Opinion of the Scientific Committee on Plants regarding the evaluation of pyridate in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market (Opinion expressed by the Scientific Committee on Plants on 6 June 2000) (SCP/PYRID/002-Final)

1. TITLE

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS REGARDING THE INCLUSION OF PYRIDATE IN ANNEX I TO COUNCIL DIRECTIVE 91/414/EEC CONCERNING THE PLACING OF PLANT PROTECTION PRODUCTS

2. TERMS OF REFERENCE

In the context of the Commission's work on the implementation of Directive 91/414/EEC [1] concerning the placing of plant protection products on the market the Scientific Committee on Plants is requested to comment on the suitability of the three-generation study in rats for the estimation of the AOEL [2] for pyridate.

3. BACKGROUND

The opinion is based on the documentation generated in the context of possible inclusion of pyridate in Annex I to Directive 91/414/EEC [3] , and on the evaluation of four original studies (1,2,3,4), relevant to the Terms of Reference.

In order to prepare its opinion, the Scientific Committee on Plants had access to documentation comprising a monograph prepared by Austria as Rapporteur Member State (RMS) and the recommendations of the ECCO [4] Peer Review Programme.

Pyridate is a pyridazine derivative, used as post-emergence contact herbicide in agriculture and horticulture. The evaluation of the toxicological dossier indicates that pyridate is of low toxicity to rats (oral LD_{50} [5] >2000 mg/kg bw), skin irritant and skin sensitizer. There is no experimental evidence of teratogenicity, mutagenicity or carcinogenicity. A neurotoxic potential of pyridate is quite consistently observed in short-term studies performed in several species (rat and dog, even if at different dose levels), with dose-dependent clinical symptoms and signs (hypoactivity, salivation, emesis, ataxia, etc.).

In the context of the ECCO [6] Peer Review Programme, the originally established AOEL of 1.2 mg/kg bw, based on clinical neurotoxic signs in the 1-year study in dog (NOAEL=30 mg/kg bw, SF [7] = 25), was revised to a new systemic AOEL of 0.036 mg/kg bw/day. The new AOEL was established by applying a SF of 100 to the NOAEL of 3.6 mg/kg bw/day in the 3-generation study in rat, based on increased relative kidney weights in the F2 and F3 generations and decreased relative thyroid weights in males of the F2 generation at 400 ppm (18.8 mg/kg bw/day).

4. OPINION OF THE COMMITTEE

4.1 Question
"Is the three generation study in rats suitable for the estimation of the AOEL for pyridate? If not, would the ninety-day study provide a more adequate basis?"

Opinion
The three generation study in rats is suitable for the estimation of the AOEL for pyridate. In the absence of a mechanistic explanation of the observed effects on organ weights, and in the absence of data to predict the relevance of similar effects to humans, it is justified to use the NOAEL of 3.6 mg/kg bw/day, based on decreased thyroid weight and increased kidney weight for AOEL setting.

4.1.1 Scientific background on which the opinion is based

The reproductive study indicates that pyridate induces dose-dependent effects in the weights of thyroid and kidney. A slight increase in kidney weights was observed in the top-dose group of both sexes in the F_1 and F_2 generation, in females of the mid-dose group of the F_2 generation, and in both sexes of the mid-dose group of the F3 generation. A dose-dependent decrease of the thyroid weights was observed in males of the mid- and top-dose groups of the F_2 generation. Liver weight was increased only in F_2 females of the top-dose group.

Effects on organ weights similar to those reported in the multigeneration study were observed also in short-term and long-term studies in rat (not in dog), even if not consistently and at higher doses.

Increased kidney weights were reported in two 90-day studies in rat: at 398 mg/kg bw (3) and at 177 mg/kg bw (2). Increased liver weights were noted in the latter study in both sexes at 177 mg/kg bw, and decreased thyroid weights were recorded in females at all dose levels (63.5, 177, and 500/600 mg/kg bw) and in males at the top dose of 500 mg/kg bw.

An increase of kidney weights in males at the top dose of 115 mg/kg bw, and a dose-dependent decrease of thyroid weights in males at all doses (lowest dose=18 mg/kg bw) were seen in the long-term study in rat, at the interim kill after one year. These effects were only transient and reverted to control values at the end of the study.

The notifier argued that, since the kidney effect observed in the reproductive study is not associated with deviations in clinical chemistry data or histopathological findings, they should not be considered as adverse but more as "adaptive" effects, "due to an overload of the organism as the result of a higher feed intake, especially in young animals". The notifier considered also that the findings on thyroid were not related to the treatment. It is opinion of the SCP, however, that the observation of similar results in the short-term study, and in the long-term study after one year may rather indicate a higher sensitivity of younger and middle age animals.

The AOEL should be based on the NOAEL in the most sensitive relevant species. In the case of pyridate, effects seen in the reproduction study represent the most sensitive end-points. The mechanism of action responsible for the observed effects is not clear from the overall body of data. The weight of evidence for the observed effects is supported by similar results observed in other studies of different design. It is important to remark that, in the absence of data to disregard the relevance of similar effects to humans, any effect in reproduction studies should be considered to be of particular biological importance.

In conclusion, the NOAEL of 3.6 mg/kg bw from the reproductive study should be regarded as relevant for AOEL setting.

5. REFERENCES

- (1) TIL, 1982, Multigeneration study with Pyridate in rats CIVO Institutes TNO Report N° V80-0696, Annex IIA, 5.6.1
- (2) HENCK, 1987, 90-day rat oral subchronic toxicity study with a 28-day recovery period of Pyridate technical Toxicity Research Lab. Report N° 043-005 Annex IIA, 5.3.2
- (3) DANKS, 1991, Pyridate technical: Toxicity study by dietary administration to CD rats for 13 weeks, Life Sci. Res. Report N° 90/AGL002/0614, Annex IIA, 5.3.2
- (4) TIL, 1990, Lifespan oral carcinogenicity study of Pyridate in rats (Revised Final Rep.), TNO-CIVO Institutes TNO Report V89.237, Annex IIA, 5.5

6. LISTE OF DOCUMENTS MADE AVAILABLE TO THE SCP

- (1) Terms of reference: Evaluation of pyridate in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market. (SCP/PYRID/1/).
- (2) Pyridate: Report from Rapporteur Member State (Austria) on the dossier.
- (3) Pyridate: Evaluation table - doc 7756/VI/97-Rev.4 (SCP/PYR/3).

7. ACKNOWLEDGEMENTS

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

Toxicology: Professor M. Maroni (Chairman), and Committee Members Dr. M.-P. Delcour-Firquet, Dr. O. Meyer, Dr A. Moretto, Prof. K. Savolainen, Prof. A. Silva Fernandes, Dr. G. Speijers and invited expert A Fait.

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[1] OJ L 230, 19. 08. 1991, p.1.

[2] Acceptable Operator Exposure Level

[3] OJ 230, 19.08.1991, p.1

[4] European Community Co-ordination

[5] Lethal Dose 50%

[6] European Community Coordination

[7] Safety Factor