Opinion of the Scientific Committee on Plants regarding the evaluation of *Flupyrsulfuron-methyl* in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market (opinion adopted by the Scientific Committee on Plants on 30 November 2000)

1. TITLE

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS REGARDING THE EVALUATION OF FLUPYRSULFURON-METHYL IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC CONCERNING THE PLACING OF PLANT PROTECTION PRODUCTS ON THE MARKET

(Opinion adopted by the Scientific Committee on Plants on 30 November 2000)

2. TERMS OF REFERENCE

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

(1) Can it be confirmed that the uses reviewed are acceptable for the aquatic environment and for earthworms?

(2) Can it be confirmed that use scenarios exist which pose no unacceptable risk to groundwater?

3. BACKGROUND

The draft Commission Directive for inclusion of flupyrsulfuron-methyl (DPX-KE459) 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.

In order to prepare the opinion the Committee had access to documentation consisting of a Monograph prepared by France as Rapporteur Member State based on a dossier submitted by the notifier (Dupont de Nemours), and a review report prepared by the Commission and the recommendation of the ECCO [1] Peer Review program.

Flupyrsulfuron-methyl is a post emergence selective herbicide belonging to the sulfonylurea class. It is for use in agricultural field situations only acting primarily through foliar uptake with little or no soil activity. Flupyrsulfuron-methyl affects sensitive weeds through inhibition of the enzyme acetolactate synthetase, which leads to the cessation of cell division and subsequent growth processes in plants. Flupyrsulfuron-methyl is used to control annual grass and broad-leaved weeds in winter and spring cereals and can be applied once per crop and season at a maximum rate of 12g a.s./ha.

4. OPINION

4.1 Question 1

"Can it be confirmed that the uses reviewed are acceptable for the aquatic environment and for earthworms?"

Opinion of the Committee:

It is the Committee's opinion that the proposed uses of flupyrsulfuron-methyl, i.e., at a maximum application rate of 12 g a.s./ha, applied once per crop and per season, will not pose an unacceptable risk to the aquatic environment. Newly submitted data allowed the SCP to conclude that no significant long term risks to earthworms are likely arise from the use of flupyrsulfuron-methyl at the recommended treatment rate.

Scientific background on which the opinion is based:

4.1.1 Degradation in soil

The active substance, flupyrsulfuron-methyl (DPX-KE459), occurs predominantly as a salt though conversion to the acid form DPX-JE138 is governed by the acid dissociation constant pK_a [2]. At environmentally relevant pH's (>5) the salt predominates. Laboratory degradation was rapid (DT50 [3] 8-26 days and DT90 27-85 days). In field dissipation trials the DT50 was 6-11 days and DT90 35-123 days.

DPX-KE459 degrades predominantly to the metabolite IN-JV460. The maximum DT50 for the metabolite IN-JV460 in laboratory soils was 373 days, although after further modelling this figure was revised to 120 days. The estimated DT50 values for the metabolite in field soils were 49-231 days for IN-JV460 (longer half-lives relate to spring applications) with a peak of 13-23% applied radioactivity (AR). Parallel laboratory work investigating aerobic degradation of the radio labelled test substance in soil extracts, similarly found that the % applied radio label reached a peak of 23.9 % after 63 days.

The maximum DT50 for the metabolite IN-KC576 in laboratory soils was 248 days, although after further modelling this figure was revised to 30 days. In several European field trials it was not detected as a major metabolite but the DT50 of this metabolite was estimated in a US field trial to be 150 days, with a peak of 58% applied radioactivity. Parallel laboratory work found that this product reached a peak of 8.8% after 30 days.

Table 1. DT50 and DT90 values of flupyrsulfuron-methyl and two soil metabolites

Analyte	DT50 lab	DT90 lab	DT50 field	DT90 field
DPX-KE459	8-26	27-85	6-11	35-123
IN-JV460	120/373		49-231	
IN-KC576	30/248		150	

In the European field dissipation studies IN-JV460 was the major soil metabolite (maximum of 27% AR, average of both radio labels) . In the US field study significant amounts of both IN-JV460 (maximum 23%, AR, average of both radio labels) and IN-KC576 (maximum of 58%, AR, average of both radio labels) were formed.

4.1.2 Aquatic environment

Flupyrsulfuron-methyl is toxic to fish and *Daphnia* at concentrations in the mg/l range and is therefore not likely to pose an unacceptable risk to these groups under the reviewed uses. As with other sulfonylurea herbicides, algae and aquatic plants (i.e., *Lemna gibba*) were the most sensitive of the aquatic species tested. Values for the acute EC50 [4] and NOEC [5] of flupyrsulfuron-methyl to *Selenastrum capricornutum* were 3.7 and 0.51 microgram/l, respectively, for the technical active substance (or 9.1 and 1.61 microgram/l for the 50% WG formulation). The 14 day EC50 and NOEC for *Lemna gibba* were 2.5 microgram/l and 0.49 microgram/l, respectively (technical active substance). Despite the high sensitivity of *Selenastrum capricornutum* and *Lemna gibba* to flupyrsulfuron-methyl, reasonable worst case PECsw [6] estimates (i.e., 0.03 microgram/l) indicated that risks to algae and aquatic plants would not be unacceptable (i.e., TER > 10) given the proposed usage pattern of one application per growing season.

The three most important metabolites formed in water/sediment studies or in an aqueous photolysis experiment (at pH 7) were IN-JV460, IN-KF526 and IN-KV994. The metabolites IN-JV460 and IN-KC576 were the most important metabolites formed in laboratory and field soil studies. It is the SCP's opinion that all of these metabolites need to be evaluated with respect to aquatic organisms as they may either be formed in (IN-JV460, IN-KF526, IN-KV994) or transported to (IN-JV460 and IN-KC576) the aquatic compartment [7].

The acute toxicity of IN-JV460 to fish and *Daphnia* was considered to be adequately covered in tests with the parent compound. For the two remaining metabolites formed in water studies, no acute effects in fish or *Daphnia* were detected at the highest concentrations tested [i.e., these were: IN-KV994, 1 microgram/l for both fish and *Daphnia*; IN-KF526: 100 microgram/l (fish) and 500 microgram/l (*Daphnia*)]. The toxicity of IN-JV460 to *Selenastrum capricornutum* was reported to be less than for the parent compound (i.e., EC50=10.1 microgram/l). There were no toxicity data for algae or aquatic plants provided for IN-KF526 or IN-KV994. However, as neither of them retains an intact sulfonylurea bridge, they are not considered to be more toxic to these groups than the active substance. IN-KC576 was tested for insecticidal activity and evaluated for its effects on earthworms (see below), but it was not tested for toxicity to aquatic organisms. However, the SCP is of the opinion that this metabolite will not pose an unacceptable risk for aquatic organisms because 1) it lacks an intact sulfonylurea bridge and should therefore be less toxic to aquatic plants and algae than the parent compound, and 2) this metabolite showed low toxicity to non-target (terrestrial) invertebrates.

4.1.3 Earthworms

The parent compound has a variety of metabolites in soil: IN-JV460 and its derivative IN-KC576 are the primary metabolites, although other metabolites IN-KV996, IN-KF311 and IN-KY374 have been detected in degradation studies.

Ecotoxicity:

Earthworms *(Eisenia fetida* andrei) were exposed for 14 days to artificial soil treated with flurpyrsulfuron-methyl at 1000 mg a.s./kg soil (14 replicates with 10 individuals, including 4 replicates as controls). There were no significant differences in mortality and weight change between treatments and controls and there were also no signs of abnormal behaviour. The test dose employed was unrealistically high compared to the maximum predicted environmental concentration of the parent in the soil (highest estimate of the maximum PECsoil [8] 0.024 mg/kg soil).

Basis for decision:

i. Annex II criteria propose that a long-term sub-lethal test on the parent compound is not required if both the DT90 [9] (field) is less than 100 days and the number of applications is less than 3, and
ii. metabolites which reach a concentration greater than a pragmatic 10% of the dose applied should also be tested for long-term sublethal effects, unless they are formed so rapidly that potential effects are covered by the available earthworm tests for the parent compound [10].

Given that:

i. flupyrsulfuron-methyl will be applied once per year,
ii. the *mean* DT90 (field) is less than 100 days, and that
iii. no sublethal effects were observed when earthworms were exposed to unrealistically high concentrations,

the SCP is of the opinion that no further evaluations of the sub-lethal effects of the parent compound on earthworms are needed.

Of all the metabolites, IN-JV460 consistently reached a peak of > 10% in European and American field studies, typically after several weeks. Where it was observed, IN-KC576 similarly reached peak concentrations > 10%. In theory (and most likely in practice), the unrealistically high concentrations used in the original test meant that earthworms were exposed to much higher concentrations of metabolites for 2 weeks from day 0 than the maximum concentration they are likely to be exposed to under field conditions. However, the SCP also notes that:

i. IN-KC576 is likely to be formed by the microbial degradation of IN-JV460. Given that artificial soils were used, we are uncertain whether IN-KC576 would indeed be capable of forming at realistic rates under the test condition, and that
ii. in general, there is often somewhat slower degradation of plant protection products at high concentrations (for example, chlorothalonil degrades to a hydroxy metabolite, which can inhibit the degradation of the parent compound if the metabolite concentration is sufficiently high). Given that extremely high concentrations were used, it is possible that the rates of degradation differed significantly from field situations [11].

Overall, since Annex II limits are exceeded and there is some question of the validity of the specific 14 day test for assessing long-term effects of metabolites, the SCP had provisionally recommended that an appropriate long-term test be conducted to evaluate the sublethal effects of flupyrsulfuron-methyl metabolites on earthworms.

In the recently submitted sub-lethal study, adult earthworms (*Eisenia fetida*) were exposed to two concentrations of the flupyrsulfuron-methyl metabolite IN-JV460 in artificial soils at rates equivalent to 1x and 5x times a proposed maximum PEC for the metabolite of 10 g IN-JV460/ha, i.e. 0.013 and 0.065 mg IN-JV460/kg dry soil. After 28 days exposure the adult worms were counted and weighed and the soil replaced with fresh soil (untreated). After a further 28 days the soil was examined for juveniles. No mortality was observed in the study, and the body weights of earthworms did not differ significantly from the controls. Similarly, the number of juveniles produced by the end of the study did not differ significantly.

The rate at which IN-JV460 is likely to break down to IN-KC576 in the above laboratory test is not known, but given the data provided in the two separate studies, it is highly unlikely that a single use of flupyrsulfuron-methyl at the recommended application rate will pose a significant risk to earthworms. The steady-state concentrations of flupyrsulfuron-methyl and its two metabolites following repeated use can be estimated by incorporating degradation data into a simple first-order kinetic model (plough layer 25 cm and dry bulk density of 1.3 kg/l). This calculation results in estimates of 0.56 micrograms/kg soil for parent, 2.4 micrograms/kg for IN-JV460 and 1.6 micrograms/kg for IN-KC576. Thus, the parent degrades so quickly that only a negligible steady state concentration builds up. If we use the NOEC of > 0.065 mg JV460/kg soil for both main metabolites then the minimum long-term TER for the main metabolites is 27.083. Given that this estimated figure is well above the standard trigger value, the SCP is of the opinion that no significant long-term risks will arise from the use of flupyrsulfuron-methyl at the recommended rate.

4.2 Question 2

"Can it be confirmed that use scenarios exist which pose no unacceptable risk to groundwater?"

Opinion of the Committee:

On the basis of field studies and the modelling data presented, neither flupyrsulfuron-methyl nor its metabolite IN-JV460 are likely to contaminate groundwater in excess of 0.1 µg/l. Insufficient data are available to reliably state that the metabolite IN-KC576 will not leach to groundwater in concentrations in excess of 0.1 µg/l. Predictions using worst case input parameters and the Dutch standard modelling scenario, indicate that the concentration of the metabolite is unlikely to exceed 0.4 µg/l. The SCP toxicological assessment indicates that there will be no direct health risk from the expected level of this metabolite in groundwater. The SCP is therefore of the opinion that use scenarios exist, which pose no unacceptable risk from drinking water derived from groundwater.

Scientific background on which the opinion is based

4.2.1 Sorption and leaching:

Flupyrsulfuron-methyl and its metabolites are weakly sorbed to soil and Koc [12] values for the active substance and the two metabolites are shown in Table 2.

Table 2. Koc values of Flupyrsulfuron-methyl and two soil metabolites

Analyte	K_{oc}
DPX-KE459	**15-23**
IN-JV460	**148-202**
IN-KC576	**19-26**

In an aged soil column leaching study DPX-JE138 constituted 2-6% and IN-JV460 16-32% of radioactivity in leachate with higher values relating to fast water fluxes (19.2ml hr^{-1}). No lysimeter studies were carried out based on the rapid field degradation of flupyrsulfuron-methyl (DT50 6-11 days) and there was no detection of any radioactivity below 60 cm in field soil dissipation studies.

4.2.2 Further assessment:

Sorption and field dissipation data indicated that the metabolites IN-JV460 and IN-KC576 can be produced in excess of 10% of the applied active substance and may have the potential to leach to groundwater. As a consequence of this assessment additional studies were requested by ECCO. The applicant submitted predictive modelling studies and subsequently responded to specific questions raised by the SCP concerning input parameters and scenario characterisation. Following continued uncertainty an assessment of the toxicity of the metabolite IN-KC576 was carried out by the SCP to determine its relevance with regard to groundwater contamination.

4.2.3 Predictive modelling

Extensive modelling data, not described in the monograph but submitted to ECCO, using PRZM-2, shows no potential for the active substance to contaminate groundwater above 0.1 µg/l. Additional modelling studies have been carried out to determine whether the two metabolites have the potential to contaminate groundwater in excess of 0.1 µg/l. Given that the modelling predictions were fundamental in determining whether the two soil metabolites pose an unacceptable risk to groundwater, the SCP was concerned that the choice of input parameters and scenarios for the modelling differed from the field study data presented, were not fully explained and therefore requested justification on a number of points. The applicant provided a comprehensive explanation and further study reports to support the basis for their choice of parameters. On the basis of these data the SCP was satisfied that the active substance and the metabolite IN-JV460 were unlikely to pose an unacceptable risk to groundwater.

The metabolite IN-KC576 appeared at a maximum concentration of 58% in the US study with a quoted half-life of 150 days. The predictive modelling study used a different half-life on the basis that the value derived in the field study was from a very poor fit due to highly variable experimental concentrations. In order to use any of the current predictive models the SCP acknowledges that it is necessary to use degradation data based on first-order kinetics and therefore the applicant fitted a first-order analytical equation to the experimental data using conventional least-squares-fit criteria to derive the 30 day half life used in the prediction. The metabolite was not found to be significant under European field study conditions (maximum 6.6%) and no further assessments of half-life were made for these studies. The uncertainty in

the variable generation of the metabolite and the possibility that the half life may be in excess of 30 days have led the SCP to the opinion that there is insufficient data to confirm that IN-KC576 will not exceed 0.1µg l^{-1} in groundwater. The SCP has therefore carried out a basic modelling using the Dutch standard scenario and worst case input parameters. The following assumptions have been made:

- the percentage of IN-KC576 formed was 58%;
- DT50 of 248 days (p. 131 of the Monograph);
- Kom [13] of 11 l/kg, based on Koc of 19 l/kg (lowest of the range);
- Application rate of 12 g a.s. ha^{-1};
- the calculation was made for 1 kg/ha giving 70.5 µg/l in groundwater;
- the actual dose of 12 g/ha was multiplied with the percentage formed and with the ratio between the molar masses of metabolite divided by parent, (357.2/487.4 = 0.73) which gives a "dose" for this metabolite of 5.1 g/ha;
- the estimated concentration in groundwater for the Dutch standard scenario is therefore 70.5*0.0051=0.4 µg/l.

4.2.4 Safety assessment of a metabolite IN-KC576 in groundwater.

The major biotransformation pathway for flupyrsulfuron-methyl forms IN-JV460 and the subsequent -desmethyl product, IN-KC576. For rat administered orally with flupyrsulfuron-methyl there are two urinary metabolites, the -desmethyl rearranged tricyclic component IN-KC576, and the pyridin mercapturic acid derivative IN-KW004. The IN-KC576 metabolite was present in higher proportions in females (8-14 %) than in males (5-9%) and, expressed as a percentage of the administered dose, was the metabolite with the largest presence. There are no toxicological data available on the metabolite IN-KC576 of flupyrsulfuron-methyl to enable a direct safety assessment of this metabolite.

However, IN-KC576 as the major metabolite of flupyrsulfuron-methyl is formed to roughly 10 % of the administered dose. Thus the metabolite can be considered to have been tested in the toxicity studies performed with the parent compound. If IN-KC576 was responsible for the toxic response seen with flupyrsulfuron-methyl then the NOAEL [14] used to derive the ADI [15] expressed as mg IN-KC576 would be 3.5/10 =0.35 mg kg bw [16] /day. The ADI would be 0.0035 mg/kg bw/day compared to the 0.035 mg/kg bw/day for flupyrsulfuron-methyl. In case IN-KC576 is not the only metabolite responsible for the toxicity, an ADI for the metabolite IN-KC576 would be expected to be higher. Therefore, with respect to the leaching of metabolites to groundwater which can be used to supply drinking water, it can be concluded that there is no direct health risk if the level reaching the groundwater is below 105 µg/l water (0.0035 mg/kg x 1 x 60 kg/2 litres).

5. REFERENCES

- 1. Opinion of the Scientific Committee on Plants regarding the draft guidance document on relevant metabolites (Document SANCO/221/2000-rev2) adopted on 30 November 2000

6. DOCUMENTATION MADE AVAILABLE TO THE COMMITTEE

- 1. Terms of reference: Evaluation of flupyrsulfuron-methyl in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market (Doc. SCP/FLUPYR/001-Rev.1) - submitted 3 August 1999.
- 2. "Model assessment of the potential groundwater concentrations of flupyrsulfuron-methyl (DPX-KE459) and its major degradates for 32 years of continuous use" - D. Esterly, E.I du Pont de Nemours and Company, 29 April 1999 (Doc. SCP/FLUPYR/003) - submitted 20 December 19999.
- 3. Questions from the SCP to the Notifier (Doc. SCP/FLUPYR/004) - submitted 31 January 2000.
- 4. Response from the Notifier to clarification sought by the SCP relating to the evaluation of flupyrsulfuron-methyl (Doc. SCP/FLUPYR/006) - submitted 8 February 2000.
- 5. "Position paper for flupyrsulfuron-methyl: calculation of half-lives of IN-JV460, the major soil degradate of flupyrsulfuron-methyl, under field conditions", S. Koch Singles, E.I. du Pont de Nemours and Company, 2 February 2000 (doc. SCP/FLUPYR/007) - submitted 8 February 2000.
- 6. Flupyrsulfuron-methyl: Draft review report 5050/VI/97-rev.2, 5 September 1999 (Doc. SCP/FLUPYR/008) - submitted 31 May 2000.
- 7. Evaluation of flupyrsulfuron-methyl in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market: appendices, 4 June 1999 (Doc. SCP/FLUPYR/009) - submitted 4 June 2000.
- 8. Evaluation of flupyrsulfuron-methyl in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market: Evaluation table, 5051/VI/98-rev.7, 2 June 1999 (Doc. SCP/FLUPYR/010) - submitted 19 June 2000.
- 9. "IN-JV460 (Metabolite of flupyrsulfuron-methyl): effects on reproduction and growth of earthworm, *Eisenia fetida* (Savigny, 1826), in artificial soil" Final report - U. Lührs, Institut für Biologische Analytik und Consulting IBACON Gmbh, 19 July 2000 [Submitted by du Pont de Nemours] (Doc. SCP/FLUPYR/011) - submitted 11 August 2000.
- 10. Flupyrsulfuron-methyl and its two metabolites: steady state concentration, submitted by Dr. Boesten. (Doc. SCP/FLUPYR/012) - 5 October 2000.
- 11. Flupyrsulfuron-methyl: Monograph prepared in the context of the inclusion of the Flupyrsulfuron-methyl in Annex I of Council Directive 91/414/EEC. Ministère de l'Agriculture, de la Pêche et de l'Alimentation, Direction générale de l'alimentation. France. October 1997. (Volumes 1, 2, 3 & 4).

7. ACKNOWLEDGEMENTS

The Committee wishes to acknowledge the contributions of the working group that prepared the initial draft opinion:

Environmental assessment WG: Prof. Hardy (Chairman) and Committee experts: Mr. Koepp, Dr. Nolting, Dr. Sherratt, Prof. Silva Fernandes, and invited experts: Dr. Boesten, Dr. Carter, Dr. Forbes and Dr. Luttik.

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

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[1] European Community Co-ordination.
[2] Dissociation Constant.
[3] Period required for 50% dissipation.
[4] Median effective concentration.
[5] No observed effect concentration.
[6] Predicted environmental concentration in surface water.
[7] See ref. 1 Opinion of the SCP on the draft guidance document on relevant metabolites.
[8] Predicted environmental concentration in soil.
[9] Period required for 90% dissipation.
[10] See also the SCP opinion on guidance document for relevant metabolites.
[11] See SCP opinion on guidance document for relevant metabolites.
[12] Organic carbon adsorption coefficient
[13] Organic matter adsorption coefficient.
[14] No observed adverse effect level.
[15] Acceptable daily intake.
[16] Body weight.