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SCIENTIFIC COMMITTEE ON PLANTS **SCP/PARAQ/002-Final**
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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

(Opinion adopted by the Scientific Committee on Plants on 20 December 2001)

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A. TITLE

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
(Opinion adopted by the Scientific Committee on Plants on 20 December 2001)

B. TERMS OF REFERENCE

The Scientific Committee on Plants (SCP) is requested to respond to the following questions in the context of the Commission's work on the implementation of Council Directive 91/414/EEC concerning the placing of plant protection products on the market.

1. Can the Committee comment on the relevance for consumers and operators of the ocular and pulmonary changes, which were observed in the long-term rat study?

2. Can the Committee comment on the risk for operators, taking into particular account potential inhalatory and dermal exposure?

3. Can the Committee comment on potential long-term effects to soil dwelling organisms?

4. Can the Committee comment on the risks the intended uses might pose to reproducing birds and hares?

C. OPINION OF THE COMMITTEE

Opinion on question 1:

The toxic effects of paraquat are due to its ability to induce the production of reactive superoxide anions from molecular oxygen.

The pulmonary lesions observed in animals after paraquat oral treatment are the critical effect and are similar to those reported to occur in humans after deliberate or accidental oral ingestion of very high doses. Such effects, however, 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.

The ocular lesions documented in the long-term rat study result from systemic action of paraquat after prolonged oral absorption and not as a result of direct local contact with the eye. This latter situation may cause irritative mucosal effects, different from the lenticular opacity observed in rats as a result of systemic toxicity. The systemic effects of paraquat on the eye, observed in rats and not in other species, are not relevant to the risk assessment for operators and consumers.

Opinion on question 2:

While the use of predictive exposure models suggests that operator exposure to paraquat may exceed the proposed AOELs[1], the results of the field studies conducted in various countries indicate that the exposure models markedly overestimate the actual exposure to paraquat in real working situations. Thus modelled exposures cannot be used as the only basis for operator risk assessment. Based on the field exposure studies, corroborated by information on health surveys on operators, the SCP is of 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 SCP is of the opinion that the NOAELs[2] based on pulmonary effects observed in dogs should represent the basis to set short-term or medium-long-term AOELs.

Opinion on question 3:

Overall the SCP is satisfied with the data presented and concluded that if paraquat is used at recommended field rates then it is unlikely to pose a significant risk to soil-dwelling organisms. However, the Committee notes that the litter bag study was conducted at too high a dose rate to allow a reliable assessment of the likely effects of paraquat on the rate of organic matter decomposition under field conditions. Given this uncertainty and the persistence of paraquat in soil, the SCP feels that the notifier should provide a more detailed appraisal of the likely effects of paraquat on the rate of degradation of organic material in soil.

Opinion on question 4:

The Committee concludes that the results of the egg-dipping study demonstrate a hazard from paraquat to avian embryos, but the available information is not adequate for an assessment of risk (i.e. the likelihood that these effects will occur in practical use of the active substance). To provide a risk assessment would require tests with paraquat involving more realistic exposures.

The Committee concludes that paraquat can be expected to cause lethal and sublethal effects for hares, and this is confirmed by field reports. However, the available data are inadequate to estimate the proportion of hares affected.

[1] Acceptable Operator Exposure Levels.
[2] No Observed Adverse Effect Levels.

A. TITLE

SCIENTIFIC REPORT 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

B. TABLE OF CONTENTS

C. BACKGROUND

Paraquat is an existing active substance (a.s.) in the context of Council Directive 91/414/EEC[3], which is covered by the first stage of the work programme established by Commission Regulation (EEC) 3600/92[4].

A draft assessment report (monograph) has been prepared by the Rapporteur Member State (RMS, the United Kingdom) on the basis of a dossier presented by the notifier (Zeneca now Syngenta AG). In order to prepare its opinion the Scientific Committee on Plants had access to the documentation listed below.

Paraquat is a broad-spectrum non selective herbicide used to control annual and perennial weeds. It is not systemic. It is used in a wide range of crops, in horticulture, and in viticulture. It is also used for weed control on non-cultivated areas. Its rate of use ranges from 0.1 to 2.2 kg a.s./ha /application.

[3] OJ N° L 230 of 19. 8.1991, p. 1.
[4] OJ N° L 366 of 15.12.1992, p. 10.

Source documents made available to the Committee:

1. Terms of Reference - Evaluation of paraquat in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market - Submitted by DG Health and Consumer Protection, 25 January 2001 (SCP/PARAQ/001).

2. Paraquat - Evaluation table doc 7755/VI/97-rev. 3 (15.11.2000) - Submitted by DG Health and Consumer Protection, 25 January 2001 (SCP/PARAQ/003).

3. Paraquat – Draft Assessment Report, Addendum to Vol 3, Annex B of monograph - Submitted by DG Health and Consumer Protection, 25 January 2001 (SCP/PARAQ/004).

4. Paraquat – Austrian comments (31/07/2000) - Submitted by DG Health and Consumer Protection, 25 January 2001 (SCP/PARAQ/005).

5. Paraquat – Austrian comments (20/11/2000) - Submitted by DG Health and Consumer Protection, 25 January 2001 (SCP/PARAQ/006).

6. Paraquat – Danish comments (10/08/2000) - Submitted by DG Health and Consumer Protection, 25 January 2001 (SCP/PARAQ/007).

7. Paraquat – Danish comments (04/12/2000) - Submitted by DG Health and Consumer Protection, 25 January 2001 - (SCP/PARAQ/008).

8. Paraquat – French comments (24/11/2000) - Submitted by DG Health and Consumer Protection, 25 January 2001 (SCP/PARAQ/009).

9. Paraquat – Comments RMS (18/05/99) - Submitted by DG Health and Consumer Protection, 25 January 2001 (SCP/PARAQ/010).

10. Paraquat – Review of the factors affecting the decline of the European Brown Hare, *Lepus europaeus* (Pallas, 1778) and the use of Wildlife Incident data to evaluate the significance of paraquat – P.J. Edwards *et al.* - Submitted by DG Health and Consumer Protection, 25 January 2001 (SCP/PARAQ/011).

11. Paraquat – Swedish comments (03/10/98) Acute toxicity - Submitted by DG Health and Consumer Protection, 25 January 2001 (SCP/PARAQ/012).

12. Paraquat – Swedish comments (29/11/2000) - Submitted by DG Health and Consumer Protection, 25 January 2001 (SCP/PARAQ/013).

13. Paraquat – Finnish comments (29/11/2000) - Submitted by DG Health and Consumer Protection, 25 January 2001 (SCP/PARAQ/014).

14. Paraquat – Notifier comments on question 1 - Submitted by the notifier 11 July 2001 (SCP/PARAQ/015).

15. Paraquat – Notifier comments on question 2 - Submitted by the notifier 11 July 2001 (SCP/PARAQ/016).

16. Paraquat – Notifier comments on question 3 - Submitted by the notifier 01 August 2001 (SCP/PARAQ/017).

17. Paraquat – Notifier comments on question 4 - Submitted by the notifier 01 August 2001 (SCP/PARAQ/018).

18. Paraquat: draft assessment report (monograph) on the evaluation of paraquat in the context of the Council Directive 91/414/EEC and Regulation 3600/92, prepared by the United Kingdom, September 1996 (Volumes 1 to 3).

D. SCIENTIFIC BACKGROUND ON WHICH THE OPINION IS BASED

I. Questions 1 and 2:

Question 1:

Can the Committee comment on the relevance for consumers and operators of the ocular and pulmonary changes, which were observed in the long-term rat study?

Opinion of the Committee:

The toxic effects of paraquat are due to its ability to induce the production of reactive superoxide anions from molecular oxygen.

The pulmonary lesions observed in animals after paraquat oral treatment are the critical effect and are similar to those reported to occur in humans after deliberate or accidental oral ingestion of very high doses. Such effects, however, 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.

The ocular lesions documented in the long-term rat study result from systemic action of paraquat after prolonged oral absorption and not as a result of direct local contact with the eye. This latter situation may cause irritative mucosal effects, different from the lenticular opacity observed in rats as a result of systemic toxicity. The systemic effects on the eye of paraquat, observed in rats and not in other species, are not relevant to the risk assessment for operators and consumers.

Question 2:

Can the Committee comment on the risk for operators, taking into particular account potential inhalatory and dermal exposure?

Opinion of the Committee:

While the use of predictive exposure models suggests that operator exposure to paraquat may exceed the proposed AOELs, the results of the field studies conducted in various countries indicate that the exposure models markedly overestimate the actual exposure to paraquat in real working situations. Thus modelled exposures cannot be used as the only basis for operator risk assessment. Based on the field exposure studies, corroborated by information on health surveys on operators, the SCP is of 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 SCP is of the opinion that the NOAELs based on pulmonary effects observed in dogs should represent the basis to set short-term or medium-long-term AOELs.

Scientific Background on which the opinions on questions 1 and 2 are based:

I.1 Mechanism of action of paraquat in plants and mammals

Paraquat is a bipyridinium contact herbicide derived from pyridine. The mode of herbicidal action of paraquat is based on its ability to induce the production of reactive superoxide anions from molecular oxygen. Superoxide anions are further metabolised to other even more reactive oxygen species that cause irreversible damage to the leaves of the plant leading to its death.

A similar mechanism of toxic action is operative for paraquat also in the cells of mammalians, where the main target organs of toxicity are represented by lungs, kidneys and eyes.

When paraquat enters mammalian cells, it quickly evokes an increase in the production of superoxide anion, which is metabolised to hydrogen peroxide by superoxide dismutase. Hydrogen peroxide, in turn can be cleaved to form free hydroxyl radical that is toxic to the cell due to its high chemical reactivity with cellular macromolecules. Hydrogen peroxide is further metabolised and detoxified by catalase that metabolises hydrogen peroxide to water and molecular oxygen. Thus, paraquat has a strong potential to induce damage of the cells in the target tissues particularly after a high single dose.

I.2 Toxicokinetics of paraquat

In experimental animals, paraquat is poorly absorbed through the gastrointestinal tract (~10 %), or through the skin (0.1-0.5 %), while it is relatively well absorbed from the lungs and mucous membranes. Paraquat does not undergo practically any biotransformation in mammalians. Most of the compound is rapidly excreted as such in faeces (> 60 %) and in the urine and <1% of the administered dose can be detected in the organism 72 hours after oral dosing. After paraquat administration, the highest concentrations of the compound can be found in the lungs, the liver, the heart, and the eyes. Of these, the lungs and the eyes are the critical targets for toxicity.

I.3 Toxicity studies on paraquat

Acute toxicity of technical paraquat is moderate (344 mg/kg bw) orally, low dermally (> 2000 mg/kg bw), and high by inhalation (0.6-1.4 mg/m^3). High acute pulmonary toxicity is found especially under experimental circumstances in which the entry of paraquat into lungs has been assured. Paraquat is a slight but persistent skin irritant, and a moderate and persistent eye irritant by direct contact. Paraquat did not induce any sensitisation in guinea pigs in Magnuson-Kligman maximisation test.

In a 90-day dietary toxicity study with rats, paraquat had a NOAEL[5] of 6.8 mg of paraquat ion/kg bw based on pulmonary and blood cell (erythrocyte microcytosis) effects. Pulmonary and blood cell changes were associated with reduced weight gain.

In a 13-week toxicity study with dogs, paraquat administered at 120 ppm or 60 ppm caused increased incidence of alveolitis in these dogs. Absolute and relative kidney weights were increased in top dose females, and swollen renal cortical tubules were noted histologically at 120 ppm. Ovary weights were decreased in top dose females with no associated pathological findings. Thymus involution was increased in top dose females as well. There were, however, no effects at 20 ppm corresponding to 0.56 mg of paraquat ion/kg body weight.

In a one-year dog study the NOAEL of paraquat was 15 ppm in the diet (0.45 mg/kg bw/day), based on pulmonary lesions, clinical chemistry, and urine analysis. Marked lung lesions were produced at 50 ppm of paraquat in the diet (about 1.3 mg/kg bw/day). This dog study has the lowest NOAEL value based on pulmonary end point among the toxicity studies on paraquat and can therefore be used as the basis for AOEL setting.

In an extended two-year rat study, paraquat did not increase the incidence of tumours in the animals. Ocular opacities were evident clinically, and confirmed by ophthalmoscopy and histology, at 75 ppm after 79 weeks of treatment and at 150 ppm of paraquat in the diet, the NOAEL thus being 25 ppm equivalent to 1.225 mg/kg bw/day according to the notifier. However, according to the RMS, similar but milder findings were also found at the lowest dose [25 ppm of paraquat in the diet (1.225 mg/kg bw/day)], suggesting the absence of NOAEL regarding eye findings. However changes were only seen at 25 ppm at termination, on 112/113 weeks of treatment for males and 118/119 weeks for females. It is worth noting that lenticular degeneration was observed exclusively in rats, and not in dogs and mice.

The other main lesions were bile duct hyperplasia, and proliferative lesions in the lungs. Testicular lesions, peripheral nerve degeneration, hydrocephalus and bile duct hyperplasia were found at 75 and 150 ppm. Based on these findings the RMS suggests 25 ppm (1.225 mg/kg bw/day) to be a minimal effect level, as the effects in eyes were considered mild.

In a study with mice that lasted for 97-99 weeks, paraquat did not increase the incidence of tumours of any kind. In this study, the kidney appeared to be the target organ with tubular lesions evident at 125 ppm (12.5 mg/kg bw/day) and pelvic dilatation seen in males at 37 ppm (3.7 mg/kg bw/day). Alveolar hypercellularity was seen at 125 ppm, and was the only sign of pulmonary toxicity. A NOAEL of 1.5 mg/kg bw/day (15 ppm) was derived from this study.

In vitro genotoxicity test indicate that at cytotoxic concentrations paraquat exhibits mutagenic potential in L5178Y cells in the presence of metabolic activation. In the absence of metabolic activation there was no clear evidence of mutagenic potential. Paraquat did not induce unscheduled DNA (UDS) synthesis in hepatocytes, but was clearly clastogenic in Chinese hamster lung cells with and without metabolic activation. In *in vivo* genotoxicity tests, paraquat was not clastogenic in the mouse or rat bone marrow micronucleus test, and did not induce UDS in rat hepatocytes. There was no evidence that technical paraquat dichloride had an effect on fertility or increased the incidence of dominant lethal mutations at doses up to 4 mg/kg bw/day in rats. The overall conclusion is that paraquat does not present a genotoxic hazard *in vivo* even though some positive effects occurred in *in vitro* genotoxicity tests.

[5] No Observed Adverse Effect Level.

Paraquat did not have an appreciable potential to affect reproduction in a three-generation reproduction study in rats even at toxic levels of 150 ppm in the diet (12 mg/kg bw). Increased incidences of lung lesions at 75 and 150 ppm indicate that the overall NOAEL is 25 ppm, equivalent to > 2.0 mg/kg bw/day. Reproduction was, however, affected only at 150 ppm of paraquat in the diet (7.5 mg/kg bw/day).

One teratogenicity study was conducted in rats and two in mice. In the rat developmental study, no overt teratogenicity occurred at maternally toxic doses (10 mg/kg bw/day) but mild foetotoxicity was evident at 4 mg/kg bw/day. A NOAEL of 1 mg/kg/day was derived from this study. In one of the mouse studies, overt teratogenicity was not seen even at maternally toxic doses. Several occasional effects were seen in foetuses without a dose-effect relationship. An increase in umbilical hernia occurred at a mid-dose level. Alterations in ossification occurred at doses exceeding 7.5 mg/kg bw/day, but this effect could not be demonstrated in another mouse study. The NOAEL derived from the mouse teratogenicity studies was 7.5 mg/kg bw/day.

In conclusion, the critical target organs in all of the short- and long-term studies were the lungs and, to a minor extent, the kidneys, with the lowest NOAEL at 0.45 mg/kg/day in the 1 year dog study. The eye effects were seen only in the two year study in rats. In the lowest dosed group (1.225 mg/kg/day), these effects were minimal and observed only after the 110th week.

I.4 Effects of paraquat on humans

Toxicity of paraquat in humans seems to be rather similar to that described in experimental animals. The critical organ in humans is represented by the lungs.

After local contact in the nose and throat, local symptoms such as nosebleed and irritation of the throat occurs.

Under normal conditions, only 0.3 % of the dose penetrates the skin and acute poisoning through intact skin exposure is virtually impossible. Exposure of extensively damaged skin has lead to systemic toxicity.

Oral ingestion of paraquat formulations leads to nausea vomiting, abdominal pain, and bloody diarrhea in addition to ulcerations of mouth and lips takes place. All these effects are only seen after high exposures, and have been reported during accidents or intentional misuse of paraquat-containing products. After oral ingestion of high doses of paraquat, severe irreversible pulmonary lesions, frequently leading to death, have been observed.

I.5 Operator Exposure to paraquat

I.5.1 *Results from predictive exposure models*

The range of paraquat containing products and application rates authorised across the European Union are broadly similar. Predictive exposure models have been used to assess the exposure of workers to paraquat when using paraquat-containing formulations. Results from the UK percent absorption model, UK absorption model, and the German model are available. The results of UK absorption rate model for knapsack sprayers indicate that the proposed

short-term AOEL[6] for paraquat would be exceeded 100 fold when protective equipment is not used and 60 fold when it is used. For tractor spraying there was 100 and 40 fold increases as compared to the proposed AOEL. The UK absorption model suggested 40 and 4 fold exceeding of the short-term AOEL when tractor spraying was used. No data were available for knapsack spraying. According to the German model, short-term AOEL for paraquat was exceeded 20 fold in the absence of protective equipment and 4 fold when protection was used.

I.5.2 *Results from field studies*

As the predictive exposure models predicted an exposure to paraquat exceeding the proposed AOELs, field studies were carried out to evaluate the exposure to paraquat in appropriate field situations.

Exposure of knapsack sprayers was studied among workers in Sri Lanka in a tea plantation (Chester G *et al.* - monograph volume 3, Annex B, p 124). The absorbed dose based on dermal exposure was 0.0004-0.009 mg/kg/day which means up to a 18 fold excess exposure in regard to the proposed short-term AOEL. In the same study, the absorbed dose based on urine and blood analyses was 0.001-0.004 mg/kg/day indicating a 2-8 fold excess exposure as compared to the proposed short-term AOEL. It has to be noted that the absorbed dose in this study was calculated assuming urinary excretion of paraquat at the limit of analytical detection, which was very high (0.03 μg/ml) in this study. Very likely, the real absorption was lower than estimated, as can be derived from another study with lower limits of detection (see below). Furthermore, the mixer/loaders did not wear the protective equipment recommended on the product label during handling of the concentrate and all operators wore minimal clothing, consisting of shorts and T-shirt with no footwear. Dermal exposure was, on average, 66 mg/day and 74 mg/day for the mixer/loaders and spray operators, respectively. Despite this dermal exposure, there was no measurable absorption of paraquat as indicated by urinary excretion of the compound following collection of complete 24 hour samples of urine for 6 days after the last day of spraying.

For comparison, it is essential to consider the biomonitoring study with hand-held knapsack sprayers for weed control in citrus orchards in Spain, which is more representative of the European scenarios of paraquat use (Findley M *et al.*, 1998 – Addendum to the monograph May 2000). In this study, the limit of detection was 0.00075 μg/ml, 40 times lower than in the Sri Lankan study. The mean absorbed dose was 0.00015 mg/kg bw/day, which is below the AOEL (i.e. 0.0005 mg/kg bw/day, Addendum to the monograph, May 2000).

Exposure during tractor spraying was studied in USA pecan orchards among workers who wore long/short sleeved shirts, long trousers, work boots, baseball caps, and gloves during mixing and loading (Meier D and Findlay M, 1995, monograph volume 3, Annex B, p127). In this study, paraquat was detected in urine samples from only six of the seventeen operators and only on the day of exposure (LOD[7] 0.005 μg/ml). The highest amount of paraquat absorbed was 0.00044 mg paraquat/kg bw/day (overall range for the six operators: 0.00007 to 0.00044 mg/kg bw/day). This operator was noted to have handled the product carelessly and did not wear any protective gloves or other protective clothing during mixing and loading. The absorbed dose based on urine and blood analyses indicated a value of 0-88 % of the short-term AOEL for paraquat.

[6] Acceptable Operator Exposure Level.
[7] Limit of Determination.

The results of the field studies greatly emphasise the importance of correct use of personal protective equipment. In fact, in the above reported field studies, the subjects who did not follow the recommended working procedures required for paraquat i.e. the use of gloves and other protective clothing, were the only ones showing absorption levels close to the AOEL values.

The results of the studies above discussed indicate that the exposure models markedly overestimate the actual exposure to paraquat in real working situations and they cannot be used as the only basis for operator risk assessment. Based on representative field exposure studies, the SCP is of the opinion that actual exposure of the operators is lower than that indicated by the exposure models and the use of paraquat according to the prescribed good working procedures does not pose a health risk for the operators.

Further reassurance that paraquat does not present a significant long-term health risk to the operators in EU Member States comes from studies conducted in countries in which exposure to paraquat markedly exceeds that in EU Member States without apparent deleterious health effects in workers. On several occasions (e.g. Malaysia, Sri Lanka, Philippines) the health of spray operators has been evaluated through a full clinical medical examination (Gurunathan *et al.*, 1990, Sabapathy & Tomenson, 1992 – monograph volume 3, Annex B p. 132-134). Additional clinical laboratory investigations were undertaken, including haematology examination, blood biochemistry (for assessment of liver and kidney function) and tests for pulmonary function. In plantations in tropical regions the climate, in particular the constant high temperatures and rainfall, promotes weed growth and control is required throughout the year on a regular basis. In each of these studies the test populations had used exclusively knapsack sprayers and, due to climatic conditions, were unlikely to have regularly used complete body clothing. Knapsack application generally presents a higher potential for operator exposure and thus represents the 'worst case' in terms of the potential for health effects. In all cases, there were no clinically significant differences in any of the measurements made between the spray operator groups and the control groups. The lung function indices, appropriate for the assessment of pulmonary paraquat toxicity, demonstrated no significant difference between the groups. From these studies it can be concluded that the normal long-term use of paraquat does not give rise to serious health problems.

I.6 Conclusions

The toxic effects of paraquat are due to the production of reactive oxygen species that damage the cells in the mammalian organisms.

The pulmonary effects observed in animals after paraquat oral treatment are the critical effect and are similar to those reported to occur in human after deliberate or accidental oral ingestion of very high doses. Such effects, however, 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 intended.

The ocular lesions documented in the long-term rat study result from systemic action of paraquat after prolonged oral absorption and not as a result of direct local contact with the eye. This latter situation may cause irritative mucosal effects, different from the lenticular opacity observed in rats as a result of systemic toxicity. The systemic effects of paraquat on the eye, observed in rats and not in other species, are not relevant to the risk assessment for operators and consumers.

The SCP is of the opinion that the NOAELs based on pulmonary effects observed in dogs should represent the basis to set short-term or medium-long-term AOELs and ADI[8].

While the use of predictive exposure models suggests that operator exposure to paraquat may exceed the proposed AOELs, the results of the field studies conducted in various countries indicate that the exposure models markedly overestimate the actual exposure to paraquat in real working situations. Thus modelled exposures cannot be used as the only basis for operator risk assessment. Based on the field exposure studies, corroborated by information on health surveys on operators, the SCP is of the opinion that when paraquat is used as a plant protection product as recommended, its use does not pose any significant health risk for the operators.

II. Question 3

Can the Committee comment on potential long-term effects to soil dwelling organisms?

Opinion of the Committee:

Overall the SCP is satisfied with the data presented and concludes that if paraquat is used at recommended field rates then it is unlikely to pose a significant risk to soil-dwelling organisms. However, the Committee notes that the litter bag study was conducted at too high a dose rate to allow a reliable assessment of the likely effects of paraquat on the rate of organic matter decomposition under field conditions. Given this uncertainty and the persistence of paraquat in soil, the SCP feels that the notifier should provide a more detailed appraisal of the likely effects of paraquat on the rate of degradation of organic material in soil.

Scientific background of which the opinion is based:

Paraquat adsorbs very strongly to soil and field dissipation studies indicate that it has a half-life of 7-20 years. The maximum proposed single application rate of the parent substance for agricultural field purposes is 1.1 kg a.s./ha (up to 1.7 kg a.s./ha for tree and shrub nurseries and 2.2 kg a.s./ha for non-crop areas), to be used up to 3 times per season. The maximum initial PEC_s[9] in the top 5 cm soil following a single application at 1.1 kg a.s. /ha has been estimated as 0.73 mg a.s./kg. As paraquat is persistent, the longer-term PEC_s following repeated applications over a number of years will depend heavily on the mean frequency of use. As an illustrative guide, the notifier estimated worst case PEC_s of 3.8 and 5.1 mg/kg following application rates of 600 and 800 g a.s./ha respectively per year after 45 years (DT_{50}[10] 20 years, 20 cm depth soil to allow for cultivation, 20% interception by foliage).

A measure of the capacity of soil to deactivate the active substance by adsorption has been estimated by employing a Strong Adsorption Capacity – Wheat Bioassay (SAC- WB). In these assays, wheat seedlings were planted in soils treated with paraquat and the concentration that reduces their growth by 50% of controls was determined. The average SAC value for sandy loam soil in Surrey, UK was 120 mg/kg soil (equivalent to 180 kg paraquat/ha incorporated to a depth of 15 cm), while the average SAC value for sandy loam soil in North

[8] Acceptable Daily Intake.
[9] Predicted Environmental Concentration in soil.
[10] Dissipation time for 50% of residue.

Carolina, USA was 25 mg /kg soil (equivalent to 57 kg paraquat/ha incorporated to a depth of 15 cm). SACs were also estimated in a comparative study of soils in Germany, Netherlands, Denmark, Greece, Italy and the UK where paraquat has previously been used. In these trials SAC-WB values showed a good correlation with soil clay content, and soil residues were a maximum of 18% of the SAC for a given soil.

The relevant ecotoxicological data that relate to the effects of paraquat on soil-dwelling organisms (with the exception of non-target plants) are summarised in tables 1 and 2 below:

Table 1. Summary of tests on surface-dwelling species

Species	Lab / field	Application rate equivalent	End point(s)
Pterostichus melanarius (Carabidae)	Lab	1 kg a.s./ ha	No statistically significant lethal or sub-lethal effects after 5 days
Aleochara bilineata (Staphylinidae)	Lab	0.6 kg a.s./ ha	20% reduction in beneficial capacity, but not statistically significant
Pardosa spp. (Lycosidae)	Lab	1 kg a.s./ ha	No statistically significant lethal or sub-lethal effects after 5 days
Various surface dwelling arthropods	Field	0.6 kg a.s./ha applied over 2 complete seasons	Linyphiid spiders adversely affected but recovered by 6 weeks (most likely through immigration). Erigonine spiders showed no significant effect. Collembola adversely affected at one site post application, but recovered within 2 months
Various surface dwelling arthropods	Field	A number of treatment regimes over several years including doses up to 1700 kg a.s./ha	Results difficult to interpret, but no effects observed that could be attributed to direct effects of active substance
Various surface dwelling arthropods	Field	1.2 kg a.s./ha. Effects monitored over 1 year	Microarthropods in general not adversely affected but 2 families of mites were reduced in numbers up to 4 months following treatment
Various soil dwelling micro-arthropods including Collembola	Field	480 mg a.s./kg soil	Some statistically significant differences between treated and untreated plots, but no consistent treatment effects.

Overall the SCP is satisfied with the data presented that if paraquat is used at recommended field rates then it is unlikely to pose a significant risk to soil-dwelling organisms. The high SAC-WB values compared to long-term PEC_S and general absence of significant effects at high field application rates, support the view that as a consequence of high adsorption, paraquat should not be bio-available in high concentrations to many soil organisms.

The SCP notes that no laboratory sub-lethal test for earthworms was conducted despite the fact that paraquat may become available to these organisms through ingestion. However the Committee notes that the LC_{50s}[11] for earthworms were generally very high, and that field trials showed no significant differences in earthworm numbers 1 year following applications up to 90 kg a.s./ha.

Of more concern, the litter bag study showed consistent treatment effects, possibly as a consequence of unrealistic high dose rates. Like the RMS, the SCP feels that the relevance of the high application rate and the method of application (dipping leaves into the products) are unclear. Given the uncertainty and the high persistence of paraquat in soil (albeit with

[11] Lethal concentration, median

potentially low bio-availability to most taxa), the SCP feels that the notifier should provide a more detailed appraisal of the likely effects of paraquat on the rate of degradation of organic material in soil.

Table 2. Summary of tests on soil-dwelling species

Species	Lab / field	Application rate equivalent	End point(s)
Eisenia foetida	Lab	1000 mg a.s./kg soil	14 d LC_{50} > 1000 mg a.s./kg soil 14 d NOEC[12] < 1000 mg a.s./kg soil (18% body weight reduction at this concentration)
1. *Lumbricus terrestris* 2. *Apporectodea caliginosa* 3. *Eisenia foetida*	Lab	Report by Hague and Ebring	14 d LC_{50}'s as follows: 1. > 1000 mg a.s./kg 2. > 580 mg a.s./kg 3. > 200 & > 3200 mg a.s./kg
Earthworms	Field	1.2 kg a.s./ha	No significant deleterious affects 1, 6 or 12 months post treatment
Earthworms	Field	15, 33, 90, 120 198, 720 kg a.s./ha in 2 experiments	Earthworm numbers significantly less on plots with application rates > 90 kg a.s./ha after 1 year. Recovery observed in 120 and 198 kg a.s./ha plots 6 years post treatment
Micro-organisms	Lab	0.8, 4 mg a.s./kg	No statistically significant differences in levels of microbial biomass carbon, nitrate or ammonium levels over a 4 week period.
Micro-organisms	Lab	0.25, 0.5, 2.5, 25 mg a.s./ kg	Only significant difference recorded was in one treated soil, which found that significantly more ammonium and nitrate was produced
Soil fungi	Lab	120, 1200, 12000, 120000 mg/L (0.1-100 times field concentration)	Sporulation rates of some species inhibited at recommended field rate, while in other species it was stimulated
Soil fungi and bacteria	Lab	0.115 and 1.15 mg a.s./cm^2	Increase in number of aerobic heterotrophic bacteria at high concentration after 14 days. Populations of fungi were 100 times higher in treated soils
Soil micro-organisms	Field	90, 198, 720 kg a.s./ha	No apparent treatment or dose-related effects after 7 years
Variety of soil dwelling organisms	Field	Litter bags (*Sorghum halepense*, 1mm^2 mesh) dipped into paraquat at concentrations 0.19% and 1.9% a.s.	Significant difference in controls and treatments in % dry weight remaining in litter bags after 70, 91 and 112 days (duration of study). Significant difference at higher treatment rate after 49 days. Mean nutrient concentrations consistently less in treatments than control.

III Question 4

Can the Committee comment on the risks the intended uses might pose to reproducing birds and hares?

Opinion of the Committee:

The Committee concludes that the results of the egg-dipping study demonstrate a hazard from paraquat to avian embryos, but the available information is not adequate

[12] No Observed Effect Concentration.

for an assessment of risk (i.e. the likelihood that these effects will occur in practical use of the active substance). To provide a risk assessment would require tests with paraquat involving more realistic exposures.

The Committee concludes that paraquat can be expected to cause lethal and sublethal effects for hares, and this is confirmed by field reports. However, the available data are inadequate to estimate the proportion of hares affected.

Scientific background of which the opinion is based:

III.1 Origin of question

The Committee restricted its assessment to the following issues, which were raised in documents SCP/PARAQ/006 and 007 with regard to:

1. Concern over the effect of paraquat on birds (SCP/PARAQ/007).

In a study carried out by Hoffman and Eastin in 1982 mallard eggs containing 3 or 8 days old embryos were dipped for 30 seconds in 0, 0.56 and 5.6 kg a.s./ha paraquat equivalents (i.e. 600 g/l and 6000 g/l). Hatching in the control group was 100% and no abnormal ducklings were seen. In the 0.56 kg/ha group, 77% of the eggs with 3 days embryos hatched and 9% was abnormal, 80% of the eggs with 8 days old embryos hatched and 13% were abnormal. In the 5.6 kg/ha group, 27% of the eggs with 3 days embryos hatched and 63% were abnormal, 53% of the eggs with 8 days old embryos hatched and 25% were abnormal. The possible effects on the reproduction from spray solutions reaching eggs in nests and resulting in reduced hatching and abnormalities could be of serious concern.

2. Concern on toxicity of paraquat to hares (SCP/PARAQ/007).

Short descriptions of four studies were presented. It was reasoned that these studies indicate that exposure of hares to freshly sprayed vegetation can cause toxic symptoms and even death.

3. Concern over the use of paraquat in relation to animal welfare (SCP/PARAQ/006).

Document SCP/PARAQ/006, submitted to the SCP states that paraquat acts very fast, but does not necessarily cause mortality within a short time. Also irreversible subchronic effects are induced (e.g. inflammation and ulceration of lips, nose tongue pharynx and oesophagus, furthermore acute inflammatory changes after eye contact, reaching a maximum after 12 to 24 hours). After ingestion of sublethal doses of paraquat, kidney failure, liver complications and pulmonary insufficiency may occur after a 2 to 3 week period. The damage of the lung is irreversible and leads to respiratory failure as a consequence of pulmonary fibrosis.

III.2 Effects of paraquat on birds

The method of dipping an egg for 30 seconds caused substantial effects, and thus demonstrates a *hazard* to avian embryos. However, the exposure in this study clearly exceeds a realistic worst case. Therefore, in order to draw conclusions about *risk*, it is necessary to assess whether effects would occur at more realistic exposures.

Overspraying with pesticide would represent a realistic worst case exposure for eggs. Document SCP/PARAQ/009 cited data on a 2,4-D dipping experiment (exposure solution 400 g/l) with two partridge species where a high rate of mortalities among embryos and of teratogenic malformations occurred (Lutz-Ostertag and Lutz, 1970). They compared this with a study by Grolleau *et al.* (1974) where eggs of the same two species were oversprayed with 2,4-D at rates of 1.2, 2.4 and 6 kg 2,4-D/ha. Only a slight decrease in the rate of viable young of one of the partridge species was observed at the dose of 6 kg/ha. This result appears to confirm that, for 2,4-D, effects of overspraying are less severe than effects of dipping.

It may be reasonable to expect that overspraying would also cause less severe effects than dipping in the case of paraquat. However, in order to reach a conclusion about the risk for paraquat, it would be necessary to estimate the degree by which effects of overspray would differ from those of dipping. The Committee considers that this cannot be estimated with sufficient confidence using the comparison of the two methods for 2,4-D, because the physico-chemical properties of the two active substances are very different. Unfortunately, none of the other information that is available can assist with this extrapolation.

The Committee therefore concludes that the results of the egg-dipping study demonstrate a hazard from paraquat to avian embryos, but the available information is not appropriate for an assessment of risk (i.e. the likelihood that these effects will occur in practical use of the active substance). To provide a risk assessment would require tests with paraquat involving more realistic exposures.

III.3 Toxicity of paraquat to hares

It is obvious from all the data presented that paraquat can cause toxic effects including lethal effects, and that such effects can be expected to occur for at least some individuals in the field and where exposure occurs a proportion may be affected. However, the available data are not adequate to determine the exact proportion of individuals that will be affected.

A scientific publication regarding the frequency of reported poisoning incidents involving hares (SCP/PARAQ/011) was submitted to the Committee. This paper cites some cases in which poisoning of hares by paraquat was demonstrated, which confirms the expectation that some individuals will be affected. The paper also reports that involvement of paraquat was not confirmed for the great majority of hare deaths that were investigated. It is concluded from this evidence that the proportion of hares poisoned by paraquat is acceptably small. However, these data are affected by a number of uncertainties:

- not all hares mentioned in SAGIR (France wildlife incident scheme) were diagnosed; a high proportion (40%) was not analysed because of poor conditions of the animals at post-mortem (SCP/PARAQ/011 page 17),
- the excretion of paraquat residues is very rapid (monograph p. 242) and can therefore obscure the outcome of a diagnosis,
- the chance of finding dead hares is small and the chance of reporting any dead hare is even less (especially if only one corpus is involved).

Attention of the Committee was drawn to a field study on the effects of paraquat on small mammals (SCP/PARAQ/007). In this study (Baumler, 1977), small populations of field voles, common shrews and pigmy shrews were exposed to 1 kg paraquat/ha. No effect was indicated for the voles. The two exposed shrew species showed declines of approximately 50% on one site; on the other site there were too few shrews for an effect to be detectable. The lack of replication precludes statistical assessment of whether the decrease in shrews was caused by

paraquat. Even if the decrease in shrews was caused by paraquat, the study does not permit a conclusion on whether the effect was due to direct toxicity or indirect effects (e.g. emigration of shrews due to the destruction of plant cover).

The Committee therefore considers this study to be inconclusive. Consequently it does not help answer the question posed to the Committee, regarding hares.

Some measures have been identified that may partially reduce the risk to hares:
- no aerial application (to avoid overspraying),
- to spray in the early morning, to prevent hares being exposed to paraquat before it has dried, as hares are active mainly at night (on the label in the UK),
- to add a repellent, if it is effective against hares (condition in France).

III.4 Animal welfare

Document SCP/PARAQ/005, submitted to the Committee, raises the issue of animals suffering following paraquat accidental ingestion. Reports of human poisonings with paraquat indicate that the victims experienced severe pain and suffering. The available data indicate that a proportion of hares will experience exposures similar to these human cases (i.e. lethal and near lethal).

Directive 91/414/EEC Article 4 states that "Member States shall ensure that a plant protection product is not authorised unless it is established, in the light of current scientific and technical knowledge and shown from appraisal of the dossier provided for in Annex III, that when used in accordance with Article 3 (3), and having regard to all normal conditions under which it may be used, and to the consequences of its use …. (iii) it does not cause unnecessary suffering and pain to vertebrates to be controlled… (v) it has no unacceptable influence on the environment, having particular regard to the following considerations…. its impact on non-target species". It seems open to interpretation whether impacts in the form of suffering and pain should be assessed for non-target species.

No specific guidance is available on how to assess the humaneness for non-target species. However, some countries (e.g. the United Kingdom) have developed guidance for the assessment of humaneness for compounds (vertebrate control agents) and target species[13]. The starting point of this document is that it should be assumed, until convincing evidence is available to the contrary, that procedures that cause pain or distress in humans would do so in animals. "Animals", in this context, are warm-blooded vertebrates since the document refers to rodent control.

If an assessment of suffering and pain is required for paraquat and hares, one possible approach could therefore be to use the one recommended by the UK for target species. This approach is divided into two steps. In the first step, the applicant would be required to conduct a literature search:
1) To discover any information relating to the experiences of humans clinically treated with, or otherwise exposed to, the test compound, or compounds with similar chemical structures and/or suspected modes of action,

[13] Chapter 9 of the Data Requirements Handbook of the UK Pesticides Safety Directorate, http://www.pesticides.gov.uk/applicant/registration_guides/data_reqs_handbook/contents.htm

2) To discover any information on the humaneness, toxicity and efficacy of the test compound in the target species (or in this case, non-target) or any related species, which may be of use in assessing the humaneness of the compound.

Depending on the outcome of the first step, a testing programme might be required in the second step.

It should be noted that the absence of comments on animal welfare in opinions of the SCP on other active substances is not to be interpreted as an absence of an animal welfare issue for all those substances.

III.5 Conclusions

In conclusion, paraquat can be expected to cause lethal and sublethal effects to hares, and this is confirmed by field reports. However, the available data are inadequate to estimate the proportion of hares affected. Some measures have been identified that may partially reduce the risk to hares. If an assessment of suffering and pain is required, it should begin with a search for relevant information on effects of paraquat in humans, hares and related species.

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