed. The amount of radioactivity remaining in the blood, selected tissues and the carcasses was estimated. Excretion of the radiolabel was rapid: in the first 24 h, in males, 9.2% of the dose was excreted in the urine and 54.5 % in the faeces. Equivalent figures for females were 11.6% and 49.6%. Of the label, 92.7% was eliminated in 72 h in the male rats and 91.7% in female rats. The highest concentrations of radioactivity were retained in the lungs and residual carcass (Lythgoe & Howard, 1995 c).

Daniel & Cage (1966) investigated the absorption and excretion of paraquat (and diquat) in albino Wistar rats given ^{14}C-labelled paraquat dichloride (0.94 mCi/mmol) as single oral doses at 4 or 6 mg/kg bw, or paraquat dimethosulfate as oral doses at 2.5-24 mg/kg bw, or subcutaneously at a dose of 21 or 23 mg/kg bw. Paraquat was poorly absorbed from the gut. After administration by either route, most of the radiolabel was found in the excreta within 2 days. After oral administration of paraquat, no radiolabel was detected in the bile (Daniel & Cage, 1966).

Dey et al. (1990) studied the pharmacokinetics of ^{14}C-labelled paraquat (111 mCi/mmol) administered to male Sprague-Dawley rats as a single subcutaneous injection at a dose of 72 µmol/kg bw. This dose was considered to be one that would produce lung damage but avoid kidney damage. Blood was sampled through indwelling cannulae, and urine and faeces were collected at 2, 4, 6, 8, 12, and 24 h and then daily for 7 days. Non-cannulated rats treated in the same way were exsanguinated at intervals from 10 min to 7 days after dosing; tissue concentrations of ^{14}C were measured in selected organs. The right lungs and kidneys were processed for histopathological examination. Histopathological examination showed changes characteristic of paraquat-induced lung pathology, without renal damage. Paraquat was rapidly absorbed, with peak blood concentrations of 58 µmol/l after 20min. The pharmacokinetics were best characterized as a two-compartment open model, the mean half-life (t½) being approximately 40 h. Highest tissue concentrations observed were in the kidney (358 nmol/g of tissue) and lung (64 nmol/g tissue), both at 40 min after administration of paraquat (Dey et al., 1990).

The distribution of paraquat in the brain was examined in male adult Wistar-derived Alderley Park rats after subcutaneous administration of paraquat (containing ^{14}C-labelled paraquat with a specific activity 2 mCi/mmol) at a dose of 20 mg of ion/kg bw. The aim of this study was to determine whether paraquat crosses the blood-brain barrier. After administration, the concentration of radiolabel in the brain reached a maximum (0.05% of administered dose) within the first hour and then rapidly disappeared. Twenty-four hours after administration, however, a residual amount of paraquat still remained in the brain (1.6 nmol/g wet weight) and could not be removed by intracardiac perfusion. Most of the paraquat was associated with five structures, two of which (the pineal gland and linings of the cerebral

ventricles) lie outside the blood-brain barrier. The remaining three brain areas (the anterior portion of the olfactory bulb, hypothalamus and area postrema) do not have a blood-brain barrier. Overall, the distribution of ^{14}C-labelled paraquat in the brain 24 h after systemic administration was highly correlated to the blood volume. The authors concluded that paraquat remaining in the brain 24 h after systemic administration was associated with elements of the cerebral circulatory system, such as the endothelial cells that make up the capillary network, and that there was limited entry of paraquat into brain regions without a blood-brain barrier (Naylor et al., 1995).

The extent to which paraquat entered the brain was compared in groups of neonatal (aged 10 days), adult (aged 3 months) and elderly (aged 18 months) Wistar-derived Alpk: ApfSD rats. Both male and female neonatal rats were studied, while the adult and elderly rats were males. Groups of six to eight rats were given a single dose of [^{14}C]paraquat (103 mCi/mmol) at 20 mg/kg, administered subcutaneously, and killed 30 min or 24 h after injection; blood was taken by cardiac puncture and brains were removed. Groups of four neonatal, adult or elderly rats were similarly injected and killed 24 or 48 h after dosing; the brains of these animals were subjected to histopathological examination. At all ages, plasma concentrations of paraquat were much higher at 30 min than at 24 h. At 30 min, the concentration of paraquat in the brain was highest in the elderly rats. While at 24 h the concentration in the brains of the adult and elderly rats had decreased, it remained high in the brains of the neonatal rats. Autoradiography showed similar distributions of paraquat in the various brain regions, paraquat being found in areas outside the blood-brain barrier or where the barrier is incomplete, e.g. the dorsal hypothalamus, area postrema and anterior olfactory bulb. There was no evidence for paraquat-induced cell damage in the neonatal brain, although there was increased paraquat entry into the brain in neonates than in older rats (Widdowson et al., 1996a).

In a study of the entry of paraquat into the brain, five male Wistar-derived Alpk: ApfSD rats were given paraquat (labelled with [^{14}C]paraquat; specific activity, 20 µCi/ml) at a dose of 5 mg of ion/kg bw per day) daily for 14 days by oral administration, and another five rats received a single oral dose of paraquat (labelled with [^{14}C]paraquat; specific activity 106 µCi/ml) at a dose of 5 mg ion/kg bw. The rats were killed 24 h after the last of the 14 doses or after the single dose. Concentrations of paraquat in the brain were 10 times higher in rats receiving multiple doses than in those receiving single doses. The same paper described a study of neuropathology, which included behavioural tests (see below) (Widdowson et al., 1996b).

In a study that used a brain microanalysis technique with detection by high-performance liquid chromatography-ultraviolet (HPLC-UV), paraquat, administered subcutaneously at a dose of 5, 10 or 20 mg/kg bw, was found to appear in the dialysate of the striatum in male Wistar rats. It was also found that paraquat did not allow 1,2,3,6-tetrahydropyridinium ion to penetrate the blood-brain barrier. Intraperitoneal injection of L-valine (200 mg/kg) 30 min before administration of paraquat at a dose of 20 mg/kg bw reduced the striatal extracellular concentrations of paraquat. The authors hypothesized that paraquat is taken up into the brain via the neutral amino acid transporter (Shimizu et al., 2001; see also McCormack & Di Monte, 2002).

In a study in anaesthetized male Wistar rats, the excretion of paraquat was found to be greater than the glomerular filtration rate, and to be concentration-dependent and saturable, implying that paraquat is secreted by a process involving active transport (Chan et al., 1997).

Groups of albino Wistar rats were given diets containing paraquat at a concentration of 50, 120 and 250 mg/kg (as paraquat ion) for 8 weeks. Groups comprised 30 animals at the two lower dietary concentrations and 40 animals at the highest concentration. After 2, 4 and 8 weeks, 10 rats per group were killed and selected organs were analysed for paraquat. At 50 mg/kg, paraquat was not detected in the kidneys, liver, brain or lung at any time, but was present in the gastrointestinal tract and, at low concentrations, in muscle. At 120 mg/kg, paraquat was detected in kidneys, lung and gastrointestinal tract. At 250 mg/kg, paraquat was detected in kidneys, lung and gastrointestinal tract (Litchfield et al., 1973).

Mice

The tissue distribution of paraquat was studied using whole body autoradiography in mice treated by intravenous injection. Mice received ^{14}C-labelled paraquat at a dose of 20 mg of paraquat ion/kg. Two mice were killed at each time-point after the paraquat injection (10 min, 1, 5, 24 and 72 h). Paraquat was found to be concentrated in the liver and cartilage, and was not detected in the central nervous system. Paraquat was also present in the lungs, notably so after 24 h. At 72 h, radioabel was only present in the stomach and intestinal contents (Litchfield et al., 1973).

Hens

Three Warren hens were given gelatin capsules containing ^{14}C-ring-labelled paraquat (purity, 99.7%; specific activity, 1.216 × 105 dpm/mg) at a daily dose of 4.52 mg of paraquat ion (0.247 mCi) for 10 days. One hen was used as the control. The hens were killed 4 h after the last dose. The highest concentration of radiolabel was found in the kidneys, while rather less was found in the gizzard and liver. Very little was found in fat. Paraquat was found at a concentration of 0.052 µg/g in eggs, mostly in the yolk (Hendley et al., 1976b).

Dogs

Greyhound dogs were given ^{14}C-labelled paraquat at a dose of 30-50 µg/kg bw. The authors of this study considered that the kinetics could be described by a three-compartment open linear system (Bennett et al., 1976).

The elimination of paraquat was studied in the female greyhound dog. After intravenous injection of low doses (30-50 µg/kg) of ^{14}C-labelled paraquat, radiolabel was found to be rapidly excreted in the urine, the clearance being greater than the glomerular filtration rate, suggesting a process of active secretion. Secretion could be inhibited by *N'*-nicotinamide. Large doses of paraquat (20 mg/kg bw) produced renal failure, as evidenced by a decrease in both renal creatinine and paraquat clearance. The elimination of paraquat could be described by a three-compartment open model (Hawksworth et al., 1981).

Goats

An English white nanny goat was dosed with ^{14}C-ring-labelled paraquat (purity, 99.7%; specific activity, 2.28 × 104 dpm/µg) in the diet at a dose equivalent to 100 µg of paraquat ion/g of diet. This was done by adding 206.6 mg of radiolabelled paraquat (as ion) to the diet at the morning and afternoon feeding, daily for 7 days. Another nanny goat was used as the control. The goats were killed 4 h after the last feeding with radiolabelled paraquat. Radioactivity was measured in the urine, faeces, stomach, milk, and in selected tissues. At sacrifice, 2.4% and 50.5% of the administered material had been excreted in the urine and faeces respectively. The stomach contents included 33.2% of the administered dose. The highest concentration of radiolabel seen in the milk was 0.009 µg/g (on the morning of day 7). The highest tissue concentrations were found in the kidney and liver (Hendley et al., 1976a).

Pigs

A pig (Large White × Welsh boar) was given 100 mg of ^{14}C-methyl-labelled paraquat (purity, 99.3%; specific activity, 4.88 × 104 dpm/µg of paraquat ion) on 7 consecutive days; this was calculated to be equivalent to about 50 µg of paraquat ion/g of diet. A second boar acted as the control. The daily dose was spotted onto the commercial pig diet. The pig was killed 2 h after the final dose. The highest concentrations of paraquat were present in the kidney and liver (Leahey et al., 1976).

In a second study in pigs, ^{14}C-methyl-labelled paraquat dichloride (purity, 99.45%; specific activity, 4.72 dpm/µg) at a daily dose of approximately 100 mg of paraquat ion was administered twice daily for 7 days to a Large White × Welsh boar. The dose contained about 2 mCi of radiolabel and the content of paraquat was calculated to be equivalent to about 50 µg paraquat ion/g of diet. The daily dose was spotted onto commercial porcine diet pellets. A second boar acted as the control. The highest concentrations of radiolabel were found in the kidney, with somewhat less being found in the liver and lung (Spinks et al., 1976).

Monkeys

Purser & Rose (1979) studied the renal handling of paraquat administered orally at a dose of 85 mg of paraquat ion/kg bw (containing 500 µCi of ^{14}C-labelled paraquat) to three male cynomolgus monkeys *(Macaca fascicularis).* In two monkeys, peak plasma concentrations were observed at 2 h in two monkeys and at 10 h in the third monkey. The renal clearance of paraquat was high during the first 10 h, but fell markedly as renal failure set in at 14 h. The clearance of paraquat was always well in excess of the clearance of creatinine, suggesting an active secretory process.

Studies in more than one species

The disposition of orally-administered ^{14}C-labelled paraquat dichloride was studied in male Sprague-Dawley rats, male and female guinea-pigs, and monkeys *(Macaca fascicularis).* The doses used were: rats, 126 mg/kg bw (0.175 µCi/mg); guinea-pigs, 22 mg/kg bw (1.25 µCi/mg); and monkeys, 50 mg/kg bw (0.4 µCi/mg). In the case of the rats and guinea-pigs, the doses used were LD_{50}s at 7 days. A total of 61 rats, 21 guinea-pigs and three monkeys were used. For the rats and guinea-pigs, urine and faeces were collected and groups were sacrificed at various times up to 21 days after the administration of paraquat. Selected organs were collected at sacrifice. For the monkeys, blood samples were taken at 30 min, 1, 2, 4, 8, 16 and 32 h after administration of paraquat and daily thereafter. In the rats, deaths were seen mainly after 5 days. A large portion of the paraquat was not absorbed from the gastrointestinal tract. Peak serum concentrations of radiolabel were seen at 30-60 min, while concentrations of radiolabel were higher in liver, kidneys and lungs than in serum. Similar results were found in the guinea-pigs. In the monkeys, one of which died on day 8, serum concentrations of radiolabel decreased rapidly after the first time-point (Murray & Gibson, 1974).

There is evidence that paraquat is taken up into the lungs by a process of active uptake, the normal substrate being endogenous diamines, e.g. putrescine and polyamines such as spermine and spermidine (see review by Smith, 1985). Diquat is not a substrate for this system and this fact accounts for the different organ-specific toxicity of these two bipyridilium herbicides (this is discussed further below).

1.2 Biotransformation

Rats

In the Daniel & Cage (1966) study in albino Wistar rats treated with ^{14}C-labelled paraquat dichloride, discussed above, some evidence of metabolism was found. Of the dose of paraquat administered orally, 30% of the radiolabel was present in the gut as metabolic products. Furthermore, a small amount of metabolite was present in the urine after oral but not subcutaneous administration, suggesting that metabolites were absorbed from the gut. Studies in vitro, using faecal homogenates, suggested that microbiological metabolism was responsible for this. In the study of Murray & Gibson (1974) in male Sprague-Dawley rats, male and female (mixed) guinea-pigs and cynomolgus monkeys *(Macaca fascicularis),* metabolites were not observed.

Urine and faeces samples from the studies in rats, described above (Lythgoe & Howard, 1995a, b, c), were pooled separately for the females and males of each study for the whole 72 h of that study. After extraction, samples were analysed by thin-layer chromatography. In all cases, paraquat accounted for the vast majority of the radiolabel in the urine (95.0% of urinary label in the males receiving the lower dose and 93.6% females receiving the lower dose). Three minor metabolites were found in urine; these were not further identified. Faecal material showed that the vast majority of the radioactivity in all cases was unchanged paraquat. It was therefore concluded that paraquat was largely unmetabolized (Macpherson, 1995).

Hens

In the study in hens, residues in tissues were generally unchanged paraquat. A small amount of a metabolite, l-methyl-(4'-pyridyl), was found in the livers and kidneys (Hendley et al., 1976b).

Goats

In the study in goats, residues in tissues were generally unchanged paraquat. In the liver, small amounts of 4-(1,2-dihydro-1-methyl-2-oxo-4-pyridyl)-1-methyl pyridinium ion and 1-methyl-4-(4'-pyridyl) pyridinium ion were found. The latter compound was also found in peritoneal fat (Hendley et al., 1976a).

Pigs

In the study by Leahey et al. (1976), all the radiolabel in the tissues, except the liver, was found to be in the form of paraquat. In the liver, 7% of the radiolabel was accounted for by l-methyl-4-(4'-pyridyl) pyridinium ion. In the study by Spinks et al. (1976), 4% of the radiolabel was accounted for by l-methyl-4-(4'-pyridyl) pyridinium and 70% by unchanged paraquat.

2 Toxicological studies

2.1 Acute toxicity

The results of studies on the acute toxicity of paraquat administered by a variety of routes are summarized in Table 1. Clinical signs seen after administration of paraquat by the oral, subcutaneous or intraperitoneal routes included decreased activity, dehydration and breathing irregularity. In animals that died after administration of paraquat by these routes, mottled areas of lung were seen. Scabbing of skin was seen after administration by the dermal route, but no systemic signs of poisoning were present. After rats had inhaled paraquat, clinical signs and appearances post mortem were similar to those seen after oral, subcutaneous or intraperitoneal administration.

Table 1. Acute toxicity of paraquat

Species	Strain	Sex	Route	LD_{50} (mg/kg bw) (95% confidence interval)	Reference
Mouse	ICR	M	Per os	360 (324-400)[a]	Shirasu & Takahashi (1977)
	ICR	F	Per os	290 (254-331)[a]	Shirasu & Takahashi (1977)
	ICR	M	Subcutaneous	41.0 (36.9-45.5)[a]	Shirasu & Takahashi (1977)
	ICR	F	Subcutaneous	36.8 (32.9-41.2)[a]	Shirasu & Takahashi (1977)
	ICR	M	Intraperitoneal	40.6 (35.6-46.3)[a]	Shirasu & Takahashi (1977)
	ICR	F	Intraperitoneal	39.2 (35.6-43.1)[a]	Shirasu & Takahashi (1977)
	Swiss-Webster	M	Intraperitoneal	39 (32.5-46.8)	Sinow & Wei (1973)
	Swiss-Webster	F	Intraperitoneal	30 (26.3-34.2)	Bus et al. (1976a)
Rat	NS	F	Per os	112(104-122)[b]	Clark et al. (1966)
	NS	F	Per os	150 (139-162)[b]	Clark et al. (1966)
	Alpk:APfSD	M	Per os	344 (246-457)[c]	Duerden (1994a)
	Alpk:APfSD	F	Per os	283 (182-469)[c]	Duerden (1994a)
	Sprague-Dawley	M	Per os	223 (199-259)[a]	Shirasu & Takahashi (1977)
	Sprague-Dawley	F	Per os	258 (228-292)[a]	Shirasu & Takahashi (1977)
	Sherman	M	Per os	100[d]	Kimbrough & Gaines (1970)
	Sherman	F	Per os	110[d]	Kimbrough & Gaines (1970)
	NS	F	Per os	150(110-173)	Mehani (1972)
	Sprague-Dawley	M	Per os	126	Murray & Gibson (1972)
	Sprague-Dawley	M	Subcutaneous	26.8 (23.9-30.0)[a]	Shirasu & Takahashi (1977)
	Sprague-Dawley	F	Subcutaneous	32.0 (28.1-36.5)[a]	Shirasu & Takahashi (1977)
	NS	F	Intraperitoneal	19 (16-21)[b]	Clark et al. (1966)
	Sprague-Dawley	M	Intraperitoneal	24.8 (21.8-28.3)[a]	Shirasu & Takahashi (1977)
	Sprague-Dawley	F	Intraperitoneal	26.8 (23.7-30.6)[a]	Shirasu & Takahashi (1977)
	NS	F	Intraperitoneal	16 (10-26)	Mehani (1972)
Rat	Sherman	M	Dermal	80[d]	Kimbrough & Gaines (1970)
	Sherman	F	Dermal	90[d]	Kimbrough & Gaines (1970)
	Alpk:APfSD	M	Dermal	>2000[c]	Duerden (1994b)
	Alpk:APfSD	F	Dermal	>2000[c]	Duerden (1994b)
	Alpk:APfSD	M	Inhalation	0.6-1.4[ef]	McLean et al. (1985)
	Alpk:APfSD	F	Inhalation	0.6-1.4[ef]	McLean et al. (1985)
Rabbit	NS	M	Per os	50 (45-58)	Mehani (1972)

	NS	M	Intraperitoneal	25 (15-30)	Mehani (1972)
Guinea-pigs	NS	M	Per os	30 (22-41)[b]	Clark et al. (1966)
	Sprague-Dawley	M&F	Per os	22	Murray & Gibson (1972)
	NS	F	Intraperitoneal	3[b]	Clark et al. (1966)
Hens	Rhode Island	F	Per os	262 (200-346)[b]	Clark et al. (1966)
Turkeys	White	F	Per os	Approx. 290	Smalley (1973)
	White	F	Intraperitoneal	Approx. 100	Smalley (1973)
	White	F	Intravenous	Approx. 20	Smalley (1973)
	White	F	Dermal	375	Smalley (1973)
Cats	NS	F	Per os	35 (27-46)[b]	Clark et al. (1966)
Dog	Beagles	M	Subcutaneous	1.8 (1.0-6.1)	Nagataetal. (1992)
	Beagles	F	Subcutaneous	3.5 (2.4-10.1)	Nagata et al (1992)
Monkeys	Cynomolgus *(M. fascicularis)*	M&F	Per os	50	Murray & Gibson (1972)
	Cynomolgus *(M. fascicularis)*	M	Per os	70[b]	Purser & Rose (1979)

NS, not stated; M, male; F, female

[a] Paraquat dichloride; purity, >98%

[b] Dose quoted as paraquat ion

[c] Technical paraquat dichloride (33% w/w paraquat ion)

[d] as dimethylsulfate

[e] LC_{50} (at 4 h) (mg of paraquat ion/m^{-3})

[f] Material used was paraquat dichloride, 21.5% w/v, but results were expressed as paraquat ion; aerosol mass median aerodynamic diameter (MMAD), <0.3 µm; rats exposed by nose only

(a) Dermal irritation

The dermal irritation potential of paraquat dichloride technical concentrate (paraquat ion, 33% w/w) was assessed in young adult female New Zealand white albino rabbits. Undiluted test material was applied to the depilated left flank of the rabbits, which was then covered by gauze and impermeable rubber. These were left in place for 4 h. After removal of the dressing and cleansing of the application site, the Draize scale was used to assess erythema and oedema, 30-60 min and 1, 2, 3, 4, 7, 14, 17, 20, 21 and 23 days after exposure. Slight erythema was observed, which regressed by 3 days and 4 days in two animals, but still remained after 23 days in the third animal. Very slight transient oedema was seen in one animal (at the 30/60 min observation time), very slight oedema was seen in the second, this still being present at 4 days but not at 7 days, while there was no oedema in the third rabbit (Duerden, 1994c).

(b) Ocular irritation

The potential for paraquat dichloride technical concentrate (paraquat ion, 33% w/w) to produce irritation of the eye was assessed in young adult female New Zealand white albino rabbits. Test material (0.1 ml) was applied to the left eye of each rabbit. Rabbits were dosed sequentially; and mild systemic toxicity was noted in the third rabbit to be dosed. Accordingly, this rabbit was killed. The fourth rabbit was collared to prevent oral ingestion of the test material. The eyes of rabbits 1, 2 and 4 were then examined and the degree of irritation was assessed using the Draize scale from 1 h to up to 28 days after instillation. Initial pain was graded as slight or was absent. Slight or mild corneal opacity was seen in all three animals, this effect resolving within 17 days. Redness and chemosis of the conjunctiva was seen in all animals and resolved by 28 days and 14 days after exposure. No effect was seen on the iris, while erythema of the eyelids and mucoid discharge was observed. Paraquat was considered to be a moderate ocular irritant (Bugg & Duerden, 1994).

In a study of ocular toxicity, paraquat was administered at a concentration of 6.25, 12.5, 25, 50 and 100% of a solution containing 242 mg of paraquat ion/ml. A total of 15 male New Zealand white rabbits were used, nine rabbits receiving

different doses in each eye and six rabbits receiving the same dose in both eyes. Control eyes received normal saline. In all cases, 0.2 ml of solution was pipetted into the lower conjunctival sac, and the eyes were examined at 12 h and then daily for 20 days, ocular lesions being scored on the Draize scale. At 6.25 and 12.5%, severe conjunctival reactions were seen, with occasional slight corneal damage at 12.5%. At higher concentrations (25 and 50%), the iris was congested and swollen and there was corneal opacification; a pannus reaction was also seen. Animals to which the 100% solution was administered died within 6 days. The time of maximal effect was around 9 days and those who received the 25% and weaker solutions showed recovery thereafter (Sinow & Wei, 1973).

(c) Dermal sensitization

A study of the sensitization potential of paraquat dichloride technical concentrate (paraquat ion, 33% w/w) was based on the maximization test of Magnusson & Kligman (1969). Female albino (Hsd/Poc: DH) guinea-pigs were used. The positive control was 2-mercaptobenzothiazole. A preliminary study was carried out to determine the concentrations of test material that gave an acceptable degree of irritancy and no signs of systemic toxicity. In the main study, 30 guinea-pigs were used (20 as test animals and 10 as controls). For induction, each animal received Freund complete adjuvant diluted 1:1 with deionized water, 0.03% w/v test material, and 0.03% w/v test material with Freund complete adjuvant 1:1 with deionized water, which were injected intradermally at three different sites in the previously depilated scapula region. One week later, the scapula region was again clipped and the test material (10% w/v) was applied topically over the injection sites. Animals serving as negative controls were treated in the same way except that the three inducing injections were Freund complete adjuvant 1:1 with deionized water, deionized water, and again Freund complete adjuvant 1:1 with deionized water. Animals serving as positive controls (20) were treated in the same way as the test animals except that the test substance administered was 2-mercaptobenzothiazole, and there were 10 negative controls for this group. For these guinea-pigs, the topical applications consisted of deionized water. Two weeks after the topical applications, both flanks of all animals were clipped free of hair and a preparation of 30% test material on an occlusive dressing was applied to one flank and a preparation of 10% test material to the other flank. These were left in place for 24 h. Erythematous reactions were recorded at 24 h and 48 h later. One animal in the test group died, but no erythema was found at either time in this group, nor in the negative control group. In contrast, erythema was seen in 19 of the positive controls, and it was concluded that paraquat had no sensitization potential (Duerden, 1994d).

2.2 Short-term studies of toxicity

(a) Oral administration

Mouse

In a 13-week dietary study, groups of 20 male and 20 female ICR-CRJ SPF mice were given paraquat dichloride (purity, 93.3%) at a dietary concentration of 0, 10, 30, 100 and 300 mg/kg, equal to 1.18, 3.65, 11.5 and 35.8 mg of paraquat dichloride/kg bw per day in males and 1.38, 3.91, 13.8 and 41.9 mg of paraquat dichloride/kg bw per day in females. These doses are equal to 0, 0.85, 2.64, 8.33 and 25.9 mg of paraquat ion/kg bw per day in males and 0, 1.00, 2.83, 9.99 and 30.3 mg of paraquat ion/kg bw per day in females. Mice were observed daily for mortality and daily clinical observations were undertaken. Animals found dead or that were killed in extremis were subjected to immediate autopsy. The mice were weighed weekly and food and water consumption were measured twice per week. On day 91, blood was collected from at least 10 mice from each group for haematological examination and for clinical chemistry. The mice were then examined post mortem. Autopsy was carried out on the remainder of the mice the next day, at which time urine was collected for urine analysis. At necropsy, selected organs were weighed and these and other organs were fixed and sections made for histopathological examination. Mortality was observed at 300 mg/kg, two females dying from pulmonary damage, one in week 2 and one in week 11. The decedents' lungs showed pulmonary oedema, small round cell infiltration with phagocytosis, and, in one animal, eosinophilic swelling of the epithelial cells of the alveoli. At 300 mg/kg in both sexes, there was reduced body-weight gain, almost from the inception of the study, however, these values were only significantly different from those of controls at a few time intervals. No intergroup difference in food intake was observed, but a slight reduction in food conversion efficiency was seen at 300 mg/kg in both sexes. No intergroup differences were seen in water intake. No test material-related intergroup differences were seen in haematological parameters (although a reduction in mean corpuscular volume at 300 mg/kg may have been test material-related in males) or in clinical chemistry findings. Terminal body weights were reduced in males at the highest dietary concentration, as were the absolute weights of the heart, liver and muscle. An increase in relative lung weight and a decrease in relative liver weight were also seen. In females at the highest dietary concentration, an increase in absolute pituitary, lung, kidney and spleen weight was observed, accompanied by a decrease in ovarian weight.

Relative weights of organs also showed some intergroup differences, those of the pituitary, thyroids, lung, kidneys and spleen being increased while that of the ovaries was decreased. Eosinophilic hypertrophy of alveolar epithelial cells was observed in both sexes (17 out of 20 males, and 12 out of 18 surviving females). Pulmonary oedema and alveolar cell proliferation was also seen in a few males and in one female. Accordingly, the no-observed-adverse-effect level (NOAEL) for the study was 100 mg/kg (equal to 11.5 mg of paraquat dichloride/kg bw per day for males and 13.8 mg of paraquat dichloride/kg bw per day for females), on the basis of decreased body-weight gain and histopathological changes in the lungs at 300 mg/kg. These NOAELs are equal to 8.33 mg of paraquat ion/kg bw per day in males and 9.99 mg of paraquat ion/kg bw per day in females (Maita et al., 1980a).

Rat

In a 13-week study, groups of 20 male and 20 female Fischer CDF (F344) CRJ rats were given diets containing paraquat dichloride (purity, 93.8%) at a concentration of 0, 10, 30, 100 or 300 mg/kg (0, 7, 22, 72 and 217 mg/kg of paraquat ion, equal to 0, 0.49, 1.44, 4.74, 14.2 mg of paraquat ion/kg bw per day for males and 0, 0.52, 1.53, 5.14 and 15.27 mg of paraquat ion/kg bw per day for females). Another group received diet containing no test material and acted as controls. The rats were examined daily for adverse clinical signs, body weight was measured weekly and food and water intake were measured twice per week. Ninety-one days after the start of the study, at least 10 animals of each sex per group were chosen for blood sampling. The samples were used for haematology and clinical chemistry and, after sampling, the animals were examined post mortem. On day 92, urine analysis was carried out on the remaining rats, which were examined post mortem. At necropsy, selected organs were weighed and these and other organs were fixed in 10% formalin; they were then processed for histopathological examination. No rats died during the study and no abnormal clinical signs were seen. At the highest dietary concentration there was markedly reduced body-weight gain and decreased food and water intake in both sexes. Neither reduced body-weight gain nor reduced food intake was seen at lower dietary concentrations. No test material-related abnormalities were found on haematological examination, clinical chemistry or urine analysis. In the males, terminal body weights and absolute weights of brains, pituitaries, thyroids, livers, kidneys, spleens and muscles were decreased at the highest dietary concentration. Also in males, relative weights of brain, pituitary, lung, kidneys, adrenals, testes and muscle were increased. In females, terminal body weights were depressed at the highest dietary concentration, together with the absolute weight of the heart, lung and liver. Relative brain, lung, kidney, ovary and muscle weights were increased at the highest dietary concentration. These changes probably reflected the reduced food intake at the highest dietary concentration. On histopathological examination, alveolar epithelial hypertrophy was observed in males (6 out of 20) while in females, there was an increased prevalence of brown pigmentation of the spleen, both at the highest dietary concentration. The NOAEL was therefore 100 mg/kg in both sexes, equal to 4.74 mg of paraquat ion/kg bw per day for males and 5.14 mg of paraquat ion/kg bw for females on the basis of reduced body-weight gain and reduced food and water intake at the highest dietary concentration, together with pathological changes in the lungs and spleen (Maita et al., 1980b).

Dog

In a 6-week study, groups of three male and three female beagle dogs received technical-grade paraquat (purity, 32.2%) at a dietary concentration of 35 or 90 mg/kg as paraquat ion (equivalent to 0.875 and 2.25 mg of paraquat ion/kg bw per day) for 6 weeks. An additional group of three males and three females received capsules containing paraquat at a dose of 0.75 mg of paraquat ion/kg bw per day, also for 6 weeks. The controls from Sheppard (1981b) were used (see below) and the results were also compared with the group receiving paraquat at 20 mg/kg in that study, as this is comparable to the dose of 0.75 mg/kg bw per day in capsules. Animals were observed periodically during the working day, and by a veterinarian before the start of the study and preterminally. Ophthalmoscopy and auscultation of the chest were undertaken before the start of the study and before termination. Body weights were recorded weekly and food consumption was measured daily. Blood was taken for clinical pathology before the start of treatment, and after 3 and 5 weeks of treatment. Urine analysis was carried out. Lungs and kidneys were weighed at necropsy, and these organs and portions of other selected organs were processed for histopathological examination. There were no adverse clinical effects, nor were there any paraquat-related effects on ophthalmoscopy. On auscultation, increased respiratory sounds were heard in animals from several groups: of these, the finding in two males and three females at 90 mg/kg may have been test material-related. Body weights decreased in males at a dietary concentration of 90 mg/kg throughout the study and in the females at 90 mg/kg towards the end of the study. Body-weight gain was reduced in those females given paraquat at 0.75 mg/kg bw per day. Food intake was reduced at 90 mg/kg in females towards the end of the study. In the males fed paraquat at a dietary concentration of 90 mg/kg, there was a reduction in erythrocyte volume fraction, haemoglobin and erythrocyte count. No test material-related findings were seen in clinical chemistry investigations or urine analysis. One female fed the diet containing paraquat at 90 mg/kg had a markedly increased

lung weight. Changes were seen at 0.75 mg/kg bw per day and at 90 mg/kg in the lungs, both macroscopically and microscopically. The macroscopic changes comprised grey, red or purple depressed areas. In all animals receiving capsules containing paraquat at 0.75 mg/kg bw per day, and in five of the six animals receiving diet containing paraquat at a concentration of 90 mg/kg, there was histopathological evidence of alveolitis, such as intra-alveolar accumulations of mononuclear cells, interstitial hypercellularity and fibrosis and alveolar hyperplasia. Occasional giant cells and pigmented macrophages were seen. It was concluded that for paraquat administered in the diet the NOAEL was 35 mg/kg (equivalent to 0.875 mg of paraquat ion/kg bw per day) and that paraquat was more toxic when administered by capsule than when mixed with the diet (Sheppard, 1981a).

In a 13-week study, groups of three male and three female beagle dogs received paraquat (paraquat ion, 32.2% w/w) at a dietary concentration of 0, 7, 20, 60 or 120 mg/kg as paraquat ion. These dietary concentrations are equal to doses of 0, 0.20, 0.55, 1.75 and 3.52 mg of paraquat ion/kg bw per day in males and 0, 0.24, 0.71, 1.92 and 4.26 mg of paraquat ion/kg bw per day in females. Animals were observed more than once daily, and by a veterinarian before the start of treatment and after 6 and 12 weeks of treatment. Ophthalmoscopy was carried out before the start of the study and after 6 weeks of treatment. Auscultation of the chest was carried out before the start of the study, 6 weeks after the start and immediately before the end of the study. The animals were weighed weekly and food consumption was measured daily. Blood samples were taken by jugular venepuncture before the start of treatment and after 6 and 12 weeks of treatment. These samples were used for haematological investigations and for clinical chemistry. At autopsy, selected organs were weighed and these and other selected organs were fixed and processed for histopathological examination. At the highest dietary concentration two males and two females were killed in extremis. These animals exhibited marked dyspnoea as well as increased respiratory sounds (harsh râles) and loss of body weight before they were killed. One female at 200 mg/kg showed pyrexia and malaise at 3 weeks; this was treated successfully with procaine penicillin and dihydrostreptomycin. The same animal showed loss of appetite from week 8; it was again treated with antibiotics. Survivors at the highest dose showed body-weight loss. Slight but significant reductions in weight gain were seen in females at 7, 20 and 60 mg/kg, compared with the controls; there was no clear dose-response relationship. These effects were not considered to be related to treatment. Food consumption was reduced in one female at the highest dietary concentration. Retinal engorgement was seen in one animal each at 7 mg/kg and 20 mg/kg, and two at 120 mg/kg. No intergroup treatment-related haematological or clinical chemistry findings were present, except in one of the decedents where haemoconcentration was seen. No test material-related effects on urinary parameters were seen. Absolute and relative lung weights were increased in all animals at 120 mg/kg and in two animals at 60 mg/kg; while not statistically significant (lungs from only two animals of each sex were weighed at the highest dietary concentration), these findings were considered to be biologically significant. Histopathological changes were seen in the lungs at 60 and 120 mg/kg. These changes consisted of proliferative alveolitis, with interstitial cellular infiltration (eosinophils and polymorphs) and exudate. Some renal (distal tubular) changes were seen in the same groups. The NOAEL was considered to be 20 mg/kg, equal to 0.55 mg/kg of paraquat ion per kg bw per day in males, and 0.71 mg/kg of paraquat ion per kg bw per day in females, on the basis of increases in lung weight and histopathological changes at the next higher dietary concentration (Sheppard, 1981b).

In a 1-year feeding study, groups of six male and six female beagle dogs were given diets containing technical-grade paraquat dichloride (paraquat ion, 32.2%) at a concentration of 0, 15, 30 or 50 mg/kg as paraquat ion for 1 year. Although no overall means were given in the study report, they were quoted in the submission document. Intakes were 0, 0.45, 0.93 and 1.51 mg of paraquat ion/kg bw per day for males and 0, 0.48, 1.00 and 1.58 mg of paraquat ion/kg bw per day for females (see Clapp, 2002). The dogs were observed twice daily, and examined by a veterinarian before the start of the study and after 13, 26 and 39 weeks, and also between weeks 48 and 51 of treatment; the examination by the veterinarian included auscultation and ophthalmoscopy. Body weights were measured weekly and food consumption daily. Haematology and clinical chemistry measurements were carried out during the study on jugular venous blood samples taken before the start of the study and at weeks 4, 8, 12, 16, 20, 39 and 52. Urine for urine analysis was collected over an 18 h period before the start of the study, and at weeks 8, 16, 24, 39 and 50. Urine samples were collected at week 39 for analysis for paraquat. At termination, necropsy was undertaken and selected organs were weighed, and these and other organs were processed for histopathological examination. Samples of kidney, liver and lung, taken at necropsy, were analysed for paraquat. Respiratory dysfunction was observed at 50 mg/kg (hyperpnea). Increased vesicular sounds were heard in the lungs at auscultation. Erythema of the dorsum of the tongue was seen at 30 and 50 mg/kg in males, and at 50 mg/kg in females. No test material-related effects were seen on ophthalmoscopy. No test material-related effect on body-weight gain was seen. Reduced food consumption was seen at 50 mg/kg. No haematological changes were seen that were attributable to paraquat. Alkaline phosphatase activity was elevated in females at 30 and 50 mg/kg, and plasma concentrations of triglycerides were raised in both sexes at 50 mg/kg. Urinary specific gravity was elevated at 50 mg/kg in males. Lung weights (both absolute and relative) were

significantly increased at 50 mg/kg. Spleen weights were elevated at 50 mg/kg in both sexes, but the biological significance was unclear, and the mean in males was influenced by one outlier. At 30 and 50 mg/kg, macroscopically there was yellow discoloration in the lungs. Microscopically, there was peribronchial mononuclear infiltration, peribronchial and interalveolar fibrosis and changes in the alveolar epithelium (alveolar cell hyperplasia and hypertrophy). These changes were accompanied by the presence of haemosiderin-laden macrophages. These changes were more severe at 50 mg/kg than at 30 mg/kg. Erythrophagocytosis in the bronchial lymph nodes was present at 30 mg/kg and 50 mg/kg. A dose-related increase in urinary paraquat was found at week 29. Paraquat was not found in the livers at any dietary concentration, but was found in the kidneys at 30 and 50 mg/kg. Paraquat was detected in the lungs. The NOAEL for the study was 15 mg/kg on the basis of erythema of the tongue at 30 mg/kg in males, elevated alkaline phosphatase in both sexes, and histopathological changes in the lung at ≥ 30 mg/kg. This NOAEL is equal to 0.45 mg of paraquat ion/kg bw per day (Kalinowski et al., 1983).

Cows

Groups of two Friesian cows were fed diets containing paraquat (as residues in dried grass) at a concentration of 25, 80 or 170 mg/kg as paraquat ion for 3 months. These dietary concentrations were equivalent to 0.375, 1.2 and 2.55 mg of paraquat ion/kg bw per day. During the trial, milk was collected from the cows. After they had been slaughtered, autopsy was carried out and organs, inter alia lung, liver and kidney, were examined histopathologically. Concentrations of paraquat were determined in the liver, kidney, renal fat and the pectoralis and adductor muscles. No adverse clinical effects were noted during the study, although the milk yield decreased (this was attributed to poor nutrition). No histopathological change attributable to paraquat was found. The concentration of paraquat in the milk was very low (in one sample, 0.001 mg/kg; in the remainder, <0.0006 mg/kg). The highest tissue residues were in the kidney (0.20-0.31) and liver (<0.01-0.09). Concentration in cardiac and skeletal muscle and renal fat were much lower. The NOAEL was the highest dietary concentration, 170 mg/kg, equivalent to 2.55 mg of paraquat ion/kg bw per day (Edwards et al., 1974).

(b) Dermal application

Rabbits

In a 21-day study of dermal toxicity, groups of six male and six female New Zealand white albino rabbits were given technical-grade paraquat (purity, 33.5%), at a dose of 0, 1.5, 3.4, 7.8 or 17.9 mg/kg bw per day (equal to 0, 0.5, 1.15, 2.6 and 6.0 mg of paraquat ion/kg bw per day), applied in distilled water under an occlusive dressing to the clipped dorsal thorax. Distilled water without paraquat was applied to the control animals. The period of exposure was 6 h per day. Animals were observed twice daily. They were more thoroughly examined and dermal irritation was assessed on days 1, 2, 4, 8, 11, 15, 18 and 21. Animals were weighed twice weekly and food consumption was measured weekly. Blood samples for haematology and clinical chemistry were collected before the start of the study and at termination. After 21 days, the animals were weighed and killed, and designated organs were weighed. These and further selected tissues were fixed and processed for microscopic pathological examination. No mortality was observed and all animals appeared to be clinically normal throughout the study. Body weights and food consumption were similar in all groups. No differences between the groups were seen in haematological measurements or clinical chemistry. Neither organ weight data nor histopathological examination showed evidence of test material-related systemic toxicity. Evidence of skin irritation was seen at the two highest doses. Microscopic evidence of skin irritation was seen in most animals at the highest dose and in some animals at a dose of 2.6 mg of paraquat ion/kg bw per day. Findings included erythema, erosion, ulceration, exudate, acanthosis and chronic inflammatory change. Accordingly, the NOAEL was 1.15 mg of paraquat ion/kg bw per day on the basis of skin changes at higher doses (Cox, 1986).

(c) Exposure by inhalation

Rats

In a 3-week inhalation study, an aerosol of technical-grade paraquat (paraquat ion, about 40%) was administered to groups of 36 male and 32 female albino Sprague-Dawley CD rats The rats were exposed for 6 h per day, 5 days per week, for 3 weeks (i.e. 15 exposures). There were two control groups, one of which received no exposure to aerosol and the other received a saline aerosol. There were two test groups, one of which received aerosolized paraquat at a concentration of 0.01 µg of paraquat ion/l and the other 0.1 µg of paraquat ion/l. Particles had aerodynamic diameters of <0.7 µm. The rats were examined twice daily and, more thoroughly, once a week. Animals were weighed daily for the first week and then twice per week. Food consumption was measured weekly. Water consumption was measured

daily, 5 days per week. Interim kills were carried out as follows: 3 days after the first exposure, four males and four females in each group were killed for histopathological examination of the nasal passages, pharynx, larynx and lungs (i.e. the rats were given a single exposure, left for 2 days, and then sacrificed). Additionally, 1 day after the third exposure, four males in each group were killed for examination of the nasal turbinates only. Eight animals of each sex per group were killed after the last exposure and the remainder (16 animals of each sex per group) were killed after a 3-week recovery period. Macroscopic examination was carried out post mortem but no microscopic pathology was performed. No treatment-related clinical signs were seen. No treatment had any effect on body-weight gain or food or water consumption. Aerosol containing paraquat ion at a concentration of 0.01 µg/l did not produce histopathological changes in the larynx, while exposure to aerosol containing paraquat ion at a concentration of 0.1 µg/l did produce such changes. In the animals examined 3 days after exposure at 0.1 µg of paraquat ion/l, there was squamous metaplasia at the base of the epiglottis. One day after the third exposure, there was ulceration, necrosis, acute inflammatory change and squamous metaplasia and/or hyperplasia especially at the base of the epiglottis and arytenoid processes. In those animals sacrificed in the interim for examination of the turbinates, no abnormalities were seen. Accordingly, the NOAEL for the study was 0.01 µg of paraquat ion/l on the basis of histopathological changes in the upper respiratory tract at the higher dose (Grimshaw et al., 1979).

2.3 Long-term studies of toxicity and carcinogenicity

Rats

In a 104-week study, groups of 80 male and 80 female Fischer (F344/DuCrj) rats were given diets containing paraquat dichloride (purity, >98%) at a concentration of 0, 10, 30, 100 or 300 mg/kg. Intakes of paraquat dichloride were 0, 0.35, 1.06, 3.52 and 10.6 mg/kg bw per day for males, and 0, 0.43, 1.34, 4.32 and 11.7 mg/kg bw per day for females. These intakes of paraquat dichloride represented intakes of 0, 0.26, 0.77, 2.55 and 7.67 mg of paraquat ion/kg bw per day in males, and 0, 0.31, 0.97, 3.13 and 8.47 mg of paraquat ion/kg bw per day in females. Eight rats of each sex were killed at 26, 52 and 78 weeks, while the survivors were sacrificed at 104 weeks. During the study, animals were observed daily and clinical findings, including mortality, were recorded. Animals that died during the study were subjected to necropsy followed by histopathological examination, as were those that were sacrificed in extremis. Body weight was measured weekly until week 26 of the study, and fortnightly thereafter. Food and water consumption was measured twice per week. At termination, haematological and clinical chemistry studies were carried out on 10 males and 10 females per group. At necropsy, selected organs were weighed and portions of these and of other organs were fixed and processed for histopathological examination. No clinical effect attributable to the test material was seen, but there was some indication of increased mortality between weeks 66 and 74 of the study in females at the highest dose. There was a reduction in body-weight gain and food and water consumption in both sexes at 300 mg/kg (the highest dietary concentration). The effect on body-weight gain was greater in the males. Some effects on haematology were observed. At 26 weeks, there was a decrease in white blood cell count at 300 mg/kg in males, but no differences between groups were seen in females. At 52 weeks, there were minor changes in mean corpuscular haemoglobin and haemoglobin concentration, and a decrease in white blood cell count at 300 mg/kg in males, but no differences between groups were seen in females. At 78 weeks, there was a decrease in white blood cell count at 300 mg/kg in males, but no test material-related differences between groups were seen in females. At 104 weeks, in males, there were minor changes in mean corpuscular volume and mean corpuscular haemoglobin. In females, at 104 weeks, there were minor changes in mean corpuscular haemoglobin concentration (a reduction) at 300 mg/kg. At 26 weeks, in males, a reduction in aspartate aminotransferase activity and globulin was observed at 300 mg/kg, as well as a rise in blood concentrations of glucose at 100 and 300 mg/kg. At 26 weeks, in females, an increase was seen in *gamma*-glutamyl transpeptidase at 300 mg/kg, and a decrease at 10 mg/kg. At 26 weeks, total protein, albumin and globulin concentrations were all decreased in females at 300 mg/kg. At 52 weeks, in males, a reduction in aspartate aminotransferase, alanine aminotransferase and *gamma*-glutamyl transpeptidase activity, and in cholesterol and calcium concentrations was seen at 300 mg/kg. At 52 weeks, females showed no test material-related changes in clinical chemistry. At 78 weeks, males showed reductions in alkaline phosphatase, alanine aminotransferase and *gamma*-glutamyl transpeptidase activity were seen accompanied by an increase in albumin and a decrease in globulin at 300 mg/kg, whereas females showed no test material-related changes in clinical chemistry. At termination at 104 weeks, a decrease in globulin was seen in males at 300 mg/kg, while no noteworthy changes in clinical chemistry parameters were seen in females. In males at the highest dietary concentration, body weight at necropsy was decreased at 26, 52 and 78 weeks and at termination. Although some changes in organ weights were observed, many of these did not appear to be test material-related. At 26 weeks in males at 300 mg/kg, however, relative but not absolute lung weight was increased, as it was at 52 weeks. At 300 mg/kg, at 78 weeks, absolute lung weight was decreased and relative lung weight in males did not differ from those of controls, while at termination, neither value was different

from that of controls. In females, at 26 weeks, a reduction in body weight was not seen at any concentration. At 26 weeks, an increase in relative lung weight was seen at the two higher dietary concentrations, and this was accompanied by an increase in absolute lung weight at 100 mg/kg only. At 52 weeks and 78 weeks, there were no differences between groups in body weight or absolute or relative lung weight in females. At termination, in females, decreased body weight and an increased relative but not absolute lung weight was observed at 300 mg/kg. A reduction in absolute and relative ovarian weight was observed at 26 weeks at the highest dietary concentration. On histopathological examination, there were changes in the lungs at 300 mg/kg in both sexes and at 100 mg/kg in males. The changes consisted of proliferation of interalveolar septum cells and hyperplasia of the alveolar epithelium. The frequency of pulmonary adenoma was increased in females at 300 mg/kg (see Table 2). Histopathological evidence of cataract was found in both sexes at 300 mg/kg (see Table 3). The NOAEL for the study was 30 mg/kg (1.06 mg of paraquat dichloride/kg bw per day and 1.34 mg of paraquat dichloride/kg bw per day in males and females respectively) on the basis of clinical chemistry changes in males, increased lung weight in females and histopathological changes in the lungs of males at ≥100 mg/kg. These NOAELs are equal to 0.77 and 0.97 mg of paraquat ion/kg bw per day in males and females respectively (Yoshida et al., 1982).

Table 2. Incidence of lung tumours in rats fed diets containing paraquat (survivors + decedents)

Sex	Lung tumour	Dietary concentration (mg/kg)				
		0	10	30	100	300
Males	Adenoma	1	2	3	4	3
	Adenocarcinoma	0	0	2	1	3
Females	Adenoma	1	2	0	1	7
	Adenocarcinoma	0	0	0	0	0

From Yoshida et al., (1982)

Table 3. Incidence of cataract in rats fed diets containing paraquat (decedents + survivors)

	Dietary concentration (mg/kg)				
	0	10	30	100	300
Males	8	4	7	9	46
Females	7	7	8	11	42

From Yoshida et al. (1982)

In a study of chronic toxicity, groups of 62 male and 62 female JCL: Wistar rats were fed diets containing paraquat (purity, 98%) at a concentration of 0, 6, 30, 100 or 300 mg/kg for up to 104 weeks. These dietary concentrations provided intakes of paraquat di chloride equal to 0, 0.25, 1.26, 4.15 and 12.25 mg/kg bw per day in males, and 0, 0.3, 1.5, 5.12, 15.29 mg/kg bw per day in females. These intakes are equal to 0, 0.18, 0.91, 3.00 and 8.87 mg of paraquat ion/kg bw per day in males, and 0, 0.22, 1.09, 3.71 amd 11.1 mg of paraquat ion/kg bw per day in females. Six rats of each sex per group were killed at 26 weeks and 52 weeks; the survivors were killed at 104 weeks. The rats were examined twice per day, deaths were recorded and clinical findings noted. Ophthalmoscopy was carried out before treatment, and before sacrifice in those killed at 26 and 52 weeks, and at termination. Body weight and food consumption were measured weekly until week 26 and thence fortnightly. Haematological and clinical chemistry end-points were measured in blood samples taken from animals killed at 26 weeks, at 52 weeks, and from the survivors at termination. Included among the clinical chemical parameters measured were activities of plasma, erythrocyte and brain cholinesterases. Urine analysis was performed on the animals killed at 26 and 52 weeks and on the survivors at termination. Animals killed at 26 and 52 weeks and survivors to termination were subjected to necropsy, as were decedents. Selected organs were weighed and these and other organs were fixed and processed for histopathological examination. No clinical effects were observed. At the highest dietary concentration in females, there was a decrease in weight gain in the middle of the study (weeks 43, 42-48 and 54), otherwise body-weight gain was unaffected. No substantial intergroup differences in food consumption or in water intake were noted. At week 26, at the highest dietary concentration, there was a decrease in erythrocyte count, erythrocyte volume fraction and haemoglobin and a reticulocytosis in males and in the erythrocyte count and haemoglobin in females. At 300 mg/kg, at week 52, decreased

erythrocyte count and increased numbers of polymorphs were seen in males, and lowered erythrocyte count, haemoglobin concentration and leukocytes were seen in females. At week 104, both sexes showed decreases in erythrocyte count, erythrocyte volume fraction and haemoglobin, and an increase in reticulocytes was observed in males. At 26 weeks, a decrease in total protein was seen in both sexes at 300 mg/kg, with a decrease in alkaline phosphatase activity in females at this dietary concentration. At week 52, decreased total protein was found in both sexes, as well as reduced blood concentrations of glucose in males and reduced aspartate aminotransferase and alanine aminotransferase activities in females. There were no differences between the groups in urine analysis at any time-point. In the rats sacrificed at week 26, there were increases in absolute kidney weights (right kidney only) in males and in both absolute kidney weights in females and absolute ovarian weights in females. At week 52, at the highest dietary concentration, in males there was an increase in both absolute thyroid and kidney weights, while females showed an increase in absolute ovarian weights and a decrease in the relative weights of the brain, heart and liver. At termination, at 300 mg/kg, males showed reductions in the absolute and relative heart weights, while females showed lowered absolute and relative liver weights and decreased absolute heart weight. At necropsy and histopathological examination, no findings could be attributed to the test material. The NOAEL was therefore 100 mg/kg in both sexes (equal to 4.15 and 5.12 mg of paraquat dichloride/kg bw per day in males and females respectively), on the basis of haematological observations and lowered plasma concentration of total protein at the highest dietary concentration. These NOAELs are equal 3.00 and 3.71 mg of paraquat ion/kg bw per day in males and females, respectively (Toyoshima et al., 1982).

Groups of 70 male and 70 female Fischer 344 rats were given diets containing paraquat (technical grade, 32.69%) at a dietary concentration of 25, 75 or 150 mg/kg as paraquat ion (equivalent to a dose of 1.25, 3.75 or 7.5 mg of paraquat ion/kg bw per day) for a period of at least 113 weeks (males) and 122 weeks (females). Two additional groups of rats served as controls. There were also additional satellite groups of five males and five females from one control group and all three test groups which were sacrificed at 1 year for estimation of paraquat concentrations in certain tissues. Ten male and ten female rats from each group were sacrificed for histopathological examination at 1 year. Rats were inspected once or twice daily, mortality was recorded and rats in extremis were sacrificed and necropsied (see below). Ophthalmoscopic examination of both eyes was carried out before the start of the study and after 4, 14, 26, 52 and 79 weeks of treatment for 20 males and 20 females from each control group; the test groups were examined in a similar manner.

Surviving males were examined ophthalmoscopic ally at 110 weeks and 112/113 weeks (termination) and surviving females at 110 and 118/119 (termination). Food consumption was recorded weekly and water consumption was recorded over 3-day periods during each of the first four weeks, and during weeks 13, 26, 41, 52, 65, 78, 92 and 101. Body weight was recorded weekly for the first 12 weeks, then fortnightly until week 68, and then weekly until termination. Before the start of treatment and after 14, 26, 40, 53, 66, 79, 92 and 102 weeks, blood was taken for measurement of haematological and clinical chemistry parameters, and additionally in males at 111/112 weeks and in females at 118/119 weeks. Urine samples were collected periodically for urine analysis and for analysis of paraquat in the urine. Five animals of each sex per group were sacrificed at 52 weeks for estimation of concentrations of paraquat in the liver, lungs, kidneys, skin, plasma and urine. Necropsy was performed on all decedents, the 10 animals of each sex per group sacrificed at 52 weeks and those surviving to termination, and selected organs were weighed. These and other selected organs were preserved and processed for histopathological examination. Mortality was not affected by treatment and survival to termination was 38-55% in males and 47-50% in females. No clinical adverse effect was seen, except corneal opacity, which was seen at 150 mg/kg in males and at 75 mg/kg in females. At ophthalmoscopy, cataracts were seen at 150 mg/kg in both sexes and, from 103 weeks, at 75 mg/kg in both sexes. In the males, the prevalence of cataracts was not unequivocally increased at 25 mg/kg; however, a statistical analysis of the eye changes revealed an increase in posterior capsular changes at week 110 in the males at 25 mg/kg. Food intake at 150 mg/kg was reduced in both sexes, in the males for the first year of the study and in the females during the first 6 weeks; these changes were small. Depression of body-weight gain was seen at 150 mg/kg in both sexes, but was more severe in males and was also present in males at 75 mg/kg. Body-weight gain in males at 25 mg/kg and in females at 75 and 25 mg/kg was not different from that in the controls. Test material-related effects were not seen on haematological or clinical chemistry parameters, or on urine analysis. At 52 weeks, the concentration of paraquat in the urine was dose-related. In rats sacrificed at 52 weeks, paraquat was detected in the plasma and kidneys at all dietary concentrations, while paraquat was present in the lungs of animals at 75 and 150 mg/kg; only at 150 mg/kg and in females was paraquat found in the liver. Paraquat was found in some skin samples taken from males at 75 mg/kg and from both sexes at 150 mg/kg. No test material-related effects were seen on organ weights, other than those attributable to changes in body weight. Macroscopically, there was an increase in corneal opacity and focal sub-pleural changes at 75 and 150 mg/kg. Proliferative alveolar changes were also seen at these dietary concentrations. Lung histopathology was

examined by two groups (Tables 4-6). An initial assessment of lung histopathology was made based on that of Life Sciences Research's own staff pathologists and of two consultant pathologists from the USA (Table 4). The other assessment was by Ishmael (Table 5), at that time Head of Pathology at Imperial Chemical Industries. There were some clear differences. Finally, the slides were examined by four independent pathologists and the results were reported by Busey (1986) (Table 6). It was concluded that the differentiation of bronchiolar adenomas and carcinomas from the non-neoplastic lesions typical of paraquat was difficult. However it was also concluded that the incidence of lung neoplasms in the test groups was comparable to that in the control groups (Ishmael & Godley, 1983; Woolsgrove, 1983; Sotheran et al., 1981; Woolsgrove, 1985; Busey, 1986; Ishmael, 1987).

Table 4. Initial assessment of lung histopathology in rats given diets containing paraquat

	Dietary concentration (mg/kg)									
	0 (Control group 1)		0 (Control group 2)		25		75		150	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Number of rats examined	70	70	69	69	70	70	70	70	69	70
Adenoma	1	0	2	0	3	1	5	2	4	8[a]
Carcinoma[b]	1	0	0	0	1	1	1	1	3	2
Total neoplasia	2	0	2	0	4	2	6	3	7	10[a]
Alveolar epithelialization	2	3	2	7	2	5	7	8	8	3

From Woolsgrove (1983)

[a] $p < 0.001$

[b] Bronchiolar-alveolar or squamous cell carcinomas

Table 5. Second assessment of lung histopathology in rats given diets containing paraquat

	Dietary concentration (mg/kg)									
	0 (Control group 1)		0 (Control group 2)		25		75		150	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Number of rats examined	70	70	69	69	70	70	70	70	69	70
Adenoma	0	0	0	0	2	0	1	1	1	0
Carcinoma	1	0	1	0	2	1	1	1	3	0
Adenomatosis	2	4	4	4	5	5	8	4	11a	13a

From Ishmael & Godley (1983)

[a] $p < 0.01$

Table 6. Final assessment of lung histopathology in rats given diets containing paraquat

	Dietary concentration (mg/kg)									
	0 (Control group 1)		0 (Control group 2)		25		75		150	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Number of rats examined	70	70	69	69	70	70	70	70	69	70
Bronchioalveolar adenoma	2	0	0	0	2	0	0	1	0	1
Bronchioalveolar carcinoma	1	0	1	0	2	1	2	1	2	1
Squamous cell	0	0	0	0	0	0	1	0	2	0

carcinoma										
Focal adenomatous hyperplasia	2	4	3	5	7	5	9	7	15	7
Diffuse adenomatous hyperplasia	0	1	0	0	0	0	0	0	1	3
Focal alveolar wall fibrosis	1	8	4	5	4	8	6	13	3	12
Diffuse alveolar wall fibrosis	0	3	0	5	2	3	3	4	8	3

From Busey (1986)
[a] $p < 0.01$

It was concluded from the data summarized in Table 6 that there was no association between the incidence of adenomas, carcinomas or the two combined, and exposure to paraquat. In contrast, there was a significantly increased incidence of adenomatosis at 150 mg/kg when all animals were included in the analysis (i.e. those sacrificed at 52 weeks, decedents and those killed at termination).

Ishmael (1987) reviewed the slides of the head region, in which squamous cell carcinomas of the skin and subcutis had been reported. In males, 11 such tumours were seen in the study (1, 2, 2, 0 and 6 in the two control groups and at the lowest, intermediate and highest doses, respectively) as originally reported and in Ishmael (1987). The site of origin of these tumours, however, differed and Ishmael (1987) suggested they should not be considered as a single phenomenon for statistical purposes. Other changes seen included dilatation of the fourth ventricle of the brain (hydrocephalus) in females at 75 and 150 mg/kg. Cysts and cystic spaces were seen in the spinal cords and, in males, prevalence was significantly greater than that in the controls in all test groups, although there was no clear dose-response relationship. This pathological change was found in females, but the frequency in test groups and control groups was similar (and similar to the frequency in the males in test groups). Degeneration of the sciatic nerve was found in males at 75 and 150 mg/kg. Changes were present in the eyes. At the highest doses, peripheral lenticular degeneration, more severe in females, and pear-shaped posterior peripheral lenticular change was seen. Mid-zonal lenticular degeneration, lens capsular fibrosis and/or lens ruptures were all seen. At 75 mg/kg, changes were milder. These changes were seen in both decedents and those rats surviving to termination. At the highest concentration, in the decedents, peripheral retinal degeneration was observed in females and proteinaceous vitreous humour was seen in males. Some changes were seen at the lowest dietary concentration; in male survivors these were moderate peripheral morgagnian corpuscles, slight peripheral lenticular degeneration, moderate mid-zonal lenticular degeneration and loss of outer nuclear layer of the retina. The last was unlikely to be a compound-related effect as the prevalence was lower in both the controls and at higher doses. In female survivors to termination, at the lowest dietary concentration, changes observed were moderate peripheral morgagnian corpuscles, slight peripheral lenticular degeneration and moderate mid-zonal lenticular degeneration.

At termination, there was no clear evidence of an effect on the retina at the lowest dose, although in males at the two higher dietary concentrations there may have been an effect on the periphery of the retina. This study was continued for a longer duration than that recommended by the OECD (104 weeks for long-term studies in rats). The NOAEL was 25 mg/kg for lenticular lesions after 103 weeks at 25 mg/kg in males and likewise in females at 103 and 110 weeks (see Table 7 for ophthalmoscopy findings at 103 weeks and Table 8 for lens findings at necropsy). This NOAEL is equivalent to 1.25 mg of paraquat ion/kg bw per day. This interpretation is supported by the findings from the other long-term studies in rats.

Table 7. Frequency of effects on the lens (in life) at 103 weeks in rats given diets containing paraquat

Finding	Dietary concentration (mg/kg)									
	0 (Control group 1)		0 (Control group 2)		25		75		150	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Opacity	1	0	4	0	0	0	0	1	0	0
Vacuolation	0	0	1	0	0	0	0	0	1	1

Suture line opacity	0	1	1	0	1	0	14*	9*	1	1
Posterior polar opacity/cataract	3	0	0	0	1	0	8	5	19	30
Posterior capsular opacity/cataract	0	2	0	5	0	4	3*	6*	24*	12*
Radial cataract	0	0	0	0	1	0	2	2*	8*	5*
Total cataract	1	1	1	1	2	1	3	1	5*	4

From Ishmael (1987)
* Greater incidence than combined control groups, statistically significant at $p = 0.05$ or less

Table 8. Frequency of effects on the lens at necropsy in rats given diets containing paraquat (all animals, regardless of time of death)

Finding	Dietary concentration (mg/kg)							
	0 (Control groups 1 and 2)		25		75		150	
	Males	Females	Males	Females	Males	Females	Males	Females
Number of eyes examined	219	226	112	112	114	107	115	114
Peripheral morgagnian corpuscles								
Slight	64	50	29	14	26	8*	7*	8*
Moderate	38	70	31	39	19	27	25	16
Marked	12	34	19*	31*	35*	52*	69*	84*
Peripheral lenticular degeneration								
Slight	18	60	25*	29	32*	23	26*	10*
Moderate	8	33	13*	30*	39*	31*	34*	43*
Marked	1	7	4	4	6*	10*	22*	32*
Pear-shaped posterior lenticular change	6	42	11*	32*	51*	48*	73*	74*
Midzonal lenticular degeneration								
Slight	7	27	5	20	18*	14	14*	19
Moderate	0	12	4*	13	19*	27*	39*	37*
Marked	0	0	0	3	3*	23*	29*	27*
Heart-shaped	0	2	0	0	1	18*	18*	15*

From Ishmael (1987)
* Greater incidence than combined control groups, statistically significant at $p = 0.05$ or less

Mice

In a 104-week study, groups of 80 male and 80 female JCL:ICR mice were given diets containing paraquat (paraquat dichloride; purity, 98%) at a dietary concentration of 0, 2, 10, 30 or 100 mg/kg, providing intakes of paraquat dichloride equal to 0, 0.26, 1.31, 3.92 and 13.09 mg/kg bw per day in males, and 0, 0.26, 1.32, 3.82 and 13.03 mg/kg bw per day in females. These intakes are equal to 0, 0.19, 0.95, 2.84 and 9.48 mg of paraquat ion/kg bw per day in males, and 0, 0.19, 0.96, 2.77 and 9.43 mg of paraquat ion/kg bw per day in females. At weeks 26 and 52, 10 male and 10 female per group were sacrificed. The mice were examined twice daily and adverse clinical effects, including mortality, were noted. Body weight and food consumption were measured weekly until week 26, and fortnightly thereafter. Blood was taken for haematology and clinical chemistry (including determination of plasma, erythrocyte and brain cholinesterase activities) from the animals killed at 26 and 52 weeks and from those that survived to

termination. Urine analysis was performed on animals killed at 26, 52 and 104 weeks. Survivors were sacrificed at 104 weeks. Necropsy was carried out on the animals killed at 26 and 52 weeks and on those that survived to termination, as well as the decedents. Selected organs were weighed and tissue from these and further selected organs was fixed and processed for histopathological examination. There were no effects of the test material on mortality. No clinical effects attributable to the test material were noted. The test material had no effect on body-weight gain or food consumption. Falls in the erythrocyte count, erythrocyte volume fraction, haemoglobin, white blood cell count and lymphocyte count were noted in males and in the haemoglobin concentration and white blood cell count in females at 100 mg/kg in week 26. At week 52, also at 100 mg/kg, a decreased erythrocyte count, and decreases in erythrocyte volume fraction and white blood cell count were observed in males and lowered erythrocyte count and haemoglobin concentration in females. At week 104, lowered erythrocyte count, erythrocyte volume fraction and polymorphonuclear leukocytes (%) were observed in males, and decreases in the erythrocyte volume fraction and haemoglobin concentration in females. Clinical chemistry findings included lowered total plasma protein in both sexes at the highest dietary concentration in week 26. At week 52, lowered total protein was seen in males and decreases in aspartate aminotransferase and alkaline phosphatase activites, with increased blood concentration of glucose, were seen in females. At week 104, reductions in total protein and increases in blood glucose were observed in both sexes. Urine analysis showed no abnormality at any time in either sex. The absolute and relative weights of the (left) adrenal at 30 mg/kg in males killed at 26 weeks was decreased in comparison with those of the controls. In male at 100 mg/kg, at 26 weeks, adrenal and thyroid absolute and relative weights were decreased in comparison with those of controls, and absolute and relative lung weights were elevated. At week 52, there was an increase in absolute heart weight in males, while at week 104, decreases in absolute thyroid, liver and bladder weight were noted in males, together with an increase in relative (left) kidney weight. A drop in the absolute brain weight was noted at week 104 in females. No macroscopic or microscopic changes that could be attributed to the test material were found in the decedents or sacrificed animals. The NOAEL was therefore 30 mg/kg on the basis of haematological and clinical chemistry changes in both sexes, at the next highest dietary concentration. This was equal to 3.92 and 3.82 mg of paraquat dichloride/kg bw per day in males and females, respectively (2.84 and 2.77 mg of paraquat ion/kg bw per day in males and females, respectively) (Toyoshima et al., 1982).

A lifetime feeding study in mice was carried out; termination was at 97-99 weeks, at which time mortality was approaching 80%. Groups of 60 male and 60 female Swiss mice were fed diets containing paraquat at a dietary concentration of 0, 12.5, 37.5 or 100 mg/kg (technical grade dichloride; paraquat ion, 32.7%) for up to 99 weeks. The dietary concentration of paraquat received by groups of mice at 100 mg/kg was increased to 125 mg/kg from week 36, as few adverse effects had been noted, other than a decrease in food consumption, up to that time. The intakes of test material were equivalent to 0, 1.88, 5.62 and 15.0/18.7 mg of paraquat ion/kg bw per day. The control groups were duplicated. Satellite groups of 10 male and 10 female mice received the diet for 52 weeks and were used for measurement of paraquat concentrations in plasma, kidney and lung; in the case of the satellite groups, the control groups were not duplicated. Further satellite groups of 15 mice of each sex were fed the diet and acted as microbiological sentinels. The mice were observed daily for clinical effects, while body-weight determinations were recorded weekly for 12 weeks, fortnightly from week 12-36, weekly from week 36-40 and thence fortnightly. Food consumption measurements were undertaken weekly for the first 12 weeks of the study, and during weeks 36-40; at all other times, it was measured for 1 week during each 4-week period. Urine samples for measurement of concentration of paraquat were collected at 3-month intervals. Mice in extremis were sacrificed, as were those that survived to termination. These mice and decedents were subjected to necropsy, after which histopathological examination was carried out. Tissues from the satellite group were not subjected to autopsy. The main clinical findings were swellings and sores in the genital area of the male and, to a lesser extent, female mice, accompanied by incontinence. Mortality was greater than in the combined control groups in male mice receiving paraquat at a dietary concentration of 37.5 mg/kg and in female mice receiving paraquat at a dietary concentration of 125 mg/kg. The former is unlikely to be a compound-related effect, as an increase in the mortality at the highest dietary concentration was not observed in males. Body-weight gain was unaffected in males, while body-weight gain was decreased in females at the highest dietary concentration (but not until this dietary concentration had been raised from 100 mg/kg to 125 mg/kg) and, after week 68, at a dietary concentration of 37.5 mg/kg. Food consumption was affected: in males, food consumption was reduced at all dietary concentrations to some extent, particularly early in the study; however, the effect did not appear to be dose-related. In females, decreased food consumption at all dietary concentrations was found, but this was more consistent and severe at the highest concentration. Concentrations of paraquat in the urine were found to be dose-related. On one occasion, paraquat was found in the urine of female controls, in trace amounts. In the satellite group, concentrations of paraquat in plasma were related to the dietary concentration that the animals had received for males, but less clearly so for females. In the case of the liver and lung tissue samples, some difficulties were encountered with some samples in analysis, but where analysis was possible, the results appeared to be related to dose. Changes in the proximal tubules of the kidneys (hydropic degeneration, eosinophilia, degeneration and/or dilatation) were seen at the

highest dietary concentration, and there was evidence that, in the decedents, the predominant change was hydropic degeneration, eosinophilia, while degeneration and/or dilatation were seen in survivors to termination. Some very mild renal changes were seen in males at 37.5 mg/kg. In the lungs, alveolar focal hypercellularity was found at a higher frequency at the highest dietary concentration than at the lower concentrations or in controls in both sexes. There was no evidence of differences in cataract formation between the groups. There was an increase in adenomas in males and females receiving paraquat at the highest dietary concentration and dying after 52 weeks and before termination than in controls, but this was not dose-related. Moreover, at termination, a lower incidence of these tumours was observed in these animals than in controls. The NOAEL was 12.5 mg/kg (equivalent to 1.88 mg of paraquat ion/kg bw per day) on the basis of decreased body-weight gain in females and renal changes in males at the next highest dietary concentration. Paraquat was not considered to be tumorigenic (Sotheran et al., 1981).

2.4 Genotoxicity

Paraquat has been the subject of many tests for genotoxicity (see Table 9). Paraquat consistently gave negative results in well-established assays for reverse mutation in strains of *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98 and TA100). There was one positive result in *S. typhimurium* TA102, a strain that is particularly responsive to reactive oxygen species. More variable results were obtained in the less well-established assays for forward mutation in *S. typhimurium* and in assays for DNA damage in bacteria, for example the *umu* test, SOS test, tests for DNA repair and the rec assay) and in an assay for gene mutation in *Aspergillus nidulans.* In comparison with the assays for reverse mutation in *S. typhimurium,* these assays are not well validated. The assays for mutation in plants are not well validated and no conclusions could be drawn from them. Paraquat gave fairly consistently positive results in assays for chromosomal damage in mammalian cells. Positive results were consistently obtained in assays for DNA damage (sister chromatid exchange, unscheduled DNA synthesis and the comet assay) in mammalian cells. These data suggest that paraquat has mutagenic potential in vitro.

Table 9. Results of studies of genotoxicity with paraquat

End-point	Test-object	Concentration/Dose	Purity	Results	Reference
In vitro					
Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100	1-1000 µg/plate	>99.9%	Negative ± S9	McGregor (1977)
Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100	0.5-500 µg/plate	100%	Negative ± S9	Shirasu et al. (1978)
Reverse mutation	*S. typhimurium,* TA1535, TA1538, TA98, TA100	0.16-5000 µg/plate	>99%	Negative ± S9	Anderson (1977)
Reverse mutation	*E. coli,* WP2 *hcr*	0.5-500 µg/plate	100%	Negative ± S9	Shirasu et al. (1978)
Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100	1-50 µg/plate	NS	Negative	Benigni et al. (1979)
Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100	Not clear	NS	Negative	Eisenbeis et al. (1981)
Reverse mutation	*S. typhimurium* TA98, TA100	0-1 mmol/l	NS	Negative	Moody & Hassan (1982)
Reverse mutation	*S. typhimurium* TA98, TA100 (not clear what other strains were used), *E coli* WP2 *hcr*	Not clear	NS	Negative, but full results not given	Shirasu et al. (1982)
Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100, *E coli* WP2 *hcr*	5000 µg/plate	NS	Negative	Moriya et al. (1983)
Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA97,	0-20 µg/plate	NS	Negative	Lin et al. (1988)

	TA98, TA100				
Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA97, TA98, TA100	0-50 µg/plate	NS	Negative	Lin et al. (1989)
Reverse mutation	*S. typhimurium* TA102	10 ng/plate	NS	Negative	Levin et al. (1984)
Reverse mutation	*S. typhimurium* TA1535, TA1537, TA1538, TA98, TA100 *E. coli* WP2 *hcr*	0.5-500 µg/plate	NS	Negative	Shirasu et al. (1978)
Reverse mutation	*E. coli* IC203, *oxyR* deficient and WP2 *uvrA*/Pkm101	1 µg/plate	NS	Negative	Martinez et al. (2000)
Reverse mutation	*S. typhimurium* TA100, TA98	0.06 µmol/plate	NS	Negative	Nishimura et al. (1982)
Reverse mutation	*S. typhimurium* TA102, TA2638, *E. coli* WP2/Pkm101 and WP2 *uvrA*/Pkm101	0-10 µg/plate	NS	Positive	Yamaguchi (1981)
Reverse mutation	*S. typhimurium* TA100	20 µg/plate	NS	Negative	Watanabe et al. (1998)
Forward mutation	Mouse lymphoma L5178Y cells $Tk^{+/-}$	31.3-1000 µg/plate	45.66%w/w technical-grade paraquat dichloride	Negative ± S9	Clay & Thomas (1985)
Forward mutation at the *Hprt* locus	Chinese hamster V79 cells	1-5 mmol/l	NS	Negative	Speit et al. (1998)
Forward mutation to azaguanine resistance	*S. typhimurium* His G46, TA92, TA1535	0.1-1 µg/plate	NS	Positive	Benigni et al. (1979)
Forward mutation to azaguanine resistance	*S. typhimurium* His G46, TA92, TA1535, TA1538, TA100	0.1-2.5 µg/plate	NS	Positive	Bignami & Crebelli (1979)
Umu test	*S. typhimurium* TA1535/Psk1002	1000-3333 µg/ml	NS	Positive	Oda et al. (1985)
Umu test	*S. typhimurium* TA1535/Psk1002	1000 µg/ml	NS	Positive	Nakamura et al. (1987)
Umu test	*S. typhimurium* TA1535/Psk1002	0.1 ml/tube	NS	Negative	Degirmenci et al. (2000)
Umu test	*E. coli* K12 AB1157, AB2463 H/r30, H/s30, NG30, R15, B/r, B_{S-1}	4 mg/ml	NS	Positive	Degirmenci et al. (2000)
SOS-induced DNA damage	*E. coli* $WP2_s$*(lambda)*	0.02-67.11 µmmol/l	NS	Positive ± S9	DeMarini & Lawrence (1992)
SOS-induced DNA damage	*E. coli* PQ300	Not clear	99	Negative	Eder et al. (1989)
SOS-induced DNA damage	*E. coli* PQ37, PM21, GC4798	Not clear	NS	Negative	Müller & Janz (1992)
DNA repair	*S. typhimurium* TA1538, TA1978	100 µg/plate	NS	Positive	Benigni et al. (1979)
Rec assay	*B. subtilis* recombination wild-type H17 and deficient M45	1-500 µg/disc	100%	Negative	Shirasu et al. (1978)
Gene mutation	*Aspergillus nidulans* (plate assay)	0-1000 µg/plate	NS	Positive	Benigni et al. (1979)
Gene mutation	*A. nidulans* (liquid assay)	20 mg/ml	NS	Negative	Benigni et al. (1979)
Lethal recessive	*A. nidulans* (liquid assay on	20 mg/ml	NS	Positive	Benigni et al.

	quiescent conidia)				(1979)
Intrachromosomal recombination	*Saccharomyces cerevisiae*	0-35 mg/ml	NS	Negative	Brennan et al. (1994)
DNA damage	*S. cerevisiae*	1-20 mmol/l	NS	Negative	Paesi-Toresan et al. (1998)
Gene conversion	*S. cerevisiae*	100-900 mg/kg	NS	Positive	Parry (1973)
Gene conversion	*S. cerevisiae*	1000 mg/kg	NS	Negative	Siebert & Lemperle (1974)
Reverse and forward mutation	*Nostoc muscorum* (blue-green alga)	50 and 75 mg/kg	NS	Positive	Vaishampayan (1984a)
Reverse and forward mutation	*N. muscorum* (blue-green alga)	25-75 mg/kg	NS	Positive	Vaishampayan (1984b)
Cytogenetics	*Vicia fava* (broad/fava bean)	NS	NS	Negative	Gopalan & Njagi (1979)
Somatic mutation (*Drosophila* wing spot test)	*Drosophila melanogaster*	2-8 mmol/l	99%	Negative	Torres et al. (1992)
SMART assay	*D. melanogaster*	NS	NS	Negative	Ramel & Magnusson (1992)
SMART assay	*D. melanogaster*	0-10 mmol/l	NS	Negative	Gaivao & Comendador (1996)
SMART assay	*D. melanogaster*	0-10 mmol/l	NS	Positive	Gaivao et al. (1999)
SMART assay	*D. melanogaster*	0-16 mmol/l	NS	Negative	Vontas et al. (2001)
Chromosome test	*D. melanogaster, mus* 302 repair-defective females	200 mg/kg	NS	Negative	Woodruff etal. (1983)
Forward mutation at *Tk* locus	Mouse lymphoma L5178Y cells	0-200 µg/ml	NS	Positive	McGregor et al. (1988)
Mutation to thioguanine resistance	Chinese hamster V79 cell lines transfected with bacterial *gpt* (G12, G10)	200-300 µmol/l	NS	Negative	Kitahara et al. (1996)
Chromosomal aberration	Chinese hamster cells	≤200 µg/ml	45% technical grade	Positive	Lin et al. (1987)
Chromosomal aberration	Chinese hamster cells resistant to hydrogen peroxided (H_2O_2)	50-400 µg/ml	NS	Positive	Sawada et al. (1988)
Chromosomal aberrations and sister chromatid exchange	Chinese hamster fibroblast cells	3-10 mmol/l for chromosomal aberrations, and 0-0.75 mmol/l for sister chromatid exchanges	NS	Positive	Nicotera et al. (1985)
Chromosomal aberrations and sister chromatid exchange	Chinese hamster lung cells	0.08-20 µmol/l	NS	Positive	Tanaka & Amano (1989)
Chromosomal aberration	Human peripheral blood lymphocyte culture	1-50 µg/ml, chromosomal aberrations	99%	Negative	Ribas et al. (1997/8)
Sister chromatid exchanges	Chinese hamster ovary cells	0.625-100 µg/ml	45% technical grade	Negative	Wang et al. (1987)
Sister chromatid	Rat tracheal epithelial cells	0.625-2.5 µg/ml	45%	Positive	Wang et al.

exchanges			technical grade		(1987)
Sister chromatid exchanges	Human peripheral blood lymphocyte culture	l-4000 µg/ml for sister	99%	Positive	Ribas et al. (1997/8)
Sister chromatid exchange	Chinese hamster lung fibroblasts	1.2-245 µg/ml	99.4% dichloride	Positive -S9, effect less +S9	Howard et al. (1985)
Cytogenetics	Human lymphocytes	250-2500 µg/ml	99.6%w/w dichloride	Clastogenic at toxic doses only	Sheldon et al. (1985a)
Micronucleus formation	Human peripheral blood lymphocyte culture	l-4000 µg/ml	99%	Negative	Ribas et al. (1997/8)
Micronucleus formation, optimized to detect excision repair	Human peripheral blood lymphocyte culture	25-100 µg/ml	99%	Negative	Surrallés et al. (1995)
Unscheduled DNA synthesis	Human epithelial-like cells	20-2000 µg/plate	NS	Positive, without dose-response relationship	Benigni et al. (1979)
Unscheduled DNA synthesis	Rat thymocytes and human peripheral blood lymphocytes	Rat thymocytes: 180-1800 µg/ml, human lymphocytes: 900 µg/ml	95%	Equivocal	Rocchi et al. (1980)
Unscheduled DNA synthesis	Rat primary hepatocytes	10^{-9}-10^{-2}mol/l	Paraquat dichloride 99.6%	Negative	Trueman et al. (1985)
Comet assay for DNA damage	Human peripheral blood lymphocytes	≤2000 µg/ml for 4 h	99%	Positive (+S9) Positive (-S9)	Ribas et al. (1995)
Comet assay for DNA damage	Rat alveolar macrophages and epithelial type II cells	10 µmol/l	NS	Positive	Dusinska et al. (1998)
Comet assay for DNA damage	Chinese hamster cells	1-5 mmol/l	NS	Negative	Speit et al. (1998)
Comet assay for DNA damage	Rat astroglial cells	20-80 µmol/l	NS	Positive	Frederiksen & Clausen (1999)
Comet assay for DNA damage	Human cell line A549 and THP-1	10-100 µmol/l	NS	Positive	Don Porto Carera et al. (2001)
Comet assay for DNA damage	Human cell lines HeLa and Hep G2 and human peripheral lymphocytes	0-350 µmol/l	NS	Positive	Petrovska & Dusinska (1999)
Chromosomal damage	Chinese hamster fibroblasts	0.2-0.8 mg/ml 3 h	NS	Positive	Sofuni & Ishidate (1988)
Chromosomal damage	Chinese hamster cells	0.8 mg/ml 3 h	NS	Positive	Sofuni et al. (1988)
Chromosomal damage	Chinese hamster V79 cells	1-5 mmol/l	NS	Negative	Speit et al. (1998)
Chromosomal damage	Mouse (male and female BALB/C) bone-marrow and germ cells	Bone marrow: 7-23 mg/kg bw (single intraperitoneal dose) or 1.5, 3.0 and 5.0 mg/kg bw per day intraperitoneally for 10 days. Germ cells: 1.5, 3.0 and 5.0 mg/kg bw per day intraperitoneally for 5 days	NS	Equivocal (repeat doses); Negative (single dose)	Rios et al. (1995)
In vivo					
Micronucleus formation	Mouse (C57 B1/6J/Alpk)	51.75, 82.8 mg of paraquat ion/kg bw	Paraquat dichloride	Negative	Sheldon et al. (1985b)

		(single dose by gavage)	33.07% w/w paraquat ion		
Micronucleus formation	Mouse (male Swiss albino)	83 mg/kg bw per os	NS	Positive	Prabakaran & Moorthy (1998)
Micronucleus formation	Mouse (male ICR)	2 × 15 mg/kg bw intraperitoneally	98%	Positive	Melchiorri et al. (1998)
Micronucleus formation	Mouse (pregnant female Swiss)	10 or 20 mg/kg bw subcutaneously	99%	Negative	Pena et al. (1999)
Micronucleus formation	Mouse (male Swiss)	2 × 20 mg/kg bw ip	NS	Positive[a]	Ortiz et al. (2000)
Cytogenetics	Rat (outbred Wistar-derived)	6.5-19.0 mg/kg bw, daily for 5 days (as paraquat ion, by gavage)	Paraquat dichloride, 100%	Negative (fuzzy banded cells were seen)[b]	Anderson et al. (1978)
Cytogenetics	Rat (Alpk: AP Wistar-derived)	15-150 mg/kg bw single dose by gavage	Paraquat dichloride, 33.07% w/w paraquat ion	Negative	Howard et al. (1987)
Chromosomal damage	Mouse (male CFLD)	Single dose 60 mg/kg bw per os; 2.4 mg/kg bw per os twice per week for 6 weeks; single dose 15 mg/kg bw intraperitoneally; 0.55-5.5 mg/kg bw × 5 intraperitoneally	25% paraquat ion	Negative	Selypes et al. (1978)
Unscheduled DNA synthesis	Rat(Alpk:AP Wistar-derived)	45-120 mg/kg bw single dose by gavage	Paraquat dichloride (technical) 33.07% paraquat ion	Negative	Trueman & Barber (1987)
DNA damage	Rat (male Wistar)	20 mg/kg bw intraperitoneally	NS	Negative	Sorensen & Loft (1999)
Dominant lethal mutation	Mouse (male Swiss-Webster)	66 mmol/kg bw per day	NS	Negative	Pasi et al. (1974)
Dominant lethal mutation	Mouse (male CD-1)	0.04-4 mg ion/kg bw per day	23.8% paraquat ion	Negative	Anderson et al. (1976)

The results of tests for genotoxicity with paraquat in *Drosophila melanogaster* were conflicting, and are in any case irrelevant to the situation in mammals in vivo. In studies of DNA damage (unscheduled DNA synthesis) in mammalian systems in vivo and of chromosome damage in germ cells (dominant lethal test), paraquat gave negative results. The results of the majority of assays for clastogenicity (metaphase analysis to investigate chromosomal aberrations or tests for micronucleus formation) in bone marrow were negative.

In three tests for micronucleus formation in vivo (two using intraperitoneal administration and one using administration per os), paraquat gave positive results. In these three tests, the doses used were high; it is thus possible to conclude that paraquat may induce chromosome damage at high doses in assays in bone marrow in vivo.

The hypothesis that these effects are caused by the well-established ability of paraquat to generate reactive oxygen species, which are not detoxified at high doses owing to saturation of cellular defensive mechanisms, is likely to be the explanation for the results discussed above. For such an effect it is likely there would be a threshold as, except at high doses, reactive oxygen species are rapidly detoxified.

A mechanistic study was carried out into the ability of paraquat to produce "fuzzy-banded" chromosomes from rat bone-marrow cells (Anderson et al., 1979). From this study, it was concluded that paraquat was interfering with staining performed by the Giemsa method.

2.5 Reproductive toxicity

(a) Multigeneration studies

Rats

In a three-generation study of reproductive toxicity, Wistar-derived Alderley Park rats were given diets containing technical-grade paraquat (25.8% paraquat ion) at a concentration of 0, 30 or 100 mg/kg. These dietary concentrations were equivalent to intakes of 0, 2.0 and 6.67 mg of paraquat ion/kg bw per day. The F_0 animals started on the test diets when aged 35 days, and they and their progeny remained on the diet throughout the study. The animals were examined daily and body weight and food consumption were recorded weekly. For the first mating, one male and two females receiving paraquat at the same dietary concentration were housed together. This was done at 105 days and produced the F_{1a} generation. The litters were examined after parturition and the number of live-born and stillborn pups recorded, together with the clinical state of the former. Offspring were examined daily for the number of live or dead offspring, and at 21 days, each litter was counted, weighed, sexed and autopsied. After 10 days, the second mating was carried out as described above. From the F_{1b} pups produced, 12 male and 24 female weanlings were selected to become the F_1 parents. The remainder of the offspring were killed and examined. At 100 days, one male and two females receiving paraquat at the same dietary concentration were housed together.

This mating produced the F_{2a} generation. The litters were examined after parturition and the number of live-born and stillborn pups was recorded, together with the clinical state of the former. Offspring were examined daily for the number of live or dead offspring, and at 21 days each litter was counted, weighed, sexed and autopsied. After 10 days, the second mating was carried out as described above. From these F_{2b} pups, 12 male and 24 female weanlings were selected to be the F_2 parents. Again two litters were produced (F_{3a} and F_{3b}), but this time all the offspring were killed and examined at 5-7 weeks. Tissues from 10 progeny of each sex per dietary concentration were examined histopathologically. No test material-related clinical effects were seen. Increased body-weight gain was seen in the groups of male rats receiving paraquat. This was particularly marked in the F_0 rats and was noted from 6 weeks onwards at both 30 and 100 mg/kg; it also occurred in the F_{1a} and F_{1b} rats, for which the body weights of females were also increased; this finding was not noted in the F_2 rats. Paraquat had no significant effect on food consumption. No adverse treatment-related effects were seen on reproductive performance (number of pregnancies to term, mean litter size, pup sex distribution and body weight at weaning). In the F_{1b} litters, the mean litter size was smaller at 30 mg/kg than in the controls or at 100 mg/kg. In the F_2 generation, litter size was increased at 100 mg/kg, but was within the range for historical controls. On histopathological examination, hydropic change was found in the renal tubules of weanlings that had been fed paraquat at a dietary concentration of 100 mg/kg. The NOAEL for the offspring was therefore 30 mg/kg (equivalent to 2.0 mg of paraquat ion/kg bw per day) on the basis of renal tubular changes in the weanlings at the highest dietary concentration. The NOAEL for the parents and for reproductive toxicity was 100 mg/kg (equivalent to 6.67 mg of paraquat ion/kg bw per day), the highest dietary concentration administered (Fletcher et al., 1972).

In another multigeneration study, Wistar-derived Alderley Park rats were fed diets containing technical-grade paraquat dichloride (32.7% w/w paraquat ion) at a concentration of 0, 25, 75 or 150 mg/kg as paraquat ion. These diets provided intakes equivalent to 0, 1.67, 5.0 and 10 mg of paraquat ion/kg bw per day. The F_0 parents comprised 15 male and 30 female rats per group; these rats were mated 12 weeks after the start of the study to produce the F_{1a} litters and 7 days after the last F_{1a} litter had been weaned (at 21 days) the F_0 parents were remated to produce the F_{1b} litters. The F_{1b} litters were weaned at 28 days. F_1 parents (30 females and 15 males per group) were selected from the F_{1b} litters and mated 11 weeks later to produce the F_{2a} and 7 days after the last F_{2a} litter had been weaned (at 28 days), remated to produce the F_{2b} litters (these were also weaned at 28 days). The F_2 parents were selected from the F_{2b} litters and mated 11 weeks later. All male parents were killed after mating to produce the F_{1b} or F_{2b} litters and the females were also killed, but after weaning of the F_{1b} or F_{2b} litters. The F_0 and F_2 parents were subjected to gross examination post mortem and the testes of all the males were fixed and processed for histopathological examination. Lungs from eight males and eight females of each group, and any abnormal tissues from all the animals were also fixed and processed for histopathological examination. Of the F_1 parents, 25 females and 10 males per group were subjected to a full autopsy and a wide range of tissues were processed for histopathological examination. Litters were examined at least

daily and dead or abnormal pups removed for examination. Live and stillborn pups were counted and sexed at 24 h and 4, 10 and 21 days post partum. Pup weights were measured at 24 h and at 4, 10, 21 and 28 days post partum. All grossly abnormal pups and those found dead up to 18 days post partum were taken for teratological examination. Those aged > 18 days were taken for histopathological examination. Of the pups of the F_{1a}, F_{2a} and F_{3a} litters, about 50% were discarded, the remainder being subjected to gross necropsy; any abnormal tissues were processed for histopathological examination. After selection of the parents for the next generation, five males and five females from the F_{1b} and F_{2b} litters and 10 males and 10 females from the F_{3b} litters were subjected to detailed histopathological examination. Test diets were fed throughout the study. The rats were observed daily, with a more detailed observation once per week, clinical observations and mortality were recorded. Body weights and food consumption were recorded weekly throughout the pre-mating period. During the premating period, urine was taken from three males and three females per group for analysis for paraquat. After the premating period, the male rats were weighed at 4-weekly intervals. No adverse effects were noted on parental clinical status, body weights or food consumption. Mortality was seen in female F_0 and F_1 parents receiving paraquat at the highest dietary concentration, mostly during or just after suckling a litter, no such effect being seen with the F_2 parents. No effect on body weight attributable to the test material was seen in the parents. There was some indication of an increase in food consumption in the F_0 parents and a decrease in food consumption in the F_1 parents. As these effects were not clearly dose-related, it is difficult to attribute them to paraquat: moreover, no effect on food consumption was noted with the F_2 parents. Measurements of urinary paraquat showed that dose-related absorption of paraquat occurred during the study. There were no adverse effects on fertility of the F_0 parents, male or female, during production of either F_1 litter. At 25 mg/kg (F_{1b}) and 75 mg/kg (F_{1b}), there was a reduction in the duration of gestation; in view of the lack of any such finding at higher dietary concentrations, this is unlikely to be related to the diet. There were no treatment-related effects on live-born offspring, maternal neglect or survival indices. In production of the F_2 litters by the F_1 parents, no effect of the paraquat was seen on fertility, body-weight gain of the pregnant dams, duration of gestation or live-born offspring, survival indices or litter size. No adverse effects on male or female fertility were noted in the F_2 parents on male or female fertility during production of the F_3 litters. Body-weight gain of the F_2 females when pregnant with F_{3a} or F_{3b} litters was increased at 75 mg/kg. The offspring of all three generations were healthy during lactation, although mortality in the F_{1b} litters was higher than that in the other litters. There were some differences in F_1 and F_3 litter weights between the groups, but they were not dose-related. Three of the F_0 female parents receiving paraquat at the highest dietary concentration died, and the lungs of these animals showed alveolar oedema, perivascular oedema and inflammatory cell infiltration (mainly macrophages, with a few neutrophils); profibroblasts and early fibrosis was also observed. Four lactating females receiving paraquat at the highest dietary concentration and suckling the F_{1b} litters died or were killed in extremis and their lungs showed similar changes. At termination, significant histopathological changes were confined to animals receiving paraquat at 150 mg/kg. These changes comprised consolidation, with alveolar fibrosis, epithelialization and infiltration with a few macrophages and profibroblasts. There was also hypertrophy and hyperplasia of the bronchial epithelium, with perivascular oedema and mixed inflammatory cell infiltration. No other treatment-related findings were seen in the F_0 female rats. In the F_0 male rats, there was an increase in focal histiocytosis at 75 and 150 mg/kg. In the F_1 parents, 13 females dying during late lactation were from the groups receiving 150 mg/kg and had lung changes similar to those described above. At termination of the F_1 females, five of the 17 surviving rats at 150 mg/kg had mild to severe lung changes. There was an increase in focal alveolar histiocytosis in the lungs at 75 and 150 mg/kg. This change was also present in the lungs of the male survivors at termination at 75 and 150 mg/kg. In the F_2 parental females, six rats at 150 mg/kg, which died or were killed in extremis, lung changes were observed at histopathological examination. At termination of the F_2 parental survivors, a proportion of both males and females at 150 mg/kg had some lung changes, as described above, and there was an increase in focal alveolar histiocytosis in the lungs at 75 and 150 mg/kg. Histopathological changes in the reproductive system were not seen in the parental animals of either sex. In the offspring, mild perivascular inflammatory cell infiltration was seen in lungs of four out of five male and two out of six female F_{1b} offspring at the highest dietary concentration. Otherwise, there were no pathological changes in the F_1, F_2 or F_3 offspring that could be directly attributed to the test material, although one F_{3b} litter starved (and died or were sacrificed in extremis) as a result as a result of the death of the mother. The NOAEL was 25 mg/kg, equivalent to 1.67 mg of paraquat ion/kg bw per day, on the basis of lung changes at 75 and 150 mg/kg in adult rats. The NOAEL for reproductive toxicity was 150 mg/kg, the highest dietary concentration administered, this being equivalent to 10 mg of paraquati on/kg bw per day. The NOAEL for toxicity in the offspring was 75 mg/kg, equivalent to 5.0 mg of paraquat ion/kg bw per day (Lindsey et al., 1982).

In another three-generation study, groups of 30 male and 30 female Sprague-Dawley (CRJ:CD) rats were fed diets containing paraquat dichloride (purity, 98.6%) at a concentration of 0, 100, 200 or 400 mg/kg. The intakes of test material achieved are given in Table 10.

Table 10. Measured intake of paraquat dichloride (mg/kg bw per day) in a three-generation study

Group	Dietary concentration (mg/kg)			
	0	100	200	400
F_0 males	0	6.6	13.0	25.1
F_0 females	0	7.2	13.8	29.3
F_{1b} males	0	9.6	19.8	38.7
F_{1b} females	0	10.2	20.8	32.9
F_{2b} males	0	8.5	16.9	40.9
F_{2b} females	0	9.6	19.6	48.7
Mean for males*	0(0)	8.2 (5.9)	16.6(12.0)	34.9 (25.3)
Mean for females*	0(0)	9.0 (6.5)	18.1 (13.1)	37.0 (26.8)

From Suzuki et al. (1983)
* Intake of paraquat ion in parentheses

The F_0 parents received the diets from week 5 weeks until after weaning of the second (F_{1b}) litters. There was a 13-week premating period after which the males and females were mated to produce the F_{1a} litters. The pups were examined for number of live born, stillbirths, sex ratio and external abnormalities. Eight pups per litter were investigated until weaning at 21 days after birth, and the pups were then examined post mortem. Two weeks after the F_{1a} litters had been weaned, the F_0 females that were successful breeders were housed with their previous mates to produce the F_{1b} litters. The F_0 females bearing the F_{1b} litters were divided into three groups, five females being used for teratology, five for postnatal investigations and 10 to produce the F_1 parents as follows. Five pregnant females of each group were killed on day 20 of gestation. After macroscopic examination, the uteruses were removed and examinations carried out to determine number of live fetuses, fetal deaths and resorptions. Live fetuses were weighed, sexed and examined for external abnormalities. One-third of all live fetuses were fixed in Bouin solution, examined in detail and dissected. The remainder were fixed in 95% alcohol, stained with alizarin red S and examined for skeletal abnormalities. Five pregnant females underwent parturition and the duration of gestation and numbers of live pups and stillbirths were recorded, together with sex ratio and any external abnormalities of the pups. Where there were more than eight pups per litter, the excess were stained with alizarin red S and examined for skeletal abnormalities. The remaining live pups were retained until weaning at 28 days, when they underwent examination post mortem. Ten pregnant females underwent parturition and the duration of gestation and numbers of live pups and stillbirths were recorded, together with sex ratio and any external abnormalities of the pups. Where there were more than eight pups per litter, 4 days after birth, the excess were killed, stained with alizarin red S and examined for skeletal abnormalities. The remaining live pups were retained until weaning at 21 days. Mortality, viability and growth status were recorded, and 30 males and 30 females at each dietary concentration were selected to be the next generation, the remainder being autopsied with their (F_0) dams. The F_1 rats, which produced the F_{2a} and F_{2b} litters, were treated similarly to the F_0 rats (see above), being fed the diets from the time they were weaned until the weaning of their second (F_{2b}) litters. Ten pregnant females were, however, used for teratology studies and 10 for postnatal investigation, any remaining being allowed to give birth, after which the dams and pups were sacrificed. The third generation (from the F_{2b} litters) were fed the diets from the time they were weaned until at least 13 weeks later.

Throughout the study, all animals were examined daily and the F_0 and F_{1b} females were weighed on days 0, 7, 14 and 20 day of gestation and on days 0, 7, 14 and 21 post partum (during lactation). The F_{1b} litters to be used for postnatal investigation were weighed 0, 4, 7, 14, 21 and 28 days after birth, and those that were used to produce the next generation were weighed 0, 4, 7, 14 and 21 days after birth. Food consumption was measured weekly for each cage, but not during dosing of the F_0 generation and not in the mating period that produced the F_{1b} litters. Water consumption by 10 males and 10 females per dietary concentration was measured weekly, except for the F_0 mating

period and the mating period that produced the F_{1b} litters. At autopsy of the parental rats, selected organs were weighed, and these and other selected organs were fixed and processed for histopathological examination.

No deaths were seen in the F_0 parents, but excess deaths were seen in the subsequent generations. At 400 mg/kg, five F_{1b} females died (compared with two of the controls). There were 14 deaths or animals killed in extremis in F_{2b} males at 400 mg/kg, and 10 deaths or rats killed in extremis in F_{2b} females at 400 mg/kg. At 400 mg/kg, wheezing was heard in rats of each generation and this was often accompanied by weight loss. At 400 mg/kg, there was a reduction in body-weight gain in male and female F_0 and F_{2b} rats at an early stage during dosing, and in female F_{1b} rats during gestation and lactation. There was a reduction in food consumption in F_0 and F_{2b} rats at 400 mg/kg early in the dosing period. No treatment-related changes were seen in reproductive parameters (corpora lutea, implantation number, implantation (%), number of dead and live fetuses, sex ratio or placental weight), nor were any teratogenic effects seen. Retarded ossification was noted in fetuses from the F_0 dams at 100 mg/kg, and in those from the F_{1b} dams at 100 mg/kg and 400 mg/kg. Furthermore, there were reductions in body weights of male fetuses from the F_{1b} females at 100 and 400 mg/kg. Retardation of ossification was also noted in fetuses from all test groups of F_{1b} dams. There were reductions in body-weight gain in F_{2b} pups at 400 mg/kg. There was retarded opening of the vagina in both the F_{1b} and F_{2b} female pups at 400 mg/kg. No effects on organ weights were seen that were clearly attributable to the test material. However, F_0 animals at 400 mg/kg showed a reduction in brain weight, both absolute and relative. Histopathologically, alveolar hyperplasia and fibrosis was found in F_0 males at 400 mg/kg, in F_{1b} females at 100, 200 and 400 mg/kg, and in F_{2b} rats of both sexes at 400 mg/kg. At 400 mg/kg, F_{1b} rats also showed atelectasis, congestion and haemorrhage, while in the decedents from F_{2b} rats at 400 mg/kg, alveolar wall hyperplasia and fibrosis, atelectasis, congestion, haemorrhage and oedema were found. The LOAEL for maternal toxicity was 100 mg/kg on the basis of lung changes seen in female F_{1b} rats (this dietary concentration is equal to 9.0 mg of paraquat dichloride/kg bw per day and 6.5 mg of paraquat ion/kg bw per day). No NOAEL for fetal toxicity was seen because of retarded ossification and decreased body weight, the LOAEL for fetal toxicity being 100 mg/kg (equal to 9.0 mg of paraquat dichloride/kg bw per day and 6.5 mg of paraquat ion/kg bw per day in the dams.fn[2] The NOAEL for pup toxicity was 200 mg/kg on the basis of decreased body weight in F_{2b} pups at 400 mg/kg and retarded opening of the vagina in F_{1b} and F_{2b} female pups at 400 mg/kg. This NOAEL is equal to 16.6 mg of paraquat dichloride/kg bw per day in males and 18.1 mg of paraquat dichloride/kg bw per day in females (12.0 and 13.1 mg of paraquat ion/kg bw per day in males and females, respectively). The NOAEL for reproductive toxicity was 400 mg/kg, (the highest dietary concentration). This is equal to 34.9 mg of paraquat dichloride/kg bw per day and 25.3 mg of paraquat ion/kg bw per day in males, and 37.0 mg of paraquat dichloride/kg bw per day and 26.8 mg of paraquat ion/kg bw per day in females. An overall NOAEL for the study was not elicited, as histopathological evidence of lung damage was found at all dietary concentrations in F_{1b} female rats, and delayed ossification and reductions in body weight in fetuses were seen at $\leq$100 mg/kg. The overall LOAEL for the study was 6.5 mg of paraquat ion/kg bw per day (Suzuki et al., 1983).

Mice

In a two-generation study of reproductive toxicity, groups of 24 pairs of ICR albino mice (paired at age 30 days) and given diets containing paraquat at a concentration of 0, 45, 90, or 125 mg/kg (equal to 0, 45, 90 or 125 mg of paraquat ion/kg feed and equivalent to 0, 6.75, 13.5 or 18.75 mg of paraquat ion/kg bw per day). Females were allowed 8 weeks from pairing to produce a litter and cages were checked daily for parental and pup mortality. The pups were weaned after 30 days and either segregated or paired for use in producing the second generation. Exposure of the parental (F_0) mice continued until the weaning of the F_1 mice, which were exposed to the diet for 49 days postnatally. Lungs were excised from sucklings, weanlings and adults in groups in which mortality had been observed, and were processed for histopathological examination. At age 30 days, randomly selected F_1 mice were paired (not siblings) to produce the next generation. The control group comprised 24 pairs and the groups receiving paraquat comprised two groups of 12 pairs at each dietary concentration. One group of 12 pairs at each dietary concentration was removed from the test diet and placed on control diet on weaning, whereas the other remained on the same diet as their parents. No differences were observed in the age of females at first parturition, pups borne/litter or in pup abnormalities; at the highest dietary concentration, however, the number of pairs of mice producing litters was reduced because of maternal deaths. Furthermore, effects on the mortality of F_1 offspring were observed at the highest dietary concentration. The age of F_1 females at second parturition was increased, and mortality in the F_2 generation at 7 weeks was increased at 125 mg/kg.

Excess mortality was not observed in the F_1 parents. Maternal and offspring lungs were histopathologically abnormal, with extensive fibrosis at the highest dietary concentration and in a few instances, in the dams, at the intermediate concentration. The NOAEL for the study was 45 mg/kg, equivalent to 6.75 mg of paraquat ion/kg bw per day. The NOAEL for pup toxicity was 90 mg/kg (equivalent to 13.5 mg of paraquat ion/kg bw per day) on the basis of excess mortality and histopathological changes in the lungs. Specific reproductive toxicity was not seen (Dial & Dial, 1987).

(b) Developmental toxicity

Rats

In a study of developmental toxicity, groups of 29 or 30 rats (strain not stated) were given paraquat dichloride (purity, 100%) at a dose of 0, 1, 5, or 10 mg of paraquat ion/kg bw per day by oral gavage on days 6-15 of gestation. Animals were examined daily and maternal body weight was measured on days 0, 3, 6, 8, 12, 16 and 21. Food consumption was not measured. On day 21 of gestation the animals were killed and their uteri were examined for live fetuses and resorptions; corpora lutea were counted. Fetuses were removed, weighed, sexed and observed for gross malformations, then preserved before examination for soft tissue or skeletal abnormalities. Alternate fetuses were examined for soft tissue or skeletal abnormalities. Maternal lungs and kidneys from at least 11 surviving rats per group were fixed and processed for histopathological examination. Observed mortality in the group receiving the highest dose was attributed to paraquat. Clinical signs of maternal toxicity occurred in many animals at 5 mg/kg bw per day and in most animals at 10 mg/kg bw per day. These signs were piloerection, weight loss, hunched appearance and, sometimes, respiratory distress. Reduced maternal body-weight gain was seen at 5 and 10 mg/kg bw per day, the effect being greater at the higher dose. The decedent dams at the highest dose showed, grossly, patchy red areas in the lungs, while microscopically there was alveolar oedema with polymorphonuclear infiltration. Proximal tubular degeneration in the kidneys was also found. These changes were not present in the groups receiving a dose of 5 mg/kg bw per day or the survivors to 21 days in any group. Slightly reduced mean fetal weights were seen at 5 and 10 mg/kg bw per day (the significance at $p < 0.05$ at 5 mg/kg bw per day depended on one female who had 12 resorptions out of 14 implants, and the two fetuses were very small). Significant intergroup differences in fetal survival, number of viable fetuses, proportion of females with resorptions, numbers of corpora lutea and sex ratios were not seen. If, however, the female receiving a dose of 5 mg/kg bw per day that had 12 resorptions out of 14 implants, and whose two fetuses were very small was included, a difference was apparent in viable fetuses as a proportion of implant numbers between the control group and the group receiving a dose of 5 mg/kg bw per day. No intergroup differences in skeletal abnormalities were found, but retarded ossification (caudal vertebrae and forelimb and hindlimb digits) was seen at 5 and 10 mg/kg bw per day. No fetal soft-limb abnormality was found that was attributable to treatment. The NOAEL for maternal and fetal toxicity was 1 mg/kg bw per day on the basis of clinical signs, and reduced body-weight gain in the dams and reduced mean fetal weights and retarded ossification in the fetuses. Teratogenicity was not observed (Hodge et al., 1978a).

In a study of developmental toxicity, groups of 24 female Alpk:ApfSD Wistar-derived rats were given technical-grade paraquat dichloride (paraquat ion, 38.2% w/v) at a dose of 0, 1, 3 or 8 mg of paraquat ion/kg bw per day by gavage on days 7-16 of gestation. Clinical observations were recorded daily and body weight was recorded on days 1, 4, 7-16, 19 and 22 of gestation. Food consumption was recorded over 3-day periods: days 1-4, 4-7, 7-10, 10-13, 13-16, 16-19 and 19-22. On day 22 of gestation, the rats were killed and their uteri weighed and examined for live fetuses and intrauterine deaths. The fetuses were weighed, examined for external and visceral abnormalities, sexed, eviscerated and stained for skeletal examination. No compound-related adverse clinical finding was recorded. There was a small amount of weight loss at the highest dose between days 1 and 2 of dosing (days 7-8 of gestation) and the difference in weight between the group receiving the highest dose and the controls was significant on days 8-14 and 16 of gestation. The effect on body weight of the dams at the highest dose (8 mg of paraquat ion/kg bw per day) was considered to be test material-related. Developmental toxicity was not seen. Paraquat was not teratogenic The NOAEL for maternal toxicity was 3 mg of paraquat ion/kg bw per day on the basis of effects on body weight at 8 mg of paraquat ion/kg bw per day, and the NOAEL for developmental toxicity was 8 mg of paraquat ion/kg bw per day, the highest dose tested (Hodge, 1992).

Mice

In a study of developmental toxicity, groups of 26-37 pregnant mice were given paraquat dichloride (purity, stated to be 100%) at a dose of 0, 1, 5 or 10 mg of paraquat ion/kg bw per day by gavage on days 6-15 of gestation. The animals were observed daily and weighed on days 0, 3, 6, 9, 12, 15 and 18 of gestation. Food consumption was not measured. On day 18, the mice were killed and their uteri were examined for resorptions. Fetuses were removed, weighed, sexed

and observed for gross abnormalities, and preserved for examination for soft tissue or skeletal changes. In the mothers, for at least eight animals per group, lungs and kidneys were fixed and processed for histopathological examination. No adverse clinical signs were noted. Maternal body-weight gain was decreased during gestation at 5 and 10 mg/kg bw per day, but only at 5 mg/kg bw per day was the difference from that of controls significant. There were no test material-related effects on maternal pathology. The numbers of implantations, viable fetuses and resorptions, sex ratio and fetal and litter weights were not different between treated and control groups. There was a higher incidence of fetal umbilical hernia at 5 mg of paraquat ion/kg bw per day, but this was considered to be unrelated to dosing. There was no increase in skeletal or soft tissue abnormalities and ossification was not retarded. The NOAEL for maternal toxicity was therefore 10 mg of paraquat ion/kg bw per day, the highest dose tested (since the effects based on reduced weight gain in pregnancy were not dose-related), while the NOAEL for fetal toxicity was also 10 mg of paraquat ion/kg bw per day, the highest dose tested (Hodge et al., 1978b).

In a study of developmental toxicity, groups of 26 Crl:CD1 (ICR) BR mice were given using technical-grade paraquat dichloride (purity, 38.2%) at a dose of 0, 7.5, 15 and 25 mg of paraquat ion/kg bw per day by gavage on days 6-15 of gestation. Maternal mortality (mice that died or were killed in extremis) and clinical signs were recorded daily from the start of gestation. Body weights were recorded on days 0, 6-15 and 18 of gestation. Food consumption was recorded over days 0-6, 6-9, 12-15 and 15-18 of gestation. The remaining females were killed on day 18 of gestation. Females were examined post mortem, when the lungs (with the trachea) and kidneys were weighed. Gestation status was assessed and the gravid uterine weight was recorded. The number of live and dead implantations was recorded. Live fetuses were weighed, examined for external abnormalities and sexed. One-half of the fetuses were examined for visceral abnormalities, and then for skeletal abnormalities, the other half being examined for visceral abnormalities. At the highest dose, there were five decedents at 15-17 days (four killed in extremis and one found dead). In the four killed in extremis, piloerection, laboured breathing, hunched posture, hypothermia, hypoactivity and pallor of the extremities and eyes were observed. No other treatment-related clinical effects were observed. Also at the highest dose, there was a decrease in body-weight gain over days 12-15 and 15-18, and over the whole period of dosing (days 6-15 of gestation); furthermore, body weight in the group receiving the highest dose was lower than that in the controls on day 15 and day 18 of gestation. Body weight and weight gain were unaffected at the lower doses. Significant differences in food consumption were seen on analysis of variance. Although food consumption between days 12 and 15 was reduced in the group receiving the highest dose compared with that in the controls, the difference was not significant. Food consumption was not reduced in mice at the lower dose. Despite the lack of statistical significance, the present reviewer considered that the reduction in food consumption between days 12 and 15 in the group receiving the highest dose compared with that in the controls may be biologically significant. At necropsy of the mice killed in extremis, dark red patches were found in the lungs. In all mice, absolute and relative lung weights were increased at the highest dose. The difference in absolute but not relative lung weights between the groups disappeared, if the decedents were excluded. The number of implantations, live fetuses, postimplantation loss and fetal sex ratio were not affected by treatment. At the highest dose, retardation of fetal growth was seen and mean fetal weight was decreased. No treatment-related effect on the prevalence of major abnormalities was seen. At 7.5 mg/kg bw per day and 15 mg/kg bw per day, but not 25 mg/kg bw per day, there were more fetuses and litters with minor external/visceral abnormalities, but as this did not appear to be dose-related, the effect was not considered to be treatment-related; this effect was due to an increase in the number of fetuses with renal pelvic cavitation. At the highest dose, there was retardation of ossification of the caudal vertebrae and the occipital and astragalus bone, with misshapen sternebrae. No treatment-related effect was seen at the lower doses. The NOAEL for maternal and fetal toxicity was 15 mg of paraquat ion/kg bw per day on the basis of effects on body weight, reduced food consumption and lung changes in the dams and retardation of ossification in the fetuses at the highest dose tested. Teratogenicity was not seen at any dose (Palmer, 1992).

Groups of Swiss-Webster mice were given paraquat at a dose of 1.67 or 3.35 mg/kg bw per day intraperitoneally or 20 mg/kg bw per day by gavage on days 6-16 of gestation. Gravid mice were sacrificed on day 19 of gestation. The number of live and dead fetuses and resorptions was recorded and the fetuses were removed, dried and examined for gross defects. Equal numbers of pups from each litter were fixed for examination of soft tissue or skeletal anomalies. No teratogenic effect was observed, although a slight degree of non-ossification of sternebrae was seen at all doses. Fetotoxicity, as evidenced by increased resorption (%), was seen at only 3.35 mg/kg bw per day intraperitoneally. At no dose was the number of fetuses, or their mean body weight affected by treatment. The amount of radiolabel reaching the mouse embryo when ^{14}C-labelled paraquat at a dose of 3.35 mg/kg bw administered intraperitoneally or 20 mg/kg bw administered orally on day 11 of gestation was small (Bus et al., 1975).

The developmental toxicity of paraquat was determined in Sprague-Dawley rats treated intravenously with paraquat at a single dose of 15 mg/kg bw on a single day, one of days 7-21 of gestation. The number of live and dead fetuses and resorptions was counted at day 22 (or before for decedent dams). Excess maternal deaths occurred with paraquat compared with controls receiving saline only, and there was an increase in the number of dead and resorbed fetuses (Bus et al., 1975).

Groups of pregnant Swiss-Webster mice were given drinking-water containing paraquat (purity unstated) at a concentration of 50 or 100 mg/l (and 150 mg/l) from day 8 of gestation until postnatal day 42. Pregnant mice receiving paraquat at 150 mg/l died during gestation (at about day 16). Treatment with paraquat at 100 mg/l and 50 mg/l did not alter the postnatal growth rate, nor was postnatal mortality increased at 50 mg/l. Administration of drinking-water containing paraquat at 100 mg/l caused an increase in postnatal mortality, and an increase in the sensitivity of pups to oxygen toxicity on postnatal days 1 and 28, while drinking-water containing paraquat at 50 mg/l did not. At both 50 and 100 mg/l, the sensitivity to oxygen toxicity and to bromobenzene at postnatal day 42 was increased. The authors considered that the effect of bromobenzene could be caused by depletion of reduced glutathione (Bus & Gibson, 1975).

2.6 Special studies

(a) Mechanistic studies

(i) Histopathological studies on the lung

Small groups of A/He mice were given drinking-water containing paraquat at a concentration of 50-300 mg/l, and retained for 1 to 16 weeks (further details of the material used are not given in the paper). Detailed light and electron microscopical studies were carried out on the mice post mortem. The main findings on light microscopy were vascular dilatation and veins filled with platelets and erythocyte aggregates. At the higher doses, interaveolar septal thickening was seen. At $\geq$ 100 mg/l, focal or, sometimes, lobar pneumonitis was observed, with small mononuclear cells, macrophages and neutrophils. In those mice receiving paraquat for 4 weeks or more, fibroblasts were seen in the septal walls. Obliteration of air spaces was seen. Type II cells were observed to be undamaged on electron microscopy in this study, but type I cells were swollen and there was evidence of oedema of interalveolar septa. The alveolar air spaces were filled with a clear exudate and where there was consolidation, fibroblasts and collagen were observed. Lymphocytes and plasma cells were noted (Brooks, 1971).

In a study of the ultrastructure of the rat lung after administration of paraquat, 51 female Wistar albino rats were divided into 17 groups, each group comprising two test animals and one control. On day 1, animals in 15 groups received paraquat at a dose of 40 mg of paraquat ion/kg bw administered intraperitoneally, while groups 16 and 17 received paraquat at a dose of 30 mg of paraquat ion/kg bw. At intervals of between 10 min and 4 h after injection, the animals were killed and the left lungs were fixed with glutaraldehyde via the main bronchus, and processed for electron microscopy. The right lungs were processed for light microscopy. Using light microscopy, changes were not seen until 24 h. After 2 days, microscopy revealed interstitial oedema and a fibrinous exudate, with a polymorph infiltration, which was more widespread after 4 days. Pro-fibroblasts were seen in the vicinity of bronchioles and major blood vessels. Using electron microscopy, after 4 days there was an increase in the quantity of rough endoplasmic reticulum and numbers of mitochondria and free ribosomes in alveolar type I cells. The cells were also thicker. These changes were followed by swelling of mitochondria, fragmentation of the rough endoplasmic reticulum and a reduction in cellular density. Later the cells disintegrated. Changes in the type II alveolar cells did not occur until 8 h and were not pronounced until 18 h after administration of paraquat. The changes consisted of swelling and rupture of the mitochondria, fusion and vacuolation of lamellar bodies and disruption of the cytoplasm. Three days after administration of paraquat, pro-fibroblasts were seen in the alveolar spaces (Smith & Heath, 1974).

In other species, such as rats and dogs, histopathological appearances after treatment with paraquat are generally similar to those in mice (Clark et al., 1966), although Butler (1975) found that the Syrian hamster relatively resistant to interstitial fibrosis. Butler & Kleinerman (1971) found that the New Zealand white rabbit did not develop pulmonary changes typical of paraquat poisoning in other species, despite intraperitoneal administration of paraquat at a dose of 2-100 mg/kg bw and sacrifice of animals being delayed up to 1 month. The only findings in the lungs were occasional small interstitial infiltrates of lymphocytes and plasma cells, minimal alveolar hyperplasia and some alveolar macrophages.

(ii) Mechanism of uptake by pneumocytes

A considerable amount of work has been done on the mechanisms that underlie the toxicity of paraquat. The fact that paraquat is concentrated by the lungs has been discussed above. Rose et al. (1976) showed that lung slices from rats Wistar-derived Alderley Park rats, beagle dogs, New Zealand white rabbits and cynomolgus monkeys *(Macaca fascicularis)* could concentrate paraquat via the polyamine active uptake system. This is the system by which paraquat and the structurally similar polyamines, such as putrescine and spermidine, are accumulated by type II alveolar cells (see reviews by Smith, 1985, Smith et al., 1990 and Lock & Wilks, 2001).

The uptake kinetics of paraquat and putrescine and their mutual inhibition in freshly isolated rat type II cell suspensions was reported. The uptake of paraquat by type II cells exhibited saturation kinetics and could be inhibited in a concentration-dependent manner by putrescine. The authors postulated that the polyamine uptake pathway in type II cells for paraquat and putrescine possessed two separate sites, one for each substrate, and that binding at one site leads to a conformational change in the other (Chen et al., 1992).

(iii) Production of cell damage in the lung

A study in which drinking-water containing paraquat at a concentration of 50 or 100 mg/l was administered to Swiss-Webster mice has already been discussed (see section on developmental toxicity). Drinking-water containing paraquat at a concentration of 100 mg/l increased postnatal mortality, and increased pups' sensitivity to oxygen toxicity at 1 and 28 days after birth, while drinking-water containing paraquat at a concentration of at 50 mg/l did not. At both 50 and 100 mg/l, drinking-water containing paraquat increased the sensitivity to oxygen toxicity and to bromobenzene at 42 days after birth (Bus & Gibson, 1975).

In a study of the hypothesis that the pulmonary toxicity of paraquat is caused by cyclic reduction-oxidation, with generation of superoxide radicals and singlet oxygen, and the production of lipid peroxidation, mouse lung microsomes in vitro were found to catalyse the nicotinamide adenine dinucleotide phosphate, reduced form (NADPH)-dependent reduction of paraquat. Incubation of paraquat with NADPH, NADPH-cytochrome reductase and purified microsomal lipid increased the production of malondialdehyde (MDA) production. Addition of superoxide dismutase or 1,3-diphenylisobenzofuran (a singlet oxygen trapper) inhibited paraquat-induced lipid peroxidation. Toxicity caused by paraquat (purity unstated) in mice (strain unstated) was decreased by phenobarbital and increased by selenium, vitamin E or reduced glutathione deficiency. The toxicity of paraquat was increased by exposure to 100% oxygen (Bus et al., 1976b).

In similar studies in rats and mice, Bus et al. (1976a) showed that pretreatment with phenobarbital increased the LD_{50} for paraquat in Swiss-Webster mice, but only when administration of the phenobarbital was continued after the administration of paraquat. Paraquat, administered intraperitoneally at a dose of 30 mg/kg bw, decreased liver concentrations of reduced glutathione and lung concentrations of lipid-soluble antioxidants. After receiving paraquat at a dose of 45 mg/kg bw, Sprague-Dawley rats habituated to 85% oxygen were found to have a longer median time to death than rats exposed to air. These rats were believed to have greater activity of lung enzymes that combat lipid peroxidation.

The effect of paraquat on oxidative radical reactions in the lung was evaluated by studying malondialdehyde production and chemiluminescence (spontaneous and induced by tertiary butyl hydroperoxide) in the isolated rat lung. After 2 h of perfusion with paraquat at 3.0 mmol/l, malondialdehyde content in lung homogenates was 16 ± 7 nmol/g of dry weight higher than in control lungs; during 30 min of perfusion, malondialdehyde efflux was 33 ± 15 nmol/g of dry weight higher than in control perfusates. Spontaneous chemilumi-nescence was not increased by 2 h of perfusion with paraquat at concentrations ranging from 0.75 to 6.0 mmol/l. Chemiluminescence induced by tertiary butyl hydroperoxide, however, was 17 ± 3% higher immediately after the addition of hydroperoxide and reached a 16 ± 6% higher plateau for lungs perfused with paraquat than for control lungs. Spectral analysis of the light emitted during induced chemiluminescence demonstrated peak intensity between 630 and 730 nm for controls and for lungs treated with paraquat. Increased production of malondialdehyde and increased induced chemiluminescence indicated that perfusion with paraquat enhances lipid peroxidation in the isolated rat lung (Aldrich et al., 1983).

The redox cycling abilities of paraquat and nitrofurantoin, compared with those of the potent redox cyclers diquat and menadione, was studied in lung and liver microsomes using the oxidation of NADPH and consumption of oxygen. In terms of relative potencies of these compounds to undergo redox cycling, diquat and menadione were similar and much greater than paraquat, which was similar to nitrofurantoin. This was partly attributed to the much lower affinity (K_m) of lung and liver microsomes for paraquat and nitrofurantoin than for diquat and menadione. These data were considered

to have important implications in assessing the risk of exposure to paraquat. Low concentrations of paraquat would not be expected to cause lung damage because insufficient compound would be present in the lung to exert toxicity by redox cycling (Adam et al., 1990).

There has been some disagreement over which cell type in the lungs is primarily affected by paraquat. Hirai et al. (1985) injected male Sprague-Dawley rats with paraquat dichloride at 40 mg/kg bw and observed mitochondrial swelling and loss of granules in alveolar type II cells at 6 h.

In a study of the effect on the lungs of paraquat applied to the skin over/next to the lungs of male Long-Evans rats, paraquat (as 1 ml of solution containing 8 g of paraquat) was applied weekly to the back of 18 rats. There were seven control rats. From week 4, two rats were killed per week. After 6 weeks, the concentration of the test solution was increased to 28.5mg/ml. Lungs, kidneys, livers and the application site were removed at autopsy and processed for histopathological examination. In some of the rats receiving paraquat, there was evidence of intra-alveolar haemorrhage. The medial thickness of large and small pulmonary arteries in the test groups was greater than in the controls. No histopathological change was present in the livers and kidneys. There was necrosis and ulceration of the application site, with acute and chronic inflammatory cell infiltration (Levin et al., 1979).

(b) Liver toxicity

Liver toxicity, as revealed by elevated liver enzymes, jaundice, and histopathological changes in the liver at examination post mortem, is sometimes seen in cases of poisoning with paraquat in humans. A number of studies examining this phenomenon (e.g. Cagen & Gibson, 1977; Burk et al., 1980). Cagen & Gibson (1977) have found that, in Swiss-Webster mice, paraquat was not hepatotoxic, unless the mice were deficient in selenium.

(c) Kidney toxicity

In cases of poisoning in humans, renal tubular damage has been noted at autopsy. In a study of the nephrotoxicity of paraquat in vitro and in vivo, proximal tubular function was monitored in vitro by measuring the accumulation of *p*-aminohippurate and *N*-methylnicotinamide using renal cortical slices from Swiss-Webster mice poisoned with paraquat at the LD_{50} for intraperitoneal administration (50 mg/kg bw). Tubular function in intact Swiss-Webster mice was estimated using disappearance of phenolsulfthalein and [^{14}C] paraquat from plasma in vivo. Glomerular function was estimated using disappearance of iothalamate from plasma in animals injected intravenously with paraquat at a dose of 50 mg/kg bw. Accumulation of *p*-aminohippurate and *N*-methylnicotinamide by renal cortical slices in vitro was not greatly altered. Disappearance in vivo of phenolsulfthalein and [^{14}C] paraquat from plasma was greatly reduced, but iothalamate disappearance was little affected. The authors concluded that nephrotoxicity attributable to paraquat affects primarily the proximal tubule (Ecker et al., 1975).

It has been noted that the uptake of paraquat by rat renal tubular cells in culture is saturable (Chan et al., 1996a). Of two renal tubular cell lines, one resembling proximal tubular cells and the other resembling distal tubular cells, the latter was found to be more resistant to the effects of paraquat (Chan et al., 1996b).

(d) Neurotoxicology

Paraquat is structurally similar to the known dopaminergic neurotoxicant 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). As a result, paraquat has been considered as a possible etiological factor in Parkinson disease. Paraquat is, however, a dication and does not readily cross biological membranes and the blood-brain barrier, whereas MPTP readily crosses the blood-brain barrier and is oxidized to the dihydropyridinium ion and then the neurotoxic methylphenylpyridinium ion. The methylphenylpyridinium ion is taken up into dopaminergic neurones by the same uptake mechanism as dopamine itself (Fonnum, 1999). Moreover, it was reported that, in a study using an inducible system in neuroblastoma cells (described only in an abstract), the toxicity of paraquat was not mediated by the dopamine transporter (Miller & Quan, 2002). Furthermore, in another abstract it was reported that, while the methylphenylpyridinium ion inhibited dopamine re-uptake in rat and mouse synaptosomes, paraquat did not, and that paraquat had no binding affinity for the dopamine transporter and the D_1 and D_2 receptors (Foster et al., 2003).

Shimizu et al. (2003) examined the mechanism by which paraquat is toxic to dopamine neurons in male Wistar rats in vivo, using GBR-12909, a selective inhibitor of the dopamine transporter. GBR-12909 reduced the uptake of paraquat into the striatal tissue, including dopaminergic terminals. Subcutaneous treatment with paraquat at 10 mg/kg bw for 5 days significantly decreased concentrations of brain dopamine and dopamine metabolites in the striatum. When

paraquat was administered through a microdialysis probe stereotaxically implanted into the striatum, a transitory increase in extracellular concentrations of glutamate, followed by long-lasting elevations of the extracellular concentrations of nitrite and nitrate and dopamine, were detected in the striatum of rats. This lasted for more than 24 h after treatment with paraquat and could be inhibited by N^G-nitro-L-arginine methyl ester, dizocilpine, 6,7-dinitroquinoxaline-2,3-dione and L-deprenyl.

The behavioural and neuropathological effects in rats of both systemic and intrahippocampal injections of paraquat dichloride were studied by Bagetta et al. (1992). Paraquat injected into the dorsal hippocampus, produced seizures within a few minutes of injection, and caused neuronal damage in the CA1 and CA3 pyramidal cell layers, pyriform cortex, dentate granule cell layer and in the hilus fascia dentata at 24 h (n = 9 rats). A smaller dose of paraquat (10 nmol) was ineffective. The effects of intrahippocampal injections of paraquat (1 µmol) were prevented by coadministration with atropine (50 nmol). Systemic injections of paraquat (20-100 mg/kg bw) produced forelimb clonus and rearing in 10 out of 15 animals. Neuronal cell death was found 24 h later in nine of these rats and was restricted to the pyriform cortex, this being the region of the brain with the highest concentrations of paraquat. Atropine (at a dose of 150 mg/kg bw given intraperitoneally 60 min previously) completely prevented the motor seizures, but cell death still occurred in two of the six animals tested. The use of certain experimental treatments for intrahippocampal toxicity of paraquat has been studied by the same group of authors (Bagetta et al., 1994).

The effects of paraquat (1-5 µg) on behaviour, morphology and neurochemistry were investigated in male Wistar rats treated by unilateral injection into the substantia nigra. There was vigorous contralateral rotational behaviour in response to administration of apomorphine. The animals were killed 2 weeks after dosing. Morphologically, there was loss of Nissl substance, glial reaction and loss of neurones in the substantia nigra, and neurochemically, there was dopamine depletion (Liou et al., 1996).

In a study of the behavioural and electrocortical effects of paraquat, Wistar-Morini rats were given paraquat administered by cannula into the substantia nigra, pars compacta, an area where dopamine-containing cell bodies are present, and into the caudate nucleus, where dopamine-containing nerve endings of the dopamine nigro-striatal system project. Paraquat was also administered into the locus coeruleus, an area containing noradrenaline cell bodies and into the nucleus raphe dorsalis or into the nucleus raphe medianus, two nuclei containing cell bodies of serotoninergic neurones. Intraventricular administration of paraquat at a dose of 10 and 50 µg caused intense behavioural stimulation and an increase in locomotor activity, circling and the wet-dog syndrome. This was accompanied by desynchronization of the electrocorticogram and the appearance of bilateral high voltage epileptiform spikes, and finally clonic convulsions occurred. The infusion of paraquat into the substantia nigra pars compacta (1 µg) produced contralateral head and neck deviation, rigidity and kyphosis as well as behavioural and motor stimulation. The electrocorticogram activity was desynchronized and characterized by high voltage spike discharges. A similar behavioural, postural and electrocorticogram pattern was seen after infusion of paraquat into the caudate nucleus (10, 25 and 50 µg). In addition, paraquat, infused into the locus coeruleus or into the raphe nuclei (5 and 10 µg), produced circling, escape responses, jumping and clonic convulsions accompanied by electrocorticogram desynchronization and epileptic phenomena. The authors concluded that paraquat was able to produce central neurotoxicological effects that did not seem to be specific, at least for the doses used, for the dopamine nigro-striatal system (Gori et al., 1988).

In a study of the pathological effects of paraquat when administered directly into different parts of the rat brain, the microinfusion of paraquat (3.2, 16, 32 or 160 nmol) into the pars compacta of the substantia nigra produced neuropathological changes culminating in neuronal necrosis. A particular feature of paraquat neurotoxicity after its microinfusion into the substantia nigra (3.2 mmol/1 at 1 µl/min for 1 min) or into the ventral tegmental area (1.6 mmol/1 at 1 µl/min for 1 min), but not into other areas of the brain, was selective vulnerability of hippocampal CA3 neurones. This initially comprised a decrease in dendritic spines, which was followed by neuronal degeneration and cell loss. No damage occurred after microinfusion of paraquat into other areas of the brain near or distant from the infusion sites. In addition, similar neuropathological alterations occurred in other non-dopaminergic areas. The authors considered that the study showed that paraquat possesses marked neurotoxicity that is not selective for dopaminergic neurones (Calò et al., 1990).

In a study of the effects of injected MPTP and analogues of MPTP inter alia, paraquat and reduced paraquat, C57 black mice were given paraquat in three subcutaneous injections of 14.5 mg/kg bw at an interval of 3 days, each injection being at a maximum tolerated dose. Reduced paraquat was administered in six daily doses increasing from 7.3 to 116.3 mg/kg bw, with a total dose of 342 mg/kg bw; this dose was well tolerated. One month after the last injection with

paraquat or reduced paraquat, striatal dopamine was not depleted, while it was severely reduced with MPTP (Perry et al., 1986).

In a study investigating the possible role of paraquat in Parkinson disease, paraquat or MPTP were administered intraperitoneally to groups of six adult C57 Bl/6 mice. The dosing regimen for paraquat was 5 or 10 mg/kg bw given as three injections at weekly intervals, while that for MPTP was 10 or 30 mg/kg administered at 7 days and 16 h later and at 15 days and 16 h later (i.e. four doses). Saline was administered to a control group of six mice. Ambulatory behaviour was monitored. Substantia nigra dopamine neurone number and striatal dopamine terminal density were quantified after death. The data indicated that paraquat elicited a dose-dependent decrease in substantia nigra dopaminergic neurones (assessed by a fluoro-gold prelabelling method), a decline in striatal dopamine nerve terminal density (assessed by measurement of tyrosine hydroxylase immunoreactivity), and a neurobehavioural syndrome characterized by reduced ambulatory activity. Similar findings were seen with MPTP. The authors suggested that systemically absorbed paraquat crossed the blood-brain barrier to cause destruction of dopamine neurones in the substantia nigra and reduction of dopaminergic innervation of the striatum. The use of a parenteral route of administration, however, means that these data are of questionable relevance for risk assessment of paraquat residues (Brooks et al., 1999).

In a study of neurotoxic effects after neonatal exposure to paraquat and MPTP, groups of mice (aged 10 or 11 days) were given vehicle (water), paraquat, or MPTP by mouth; MPTP was administered at a dose of 0.3 or 20 mg/kg bw, and paraquat at a dose of 0.07 or 0.36 mg/kg bw. Neonatal spontaneous motor activity was tested on day 18 in mice given paraquat at 0.36 mg/kg bw. Adult spontaneous motor activity was tested at ages 60 and 120 days. On day 125, the mice were decapitated and the contents of dopamine and serotonin and metabolites in striatum were analysed. Acute toxicity was not observed in any of the groups. No respiratory distress or motor performance dysfunction was seen on day 18 in mice given paraquat at 0.36 mg/kg bw. The results of behavioural tests carried out at age 60 days showed a marked hypoactive condition in the mice given paraquat (at both doses) and MPTP (at both doses). At age 120 days, the hypoactivity persisted and appeared even more pronounced. Reduced striatal content of dopamine and metabolites was seen in the striatum with both compounds, but concentrations of serotonin were unaffected. The effect was greater at the higher doses (Fredriksson et al., 1993).

In a study in two strains of mice, one (C57 black) being the same as that used by Fredriksson et al. (1993), paraquat was administered as single daily doses at 0.36 or 3.6 mg/kg bw to pups aged 10 or 11 days, and appropriate controls were used (Ray, personal communication, 2003). Testing for spontaneous behaviour was carried out at 4 months, and approximately 1 week later the mice were killed and analysed for neurotransmitters in the brain, as well as muscarinic receptor density. In the C57 black mice at 4 months, there was hyperactivity at 0.36 mg/kg bw compared with the controls, while at 3.6 mg/kg bw and in the other strain of mice used (NMRI) at both doses there were no significant differences from the controls. There were no significant intergroup differences in muscarinic receptor density nor in striatum or hippocampus dopamine, metabolites of dopamine or 5-hydroxyindoleacetic acid. The authors concluded that, using similar conditions, they could not replicate the results of the Fredriksson et al. (1993) study.

In the study by Widdowson et al. (1996b) on the entry of paraquat into the brains of male Wistar-derived Alpk: Apfsd rats, discussed above, groups of four rats were dosed daily for 14 days with water (controls) or 5 mg of paraquat ion/kg bw, orally. The rats were killed 24 h after the last of the 14 doses or after the single dose. On days 4 and 12, open field testing was carried out. On day 15, activity was measured over 50 min using an animal activity monitor, while animal grip strength and coordination was tested on days 4, 8 and 15 of the study. The brains were processed for histopathological examination after fixation by intracardiac perfusion. Brain catecholamines were measured by high-performance liquid chromotography using electrochemical detection, while dopamine D_1 and D_2 receptors were labelled using ^{3}H-labelled SCH23390 and spiperone respectively. The density of muscarinic acetylcholine receptors was estimated with ^{3}H-*N*-methyl scopolamine, and of *N*-methyl-D-aspartate (NMDA) receptors by ^{3}H MK-801 binding. The density of benzodiazepine sites on $GABA_A$ receptors was measured by ^{3}H-labelled Ro 15-1788 binding. Body-weight gain was decreased in the test animals in comparison with the controls. No differences between the groups were seen in the results of behavioural tests. There was no sign of neuronal cell damage in the test group, in particular in the substantia nigra. The concentration of dopamine was significantly higher in the striatum of rats treated with paraquat than in controls, but this was not the case in the hypothalamus. Differences in D_1, D_2, muscarinic, *N*-methyl-D-aspartate and benzodiazepine sensitive $GABA_A$ receptors was not seen. The authors concluded that paraquat did not behave in the same way as MPTP in the tests used (Widdowson et al., 1996b).

(e) Possible neurotoxic interactions

Thiruchelvam et al. (2000a, 2000b) carried out studies to assess the potential involvement of combined exposure to the herbicide paraquat and to maneb, a manganese-containing ethylene*bis*dithiocarbamate fungicide, in the etiology of idiopathic Parkinson disease.

Male C57 Bl/6 mice were given paraquat dichloride at a dose of 5 or 10 mg/kg bw and/or maneb at a dose of 15 or 30 mg/kg bw, once weekly for a total of 4 weeks, by intraperitoneal injection. End-points assessed were: effects on locomotor activity, density of tyrosine hydroxylase positive neurones, concentrations of dopamine and metabolites, and dopamine turnover. The authors noted that decreases in motor activity immediately after injections were observed more consistently with combined exposures to maneb and paraquat. Concentrations of dopamine and metabolites and dopamine turnover were slightly increased immediately after injection of combined maneb and paraquat, compared with injection of maneb alone. In addition, significant reductions in tyrosine hydroxylase immunoreactivity, measured 3 days after the last injection, were detected in the dorsal striatum of animals given combined treatments, but not those treated with single compounds. The authors concluded that these results demonstrated potentiating effects of combined exposures to paraquat and maneb on nigrostriatal dopamine systems (Thiruchelvam et al., 2000a).

In similar experiments, male C57 Bl/6 mice were given single compounds (paraquat at a dose of 10 mg/kg bw or maneb at a dose of 30 mg/kg) or a combination (paraquat at 10 mg/kg bw paraquat plus maneb at 30 mg/kg bw), twice weekly by intraperitoneal injection for 6 weeks. It was reported that maneb, but not paraquat, reduced motor activity immediately after treatment, and that this effect was potentiated by combined treatment with paraquat and maneb. As treatments progressed, only the groups receiving combined paraquat and maneb showed a failure of motor activity recovery within 24 h. Paraquat and maneb in combination, but not alone, reduced tyrosine hydroxylase and dopamine transporter immunoreactivity in the dorsal striatum, but not in the nucleus accumbens. Reactive gliosis occurred only in response to combined paraquat and maneb in dorsal-medial but not ventral striatum. Tyrosine hydroxylase immunoreactivity and cell counts were significantly reduced only by the mixture of paraquat and maneb, and not by the pesticides alone, in the substantia nigra, while no treatment produced significant effects on tyrosine hydroxylase immunoreactivity and cell counts in the ventral tegmental area. The authors suggested that the combination of paraquat and maneb showed synergistic effects, preferentially expressed in the nigrostriatal dopamine system, and suggested that such mixtures could play a role in the etiology of Parkinson disease. The study was not designed appropriately to investigate potentiation and the results could have reflected dose-additivity (Thiruchelvam et al., 2000b).

(f) Experimental therapies

Among treatments for poisoning with paraquat that have been studied in experimental animals is the injection of the enzyme superoxide dismutase. Steroids have also been studied (Kitazawa et al., 1988; Chen et al., 2003), without apparent benefit. This appeared to be beneficial in rats that had been given paraquat administered by gavage (Autor, 1974). The results of studies in rats suggested that paraquat might potentiate the toxic effects of oxygen (Fisher et al., 1973; Keeling et al., 1981). Prolonged (6 h) haemoperfusion was reportedly successful in saving three out of four pigs (Landrace × Yorkshire gilts) to whom paraquat at a dose of 70 mg/kg bw had been administered by stomach tube. This dose was fatal in untreated pigs and 2 h of haemoperfusion was ineffective. The purity of the paraquat used was not stated, nor is it clear whether the dose was expressed as paraquat ion or dichloride (Yang et al., 1997).

(g) Poisoning of animals

Paraquat poisoning in animals is rare (Blood et al., 1983). Nevertheless, from time to time paraquat is reported as the causative agent in animal poisoning, Longstaffe et al. (1981), for example, reported malicious and accidental poisoning of cats and dogs, and Aleksic-Kovacevic et al. (2003) reported the accidental poisoning by paraquat of five German shepherd dogs.

3. Observations in humans

3.1 Poisoning incidents

Intentional ingestion of paraquat is a major cause of death from poisoning. Casey & Vale (1994) tabulated deaths from pesticide poisoning from 1945-1989 in England and Wales and found that paraquat was responsible for 570 deaths, or

56.3% of all deaths caused by pesticides. From 1982, however, there has been a progressive decline in the annual number of poisonings after the inclusion of emetic, stench and dye into gramoxone formulations.

There are numerous case reports and case series of poisonings with paraquat (e.g. Bullivant, 1966; Campbell, 1968; Malone et al., 1971; Douze et al., 1974; Carson & Carson, 1976; Bismuth et al., 1982; Bramley & Hart, 1983; Naito & Yamashita, 1987; Wesseling et al., 1993; Hall, 1995; Tsatsakis et al., 1996; van Wendel de Joode et al., 1996; Wesseling et al., 1997; Papanikolaou et al., 2001). The effects can be divided into local and systemic effects. Local effects may comprise damage to the skin, nails, and nose (Samman & Johnston, 1969; Hearn & Keir, 1971; Vale et al., 1987; Bismuth et al., 1995), and sore throat, dysphagia and epigastric pain may also occur. Local effects to the eye may heal only slowly and with scarring (Peyresblanques, 1969; Deveckova et al., 1980). After ingestion of formulation concentrate, ulceration of the upper gastrointestinal tract is often observed. Although these effects are unpleasant, the findings from those poisonings with a fatal outcome are generally referable to the respiratory system, death being preceded by dyspnoea and cyanosis. Crepitations may be heard. Radiology initially reveals diffuse fine mottling of the lungs. Renal dysfunction may partly be a direct effect of paraquat and partly be caused by hypovolemia; often mild, renal dysfunction impairs the only route of elimination available (Marrs & Proudfoot, 2003). Lung function tests are commonly abnormal (Bismuth et al., 1982). At autopsy, there may be a pleural effusion, and damage to the upper respiratory tract. Grossly, the lungs appear solid, with haemorrhages, including subpleural ones. Histologically, there is oedema and the alveoli are airless with fibroblastic proliferation in the alveolar walls. Infiltration with mononuclear cells, polymorphs, macrophages and eosinophils has been reported. The longer the survival time, the greater the proliferation of epithelium and fibroblasts in the alveoli (Carson & Carson, 1976). Tubular damage in the kidney has been reported as well as mid-zonal and centrilobular degeneration in the liver. Proudfoot et al. (1979) reported that the plasma concentration of paraquat was a good predictor of the outcome in that persons whose plasma concentrations were below 2.0, 0.6, 0.3, 0.16 and 0.1 mg/l at 4, 6, 10, 16 and 24 h respectively after ingestion survived. Scherrmann et al. (1987) reported that plasma concentrations of paraquat in persons admitted more than 24 h after poisoning were predictive of the outcome of the poisoning in most patients. Furthermore, they concluded, on the basis of study of 53 patients, that persons with urinary concentrations of paraquat of <1 mg/l within 24 h of exposure would survive, while a fatal outcome could be anticipated in most persons in whom the urinary concentration of paraquat was >1 mg/l.

In a fatal case of paraquat poisoning in a pregnant woman, who developed the typical symptoms and signs of paraquat poisoning and at postmortem had the typical lung pathology of paraquat poisoning, the fetal lungs were normal (Fennelly et al., 1968). Talbot & Fu (1988), however, who reported the details of nine pregnant women who deliberately ingested paraquat, stated that paraquat in one case was concentrated 4-6 times in the fetus. In another of the cases, the amniotic fluid contained paraquat at twice the concentration of that in the maternal blood. All the fetuses died, whether or not caesarian section was carried out. A case of paraquat poisoning in early pregnancy was reported from French Guiana. A woman who was 10 weeks pregnant took Grammoxone®, in a suicide attempt. She developed oliguria and underwent dialysis. The blood concentration of paraquat was 0.22 mg/l. No pulmonary symptoms or signs were noted and renal function progressively returned to normal. The woman gave birth normally at 39 weeks and both mother and baby remained well during 4 years of follow-up (Raynal et al., 2003).

Although most patients who have radiological lung changes go on to develop progressive and ultimately fatal lung damage, there are a few case reports in which patients have developed persistent radiological changes but have survived (e.g. Hudson et al., 1991).

There is also evidence that, in such patients, some recovery may occur over time (Ming et al., 1980; Lin et al., 1995; Papiris et al., 1995).

It has been reported that alcohol may increase the severity of paraquat poisoning (Ernouf et al., 1998), but the reverse has also been suggested (Ragoucy-Sengier et al., 1991).

The vast majority of paraquat intoxications are by ingestion. Athanaselis et al. (1983), however, reported the poisoning via the skin of a 64-year-old spray operator. Fluid had leaked down his back for several hours, causing irritation of the skin. Two days later, the spray operator visited a doctor, who advised hospitalization. The patient rejected this advice, but was admitted into hospital 3 days later. He died of toxic shock and renal and respiratory insufficiency 12 h after admission. At autopsy, the findings were typical of paraquat poisoning with fibrosing interstitial pneumonitis and intra-alveolar haemorrhage in the lungs, renal tubular cell degeneration, cholestasis and necrosis of the skin of the back. A further case of a fatality from transdermal exposure to paraquat was reported from Papua New Guinea, the patient evidently thinking that Gramoxone (20% paraquat w/v) would kill lice, for which purpose he applied the material to his scalp and beard. This produced painful sores and his condition steadily deteriorated until death 6 days after applying

the paraquat to his skin. At autopsy, there were skin lesions as well as solid and haemorrhagic lungs (Binns, 1976). In a further report, Garnier et al. (1994) reported two cases of percutaneous exposure. In the first case, a man aged 36 years applied 20% paraquat concentrate to his whole body to cure scabies. He developed extensive erythema followed by blistering and 2 days later he was admitted to hospital. He developed transient renal failure. Dyspnoea appeared 1 week after admission and he deteriorated, dying 26 days after exposure. The other case reported by Garnier et al. (1994) was much milder, with mainly skin effects, and the outcome was not fatal. Additional cases of fatal percutaneous paraquat intoxication were reported by Newhouse et al. (1978), Levin et al. (1979), Wohlfahrt (1982), Okonek et al. (1983) and Papiris et al. (1995). In general, systemic toxicity after percutaneous exposure of humans seems to be unusual (Hoffer & Taitelman, 1989).

There is evidence that as well as the route of exposure, the formulation may be important in determining the severity of effects. A case series of 14 instances of poisoning with granular paraquat and diquat at low concentrations was reported by Fitzgerald & Barniville in 1978. No deaths occurred, the illness was mild and necrotic lesions of the mouth and pharynx were not seen.

Initial management of cases of poisoning with paraquat comprises replacement of fluid loss, determination of the prognosis by measurement of the plasma concentration of paraquat, treatment of local damage to the oropharynx, and supportive care (Vale et al., 1987).

Numerous treatments have been tried in the management of cases of poisoning with paraquat, many concentrating on the prevention of absorption (Meredith & Vale, 1987). Gastric lavage, fuller's earth and activated charcoal have all been tested: other therapies that have been investigated include removal of paraquat from the blood by forced diuresis, peritoneal dialysis, haemodialysis or haemoperfusion using sorbent materials, including charcoal haemoperfusion (Tabei et al., 1982). Corticosteroids have also been tried (Bismuth et al., 1982; Chen et al., 2002), as have acetylcysteine and deferoxamine (Lheureux et al., 1995), and *S*-carboxymethylcysteine (Lugo-Vallin et al., 2003) and radiotherapy (Talbot & Barnes, 1988). Addo et al. (1984) reported that treatment with cyclophosphamide, dexamethasone, forced diuresis with frusemide, triamterine and hydrochlorothiazide enabled the survival of 15 of 20 patients. This therapy was combined with routine measures, such as fuller's earth, activated charcoal and magnesium sulfate to eliminate paraquat from the gut. Time has, however, shown that none of the measures discussed above are consistently successful, therefore treatment is perforce symptomatic (Vale et al., 1987). The use of oxygen may increase the severity of pulmonary fibrosis (Bismuth et al., 1982) and should be delayed as long as possible. The therapy of paraquat poisoning has been reviewed (Flanagan & Jones, 2001).

3.2 Epidemiological studies

In an analysis of all cases of early onset Parkinson disease in persons born and raised in Saskatchewan, Canada, it was found that 20 out of 22 cases were exclusively exposed to a rural environment during the first 15 years of life. This distribution was significantly different from that of the general population ($p = 0.0141$). Further study included sampling and metal analysis of sources of drinking-water in childhood in 18 cases and in 36 age- and sex-matched controls. Drinking-water to which the individuals in the cases and controls had been exposed was collected and analysed for 23 metals. There was no difference in the metal composition of the water between the two groups. A review of pesticide usage from Saskatchewan agricultural records was undertaken to determine if there was an increased incidence of early onset Parkinson disease after use of any particular chemical. No increase was found in the incidence of the disease with the introduction of any pesticide, including paraquat, for agricultural use (Rajput et al., 1987).

In a case-control study, the personal histories of 57 cases and 122 age-matched controls were compared to identify possible determinants of Parkinson disease. Odds ratios (OR) adjusted for sex, age, and smoking were computed using stepwise logistic regression. A statistically significant increased risk for working in orchards was found (OR, 3.69; 95% CI, 1.34-10.27; $p = 0.012$). The relative risk of Parkinson disease decreased with smoking, an inverse relationship that was supported by the results of many studies (Hertzman et al., 1990).

A questionnaire-based case-control study to investigate possible risk factors for Parkinsonism involved 150 patients with Parkinson disease and 150 controls matched by age and sex. Use of well water and rural living were associated with Parkinsonism, but farming and pesticide/herbicide use was not (Koller et al., 1990).

In a case-control study of 130 cases of Parkinson disease and 260 age- and sex-matched controls from Calgary, Alberta, Canada, no significant association of Parkinson disease with rural or farm living or drinking well water in early childhood was found (Semchuk et al., 1991).

A retrospective case-control study, with 127 cases and 245 controls was carried out to identify possible risk factors for idiopathic Parkinsonism. Of the controls, 121 had cardiac disease and 124 were randomly selected from electoral lists. An occupational history was collected, and known contact with all pesticides associated with the tree-fruit sector of the agricultural industry was recorded. There was a significant association between Parkinsonism and having had an occupation in which exposure through handling or directly contacting pesticides was probable, but no specific chemicals were associated with the condition. The authors concluded that although occupations involving the use of agricultural chemicals might predispose to the development of Parkinsonism, it was likely that the pathogenesis is multifactorial rather than related to a specific agent (Hertzman et al., 1994).

In a cross-sectional study undertaken in the Republic of Nicaragua to evaluate any relationship between respiratory health and paraquat exposure, the study population was selected from among workers at 15 banana plantations that used paraquat as a herbicide. All workers who reported never having applied paraquat and all who reported more than 2 years of cumulative exposure as knapsack sprayers of paraquat were invited for medical examination. There were 134 workers in the group that was exposed to paraquat and there were 152 workers that were not exposed. All took part in a questionnaire interview asking about exposure and respiratory symptoms, and underwent spirometric testing of forced expiratory volume in 1 s ($FEV_{1.0}$) and forced vital capacity (FVC). Of the persons in the exposed group, 53% reported having experienced a skin rash or burn resulting from exposure to paraquat, 25% reported epistaxis, 58% reported nail damage, and 42% reported paraquat splashes to the eyes. There was a consistent relationship between a history of skin rashes or burns and the prevalence of dyspnoea. This relationship was more marked for more severe dyspnoea. There was a three-fold increase in episodic wheezing accompanied by shortness of breath among the more intensely exposed workers. There was no relationship between exposure and $FEV_{1.0}$ or FVC. The authors considered that the high prevalence of respiratory symptoms associated with exposure, in the absence of spirometric abnormalities associated with exposure, could be a result of unmeasured gas exchange abnormalities among workers with long-term exposure to paraquat. They could also have been caused by recall bias (Castro-Gutiérrez et al., 1997).

3.3 Studies in human volunteers

A study of the percutaneous absorption of paraquat in vivo was undertaken in six human volunteers by Wester et al. (1984). ^{14}C-Labelled paraquat dichloride at a dose of 9 mg/cm^2 was applied to a 70 cm^2 area of the skin of the back of the leg, the back of the hand or the ventral surface of the forearm. The specific activity of the paraquat was 2.0 mCi per mmol per l and the concentrations of the solution were given as paraquat dichloride, not as paraquat ion. Urine samples were collected at 4, 8, 12, and 24 h, and then every 24 h for 5 days. The extent of percutaneous absorption was measured by comparing the excretion of ^{14}C after parenteral and topical administration; rather than administer the paraquat to humans, it was administered to rhesus monkeys. The percentage of the applied dose that was absorbed was 0.29 ± 0.2 (mean ± SD) for the leg, 0.23 ± 0.1 for the hand and 0.29 ± 0.1 the forearm. The absorption rate for the 24 h of exposure was 0.03 µg/cm^2. It was concluded that paraquat was poorly absorbed through human skin and that there was little difference between skin at different sites in ability to absorb paraquat.

Comments

The pharmacokinetics and metabolism of paraquat have been the subject of many studies. Paraquat is not well-absorbed when administered orally. After oral administration of radiolabelled paraquat to rats, more than half the administered dose (60-70%) appeared in the faeces and a small proportion (10-20%) in the urine. In studies involving single or repeated doses, excretion of the radiolabel was rapid; about 90% was excreted within 72 h. Residual radioactivity was primarily found in the lungs, liver and kidneys. Some studies have found small amounts in the brain, but only in structures outside the blood-brain barrier or in structures without a blood-brain barrier (the pineal gland and linings of the cerebral ventricles, the anterior portion of the olfactory bulb, hypothalamus and area postrema). Paraquat is taken up into the lungs by an active process, whose normal substrate is endogenous diamines, e.g. putrescine and polyamines such as spermine and spermidine. In rats, dogs and monkeys, there are indications that paraquat is actively secreted in the kidneys.

Paraquat is largely eliminated unchanged; in rats, approximately 90-95% of radiolabelled paraquat in urine was excreted as the parent compound. Some studies have failed to show the presence of any metabolites after oral administration of paraquat, while others have shown a small degree of metabolism, which probably occurs in the gut as a result of microbial metabolism. Paraquat was not found in the bile.

The acute LD_{50} after oral administration was 290-360 mg/kg bw in mice and 112-350 mg/kg bw in rats, while the guinea-pig was more sensitive (LD_{50} of 22-30 mg/kg bw). The LD_{50}in cynomolgus monkeys was 50-70 mg/kg bw. Paraquat was considered to be a mild skin irritant and a moderate ocular irritant and was not a skin sensitizer in the Magnusson and Kligman test.

The predominant feature of exposure to repeated doses of paraquat was lung toxicity. Renal toxicity (proximal tubular damage) and toxicity to the liver (jaundice and elevations of enzyme activity) were also found. In some studies, lens opacities were seen. At higher doses, decreased body-weight gain, clinical signs (dyspnoea, increased respiratory sounds, swellings and sores in the genital area), haematological changes and effects on organ weight were reported, as well as increased mortality.

Lung abnormalities observed in mice, rats and dogs consisted of increased lung weight and gross pathological changes. Associated histopathological changes included cell necrosis, alveolar cell proliferation and hypertrophy, oedema, infiltration of macrophages and mononuclear cells and exudate. Dogs were most sensitive to paraquat-induced lung toxicity, followed by rats and mice; a NOAEL of 0.45 mg of paraquat ion/kg bw per day was found in a 1-year study in dogs, on the basis of signs of respiratory dysfunction and histopathological changes at higher doses. This finding was supported by the NOAEL of 0.55 mg of paraquat ion/kg bw per day from a 13-week study in dogs.

Ophthalmoscopy in-life and histopathological examination of eyes at necropsy revealed corneal opacity and cataracts in animals receiving doses of 3.75 mg and 7.5 mg of paraquat ion/kg bw per day in a lifetime study in Fischer rats. Other ocular effects included lenticular degeneration, lens capsular fibrosis and/or lens ruptures, peripheral retinal degeneration, and proteinaceous vitreous humour. At time-points after 2 years (i.e. after the study would have ended according to current guidelines), rats receiving the lowest dose exhibited age-related peripheral morgagnian corpuscles and slight peripheral and moderate mid-zonal lenticular degeneration. Histopathological evidence of cataracts was also found at the highest dose (7.67 mg of paraquat ion/kg bw per day) in a 2-year study in Fischer rats, but not at lower doses. In another 2-year study in Wistar rats, no intergroup differences in the prevalence of cataracts were seen. These differences between effects on the lens in the three long-term studies in rats may be indicative of a difference between Wistar and Fischer rats.

Paraquat elicited renal toxicity, which comprised changes in the proximal tubules of the kidneys (hydropic degeneration, eosinophilia and dilatation) in mice fed with 15.0 mg of paraquat ion/kg bw per day in a lifetime study. Some very mild changes were also observed in males at 5.62 mg of paraquat ion/kg bw per day, however, there was a clear NOAEL at 1.88 mg of paraquat ion/kg bw per day. There were some histopathological effects on renal distal tubular cells at 1.75 mg and 3.52 mg of paraquat ion/kg bw per day in a 13-week study in dogs, the NOAEL being 0.55 mg of paraquat ion/kg bw per day.

The frequency of pulmonary adenoma was increased in females in a 2-year study in rats receiving a dose of 8.47 mg of paraquat ion/kg bw per day; however, there was a clear NOAEL at 3.13 mg of paraquat ion/kg bw per day. In males, adenocarcinoma was found in three animals (out of 80) receiving a dose of 10.6 mg of paraquat ion/kg bw per day, one animal (out of 80) receiving 3.52 mg of paraquat ion/kg bw per day and two animals (out of 80) receiving 1.34 mg of paraquat ion/kg bw per day. The NOAEL for males in this study was 0.77 mg of paraquat ion/kg bw per day on the basis of histopathology of the lungs. In a second 2-year study in rats, no intergroup differences in tumour incidence were seen at any site. After review of the histopathological findings in the lifetime study in rats, it was concluded that the incidence of lung neoplasms in the test groups was comparable to that in the control groups. Thus tumours were seen in only one out of three long-term studies in rats. The Meeting concluded that the weight of evidence suggested that paraquat was not carcinogenic in the rat. Paraquat was not considered to be tumorigenic in two studies in mice.

Paraquat has been tested extensively in a broad range of assays for genotoxicity in vitro and in vivo, with mixed results. Studies more commonly gave positive results when DNA damage or clastogenicity were the end-points. Paraquat is known to produce active oxygen species and the available evidence indicates that it is probably this property that is responsible for its genotoxicity. Consequently, there is a threshold below which genotoxic activity will

not be evident, provided that normally functioning antioxidant defence mechanisms have not been overwhelmed. The Meeting concluded that paraquat is unlikely to pose a genotoxic risk to humans.

Because of the nature of the genotoxicity observed and the lack of carcinogenicity in rats and mice, the Meeting concluded that paraquat was unlikely to pose a carcinogenic risk to humans.

Three studies of reproductive toxicity in rats were reported. The overall NOAEL for parental toxicity was 1.67 mg of paraquat ion/kg bw per day, and the NOAEL for pup toxicity was 5.0 mg of paraquat ion/kg bw per day. Impaired fertility was not seen in these studies. Two studies of developmental toxicity in rats and two in mice were available for evaluation. The lowest NOAELs observed for both maternal and developmental toxicity in rats were 1 mg of paraquat ion/kg bw per day on the basis of clinical signs, and reduced body-weight gain in the dams and reduced mean fetal weights and retarded ossification in the fetuses. Higher NOAELs for maternal and developmental toxicity were seen in mice. Teratogenicity was not seen at any dose in any study in either rats or mice.

Paraquat is structurally similar to the known dopaminergic neurotoxicant 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). As a result, paraquat has been considered as a possible etiologic factor in Parkinson disease. However, paraquat is a quaternary nitrogen compound and therefore crosses biological membranes poorly, unlike MPTP, the precursor of the neurotoxicant methylphenylpyridinium ion. Data made available to the Meeting suggested that paraquat is not taken up by the dopamine transporter. Studies on the effects of paraquat on the central nervous system have used a variety of routes, including subcutaneous or intraperitoneal injection and direct injection into the central nervous system, and end-points observed have been behavioural, morphological and neurochemical. Behavioural effects and loss of neurones in the substantia nigra were observed and, neurochemically, depletion of dopamine was reported in many, but not all of these studies. The design of these studies, however, renders the relevance of these data questionable for the risk assessment of dietary exposure to paraquat residues.

Persistent hypoactivity was observed in mice given paraquat by mouth on postnatal days 10 and 11. Reduced striatal content of dopamine and its metabolites was seen, but concentrations of serotonin were not affected. In a similar study of which the Meeting was aware, these findings had not been reproduced.

The Meeting concluded that the available mechanistic and other animal studies did not support the hypothesis that paraquat residues in food are a risk factor for Parkinson disease in humans.

Two studies carried out to assess the potential involvement of combined exposure to paraquat and maneb, a manganese-containing ethylene*bis*dithiocarbamate fungicide, in the etiology of idiopathic Parkinson disease were evaluated by the Meeting. Paraquat or maneb, or a combination of the two, was given intraperitoneally to mice. The study was not designed appropriately to investigate potentiation and the results could have reflected dose-additivity.

Intentional and accidental poisonings with paraquat have been a major cause of death in many countries. Most incidents are caused by ingestion of the concentrate intended for agricultural use. Local effects include damage to the skin, nails, mouth, eyes and nose. Sore throat, dysphagia and epigastric pain may occur. Systemic effects, which produce the fatal outcome seen in those who have ingested a sufficient quantity of paraquat, mainly involve the respiratory system. The changes in the lungs that underly the symptoms and clinical signs comprise a proliferative alveolitis similar to that seen in most experimental animals treated with paraquat. In most, but not all, patients who develop the characteristic lung changes, the condition progresses inevitably towards a fatal outcome, death being due to respiratory failure. Numerous therapies have been tested, but none has been consistently successful.

A number of epidemiological (case-control) studies have been carried out in humans with Parkinson disease. In some of these, associations with exposure to chemicals including pesticides (in some cases specifically paraquat) were sought. Some but not all studies have shown a relationship between working in situations that might involve contact with or use of pesticides and Parkinson disease, but associations with exposure to specific pesticides have not been shown consistently.

The Meeting established an ADI of 0-0.005 mg of paraquat ion/kg bw based on a NOAEL of 0.45 mg of paraquat ion/kg bw per day in the 1-year study in dogs and using a safety factor of 100. Although a 1-year study in dogs is not considered to be a long-term study, the nature and time-course of the pathogenesis of the lung lesions were such that the application of an additional safety factor was not considered to be necessary.

The Meeting established an acute RfD of 0.006 mg of paraquat ion/kg bw based on the NOAEL of 0.55 mg of paraquat ion/kg bw per day in the 13-week study in dogs, with a safety factor of 100. Histopathological changes in the lungs were present at higher doses in both studies in dogs.

Toxicological evaluation

Levels relevant to risk assessment

Species	Study	Effect	NOAEL[a]	LOAEL[a]
Mouse	13-week study	Toxicity	300 mg/kg, equal to 8.33 mg of ion/kg bw per day	300 mg/kg, equal to 25.9 mg of ion/kg bw per day
	97-99-week study	Toxicity	12.5 mg/kg, equivalent to 1.88 mg of ion/kg bw per day	37.5 mg/kg, equivalent to 5.62 mg of ion/kg bw per day
		Carcinogenicity	100 mg/kg equivalent to 15.0 mg of ion/kg bw per day[b]	—
	Study of developmental toxicity	Maternal toxicity	10 mg/kg bw per day[b]	—
		Embryo- and fetotoxicity	10 mg/kg bw per day[b]	—
Rat	13-week study	Toxicity	300 mg/kg, equal to 4.74 mg/kg bw per day	300 mg/kg, equal to 14.2 mg/kg bw per day
	104-week study	Toxicity	30 mg/kg, equal to 0.77 mg/kg bw per day	100 mg/kg, equal to 2.55 mg/kg bw per day
		Carcinogenicity	300 mg/kg, equal to 7.67 mg of ion/kg bw per day[b]	—
	Multigeneration study of reproductive toxicity	Parental toxicity	25 mg/kg, equivalent to 1.67 mg/kg bw per day	75 mg/kg, equivalent to 5.0 mg/kg bw per day
		Pup toxicity	150 mg/kg, equivalent to 5.0 mg/kg bw per day	150 mg/kg, equivalent to 10.0 mg/kg bw per day
	Study of developmental toxicity	Maternal toxicity	1 mg/kg bw per day	5 mg/kg bw per day
		Embryo- and fetotoxicity	1 mg/kg bw per day	5 mg/kg bw per day
Dog	13-week study	Toxicity	20 mg/kg, equal to 0.55 mg/kg bw per day	60 mg/kg, equal to 1.75 mg/kg bw per day
	1-year	Toxicity	15 mg/kg, equal to 0.45 mg/kg bw per day	30 mg/kg, equal to 0.93 mg/kg bw per day

[a] Dietary concentrations are expressed as dichloride or paraquat ion as in the study report; intakes and doses are expressed as paraquat ion
[b] Highest dose tested

Estimate of acceptable daily intake for humans

0-0.005 mg of paraquat ion/kg bw

Estimate of acute reference dose

0.006 mg of paraquat ion/kg bw

Studies that would provide information useful for continued evaluation of the compound

Further observations in humans

Summary of critical end-points for paraquat

Absorption, distribution, excretion and metabolism in mammals

Rate and extent of oral absorption	Poor
Dermal absorption	Poor; 0.25-0.29% absorbed (humans)
Distribution	Highest concentrations found in the lungs, liver and kidneys
Potential for accumulation	No potential for passive accumulation; active uptake into type II pneumocytes
Rate and extent of excretion	Rapid, about 64% in 24 h; 10% in urine, the remainder in the faeces; none is found in bile
Metabolism	Some metabolism (<5%) in gut (probably microbial); paraquat is largely excreted unchanged
Toxicologically significant compounds (animals, plants and environment)	Parent compound
Acute toxicity	
Rat, LD_{50}, oral	100-300 mg paraquat ion/kg bw
Rat, LD_{50}, dermal	80>660 mg of paraquat ion/kg bw
Rat, LC_{50}, inhalation	0.0006-0.0014 mg of paraquat ion/l (4 h exposure)
Rabbit, skin irritation	Mild
Rabbit, eye irritation	Moderate
Skin sensitization	Not sensitizing (Magnusson and Kligman test)
Short term toxicity	
Target organ/critical effect	Lung toxicity
Lowest relevant oral NOAEL	0.55 mg of paraquat ion/kg bw per day (13-week study in dogs); 0.45 mg of paraquat ion/kg bw per day (1-year study in dogs)
Lowest relevant dermal NOAEL	1.15 mg of paraquat ion/kg bw per day (21-day study in rabbits)
Lowest relevant inhalation NOAEC	0.00001 mg/l (21-day study in rats)
Genotoxicity	Paraquat was clastogenic at high concentrations
	Unlikely to pose a genotoxic risk to humans at dietary concentrations
Long term studies of toxicity and carcinogenicity	
Target organ/critical effect	Lung toxicity
Lowest relevant NOAEL	0.77 mg of paraquat ion/kg bw per day (2-year study in rats)
Carcinogenicity	Not carcinogenic; unlikely to pose a carcinogenic risk to humans
Reproductive toxicity	
Reproduction target/critical effect	Lung toxicity in pups
Lowest relevant reproductive NOAEL	5 mg of paraquat ion/kg bw per day (three-generation study in rats)
Developmental target/critical effect	Not teratogenic; reduced fetus weight and ossification at maternally toxic dose
Lowest relevant developmental NOAEL	1 mg of paraquat ion/kg bw per day (rats)
Neurotoxicity/delayed neurotoxicity	
	Not neurotoxic by oral route
Other toxicological studies	Mechanistic studies on lung, liver and kidney toxicity
Medical data	Causes acute poisoning

Summary	Value	Study	Safety factor
ADI	0-0.005 mg/kg bw	Dog, 1-year study	100
Acute RfD	0.006 mg/kg bw	Dog, 13-week study	100

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ENDNOTES:

1. The relative molecular mass of paraquat is 186.3; the relative molecular mass of paraquat dichloride is 257.2; therefore 1 g of paraquat dichloride = 0.724 g of paraquat ion.
2. Assuming no paternal effect.

See Also:
Toxicological Abbreviations
Paraquat (HSG 51, 1991)
Paraquat (PIM 399)
Paraquat (AGP:1970/M/12/1)
Paraquat (WHO Pesticide Residues Series 2)
Paraquat (Pesticide residues in food: 1976 evaluations)

Paraquat (Pesticide residues in food: 1978 evaluations)
Paraquat (Pesticide residues in food: 1981 evaluations)
Paraquat (Pesticide residues in food: 1982 evaluations)
Paraquat (Pesticide residues in food: 1986 evaluations Part II Toxicology)

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R.E.D. FACTS

Paraquat Dichloride

Pesticide Reregistration

All pesticides sold or distributed in the United States must be registered by EPA, based on scientific studies showing that they can be used without posing unreasonable risks to people or the environment. Because of advances in scientific knowledge, the law requires that pesticides which were first registered before November 1, 1984, be reregistered to ensure that they meet today's more stringent standards.

Under the Food Quality Protection Act of 1996, EPA must consider the increased susceptibility of infants and children to pesticide residues in food, as well as aggregate exposure of the public to pesticide residues from all sources, and the cumulative effects of pesticides and other compounds with a common mechanism of toxicity in establishing and reassessing tolerances.

In evaluating pesticides for reregistration, EPA obtains and reviews a complete set of studies from pesticide producers, describing the human health and environmental effects of each pesticide. The Agency develops any mitigation measures or regulatory controls needed to effectively reduce each pesticide's risks. EPA then reregisters pesticides that can be used without posing unreasonable risks to human health or the environment.

When a pesticide is eligible for reregistration, EPA explains the basis for its decision in a Reregistration Eligibility Decision (RED) document. This fact sheet summarizes the information in the RED document for reregistration case 0262, paraquat dichloride (commonly referred to as paraquat).

Use Profile

Paraquat dichloride is a herbicide currently registered to control weeds and grasses in many agricultural and non-agricultural areas. It is used preplant or preemergence on vegetables, grains, cotton, grasses, sugar cane, peanuts, potatoes, and tree plantation areas; postemergence around fruit crops, vegetables, trees, vines, grains, soybeans, and sugar cane; during the dormant season on clover and other legumes; as a desiccant or harvest aid on cotton, dry beans, soybeans, potatoes, sunflowers, and sugar cane; and as a post harvest desiccant on staked tomatoes. It also is applied to pine trees to induce resin soaking. Paraquat dichloride is also used on non-crop areas such as public airports, electric transformer stations and around commercial buildings to control weeds.

Paraquat dichloride is applied aerially, by groundboom, backpack sprayer, and low pressure handwand.

A soluble concentrate/liquid (SC/L) is the sole paraquat formulation type registered for all uses. This formulation may be applied to crops pre-plant, at planting, pre-emergence (broadcast or band), post-emergence (broadcast, band, split, directed, or spot), post-harvest (as a pre-harvest desiccant or harvest aid), and for suckering and stripping of hops.

Regulatory History

Paraquat dichloride was first registered as a pesticide in the U.S. in 1964. EPA issued a Registration Standard for paraquat dichloride in June 1987 (NTIS# PB88-217005). A December 1991 Data Call-In (DCI) required additional ecological effects, environmental fate and residue chemistry data.

Currently, 7 pesticide products are registered which contain the active ingredient paraquat dichloride. All paraquat products are classified as Restricted Use Pesticides.

Human Health Assessment

Toxicity

In acute toxicity studies using laboratory animals, paraquat has been shown to be highly toxic by the inhalation route and has been placed in Toxicity Category I (the highest of four levels) for acute inhalation effects. However, the Agency has determined that particles used in agricultural practices (400 to 800um) are well beyond the respirable range and therefore inhalation toxicity is not a toxicological endpoint of concern. Paraquat is moderately toxic (Category II) by the oral route and slightly toxic (Category III) by the dermal route. Paraquat will cause moderate to severe eye irritation and minimal dermal irritation, and has been placed in Toxicity Categories II and IV for these effects.

In a subchronic toxicity study using rats, paraquat caused changes in the lungs. A dermal toxicity study using rabbits resulted in scabbing and inflammation when tested at the two highest doses (2.6 mg cation/kg group and 6.0 mg cation/kg group). In an inhalation toxicity study, rats were exposed to respirable aerosols (particle size - less than 2 um in diameter) of paraquat dichloride which resulted in lung changes and extensive sores and swelling in the larynx.

A chronic toxicity study using dogs resulted in an increase in the severity and extent of chronic pneumonitis in the mid dose and high dose male and female dogs. Two chronic toxicity/carcinogenicity studies using rats were conducted with paraquat. In the first chronic toxicity study, paraquat did not appear to be carcinogenic in the lungs or the head region (middle ear, hard palate, head tissue and skin) of the rat. In the second study, paraquat resulted in non-tumor lesions in various organs and no evidence of carcinogenicity. Two chronic toxicity/carcinogenicity studies using mice were also conducted with paraquat. The first study resulted in

decreased body weight gain, kidney changes and no evidence of carcinogenicity. The second study using mice also resulted in no evidence of carcinogenicity. Based on these studies, paraquat was classified as a "Group E" chemical--one showing evidence of noncarcinogenicity for humans.

Four developmental/maternal toxicity studies were evaluated for paraquat. Treatment-related effects were seen (i.e., delayed hardening [ossification] in the forelimb and hindlimb digits, or retarded ossification of the posterior portion of the skull) in the fetuses only at the same or higher dose levels than effects in the mother. Therefore, the no-observed effect dose levels (NOEL) for maternal toxicity are at least or more conservative (protective) than the NOEL based on developmental toxicity.

There is no evidence that paraquat is associated with reproductive effects. In a reproduction study using rats, paraquat had no effect on body weight gain, food consumption/utilization, fertility or length of gestation. Paraquat also shows no evidence of causing mutagenicity.

Dietary Exposure

People may be exposed to residues of paraquat through the diet. Tolerances or maximum residue limits have been established for well over 80 raw agricultural commodities, processed foods and feed (please see 40 CFR 180.205(a), (b); 185.4700; 186.4700). EPA has reassessed the paraquat tolerances and found that numerous revisions are necessary. Most of these revisions will be handled administratively.

The available data support the established tolerances on all but sorghum forage, ruminant kidney, oats, rye, soybeans and hops. The tolerance for sorghum forage was reassessed from 0.05 to .1 ppm, while kidney was reassessed from 0.3 ppm to 0.5 ppm, soybeans from 0.05 ppm to 0.25 ppm, and hops from 0.2 ppm to 0.5 ppm. As there are presently no registered uses of paraquat on rye, the tolerances for this commodity will be revoked. Also the tolerance on oats will be revoked, as the registrant has indicated that they do not wish to support this use. Additionally, the tolerances for poultry (except for eggs) will be revoked. Finally, a tolerance for popcorn (0.05 ppm) will be established (See Section IV, Tolerance Reassessment Summary and Table in the paraquat RED for further specifics).

Numerous international Codex maximum residue limits (MRLs) have been established for paraquat. Harmonization of Codex MRLs and U.S. tolerances for paraquat exists for many crops. However, at this time there remain some incompatibilities between U.S. tolerances and Codex MRLs on the following raw plant commodities because of differences in agricultural practices: cottonseed, dry hops, maize, olives, potatoes, rice, sorghum, and dry soya beans.

EPA has assessed the dietary risk posed by paraquat. The Theoretical Maximum Residue Contribution (TMRC) for the overall U.S. population

represents 10% of the Reference Dose (RfD), or amount believed not to cause adverse effects if consumed daily over a 70-year lifetime. The highest subgroup, non-nursing infants (<1 year old) occupies 31% of the RfD. This fraction of the allowable RfD is considered to be an acceptable dietary exposure risk.

Occupational and Residential Exposure

Exposure to homeowners is not expected since there are no residential uses. Based on current use patterns, handlers (mixers, loaders, and applicators) may be exposed to paraquat dichloride during and after normal agricultural use. Ground, aerial and backpack application methods were considered. All the dermal and inhalation Margins of Exposure (MOEs) were acceptable (greater than 100) except backpack applicators and resin-soaking uses. The registrant has agreed to reduce the concentration of paraquat dichloride allowed when using a backpack sprayer and make label changes for tree injection (resin soaking) use.

Human Risk Assessment

Paraquat generally is of moderate to high acute toxicity based on inhalation toxicity (Toxicity Category I), oral toxicity, and moderate to severe eye irritation (Toxicity Category II). It is a Group E chemical--one showing no evidence of carcinogenicity.

Although people may be exposed to residues of paraquat in many food commodities, the chronic dietary risk from all uses is considered minimal.

Of greater concern is the risk posed to paraquat handlers, particularly mixers/loaders/applicators. A dermal endpoint--based on maternal toxicity effects-- was used to assess risks to handlers. Margins of Exposure (MOEs) for dermal effects to paraquat are adequate (greater than 100) for all exposure scenarios considered except for backpack sprayer applicators (non-spot treatment) and low pressure sprayer (resin soaking) for mixer/loader/applicators. Even with gloves, the margin of exposure for handlers using a backpack sprayer was too low. Exposure and risk to workers will be mitigated by reducing the concentration of paraquat in backpack sprayers, and through the use of Personal Protective Equipment (PPE) required by the WPS, supplemented by gloves, a chemical-resistant apron and face shield for all occupational uses of paraquat end-use products, as required by this RED. PPE requirements for applicators and other handlers (other than mixers and loaders) include a long-sleeved shirt and long pants, chemical-resistant gloves and shoes plus socks. Based on a biological monitoring study, post-application reentry workers will be required to observe a 12-hour Restricted Entry Interval for the uses of paraquat for preemergent or early-season weed control and weed control for orchard and vegetable crops where the spray is directed solely at the weeds (not broadcast over the entire crop area). A 24-hour Restricted Entry Interval is required for desiccation and harvest aid applications of paraquat

since the Agency concludes such uses result in a greater degree of exposure to workers.

Food Quality Protection Act Considerations

In establishing or reassessing tolerances, FQPA requires the Agency to consider aggregate exposures to pesticide residues, including all anticipated dietary exposures and other exposures for which there is reliable information, as well as the potential for cumulative effects from a pesticide and other compounds with a common mechanism of toxicity. The Act further directs EPA to consider the potential for increased susceptibly of infants and children to the toxic effects of pesticide residue.

The Agency considered the appropriateness of an additional uncertainty factor to account for situations where available data indicate increased sensitivity of infants and children and concluded that it is not warranted based on an evaluation of the toxicology database. Regarding aggregate exposure, the Agency only considered dietary exposure because there are no residential or other non-occupational uses of paraquat, and exposure to paraquat in drinking water is not expected. The EPA estimates that paraquat residues in the diet of the general U.S. population account for 10% of the RfD, 24% of the RFD for children aged 1-6 years and 31% of the RfD for non-nursing infants (less than 1 year). Therefore, the Agency has determined that there is a reasonable certainty that no harm will result to infants and children or to the general population from aggregate exposure to paraquat dichloride residues. Further, based on the available data, the Agency does not believe that the effects produced by paraquat would be cumulative with those of other structurally related compounds. Therefore, based on these conclusions, the Agency considers the tolerances in the RED to be reassessed with regard to FQPA requirements.

Environmental Assessment

Environmental Fate

Paraquat dichloride was shown to be very immobile in soil. Paraquat does not hydrolyze, does not photodegrade in aqueous solutions, and is resistant to microbial degradation under aerobic and anaerobic conditions. The primary route of environmental dissipation of paraquat is adsorption to biological materials and soil clay particles. Due to the apparent adsorption strength of paraquat for soil clays, these bound residues do not appear to be environmentally available. Nevertheless, since paraquat is persistent, it could potentially be found in surface water systems associated with soil particles carried by erosion. However, detections would not be considered to be representative of normal paraquat use (since it binds so strongly to soil clay particles and becomes environmentally inactive). Therefore, paraquat is not expected or considered to be a groundwater concern from normal paraquat dichloride use patterns.

Ecological Effects

Paraquat is practically non-toxic to honey bees and slightly toxic to fish on an acute basis. Paraquat is moderately toxic to non-endangered and endangered terrestrial animals (birds and mammals), non-target terrestrial and semi-aquatic plants. Acute toxicity to terrestrial animals (birds) and mammals only exists immediately after application.

Ecological Effects Risk Assessment

Paraquat exposure to birds, mammals, non-target terrestrial and semi-aquatic plants including endangered species may result from paraquat spray drift during application.

The Agency levels of concern (LOCs) have been exceeded for acute effects for birds and small (herbivorous and insectivorous) mammals and for acute effects on semi-aquatic and terrestrial plants. However, the risk for birds and small mammals only exists shortly after application. Once the applied paraquat has dried (or becomes bound) its risk is greatly reduced. Therefore, the Agency concludes the registered uses of paraquat are not expected to pose significant risk to birds or mammals. The Agency LOCs have also been exceeded for non-endangered and endangered non-target terrestrial and semi-aquatic plants. Depending on the application method and application rate, the risk quotients ranged from acceptable to acute effects. To mitigate these risks, the registrant has agreed to lower the maximum use rate, amend all paraquat labels to include a warning about possible adverse effects to non-target and semi-aquatic plants due to drift and include spray drift language.

Risk Mitigation

To lessen the occupational and ecological risks posed by paraquat, EPA is requiring the following risk mitigation measures.

- For all risk concerns:

  Reduce the maximum rate of application from 1.6 lb cation/A to 1.0 lb cation/A and maintain the Restricted Use Classification.

- To protect workers:

  Additional PPE are being required for mixers and loaders: gloves, chemical-resistant apron and face shield. PPE requirements for applicators and other handlers (other than mixers and loaders) include: long-sleeved shirt and long pants, chemical-resistant gloves, and shoes plus socks.

  Further, the concentration of paraquat in backpack sprayers will be reduced and the resin soaking sections on the paraquat labels amended (i.e., delete plastic acid bottle use) to lessen the exposure and risk to applicators.

- To protect non-target terrestrial and semi-aquatic plants from drift:

  Aerial applications will include the most current spray drift language and all paraquat products must place a statement in the “Environmental Hazard”section of the label that warns the user about possible adverse effects to non-target and semi-aquatic plants due to drift.

Additional Data Required

EPA is requiring data to establish tolerances for paraquat dichloride on taro foliage, corn and soybean aspirated grain fractions, wheat and hay, cotton and gin byproducts and processed grapes. The Agency is also requiring data to confirm that the existing tolerances for field corn is adequate to cover the specialized use of paraquat as a harvest aid.

Additionally, the Agency is requiring product-specific data including product chemistry and acute toxicity studies, revised Confidential Statements of Formula (CSFs), and revised labeling for reregistration.

Product Labeling Changes Required

All paraquat dichloride end-use products must comply with EPA's current pesticide product labeling requirements and with the following. For a comprehensive list of labeling requirements, please see the paraquat dichloride RED document.

Application Rates and Label Deletions for End-Use Products

In cooperation with the Agency the registrant has agreed to the following application rates and label deletions:

○ The maximum paraquat dichloride application rate for all products will be lowered from 1.6 lb cation/A to 1.0 lb cation/A.

- For broadcast applications of paraquat with backpack sprayers, **non-spot**, the application rate should not exceed 0.625 lb cation/A and the application volume should be no less than 20 gallons per acre.
- The maximum application rate for **spot spraying** on all paraquat labels will be no more than 0.0195 lbs cation/gallon.

○ Delete the plastic acid bottle and the tree injection directions for use from the resin soaking sections of all paraquat dichloride labels.

Hazard Statement

The following hazard statement must be placed in the "Environmental Hazard" section of all paraquat labels to warn the user about possible adverse effects to non-target terrestrial and semi-aquatic plants due to drift:

> "Paraquat dichloride is toxic to nontarget crops and plants if off-target movement occurs. Extreme care must be taken to ensure that off-target drift is minimized to the greatest extent possible."

PPE/Engineering Control Requirements for Pesticide Handlers

For **sole-active-ingredient** end-use products that contain paraquat, the product labeling must be revised to adopt the handler personal protective equipment/engineering control requirements set forth in this

section. Any conflicting PPE requirements on the current labeling must be removed.

For **multiple-active-ingredient** end-use products that contain paraquat, the handler personal protective equipment/engineering control requirements set forth in this section must be compared to the requirements on the current labeling and the more protective must be retained. For guidance on which requirements are considered more protective, see PR Notice 93-7.

Products Intended Primarily for Occupational Use (WPS and nonWPS)

Minimum (Baseline) PPE/Engineering Control Requirements

Although the MOE's were greater than 100 for all but two scenarios (backpack applicators and resin-soaking uses) without personal protective equipment requirements beyond long-sleeve shirt, long pants, shoes and socks, the Agency notes the relatively significant epidemiological evidence of poisonings from intentional/accidental swallowing and numerous non-systemic skin and eye effects in California (see OREB J. Blondell memo, 12/5/95). These considerations have led to the Agency establishing the following minimum (baseline) PPE is required for all occupational uses of paraquat end-use products:

"Mixers and loaders must wear:

--long-sleeved shirt and long pants,

--chemical-resistant gloves*,

--shoes plus socks,

--chemical-resistant apron,

--face shield"

Although there is no direct evidence that occupational handlers have ever ingested a lethal amount of paraquat from a splash or spill, the requirement for a face shield for all mixers and loaders reflects the Agency's particular concern about accidental swallowing in case of a spill or splash back.

"Applicators and other handlers (other than mixers and loaders) must wear:

--long-sleeved shirt and long pants,

--chemical-resistant gloves*,

--shoes plus socks"

* For the glove statement, use the statement established for paraquat through the instructions in Supplement Three of PR Notice 93-7.

Determining PPE Requirements for End-use Product Labels

The PPE that would be established on the basis of the acute toxicity category of the end-use product must be compared to the active-ingredient-based minimum (baseline) personal protective equipment specified above. The more protective PPE must be placed on the product labeling. For guidance on which PPE is considered more protective, see PR Notice 93-7.

Placement in Labeling

The personal protective equipment requirements must be placed on the end-use product labeling in the location specified in PR Notice 93-7, and the format and language of the PPE requirements must be the same as is specified in PR Notice 93-7.

Products Intended Primarily for Occupational Use

There are no registered homeowner-use products.

Entry Restrictions

For **sole-active-ingredient** end-use products that contain paraquat the product labeling must be revised to adopt the entry restrictions set forth in this section. Any conflicting entry restrictions on the current labeling must be removed.

For **multiple-active-ingredient** end-use products that contain paraquat the entry restrictions set forth in this section must be compared to the entry restrictions on the current labeling and the more protective must be retained. A specific time period in hours or days is considered more protective than "sprays have dried" or "dusts have settled."

Products Intended Primarily for Occupational Use - Entry Restrictions and Labeling

WPS Uses

Restricted-entry interval:

"For preplant or preemergence (broadcast or banded) applications, post-emergence directed-spray applications, dormant-season applications, and "between cutting" alfalfa applications: Do not enter or allow worker entry into treated areas during the restricted entry interval (REI) of 12 hours."

"For harvest-aid and desiccation applications: Do not enter or allow worker entry into treated areas during the restricted entry interval (REI) of 24 hours."

Early-entry personal protective equipment (PPE):

The PPE required for early entry is:

-- coveralls,

-- chemical-resistant gloves*,

-- shoes plus socks,

-- protective eyewear.

* For the glove statement, use the statement established for paraquat through the instructions in Supplement Three of PR Notice 93-7.

WPS Notification Statement:

Not required on label.

NonWPS uses

Entry restrictions:

The Agency is establishing the following entry restrictions for nonWPS occupational uses of paraquat end-use products:

"Do not enter or allow others to enter the treated area until sprays have dried."

Placement in labeling:

If WPS uses are also on label -- Follow the instructions in PR Notice 93-7 for establishing a Non-Agricultural Use Requirements box, and place the appropriate nonWPS entry restrictions in that box.

If no WPS uses are on the label -- Place the appropriate nonWPS entry restrictions in the Directions for Use, under the heading "Entry Restrictions."

Products Intended Primarily for Homeowner Use

Entry restrictions:

There are no registered homeowner-use products.

Other Labeling Requirements

Products Intended Primarily for Occupational Use

The Agency is requiring the following labeling statements to be located on all end-use products containing paraquat that are intended primarily for occupational use.

Application Restrictions

"Do not apply this product in a way that will contact workers or other persons, either directly or through drift. Only protected handlers may be in the area during application."

Engineering Controls

"When handlers use closed systems, enclosed cabs, or aircraft in a manner that meets the requirements listed in the Worker Protection Standard (WPS) for agricultural pesticides (40 CFR 170.240(d)(4-6), the handler PPE requirements may be reduced or modified as specified in the WPS."

User Safety Requirements

"Discard clothing or other absorbent materials that have been drenched or heavily contaminated with this product's concentrate. Do not reuse them."

"Follow manufacturer's instructions for cleaning/maintaining PPE. If no such instructions for washable, use detergent and hot water. Keep and wash PPE separately from other laundry."

"DO NOT USE AROUND HOMES, SCHOOLS, RECREATIONAL PARKS, GOLF COURSES, OR PLAYGROUNDS"

User Safety Recommendations

- "Users should wash hands before eating, drinking, chewing gum, using tobacco, or using the toilet."
- "Users should remove clothing immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing."
- "Users should remove PPE immediately after handling this product. Wash the outside of gloves before removing. As soon as possible, wash thoroughly and change into clean clothing."

Spray Drift Labeling

Please see the paraquat dichloride RED document for the text of this Advisory, which must be contained on each paraquat product label that can be applied aerially.

Regulatory

The use of currently registered products containing paraquat

Conclusion

dichloride in accordance with approved labeling will not pose unreasonable risks or adverse effects to humans or the environment. Therefore, all uses of these products are eligible for reregistration.

Paraquat products will be reregistered once the required product-specific data, revised Confidential Statements of Formula, and revised labeling are received and accepted by EPA.

For More Information

EPA is requesting public comments on the Reregistration Eligibility Decision (RED) document for paraquat dichloride during a 60-day time period, as announced in a Notice of Availability published in the Federal Register. To obtain a copy of the RED document or to submit written comments, please contact the Pesticide Docket, Public Response and Program Resources Branch, Field Operations Division (7506C), Office of Pesticide Programs (OPP), US EPA, Washington, DC 20460, telephone 703-305-5805.

Electronic copies of the RED and this fact sheet can be downloaded from the Pesticide Special Review and Reregistration Information System at 703-308-7224. They also are available on the Internet using ftp on *FTP.EPA.GOV*, or using WWW (World Wide Web) on *WWW.EPA.GOV*.

Printed copies of the RED and fact sheet can be obtained from EPA's National Center for Environmental Publications and Information (EPA/NCEPI), PO Box 42419, Cincinnati, OH 45242-2419, telephone 1-800-490-9198, fax 513-489-8695.

Following the comment period, the paraquat dichloride RED document also will be available from the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161, telephone 703-487-4650.

For more information about EPA's pesticide reregistration program, the paraquat dichloride RED, or reregistration of individual products containing paraquat dichloride, please contact the Special Review and Reregistration Division (7508W), OPP, US EPA, Washington, DC 20460, telephone 703-308-8000.

For information about the health effects of pesticides, or for assistance in recognizing and managing pesticide poisoning symptoms, please contact the National Pesticides Telecommunications Network (NPTN). Call toll-free 1-800-858-7378, between 9:30 am and 7:30 pm Eastern Standard Time, Monday through Friday.