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OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON THE EVALUATION OF CYHALOFOP-BUTYL [DE-537] IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC FOR PLACING PLANT PROTECTION PRODUCTS ON THE MARKET

(Opinion adopted by the Scientific Committee on Plants on 7 March 2001)

Rue de la Loi 200, B-1049 Bruxelles/Wetstraat 200, B-1049 Brussel - Belgium - Office: B232 6/18.
Telephone: direct line (+32-2)296.58.91, switchboard 299.11.11. Fax: 295.73.32.

Internet: Jean.Ferriere@cec.eu.int

1. TITLE

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON THE EVALUATION OF CYHALOFOP-BUTYL [DE-537] IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC FOR PLACING PLANT PROTECTION PRODUCTS ON THE MARKET

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2. 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 confirm that a use exists which is acceptable for aquatic organisms and for non-target arthropods?

2. Can the Committee confirm that the operator exposure has been sufficiently addressed?

3. BACKGROUND

Cyhalofop-butyl is a new active substance in the context of Council Directive 91/414/EEC[1]. The draft Commission Directive for inclusion of cyhalofop-butyl [DE-537] in Annex I to Directive 91/414/EEC concerning the placing of plant protection products on the market was submitted to the Committee for opinion. The Committee had been supplied with documentation comprising a draft assessment report (monograph) prepared by the Rapporteur Member State (RMS, Italy) based on a dossier submitted by the notifier (Dow AgroSciences), a review report prepared by the Commission and the Recommendations of the ECCO[2] Peer Review Programme.

Cyhalofop-butyl is a herbicide for use on rice. It is intended to be applied using aerial and terrestrial means at a rate between 200 and 300 g a.s./ha.

4. OPINION

4.1 Question 1

Can the Committee confirm that a use exists which is acceptable for aquatic organisms and non-target arthropods?

<u>Opinion of the Committee:</u>

The Committee concludes that terrestrial application of cyhalofop-butyl to either flooded or drained paddy fields at a maximum rate of 300 g/ha is not likely to pose an

[1] OJ N° L 230, 19. 8.1991, p.1.
[2] European Commission Co-ordination.

unacceptable risk to aquatic organisms occupying adjacent surface water. It can also be confirmed that terrestrial application to drained paddies (allowing a minimum of 24 hours before re-flooding) is not likely to pose an unacceptable risk to aquatic organisms within the paddy field. However, aerial application may pose an unacceptable risk to aquatic organisms both within paddies and in adjacent surface waters, and terrestrial application to flooded paddies may pose an unacceptable risk to aquatic organisms within the paddy fields.

With regard to non-target arthropods, there is no indication of unacceptable risk to bees. However, there remains some uncertainty with regard to other non-target arthropods which should be addressed by an extended test on an appropriate predatory arachnid species.

Scientific background on which the opinion is based:

Cyhalofop-butyl is a new post emergence herbicide for use in rice at proposed application rates of 200-300 g a.s./ha, given as 1-2 applications. It may be used in drained or flooded paddies, and applied via broadcast or aerial methods. A minimum no-spray zone of 1 m for static water bodies has been suggested by the RMS, who also concluded that aerial application should be avoided because of high probability of overspray.

4.1.1 Environmental Fate

In both soil and sediment/water tests, the parent ester, cyhalofop-butyl (DE-537) degrades rapidly to DE-537 ACID through cleavage of the ester linkage which is further degraded by sequential oxidation of the cyano group to form DE-537 AMIDE and DE-537 DIACID. All three of these metabolites formed at levels > 10% of applied radioactivity (i.e., cyhalofop-ACID: 13-38% AR[3] after 1-4 hr; cyhalofop-AMIDE: 16-36% AR after 8 hr; cyhalofop-DIACID: 22-40% AR after 8-24 hr). These metabolites were more rapidly degraded in aerobic- than in anaerobic soil and were more rapidly degraded in soil than in sediment/water tests, with half-lives shown in Table 1. Other metabolites forming in soil at levels < 10% are 3-fluoro-4-(4-hydroxyphenoxy)benzoic acid and 2-(4-hydroxyphenoxy)propanoic acid.

Table 1. Mean DT_{50}[4] values for DE-537 and its metabolites (values taken from SCP/CYHALO/003; pp. 11-18).

Metabolite	DT_{50lab} in aerobic soils (20°C)	DT_{50lab} in anaerobic soil (20°C)	DT_{50lab} in sediment: water (whole system)
DE-537	3.4-9.8 hours	< 1 day	1.4-5.3 hours
DE-537 ACID	8-21 hours	3.2 days	4.5-8.5 days
DE-537 AMIDE	5-24 hours	4.8 days	3.9-17 days
DE-537 DIACID	0.8-3.9 days	21 days	8-43 days

[3] Applied radioactivity.
[4] Period required for 50% dissipation.

4.1.2 Effects of parent substance and metabolites on aquatic organisms

Acute toxicity of cyhalofop-butyl has been tested on a range of aquatic species including rainbow trout (*Oncorhynchus mykiss*; 96h LC_{50}[5]=1.65 mg/l, nominal), bluegill sunfish (*Lepomis macrochirus*, 96h LC_{50}=0.637 mg/l, measured), daphnids (*Daphnia magna;* 48h EC_{50}[6]=3.62 mg/l, measured), green algae (*Selenastrum capricornutum*; 72h EC_{50}=9.71 mg/l, measured), blue-green algae (*Anabaena flos-aquae*; 72h EC_{50}>8.44 mg/l, measured ester & acid)), duckweed (*Lemna minor*; 14d EC_{50} >5.3 mg/l, measured ester & acid), and diatoms (*Navicula pelliculosa*; 120h EC_{50}=1.33 mg/l).

Acute toxicity of cyhalofop-ACID was tested in the bluegill sunfish, (96h LC_{50} >99.2 mg/l, measured), rainbow trout (96h LC_{50} >100 mg/l, nominal), daphnids (48h EC_{50} >100 mg/l, nominal) and a green alga (72h EC_{50} >78.2 mg/l, measured, and NOEC[7] ≥78.2 mg/l, measured).

Acute toxicity of cyhalofop-AMIDE was tested in the bluegill sunfish (96h LC_{50} >88.4 mg/l, measured), daphnids (48h EC_{50} >100 mg/l, nominal), and a green alga (72h EC_{50} *ca.* 42.4 mg/l, measured, and NOEC 24.9 mg/l, measured).

Acute toxicity of cyhalofop-DIACID was tested in the bluegill sunfish (96h LC_{50} >98.7 mg/l, measured), daphnids (48h EC_{50} > 100 mg/l nominal), and a green alga (72h EC_{50} > 100 mg/l, nominal).

Chronic toxicity of cyhalofop-butyl was tested in an early life-stage test with the fathead minnow (*Pimephales promelas*). The NOEC was 0.134 mg a.s./l, measured (ester plus acid as ester equivalents), determined on the basis of a reduction in survival at exposure levels ≥ 0.287 mg/l. From analysis of the DE-537 ACID component in the exposure media, it was determined that the chronic NOEC for the DE-537 ACID metabolite is greater than 0.0666 mg/l. Chronic effects of the DIACID metabolite were tested with fathead minnow (28 days NOEC > 9.41 mg a.s./l, measured) and daphnids (21 days NOEC ≥ 98.3 mg a.s./l measured), and chronic toxicity of cyhalofop-butyl (plus any metabolites formed during the study) was tested with the sediment-dwelling midge, *Chironomus riparius* (NOEC = 10 mg/l nominal).

Thus, the lowest measured ecotoxicological end-point for cyhalofop-butyl identified in the dossier is 0.134 mg/l (i.e. the chronic NOEC for fathead minnows, Ref. J49), and in general, the three main metabolites were less toxic than the parent compound.

4.1.3 Risk assessment for aquatic organisms

In order to estimate risk of cyhalofop-butyl to aquatic organisms the Committee considered terrestrial and aerial application methods, application to drained and flooded paddies, and aquatic organisms within and adjacent to the paddies, giving a total of eight scenarios (Table 2). To assess the risk to aquatic organisms within paddy fields from both terrestrial and aerial application to flooded paddy fields, PECs[8] were calculated as direct overspray to a 10 cm deep water body (SCP/CYHALO/006, p. 81). To assess risk to aquatic organisms inhabiting adjacent surface water, PECs for aerial application to flooded paddies were calculated as

[5] Lethal concentration, median.
[6] Median effective concentration.
[7] No observed effect concentration.
[8] Predicted environmental concentration.

direct overspray to a 30 cm deep water body (volume 3 of draft evaluation report p. 22), and PECs for terrestrial application to flooded paddies were based on 4% drift (i.e., 1 m buffer zone) to a 30 cm deep static water body (SCP/CYHALO/006, p. 79). For applications (terrestrial and aerial) to drained paddy fields, the PECs for organisms within the paddy were calculated assuming that the paddy was flooded 24h following application (SCP/CYHALO/003; p. 19); PECs for organisms outside of the paddy were assumed to be the same regardless of whether the application is made to drained or flooded paddies (based on the assumption that exposure would occur primarily by spray drift).

Table 2. PECs based on different application scenarios used for TER[9] calculations. A maximum application rate of 300 g a.s./ha is assumed throughout.

		PEC_{sw}[10] (μg/l) within paddy field	PEC_{sw} (μg/l) for adjacent surface water
Aerial application	Flooded	300	100 (30 for 1 m depth)
	Drained	10.7	100
Terrestrial application	Flooded	300	4.0
	Drained	10.7	4.0

Taking the lowest acute toxicity values for fish (637 μg/l), daphnids (3620 μg/l) and aquatic plants/algae (1330 μg/l) and dividing by the PEC_{sw} values for each application scenario leads to the following TER values:

Table 3. TER calculations using lowest acute effect level for fish, daphnids and algae and PEC_{sw}s from Table 2.

		TER (fish, daphnids, algae) within paddy field	TER (fish, daphnids, algae) for adjacent surface water
Aerial application	Flooded	2.1, 12.1, 4.4	6.4, 36.2, 13.3
	Drained	59, 338, 124	6.4, 36.2, 13.3
Terrestrial application	Flooded	2.1, 12.1, 4.4	159, 905, 332
	Drained	59, 338, 124	159, 905, 332

It was noted in the draft evaluation report (Volume 3, p. 222) that 1 m is more typical for the depth of water in irrigation channels. In such case the estimated PEC_{sw} is 30 μg/l and the corresponding TER values for fish, daphnia, and algae in the adjacent channels would be 21, 121, 44 respectively for aerial application. For terrestrial application, TER values for organisms inhabiting adjacent 1 m deep drainage channels, assuming 4% spray drift would all be well above trigger values.

An important source of uncertainty in all of the above TER calculations for cyhalofop-butyl is that effect concentrations are based on a minimum exposure period of 24h, whereas exposure concentrations in the field are expected to decline markedly during this time period. For fish, TER values based on initial PECs indicate an unacceptable risk, but those based on PECs 24h following application are well above the trigger values (SCP/CYHALO/006, p. 79). The extent to which TERs based on initial PECs overestimate risk is unclear from the

[9] Toxicity over exposure ratio.
[10] Predicted environmental concentration in surface water.

data provided because it is partly dependent on the rate at which the LC_{50} declines during the first 24h of exposure. As a general rule, effect concentrations decline with exposure period, though at widely varying rates, depending on the chemical's mode of action, uptake route, etc. For cyhalofop-butyl, toxic effects appear very quickly. In bluegill sunfish the $L(E)C_{50}$ does not appear to decline substantially between 24h (the earliest time at which LC_{50} was calculated) and 96h (Jenkins 1997, J14), and after as little as 2 hours of exposure to 2.3 mg/l all fish were observed to show signs of hyperventilation and loss of coordination. Likewise, the LC_{50} of cyhalofop-butyl to *Daphnia magna* declined very little between 24h (EC_{50}=3.8 mg/l) and 48h (EC_{50}=3.62 mg/l) (Jenkins 1996, MJ03). There was 100% immobility of *Daphnia* exposed to an initial measured (acid + ester) concentration of 8.02 mg/l in a static test, giving a TER of 8.02/0.3=26.7, which is well below the 'acceptable' trigger of 100. In summary, without knowing the rate at which the $L(E)C_{50}$ declines during the first 24h of exposure, it is impossible to determine by how much the ratio of 24h $L(E)C_{50}/PEC_{initial}$ overestimates risk.

The TER values for daphnids and algae within paddy fields following terrestrial application to drained paddies are above critical values, whereas the TER for fish (59) is below the critical trigger of 100. However, several lines of evidence suggest that risks to fish within paddy fields following terrestrial application to drained paddies may be considered acceptable:

- As indicated above, the initial TER of 59 is likely to increase markedly during the first day of exposure due to rapid breakdown and partitioning of the parent giving an additional margin of safety for fish re-entering the paddy;
- Results of a field study with Japanese carp at 1 and 2x the maximum application rate showed no detectable effects on caged fish that were placed inside the paddy field either immediately or after 1, 3, or 5 days following application (Nakamura 1995, Ref. J12);
- In the documentation provided to the Committee (SCP/CYHALO/006; p. 78) it is stated that 'Typically, application is made to the drained field which is then re-flooded approximately 2 days later.' The TER value of 59 in Table 3 assumes that the paddy was refilled after 24h and would therefore overestimate exposure for situations in which more time elapses prior to re-flooding.

Acute effects of the metabolites, cyhalofop-ACID, cyhalofop-AMIDE and cyhalofop-DIACID generally occur at concentrations two orders of magnitude higher than for the parent compound in those aquatic organisms that have been investigated (SCP/CYHALO/003; p. 29). Given that the initial PEC_{sw}s of the metabolites will be no higher that those of the parent compound for any application scenario, and given that the metabolites are not persistent, risks to aquatic organisms from exposure to metabolites are not likely to be any greater than risks estimated for the parent compound for any given scenario. TER calculations for the metabolites (SCP/CYHALO/006, p. 81) confirm low risk to aquatic organisms.

On the basis of the TER values shown in Table 3, the Committee concludes that terrestrial application to either flooded or drained paddy fields at a maximum rate of 300 g a.s./ha is not likely to pose an unacceptable risk to aquatic organisms occupying adjacent surface water. It can also be confirmed that terrestrial application to drained paddies (allowing a minimum of 24 hours before re-flooding) is not likely to pose an unacceptable risk to aquatic organisms within the paddy field. However, aerial application may pose an unacceptable risk to aquatic organisms both within paddies and in adjacent surface waters, and terrestrial application to flooded paddies may pose an unacceptable risk to aquatic organisms within the paddy fields.

4.1.4 Risk assessment for non-target arthropods

Cyhalofop-butyl was tested for effects on bees and on several crop-relevant arthropod species. Hazard quotients for bees were estimated for contact (< 3) and oral (< 7.5) exposure to the formulation (EF-1218) and were below the Annex VI trigger of 50. Exposure to the formulated product (EF-1218) at 300 g a.s./ha caused 100% mortality to the predatory wasp, *Aphidius rhopalosiphi*, when applied to artificial substrates in the laboratory but only 8% mortality when applied to a natural substrate of barley seedlings. Laboratory tests with five other species at the same exposure concentration gave the following mortalities: *Orius laevigatus*, 10%; *Pardosa spp*., 10%; *Poecilus cupreus*, 3%; and *Lepthyphantes tenuis*, 30%. The Annex VI trigger for these kinds of test, is 30%, and thus the observed levels of mortality would be classified as "harmless". On the basis of these results it was concluded by the Rapporteur Member State that when used under conditions of good agricultural practice, cyhalofop-butyl is unlikely to be harmful to the majority of non-target arthropod species present in European rice crops.

Laboratory tests on the predatory mite *Typhlodromus pyri* at 1x and 2x application rates resulted in 82% and 93% mortality after 7 days respectively, compared to 14% in controls. Differences in fecundity per surviving female compensated for this mortality to a degree (6.08 and 5.28 eggs/female respectively compared to 3.01 in the control), resulting in the classification of "slightly/moderately harmful". Therefore, an extended test on this species should have been triggered.

The justification of the notifier for not conducting an extended laboratory test on *Typhlodromus* (class Arachnida, order Acari) is based on the fact that such a test (using grape vines, for instance) would not have been particularly relevant to rice. This is of course correct (*T. pyri* is primarily a beneficial within fruit crops), but it should be noted that: (i) there are important arachnids within these agroecosystems (e.g., Hidaka 1997, Oraze *et al.* 1988, Tanaka *et al.* 2000) and (ii) the overall sensitivity of this species has recently led to a recommendation that it be employed as one of two primary "indicator species" (ESCORT[11] 2000). While laboratory tests on another Arachnid, the linyphiid spider *Lepthphantes tenuis* (order Araneae) generated only "harmless, or slightly harmful" classifications, it should be also noted that mortality was *at*, or higher, than the trigger value (30% and 75% at 1x and 2x concentration respectively, compared to 0% controls) and that these trials involved relatively few spiders ($n \leq 10$). Given the inconclusiveness of these results, the Committee recommends that some form of extended study, either with *T. pyri*, *L. tenuis* or another predatory arachnid (such as a lycosid) be conducted to allow a better assessment of risk to members of this taxonomic group.

In summary, cyhalofop-butyl applied at a maximum of 300 g a.s./ha under conditions of good agricultural practice is unlikely to be harmful to bees. However, there remains some uncertainty with regard to other non-target arthropods which should be addressed by an extended test on an appropriate predatory arachnid species.

[11] European Standard Characteristics Of non-target arthropod Regulatory Testing.

4.2 Question 2

"Can the Committee confirm that the operator exposure has been sufficiently addressed?"

<u>Opinion of the Committee:</u>

The Committee is of the opinion that the operator exposure to cyhalofop-butyl has been adequately addressed.

<u>Scientific background on which the opinion is based</u>:

Cyhalofop-butyl has not demonstrated a carcinogenic, genotoxic, developmental, reproductive, or neurotoxic potential in experimental animals. In both short- and long-term studies the target organ was the liver which increased in weight with associated hepatocellular hypertrophy occurring at comparable dose-levels. Increased kidney weight and alteration of some blood clinical chemistry parameters were also observed in long term studies in certain species or sexes.

The NOAELs[12] in 13-week studies were 3 (rats and mice, based on increased liver weight and hepatocellular hypertrophy), and 3.2 (dogs, based on increased liver weight in females) mg/kg bw[13] per day and those in long-term studies were 0.3 (mice, based on microgranulomas in liver in females) and 0.8 (rats, based on increased kidney weight and deposition of brown pigment in renal proximal tubules in males) and 1.2 mg/kg bw per day in one-year dog study (based on reduced body weight gain and sandy material in gall bladder).

Studies on dermal absorption in rats showed that cyhalofop-butyl concentrate and spray formulation are absorbed after 24 hours of occlusive application by 16% and 25% on average, respectively. Comparative human: rat skin *in vitro* experiments showed that rat skin is approximately 12-times and approximately two times more permeable than human skin to the concentrated and spray formulation, respectively. When these *in vitro* ratios are used to adjust the *in vivo* rat data, 1.3% and 11% are approximately the rates of absorption which can be extrapolated to the human situation for the concentrated and spray solution, respectively.

Operator exposure was estimated as based on the UK POEM[14], the German model for tractor application, and the USA PHED[15] for aerial application. Modifications of the value of some default parameters (20 ha/day instead of 50 ha/day, and body weight of 70 kg) did not substantially affect the estimation of the exposure which was found to be up to 114% of the AOEL according to the UK model (based on a spray volume of 100 l/ha and the assumption that gloves are worn; exposure was found to be up to 40% if the spray volume is of 300 l/ha) and 73% according to the German model. For aerial application, the estimation of exposure was found to be up to 6% of the AOEL according to the PHED model. The SCP is of the opinion that the overall assessment indicates an acceptable margin of safety.

The Committee concluded that the operator exposure has been adequately addressed.

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[12] No observed adverse effect levels.
[13] Body weight.
[14] Pesticide operator exposure model.
[15] Pesticide handler's exposure data.

5. REFERENCES

1. ESCORT (2000). Guidance document on regulatory testing and risk assessment procedures for plant protection products with non-target arthropods. Candolfi MP, *et al.* (eds). European Standard Characteristics Of non-target arthropod Regulatory Testing (ESCORT) 2 Workshop, Wageningen, Netherlands 21-23 March 2000.

2. Hidaka, K. (1997) Community structure and regulatory mechanism of pest populations in rice paddies cultivated under intensive, traditionally organic and lower input farming in Japan. Biological Agriculture and Horticulture, 15, 35-49.

3. Jenkins CA. 1996. EF-1218: Acute toxicity to *Daphnia magna*. Huntingdon Life Sciences. Biblio. Ref. MJ03.

4. Jenkins CA. 1997. DE-537 Technical: Acute toxicity of DE-537 to bluegill sunfish. Huntingdon Life Sciences, Biblio. Ref. J14).

5. Oraze, M.J., Grigarick, A.A., Lynch, J.H. & Smith, K.A. (1988) Spider fauna of flooded rice fields in northern California. Journal of Arachnology 16, 331-337.

6. Tanaka, K. Endo, S. & Kazano, H. (2000) Toxicity of insecticides to predators or rice planthoppers: spiders, the mirid bug and the dryinid wasp. Applied Entomology and Zoology, 35, 177-187.

6. DOCUMENTATION MADE AVAILABLE TO THE COMMITTEE

1. Evaluation of cyhalofop-butyl in the context of directive 91/414/EEC concerning the placing of plant protection products on the market. Terms of reference (Doc. SCP/CYHALO/001 submitted by DG SANCO 8 August 2000).

2. Cyhalofop-butyl: list of end points (Doc. SCP/CYHALO/003 submitted by DG SANCO 16 November 2000).

3. Gap forms on both food and feed crops and non food and feed corps in the territory of EU (Doc. SCP/CYHALO/004 submitted by DG SANCO 16 November 2000).

4. Cyhalofop-butyl: Comments from Sweden 12. 1.2000 (Doc. SCP/CYHALO/005 submitted by DG SANCO 16 November 2000).

5. Cyhalofop-butyl: Addendum to the Monograph, March 2000 (Doc. SCP/CYHALO/006 submitted by DG SANCO 16 November 2000).

6. Cyhalofop-butyl: Evaluation table - Doc. 6484/VI/99 rev. 7 (12.07.2000) (Doc. SCP/CYHALO/007 submitted by DG SANCO 16 November 2000).

7. Cyhalofop-butyl: draft evaluation report (monograph) prepared by Italy, as Rapporteur Member State (Volumes 1 to 3) – November 1998.

7 ACKNOWLEDGEMENTS

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Environmental assessment WG: Prof. Hardy (Chairman) and Committee members: Mr. Koepp, Prof. Leszkowicz, Dr. Sherratt, Prof. Papadopoulou-Mourkidou, Prof. Silva Fernandes, and invited experts: Dr. Boesten, Dr. Carter, Dr. Forbes, Dr. Hart, Dr. Luttik.

Toxicology WG: Prof. Maroni (Chairman) and Committee members: Dr. Delcour-Firquet, Prof. Leszkowicz, Dr. Meyer, Dr. Moretto, Dr. Petzinger, Prof. Savolainen, Prof. Silva Fernandes, Dr. Speijers and invited experts Dr. Fait, Dr. McGregor.