Opinion regarding the evaluation of Pymetrozine in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market (opinion adopted by the Committee on 26 January 2001)

1. TITLE

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

(Opinion adopted by the Committee on 26 January 2001)

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 give its opinion on the significance of the changes in serum sodium levels observed in the long-term and carcinogenicity study in rats and should these be considered as an adverse effect in the context of estimating an ADI (Acceptable Daily Intake)?

2) Can the Committee give its opinion on the significance of effects seen in the acute neurotoxicity study and should these be considered as an adverse effect in the context of estimating an acute reference dose?

3. BACKGROUND

The draft Commission Directive for inclusion of pymetrozine in Annex I to Directive 91/414/EEC [1] 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 evaluation report (monograph) prepared by the Rapporteur Member State (Germany) on the basis of dossier submitted by the notifier (Novartis now Syngenta), a review report prepared by the Commission and the Recommendations of the ECCO [2] Peer Review Programme.

Pymetrozine is a systemic insecticide derived from a novel type of chemistry. It acts selectively against a wide range of aphids and whiteflies. It penetrates green leaves and is transported acropetally within plants. It stops feeding activity of sucking insects. Death will occur after 1 - 3 days because of missing food. It is intended for use in a wide range of crops, such as cotton, tobacco, vegetable and fruit crops, in field and in glasshouse where aphids and whiteflies occur as pests. Its intended rate of use ranges from 0.1 kg a.s./ha to 0.45 kg a.s./ha.

4. OPINION

4.1 Question 1

"Can the Committee give its opinion on the significance of the changes in serum sodium levels observed in the long-term and carcinogenicity study in rats [3] and should these be considered as an adverse effect in the context of estimating an ADI [4] ?"

Opinion of the Committee:

In the long-term toxicity and carcinogenicity study with pymetrozine in rats transient and slight, but statistically significant, decreases in serum sodium and chloride levels were observed. Similar changes were not reported in other studies nor were effects of pymetrozine on the morphology and function of the kidneys ever reported. The Committee concluded that these changes in serum sodium and chloride levels should not be considered adverse in the context of deriving an ADI.

Scientific background on which the opinion is based:

The kidneys play the main role in osmoregulation by which serum sodium and chloride levels are controlled, and small fluctuations within the physiological range are observed due to variation of dietary salt or water intake.

Slight, though statistically significant, changes in the serum sodium and chloride levels were only observed in the early intervals (week 13, 27 and 53) of the long-term toxicity and carcinogenicity study with pymetrozine in rats, at dose levels equivalent to 5 mg/kg body weight or higher. After week 53 no changes in serum sodium and chloride levels were noted in any dose group. These transient changes were not accompanied by any alteration in the function (serum creatinine and urea) or in morphology of the kidneys.

No decreases in serum sodium and chloride levels were observed in the other toxicity studies in mice, rats and dogs.

In conclusion, the transient slight changes in serum sodium and chloride levels only seen at few intervals in the long-term study in rats are not considered relevant for the derivation of an ADI.

4.2 Question 2

"Can the Committee give its opinion on the significance of effects seen in the acute neurotoxicity study [5] and should these be considered as an adverse effect in the context of estimating an acute reference dose?"

Opinion of the Committee:

The Committee considers that the reversible effects, such as, lower body temperature (both sexes), decreased numbers of rearings (males) and reduced responsiveness to tail pinch (females) observed in the acute gavage neurotoxicity study in rats at lower doses were compound related and as such should be considered in the context of estimating an Acute Reference Dose. In this study a clear NOAEL [6] was not observed (LOAEL [7] 125 mg/kg body weight). However, the reversibility of effects, the dose-response curve, the mode of administration and the lack of neurotoxic effects in the 13 week dietary study in rats at doses

up to 201 mg/kg body weight per day (3000 ppm) should be taken into account when deriving the Acute Reference Dose.

Scientific background on which the opinion is based:

Pymetrozine is rapidly and almost completely absorbed after oral administration. It is extensively and rapidly metabolised with no indication of accumulation. Its acute toxicity is low (oral rat LD_{50} [8] 5820 mg/kg body weight), it is not a skin sensitiser, and is not genotoxic. It is not teratogenic but caused skeletal variations and anomalies at maternally toxic doses (NOAEL 30 and 10 mg/kg body weight in rats and rabbits, respectively). Pymetrozine causes increased incidence of liver tumours in both rats and mice at very high doses but this effect is not considered to be relevant in human risk assessment. The lowest dose target organ for toxicity in all tested animals is the liver with anemia (possibly haemolytic) and decreased spermatogenesis occurring at higher doses. The Acute Refence Dose of 0.1 mg/kg body weight derived by the Rapporteur Member State is based on the NOAEL of 10 mg/kg body weight in the rabbit developmental study.

Neurotoxicity studies:

Groups of CD rats (10/sex) received pymetrozine at 0, 125, 500 or 2000 mg/kg body weight by gavage in water [9]. Animals were subjected to a functional observation battery (FOB) and assessments of locomotor activity at 4 to 5 hours and at 7 and 14 days post dosing. The FOB included open field, reflex, neuromuscular and physiological assessments. At sacrifice, a full post-mortem was performed. Three top dose males died or were sacrificed by day 3. Body weight gain was reduced at 2000 mg/kg body weight in both sexes (<10%). Dose-related reductions in locomotor activity (figure of 8 maze activity counts) were seen in all treated groups at 4 - 5 hours but not at later intervals. Variations in a number of FOB parameters were seen at 4 - 5 hours, occasionally persisting until day 8 in the top dose group (note the general toxicity of this dose). In the low dose animals only lower body temperature (both sexes), decreased numbers of rearings (males) and reduced responsiveness to tail pinch (females) were observed at 4-5 hours. There were no abnormal findings in the nerve or muscular tissue samples examined histologically.

Groups of CD rats (10/sex) received pymetrozine at 0, 500, 1000 or 3000 ppm in the diet for 13 weeks [10]. Animals were subjected to a functional observation battery and assessments of locomotor activity at 4, 8 and 13 weeks. At sacrifice a post-mortem was performed focusing on nervous and muscular tissue. There were no deaths and no substance related clinical observations during the study. Body weight gain was reduced (15 - 25%) in both sexes at 3000 ppm while food consumption was reduced by 10%. There were no adverse findings in the microscopic examination of nervous and muscular tissue. Some behavioural changes were seen but were considered not treatment related. Motor activity, hind limb foot splay and body temperature were also not affected by pymetrozine in this study. It is concluded that administration of pymetrozine for 13 weeks in the diet to rats did not shown any signs of neurotoxicity at doses up to 3000 ppm (equal to 201 mg/kg body weight per day) (highest dose tested).

In conclusion, some reversible neurotoxic effects were observed in the acute gavage study in rats without a clear NOAEL, the LOAEL being 125 mg/kg body weight. These effects are probably related to the peak tissue concentration reached after gavage, since these were not observed in the 13-week dietary study up to 3000 ppm (equal to 201 mg/kg body weight per

day) where the intake is more gradual leading to a lower peak concentration. These effects should be considered when deriving the Acute Reference Dose, taking also into account their reversibility, the shape of the dose-response curve, the mode of administration and the lack of neurotoxic effects in the 13-week rat study.

5. REFERENCES

1. Gerspach R. (1995) 24-Month carcinogenicity and chronic toxicity study in rats. Ciba-Geigy report n. 901483, 19-10-95, owned by Novartis Crop Protection AG, submitted by Novartis Crop Protection AG

2. Ferkany, J.WM. 1997: An Acute Neurotoxicity Study with CGA-215944. Technical in Rats. Rep. No. A108-017, Oread Biosafety Incorporated, Farmington, Connecticut, USA, 03.09.1997; Owned by: Novartis Crop Protection AG; Submitted by: Novartis Crop Protection AG; Novartis File 215944 / 653. Dates of experimental work February 1997

3. Weiler S., 1997: 13-Week Dietary Neurotoxicity Study with CGA-215944. Technical in Rats. Rep. No. 6804-100, Covance laboratories Inc., Madison, Wisconsin, USA, 03.09.1997; Owned by: Novartis Crop Protection AG; Submitted by: Novartis Crop Protection AG; Novartis File 215944 / 659. Dates of experimental work January to September 1997.

6. DOCUMENTS MADE AVAILABLE TO THE COMMITTEE

1. Evaluation of pymetrozine in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market: Terms of reference (Doc. SCP/PYMET/001).

2. Pymetrozine - Evaluation table - Doc. 7454/VI/98-rev.7 (Doc. SCP/PYMET/003).

3. Pymetrozine - Appendices [Appendix I Identity, physical and chemical properties - Appendix II End points and related information - Appendix III List of studies which were submitted during the evaluation process and were not cited in the draft assessment report] (Doc. SCP/PYMET/004).

4. Pymetrozine: Addendum 3 to the Monograph - prepared by Rapporteur Member State: Germany, 3 March 2000 (Doc. SCP/PYMET/005).

5. German comments to UK concerns regarding the proposed ADI and ARfD for Pymetrozine, 19 November 1999, submitted by DG Health and Consumer Protection (Doc. SCP/PYMET/006).

6. Pymetrozine (Monograph) Report of the evaluation of a dossier submitted by Novartis, prepared by Germany made to the European Commission under Article 8(1) of Council Directive 91/414/EEC Volume 1, April 1998.

7. Pymetrozine (Monograph) Report on the evaluation of a dossier submitted by Novartis, prepared by Germany made to the European Commission under Article 8(1) of Council Directive 91/414/EEC Volume 1 **Addendum,** May 1998.

8. Pymetrozine (Monograph) Report on the evaluation of a dossier submitted by Novartis, prepared by Germany made to the European Commission under Article 8(1) of Council Directive 91/414/EEC Volume 2 Annex A, List of tests and studies, April 1998.

9. Pymetrozine (Monograph) Report on the evaluation of a dossier submitted by Novartis, prepared by Germany made to the European Commission under Article 8(1) of Council Directive 91/414/EEC Volume 3 Annex B, Summary, scientific evaluation and assessment, April 1998.

10. Pymetrozine (Monograph) Report on the evaluation of a dossier submitted by Novartis, prepared by Germany made to the European Commission under Article 8(1) of Council Directive 91/414/EEC Volume 4 Annex C, Confidential information, April 1998.

7 ACKNOWLEDGEMENTS

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

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[1] **OJ N° L 230 of 19. 8.1991, p. 1.**

[2] **European Commission Co-ordination.**

[3] **Reference 1 under section 5.**

[4] **Acceptable daily intake.**

[5] **Reference 2 under section 5.**

[6] **No observed adverse effect level.**

[7] **Lowest observable adverse effect level.**

[8] **Lethal dose, median.**

[9] **Reference 2 under section 5.**

[10] **Reference 3 under section 5.**