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SCIENTIFIC COMMITTEE ON PLANTS

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OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON SPECIFIC QUESTIONS FROM THE COMMISSION CONCERNING THE EVALUATION OF FAMOXADONE [DPX-JE874] IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC

(Opinion expressed by the Scientific Committee on Plants, 20 July 2001)

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A. TITLE

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS ON SPECIFIC QUESTIONS FROM THE COMMISSION CONCERNING THE EVALUATION OF FAMOXADONE [DPX-JE874] IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC
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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. The Committee is requested to comment whether the long-term risk to Daphnia, in particular in relation to metabolites, has been sufficiently addressed.

2. Can the Committee confirm that the risk from the metabolites IN-KZ007 and IN-JS940, to earthworms, has been sufficiently addressed?

3. Can the Committee comment on the relevance of the eyes effect observed in the 12 months dog study to human? Should mechanistic study on eyes be required?

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

C. OPINIONS

Question 1

The Committee is requested to comment whether the long-term risk to Daphnia, in particular in relation to metabolites, has been sufficiently addressed.

Opinion of the Committee:

The Committee concludes that the long-term risk to Daphnia of famoxadone and its metabolites has been sufficiently addressed. Famoxadone is acutely toxic to both fish and Daphnia, and therefore substantial risk mitigation measures would be necessary to prevent unacceptable acute effects of the active substance from occurring in aquatic organisms. Such buffer zone would be sufficient to cover chronic risk to Daphnia from famoxadone or its metabolites.

Question 2

Can the Committee confirm that the risk from the metabolites IN-KZ007 and IN-JS940, to earthworms, has been sufficiently addressed?

Opinion of the Committee:

On the basis of the submitted data, the SCP considers that the metabolites IN-KZ007 and IN-JS940 are unlikely to present an acute risk to earthworms. However no longer-term sub-lethal tests have been conducted, so the Committee is unable to evaluate the likely

chronic risks of the parent substance or metabolites to earthworms when the number of applications per season is high (> 6).

Question 3

Can the Committee comment on the relevance of the eyes effect observed in the 12 months dog study to human? Should mechanistic study on eyes be required?

Opinion of the Committee:

Available data show that famoxadone is clearly cataractogenic in Beagle dogs, while milder effects were seen in rats and no effect in monkeys and in mice. The mechanism of action is unknown. The provided data are not sufficient to support a species specificity of cataract induction in dogs. Therefore, the Committee is of the opinion that the eye effect of famoxadone in dogs is to be considered relevant for humans. This opinion could be revised with a more complete understanding of the mechanism of action of famoxadone on the eyes in the various species.

Question 4

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

Opinion of the Committee:

The Committee is of the opinion that the risk to operator has not been adequately assessed and needs to be reassessed using the AOEL derived from the NOAEL based on cataracts induction in dogs (see opinion on question 3).

A. TITLE

REPORT OF THE SCIENTIFIC COMMITTEE ON PLANTS ON SPECIFIC QUESTIONS FROM THE COMMISSION CONCERNING THE EVALUATION OF FAMOXADONE [DPX-JE874] IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC

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C. BACKGROUND

Famoxadone is a new active substance (a.s.) in the context of Council Directive 91/414/EEC[1]. A draft evaluation report (monograph) has been prepared by the Rapporteur Member State (RMS, France) on the basis of a dossier presented by the notifier (DuPont). In order to prepare its opinion the Scientific Committee on Plants had access to this draft evaluation report, the evaluation table and other documents listed below.

Famoxadone is a new fungicide proposed to control fungal diseases, such as potato blight, tomato late blight in horticulture, downy mildew in viticulture as well as cereal diseases (eyespots, Septoria, yellow and brown rusts, powdery mildew, etc.). Famoxadone belongs to the group of phenylamide fungicides known to inhibit mycelial growth and zoospore survival of various Oomycete fungi. It is intended for use at a maximum dose of 280 g a.s./ha in cereals and 90 g a.s./ha in grapes (up to 12 times/season) and tomatoes (up to 8 times/season).

Source documents made available to the Committee:

1. Famoxadone – Terms of reference submitted by DG Health & Consumer Protection, 7 August 2000 (SCP/FAMOX/001).
2. Famoxadone – Addendum to the evaluation table section 1 physico and chemical properties submitted DG Health & Consumer Protection, 11 December 2000 (SCP/FAMOX/003).

[1] OJ N° L 230, 19. 8.1991, p. 1.

3. Famoxadone – Evaluation table doc. 6489/VI/99 rev5 12-07-2000, submitted by DG Health & Consumer Protection, 7 August 2000 (SCP/FAMOX 004).

4. Famoxadone – Addendum to Volume 3 physical and chemical properties, 01.08.2000 submitted by DG Health & Consumer Protection, 12 October 2000 (SCP/FAMOX/005).

5. Famoxadone – Second addendum to the monograph, Ecotoxicology sections 02-10-2000, submitted by DG Health & Consumer Protection, 12 October 2000 (SCP/FAMOX/006).

6. Famoxadone - End points ecotoxicology, 02-10-2000 submitted by DG Health & Consumer Protection, 12 October 2000 (SCP/FAMOX/007).

7. Famoxadone – RMS comments concerning question 1 to the SCP, 10 October 2000, submitted by DG Health & Consumer Protection, 8 January 2001 (SCP/FAMOX/008).

8 Famoxadone – Appendices I, II and III to end points, June / October 2000, submitted by DG Health & Consumer Protection, 8 January 2001 (SCP/FAMOX/009)

9. Famoxadone – Letter from notifier, list of additional data available, 30 August 2000, submitted by Notifier, 30 August 2000 (SCP/FAMOX/010).

10. Famoxadone – Notifer comments on questions referred to the SCP, submitted by Notifier, 2 February 2001 (SCP/FAMOX/011).

11. Famoxadone: draft evaluation report (volumes 1 to 3) prepared by France, Rapporteur Member State, July 1998.

12. Famoxadone: Ecotoxicology end points, 26 Feb 2001, submitted by DG Health & Consumer Protection, 1 March 2001 (SCP/FAMOX/012).

13. Famoxadone: Addendum 2 to the draft evaluation report, Ecotoxicology, volume 3 Annex B9, 26 Feb 2001, submitted by DG Health & Consumer Protection, 1 March 2001 (SCP/FAMOX/013).

14. Famoxadone (DPX-JE874), relevance of ocular findings in animals for human risk, Ralph Heywood, 12 August 1999, submitted by Notifier.

15. Answer to the EU June evaluation working group questions on famoxadone eye effect in the dog, Ralph Heywood, undated – submitted by Notifier.

16. Comparative aspects of human, primate and canine lens and lenticular opacities – Susan A. MacKenzie, 27 August 1998 – Report n° DuPont-1441, submitted by Notifier.

17. Famoxadone technical: basis for setting the ADI and AOEL for the European Union - Susan A. MacKenzie, 28 April 2000 – Report n° DuPont-4243, submitted by Notifier.

18. IN-KZ007: Acute toxicity to the earthworm *Eisenia foetida* Michaelsen in artificial soil – R.W.J. Hardwood and J. Allen, 30 January 2001 – Report n° DuPont-3796, submitted by Notifier.

19. IN-JS940: Acute toxicity to the earthworm *Eisenia foetida* Michaelsen in artificial soil – B. Knight and J. Allan, 25 January 2001 – Report n° DuPont-3797, submitted by Notifier.

20. Flow through 21 Day Toxicity of DPX-JE874-221 to *Daphnia magna*, M. R. Brown, Haskell Laboratory for Toxicology and Industrial Medicine, 4 March 1996, Report n° 90-95, volumes 1 and 2 376 pages), submitted by Notifier.

D. SCIENTIFIC BACKGROUND ON WHICH THE OPINIONS ARE BASED

I Question 1

The Committee is requested to comment whether the long-term risk to Daphnia, in particular in relation to metabolites, has been sufficiently addressed.

Opinion of the Committee:

The Committee concludes that the long-term risk to Daphnia of famoxadone and its metabolites has been sufficiently addressed. Famoxadone is acutely toxic to both fish and Daphnia, and therefore substantial risk mitigation measures would be necessary to prevent unacceptable acute effects of the a.s. from occurring in aquatic organisms. Such buffer zone would be sufficient to cover chronic risk to Daphnia from famoxadone or its metabolites.

Scientific background on which the opinion is based:

A summary table of the degradation products of famoxadone observed in environmental fate studies is provided in Table B. 8-37 (Monograph Volume 3, p. 297). The dominant metabolites of famoxadone formed in soil are IN-KZ007 and IN-JS940; IN-MN467 and IN-MN468 were also detected in small amounts (<2% of applied radioactivity). A soil photolysis study detected IN-KF015 (max. 22% on day 1; degrades further to IN-JS940 which degrades to IN-H3310), IN-H3310 (increased to 27%), IN-MN468 (increased to 13%), IN-MN467 (increased to 18%) and IN-JS940 (<7%). No lysimeter studies were performed because column leaching tests indicated low mobility of famoxadone and its degradation products in soil. In water, several degradation products were formed due to hydrolysis, but only IN-JS940 and IN-H3310 were stable (SCP/FAMOX/009, p.12). In water-sediment studies IN-JS940 reached a maximum of 20.5 % in water and 3.5 % in sediment on day 3, whereas IN-H3310 reached a maximum of 2.3 % in water and 10.7 % in sediment on day 7. In addition, IN-JL856 and IN-KZ007 were detected in small amounts (max. 5% each).

Five of the metabolites of famoxadone, including the two degradation products formed in sediment-water studies in large amounts (IN-JS940 and IN-H3310), were tested for acute toxicity to *Daphnia magna*. The corresponding EC_{50}[2] values are shown in Table 1.

[2] Median effective concentration.

Table 1. Degradation products of famoxadone observed in various environmental fate studies (Monograph Volume 3, p. 297) and acute toxicity of famoxadone and its metabolites to *Daphnia magna*.

Chemical	48 h EC_{50} for *Daphnia magna* (mg/L)
Famoxadone	0.012
IN-JS940	> 9.6
IN-H3310	> 2.7
IN-JL856	> 0.19
IN-MN468	> 0.012
IN-KF015	> 8.3
IN-MN968	Not tested; unstable intermediate in hydrolysis; observed in sterile samples at pH 9.
IN-KZ007	Not tested; observed in aerobic soil where it rapidly degraded and did not leach; observed in water/sediment tests at a maximum of 5%
IN-MN467	Not tested; observed in aerobic soil at generally less than 10%

Thus, metabolites IN-JS940 and IN-H3310 that formed in relatively large amounts in sediment-water tests are over 100 times less toxic to *Daphnia magna* than the active substance. TER^3_{acute} values for *Daphnia magna* were only estimated for IN-JS940, and these were two orders of magnitude above the Annex VI trigger of 100. Given that the half-life of this metabolite was determined to be < 3 days, risks to Daphnia from chronic exposure are not likely. As metabolite IN-H3310 was detected primarily in the sediment of sediment-water systems, it is unlikely that this metabolite would pose an unacceptable risk to Daphnia. Four of the five metabolites tested were one to two orders of magnitude less toxic to Daphnia than the parent substance. The exception is IN-MN468, however this metabolite is rapidly hydrolysed in water with a half-life of 10 hours. The Committee thus concludes that the long-term risks of famoxadone's metabolites to Daphnia have been sufficiently addressed.

In performing its evaluation the Committee noted that famoxadone is acutely toxic to both fish and Daphnia, and that fairly substantial risk mitigation (i.e., buffer zones on the order of 20 meters for grapes and 15 meters for wheat) would be necessary to prevent unacceptable acute effects of the a.s. from occurring in aquatic organisms. There was disagreement between the RMS, notifier, and the ECCO[4] group as to whether a chronic NOEC[5] of famoxadone for Daphnia should be taken as 3.7 or 0.29 µg/L. This was largely due to the fact that the concentration-response curve for the measured endpoints was not monotonic. However, the outcome of this discussion does not affect the risk assessment. If the more conservative value of 0.29 µg/L is chosen for *Daphnia magna*, then Daphnia would be the most sensitive trophic group (next most sensitive would be fish with a chronic NOEC of 1.4 µg a.s./L for *Oncorhynchus mykiss*). TER calculations indicate that a minimum buffer zone of 10 meters for grapes and 3 meters for wheat would be needed to protect against chronic effects in this group of aquatic organisms (SCP/FAMOX/004, p. 34-35). Since this is less than the width of the buffer zones already indicated to be necessary to prevent unacceptable acute effects in aquatic organisms, the choice of chronic effect value, in this case, has little influence on the overall conclusions of the risk assessment.

[3] Toxicity exposure ratio.
[4] European Commission Co-ordination.
[5] No Observed Effect Concentration.

II Question 2

Can the Committee confirm that the risk from the metabolites IN-KZ007 and IN-JS940, to earthworms, has been sufficiently addressed?

Opinion of the Committee:

On the basis of the submitted data, the SCP considers that the metabolites IN-KZ007 and IN-JS940 are unlikely to present an acute risk to earthworms. However no longer-term sub-lethal tests have been conducted, so the Committee is unable to evaluate the likely chronic risks of the parent or metabolites to earthworms when the number of applications per season is high (> 6).

Scientific background on which opinion is based:

As the TER_{acute} values for IN-KZ007 and IN-JS940 are considerably greater than 100, then the acute risks to earthworms from exposure to both metabolites are likely to be small. However, the Committee notes that intended use of the product includes up to 12 applications per year on grapes, and up to 8 applications per year on tomatoes. The Guidance Document on Terrestrial Ecotoxicology (European Commission, 2000) maintains that sub-lethal testing on the parent compound and major metabolites is necessary if the number of applications per year is greater than 6. The Committee recognises that the acute TER is high, but supports the view that such data do not in themselves allow to conclude that longer-term sub-lethal effects are unlikely to occur.

III Question 3

Can the Committee comment on the relevance of the eyes effect observed in the 12 months dog study to human? Should mechanistic study on eyes be required?

Opinion of the Committee:

Available data show that famoxadone is clearly cataractogenic in Beagle dogs, while milder effects were seen in rats and no effect in monkeys and in mice. The mechanism of action is unknown. The provided data are not sufficient to support a species specificity of cataract induction in dogs. Therefore, the Committee is of the opinion that the eye effect of famoxadone in dogs is to be considered relevant for humans. This opinion could be revised with a more complete understanding of the mechanism of action of famoxadone on the eyes in the various species.

Scientific background on which opinion is based:

III.1 Pathogenicity of cataract

The lens epithelium and the differentiating fibre cells in the lens bow are crucial for maintaining the state of hydration of the lens which is strongly dependent on the energy (ATP[6]) content of the cells and on the activities of ion and water channels. The normal lens is in a "dehydrated" state. This strongly depends on the proper functioning of the ion and water pumps which derive their energy from the ATP delivered by lens epithelium and

[6] Adenosine triphosphate.

superficial lens fibres. The lens osmolarity is maintained by cations (Na^+ and K^+) and anions (Cl^-, bicarbonate, sulfate, ascorbate, glutathione, acidic groups of lens proteins and glycoproteins). Some of the markers used in various studies on cataractous ion changes in the lens include ATP-content, glutathione peroxidase and reductase activities, and ascorbate content.

Lenticular opacities can be caused by different mechanisms such as:

- changes in osmotic pressure caused by accumulation of active osmolytes, leading to an increased water content and lens weight which change the refractive properties and clarity of the lens (e.g. diabetic cataract);
- post-translational denaturation of lens proteins, especially the crystallins, which are critical for maintaining lens clarity and refractive index (e.g. nuclear and cortical age-related cataracts);
- impairment of the normal differentiation process, including synthesis of crystallins, which is strongly dependent on unrestricted energy and nutrient supply. Dose-dependent reductions in lenticular ATP content correlate with a dose-dependent decrease in lenticular crystallin content. This effect seems not to be species specific (e.g. X-ray and steroid cataracts).

Chemicals with widely differing structures and pharmacological activities have been reported in the literature to cause cataract in laboratory animals. These compounds defy easy classification because the mechanisms of their cataractogenicity are poorly understood. Several mechanisms of action are proposed (Brown and Bron, 1996). Nevertheless, the vast majority of chemicals induce cataracts with unknown mechanisms. In a survey of the ocular toxicological profiles, the correlation between rodent and non-rodent toxicity was not established; few compounds are known to cause cataracts in both rats and non-rodents (Heywood, a & b). The toxic effects of various substances on the lens are quantitatively very different in different species. Extrapolation of animal data to humans must therefore be done with great caution.

III.2 Eye effects of famoxadone

Famoxadone has a low acute toxicity, has no dermal or ocular irritancy potential and is not a sensitizer. Ocular effects are observed in short and long term dog studies and in a two year rat study. The toxicological effects of famoxadone are summarised in table 2 hereafter.

Table 2: Toxicological findings in repeated toxicity studies with famoxadone:

Species	Exposure	Eye effects	NOAEL ppm (mg/kg/d)	Comments
Rat (CD)	Oral 90-days 0, 50, 200, 800, 1600 ppm in diet (M : 3.34, 13, 52.1, 106 mg/kg/d, F : 4.24, 16.6, 65.7, 130 mg/kg/d)	No test substance-related ophthalmological effect	50 (4.24)	Based on female body weight changes
Mouse (CD-1)	Oral 90-days 0, 35, 350, 3500, 7000 ppm in diet (M : 5.89, 62.4, 534, 1149 mg/kg/d, F : 8.21, 79.7, 757, 1552 mg/kg/d)	No test substance-related ophthalmological effect	350 (62.4)	Based on haemolysis and hepatic and splenic alterations
Dog (Beagle)	Oral 90-days 0, 40, 300, 1000 (or 600 ppm test week 6-13) in diet (M : 1.3, 10, 23.8-21.2 mg/kg/d, F : 1.4, 10.1, 23.3-20.1 mg/kg/d)	Ophthalmology: Bilateral posterior cortical cataracts at wk 12 at 300 ppm (2 M/4 & 1F/4) and at 1000/600 ppm (2 M/4 & 2 F/4) Histopathology: minimal to mild compound-rel. changes in the lenses at 40 ppm (1F/4), 300 ppm (4M/4) and 1000/600 ppm (3M/4 & 4F/4)	Taking account of the eye effects : M : 40 (1.3) ; F : no With the exception of eye effects : 40 (1.3)	Excluding lens effects, 300 ppm (10.0 mg/kg bw/d) is NOAEL based on haematological effects and hyperkalemia
Dog (Beagle)	Oral 1-year 0, 10, 20, 40, 300 + 300 ppm in diet during 3-months and basal diet for the remaining 9 months (M : 0.3, 0.6, 1.2, 8.8-10.1 mg/kg/d, F : 0.3, 0.6, 1.2, 9.3-9.9 mg/kg/d)	Ophthalmology : Posterior subcapsular lens opacities at 300 ppm (2M/4 & 2F/4 in the main group and 4M/4 & 4F/4 in the recovery group) most of the lesions first appeared between the 2-month and 3-month examinations. Histopathology: Lenticular degeneration (posterior subcapsular and equatorial) observed at 300 ppm (3M/4 & 2F/4 in the main group and 2M/4 & 4F/4 in the recovery group)	40 (1.2)	Based on ophthalmological changes
Rat (CD)	Oral 2-years 0, 10, 40, 200, 400 ppm in diet (M : 0.42, 1.62, 8.37, 16.8 mg/kg/d, F : 0.53, 2.15, 10.7, 23 mg/kg/d)	Ophthalmology: posterior cortical cataract in 1/78 M at 400 ppm on d 346 and posterior capsule cataract in 1 M/31 at 40 ppm and 1 M/21 at 400 ppm Histopathology: 400 ppm : ↑ i. cataracts in M (3/62, 0/43, 1/34, 1/38, 7/62) Microscopy: 5/59, 4/56, 10/58, 4/60, 9/60	40 (1.62)	Based on haemolytic anaemia (increase in pigmentation in splenic macrophages and reticular sites)
Mouse (CD-1)	Oral 18-months 0, 5, 50, 700, 2000 ppm in diet (M : 0.70, 6.78, 95.6, 274 mg/kg/d, F : 0.96, 9.84, 130, 392 mg/kg/d)	Ophthalmology : No abnormalities rel. to treatment Histopathology : Cataracts : no test substance-rel. effect (M : 22/60, 0/19, 1/16, 1/15, 26/60, F : 28/60, 3/13, 5/19, 9/20, 21/60)	700 (95.6)	Borderline increased liver weight and increased foci of cellular alteration
Monkey (Cynomolgus) 4/sex/group	Oral (gavage) 52-weeks 0, 1, 100, 1000 mg/kg/d	No test substance-related ophthalmological effect	(100)	Based on haematological changes

III.3 Biochemical and pharmacodynamic properties of famoxadone

The known biochemical mechanism of famoxadone is inhibition of the mitochondria respiratory chain at complex III resulting in decreased production of ATP by the cell (SCP/FAMOX/011).

In the dog study in which high dosages of famoxadone were given an increase in serum K^+ was found, indicating an effect on ion homeostasis at toxic doses.

Metabolic studies conducted with famoxadone in rats and dogs demonstrated a longer half-life for radioactivity (parent and/or metabolite) in the dog, but no major qualitative differences in metabolic profile were found and the quantitative differences were only small (monograph, volume 3, annex B).

III.4 Differences between species

Corticosteroid treatment and X-ray irradiation are known to lead, with a considerable delay of many months, to abnormal differentiation and migration of lens fibres due to DNA damage and reduction of normal energy supply, and are finally leading to posterior subcapsular cataract. It seems possible that reduced energy supply and therefore lower ATP levels also impair the normal differentiation process leading to abnormal growth and migration of lens fibres which eventually lead to posterior cataract. In conjunction with postulated effects on ion and water homeostasis, this may provide a mechanistic explanation of the observed posterior subcapsular changes in the Beagle dog after famoxadone treatment. Since this is a general cell biological mechanism, similar changes in rats and monkeys would be expected.

There are no qualitative differences between mammalian species and strains with respect to the differentiation process of lens fibres. Thus, a conclusion that the observed posterior subcapsular cataract is species specific and restricted to the Beagle dog is not sufficiently supported at the moment. Such a conclusion would require a full understanding of the mechanism of action of famoxadone on the eyes in the various species and especially knowledge on the concentration of famoxadone in the aqueous humour and the lens.

The absence of effects in monkeys may be due to the relative short exposure period in comparison to their life span or to non-toxic dosage. The exposure time might have been too short to lead to manifest equatorial and posterior subcapsular changes detectable using routine clinical and histopathological methods. Monkeys seem also particularly less sensitive to the toxic effects of famoxadone since at 1000 mg/kg bw/day the sole observed effect is a mild anaemia. In addition other parameters, which were assumed by the notifier to explain the appearance of cataracts, have not been measured in monkeys.

Furthermore it must be realised that there is accumulating evidence that albino and pigmented rats have differential sensitivity to cataractogenic factors, albino rats being less sensitive (Eiben R. and Wegener A., 1995 and Wegener A. and Eiben R., 1992).

In the multigeneration study in rats, it seems that only gross pathological examination was done. Histopathological examination was performed only on reproductive organ tissues and selected gross lesions, while livers and eyes were not examined.

III.5 Conclusions

Experimental data show that famoxadone has a clear cataractogenic effect in Beagle dog. The precise mechanism of action of famoxadone is unknown. Results from studies carried out with other species (rats, mice and monkeys) do not allow a definite conclusion on the absence of cataractogenic effect in these species.

Many compounds have been shown to be cataractogenic in either rats or Beagle dogs but very few compounds are cataractogenic in both species. The extrapolation of animal data to human is therefore difficult.

The Committee is of the opinion that the eye effect of famoxadone in dogs is to be considered relevant for humans. This opinion could be revised with a more complete understanding of the mechanism of action of famoxadone on the eyes in the various species.

IV Question 4

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

Opinion of the Committee:

The Committee is of the opinion that the risk to operator has not been adequately assessed and needs to be reassessed using the AOEL derived from the NOAEL based on cataracts induction in dogs (see opinion on question 3).

Scientific background on which opinion is based:

Famoxadone is applied by spray application with standard field sprayers at a maximum rate of 0.15 kg a.s./ha to cereals, or 0.09 kg a.s./ha to grapes, potatoes and tomatoes. Operator exposure was estimated by using the German model and the UK POEM[7] for tractor-mounted applications, assuming the maximum rate of applications for each crop, and a work rate of 20 (8 for grapes) ha/day (German model) or 50 (10 for grapes) ha/day (UK POEM). TERs[8] were calculated on an AOEL[9] derived from NOAEL[10] based on hematological effects in 90-day and 2-year rat studies. With one exception (UK POEM for application to cereals) TERs calculated for workers without PPE[11] were higher than 100. Since the relevance for humans of induction of cataracts in dogs (see opinion 3) cannot be excluded, the NOAEL from which the AOEL should be derived is lower than that used for risk assessment for worker exposure as described above. The Committee is of the opinion that the risk to operator has not been adequately assessed and needs to be reassessed using the AOEL derived from the NOAEL based on cataracts induction in dogs (see opinion on question 3).

[7] Predictive Operator Exposure Model.
[8] Toxicity Exposure Ratio.
[9] Acceptable Operator Exposure Level.
[10] No Observed Adverse Effect Level.
[11] Personal Protection Equipment.

E. REFERENCES

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