EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Scientific Opinions
C3 - Management of scientific committees II; scientific co-operation and networks

SCIENTIFIC COMMITTEE ON PLANTS

SCP/ETHOXY/002-Final
22 September 2000

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS REGARDING THE EVALUATION OF ETHOXYSULFURON 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 22 September 2000)

Rue de la Loi 200, B-1049 Bruxelles/Wetstraat 200, B-1049 Brussel - Belgium - Office: B232 6/25.
Telephone: direct line (+32-2)295.77.05, switchboard 299.11.11. Fax: 295.73.32.

Internet: Michael.Walsh@cec.eu.int
F:\WebDev\4298.doc

1. TITLE

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS REGARDING THE EVALUATION OF ETHOXYSULFURON IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC CONCERNING THE PLACING OF PLANT PROTECTION PRODUCTS ON THE MARKET (PRELIMINARY OPINION).

2. TERMS OF REFERENCE

The Scientific Committee on Plants (SCP) is requested to respond to the following question 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.

"Can the committee comment on the occurrence of uterine tumours and changes in weight of endocrine-sensitive tissues of rats and should mechanistic studies be provided?"

3. BACKGROUND

Ethoxysulfuron is a new active substance in the context of Directive 91/414/EEC[1] which has been notified by AgrEvo (now Aventis CropSciences) to Italy.

During the ECCO[2] Peer Review Programme, the Commission identified an important issue of concern. Despite the evaluation by the ECCO Peer Review Programme was not completed, the Commission decided to refer to the Scientific Committee on Plants to issue a preliminary opinion on the evaluation of ethoxysulfuron.

The Committee had been supplied with a monograph prepared by the Rapporteur Member State (Italy), a draft review report prepared by the Commission and the draft recommendations of the Peer Review Programme.

Ethoxysulfuron is a herbicide of the sulfonylurea family, with a broad spectrum pre- and post-emergence activity. In Europe, its current intended use is on rice at a maximum rate of 0.06 g a.s./ha with only one application/ year.

4. OPINION

Question:

"Can the committee comment on the occurrence of uterine tumours and changes in weight of endocrine-responsive tissues of rats and should mechanistic studies be provided?"

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

Opinion of the Committee

The increase in uterine tumour incidence in rats is considered of no relevance to human risk as it occurred only at a high dose causing marked general toxicity. In addition, no carcinogenic effect was found in male rats, nor in male and female mice and no evidence for genotoxicity was found. For endocrine responsive tissues of rats, only ovary and uterus weight were decreased in a reproduction study, but without histological abnormalities and at clearly toxic doses. For these reasons no additional mechanistic studies are deemed necessary.

Scientific background on which the opinion is based

4.1. Occurrence of uterine tumours

4.1.1. Genotoxicity

Ethoxysulfuron was shown to be consistently negative in the following test systems:

- Reverse mutation (Ames test, *S. typhimurium* and *E. coli*),
- Gene mutation in somatic cells,
- Unscheduled DNA synthesis,
- Chromosome aberration *in vitro*,
- Micronucleus test *in vivo*.

Therefore ethoxysulfuron can be considered as a non-genotoxic compound.

4.1.2 Carcinogenicity

Two carcinogenicity studies (dietary exposure) have been performed, one in mice and one in rats.

The study in mice (NMRI strain) was conducted with a dietary concentration of 7000 ppm (1005 mg/ kg bw[3] /day) for 102 weeks, and produced no evidence of carcinogenicity.

In Wistar rats, a study (104 or 118 weeks) was performed with doses up to 8000 ppm. In males, no evidence for carcinogenicity was seen. In females, an increase in uterine adenocarcinomas was found exclusively in the highest dose (8.6% in controls, 27.5% in 8000 ppm animals, 104 week and 118 week animals combined). No trend for dose relationship was seen in the intermediate dose groups, and no uterine preneoplastic effects were reported in the lower dose groups. It should be noted that in the high dose group a significant general toxicity was observed, such as, decreased food intake and decreased body weight gain (30%), along with other significant physiological disturbances as indicated by various clinical chemistry parameters, while survival was increased.

4.1.3 Comment

The uterine tumour observed is a common tumour in this rat strain, showing 8.7% in concurrent controls. It is a frequent and well-established finding that the incidence of common

[3] Body weight.

tumours in laboratory species can be influenced by physiological disturbances, including those produced by environmental factors. For this reason, it is of great importance to have no or minimal differences in physiological conditions compared to control animals.

When a tumour type occurs at relatively high spontaneous incidence, it may be considered as not representative for a human tumour type analogue and probably has a species / tumour type-specific mechanism of action.

In this perspective, the MTD[4] concept has been established and should be respected in carcinogenicity studies, or a paired fed control group should be included. In the present study, the MTD has been significantly exceeded (see above). Moreover, an additional study was conducted in this rat strain with a low nutrient (protein and fat) diet and without any test agent, which showed an increase in uterine adenocarcinomas in the same proportion as in the ethoxysulfuron study with this rat strain. This demonstrates that the occurrence of this tumour type in this rat strain is influenced by nutritional / physiological imbalance, which renders the tumour findings in the highest dose of the present study of no relevance to humans.

4.1.4 Conclusion

For the reasons described above, it seems to be justified to disregard this increase in tumour incidence observed exclusively in the high dose group of rats. In addition, no carcinogenic effect was found in male rats, nor in male and female mice, and the compound was not genotoxic.

4.2. Changes in weight of endocrine-responsive tissues

According to the specific definition adopted by the EC (Report SCTEE[5], March 1999):
"An endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)-populations."

Thus endocrine disruption mechanisms become toxicologically important when they cause adverse health effects. No specific tests for endocrine function have been supplied, but toxicity studies including 90-day and reproductive toxicity studies as provided can be considered suitable for a first step evaluation of endocrine function.

4.2.1 Observations in endocrine responsive tissues

The following findings were reported:

4.2.1.1 *Short term toxicity*:

– 90 day feeding study, beagle dogs:

[4] Maximum Tolerated Dose.
[5] Scientific Committee for Toxicity, Ecotoxicity and the Environment.

Occasional slight increased thyroid weight, mild thyroid hyperplasia and decreased thyroxine levels. These observations were not dose related, and are of questionable significance.

– No such effects were observed in rats and mice.

4.2.1.2 *Long term toxicity*

– 52 / 104 week toxicity / carcinogenicity study in Wistar rats:

No treatment related effects on organ weights were seen (up to 8000 ppm). Slightly decreased thyroid hormone levels (along with an increase in TSH) were found but without histological changes. The observed changes were attributed to lower levels of thyroxin binding proteins (8000 ppm).

– 52 / 102 week toxicity / carcinogenicity study in NMRI mice:

A decrease in absolute and relative adrenal weight was seen in the top dose only (7000 ppm), without histological changes.

4.2.2 Reproductive toxicity

Decreased ovarian weight was reported in the 2000 and 8000 ppm exposed rats of parent generation (preliminary study). Decreased ovarian and uterus weights in the parent and F1 generation of 5000 ppm group were reported, along with decreased food intake and body weight in this dose group, but without histopathological correlates (2-generation study). No adverse effects were reported in the reproductive parameters. In addition, no adverse effect was seen in pre-natal development studies in rats and rabbits.

4.2.3 Conclusion

Changes in weight of endocrine responsive tissues in laboratory rats were limited to the ovary and uterus (but without histopathologically detected abnormalities) and then only at doses that induced significant systemic toxicity. This systemic toxicity might itself be responsible for the organ weight changes. Importantly, these effects were not associated with reproductive / developmental disturbances, which are the major concerns related to endocrine disrupting chemicals. Therefore, further mechanistic studies are not considered necessary.

5. REFERENCES

1. International Agency for Research on Cancer, 1980. Long-term and short-term screening assays for carcinogens: a critical appraisal. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, Supplement 2. IARC, Lyon.

2. Opinion on Human and Wildlife Health Effects of Endocrine Disrupting Chemicals, with Emphasis on Wildlife and on Ecotoxicological Test Methods. Report of the Scientific Committee for Toxicity, Ecotoxicity and the Environment (SCTEE), March 1999. http://europa.eu.int/comm/food/fs/sc/sct/out37_en.html

6 DOCUMENTATION MADE AVAILABLE TO THE COMMITTEE

1. Evaluation of ethoxysulfuron in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market (SCP/ETHOXY/001).

2. Ethoxysulfuron: Evaluation table – 7460/VI/98 rev.5 (Doc. SCP/ETHOXY/003-Rev.1).

3. Ethoxysulfuron: proposed good agricultural practices (Doc. SCP/ETHOXY/004).

4. Ethoxysulfuron: List of end points (Doc. SCP/ETHOXY/005).

5. Ethoxysulfuron (Hoe095404) – Annex B: B.1.1.11, B.1.3 (Doc. SCP/ETHOXY/006).

6. Ethoxysulfuron (Hoe095404) – Annex B: B.2, B.2.1, B.2.2 (Doc. SCP/ETHOXY/007).

7. Ethoxysulfuron (Hoe095404) – Annex B: B.3.1.8? B.3.4.3, B3.5.2, B.3.5.4, B.3.5.5, B3.5.5.1, B.3.4.5.3, B.3.6 (Doc. SCP/ETHOXY/008).

8. Ethoxysulfuron: B7.4 Fate and behaviour in water (Annex IIA 7.2.1; Annex IIIA 9.2 (Doc. SCP/ETHOXY/009).

9. Ethoxysulfuron (Hoe095404) – Annex B: B8.2.8.1, B8.11 (Doc. SCP/ETHOXY/010).

10. Ethoxysulfuron (1997), Monograph prepared in the context of inclusion in Annex I to Council Directive 91/414/EEC - Ministerio della Sanita, Italy.

7. ACKNOWLEDGEMENTS

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

Carcinogenicity WG: Prof. Maroni (Chairman) and Committee members: Dr. Delcour-Firquet, Dr. Meyer, Dr. Moretto, Prof. Savolainen, Prof. Silva Fernandes, Dr. Speijers and invited experts Prof. Galli, Prof. Parry, Dr. Rice, Prof. Schulte-Hermann and Dr. Wester.