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SCIENTIFIC COMMITTEE ON PLANTS **SCP/PROSULF/002-Final**
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OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS REGARDING THE EVALUATION OF PROSULFURON [CGA-152005] 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 7 June 2001)

A. TITLE

OPINION OF THE SCIENTIFIC COMMITTEE ON PLANTS REGARDING THE EVALUATION OF PROSULFURON [CGA 152005] IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC CONCERNING THE PLACING OF PLANT PROTECTION PRODUCTS ON THE MARKET

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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. Can the Committee comment on the acceptability of the risk of metabolites M5 and CGA 349707 to sediment dwelling organisms?

2. The Committee is requested to comment on possible hormonal disruption effects on uterus and mammary glands in test animals and possible relevance to humans

C. OPINION OF THE COMMITTEE

Opinion on question 1:

The Committee concludes that the risks of the metabolites M5 and CGA 349707 of prosulfuron to sediment-dwelling species have not been adequately assessed. In addition the Committee notes that other persistent metabolites are formed in significant quantities in sediment-water tests. The risks associated with these other metabolites do not appear to have been assessed.

Opinion on question 2:

The Committee concludes that the possibility that prosulfuron might have a mild oestrogenic effect at high doses in rats cannot be excluded. However, since this possible effect is observed in rats well above the NOAEL[1]/LOAEL[2] used for setting the ADI[3] and AOEL[4] and is not observed in other species, it is not considered relevant for human risk assessment of prosulfuron in the context of its intended uses.

[1] No Observed Adverse Effect Level.
[2] Lowest Observed Adverse Effect Level.
[3] Acceptable Daily Intake.
[4] Acceptable Operator Exposure Level.

A. TITLE

SCIENTIFIC REPORT ON THE EVALUATION OF PROSULFURON [CGA 152005] IN THE CONTEXT OF COUNCIL DIRECTIVE 91/414/EEC CONCERNING THE PLACING OF PLANT PROTECTION PRODUCTS ON THE MARKET

B. TABLE OF CONTENTS

C. BACKGROUND

Prosulfuron is a new active substance in the context of Directive 91/414/EEC. The draft Commission Directive for inclusion of prosulfuron [CGA-152005] 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. The Committee had been supplied with the documentation listed below.

Prosulfuron is a new herbicide of the sulfonylurea family for the control of broad-leaved weeds in maize at a maximum rate of 15 g a.s./ha in association with bromoxynil (maximum rate of use 300 g a.s/ha) with one application per season. It acts by inhibiting the enzyme acetolactase synthase (ALS) which is required for the synthesis of essential amino acids.

In a water/sediment study, two secondary metabolites (M5 and CGA 349707) were found in significant concentrations. On the basis of the data available, the RMS concluded that no particular risk is expected. The Committee is requested to comment on the acceptability of the risk of secondary metabolites M5 and CGA 349707 to sediment dwelling organisms.

In addition, in the evaluation process, the Rapporteur Member State (RMS) considered possible indication of hormonal disruption on uterus and mammary glands in rats at high dose levels. However, in the absence of specific studies and taking into account the prosulfuron properties and the specific sensitivity of the rat, it was concluded that the possible hormonal disruption was overestimated. The Committee is now requested to comment on the possible hormonal disruption effects in rats and its possible relevance to human.

Source documents made available to the Committee:

1. Prosulfuron: Terms of reference, submitted by DG Health and Consumer Protection, 7 August 2000 (SCP/PROSULF/001).

2. Prosulfuron: Evaluation table - Doc. SANCO/3054/99 rev. 0 (03.07.00) submitted by DG Health and Consumer Protection, 7 August 2000 (SCP/PROSULF/003).

3. Prosulfuron: Addendum to the Monograph of the active substance: prosulfuron – Ecotoxicology, prepared by France, submitted by DG Health and Consumer Protection, 7 August 2000 (SCP/PROSULF/004).

4. Prosulfuron: Danish comments (microcosm study), Ecotoxicology, submitted by DG Health and Consumer Protection, 7 August 2000 (SCP/PROSULF/005).

5. Prosulfuron: draft evaluation report (monograph) on the evaluation of prosulfuron in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market, prepared by France as Rapporteur Member State (volumes 1 to 3), December 1998.

6. Prosulfuron: Syngenta assessment of the Risk of Metabolites M5 and CGA 349707 to Sediment dwelling Organisms, 3 pages – submitted by the notifier (property of Syngenta).

D. SCIENTIFIC BACKGROUND ON WHICH THE OPINION IS BASED

I. Question 1:

Can the Committee comment on the acceptability of the risk of metabolites M5 and CGA 349707 to sediment dwelling organisms?

Opinion of the Committee:

The Committee concludes that the risks of the metabolites M5 and CGA 349707 of prosulfuron to sediment-dwelling species have not been adequately assessed. In addition the Committee notes that other persistent metabolites are formed in significant quantities in sediment-water tests. The risks associated with these other metabolites do not appear to have been assessed.

Scientific background on which the opinion is based:

Metabolites of prosulfuron identified in aerobic and anaerobic water-sediment studies include CGA 159902 (max. 51% in water in anaerobic systems), CGA 300406 (max. 27% in anaerobic systems), CGA 150829 (max. 11% in sediment in anaerobic systems), CGA 325025 (max. 6% in water in aerobic systems), CGA 325028 (max. 22% in water in anaerobic systems) and CGA 349707 + M5 (max 44% in aerobic systems) (Monograph Volume 3, pp. 234-235). After one year, significant amounts of the applied radioactivity (AR) were recovered as extractable (up to 51%) and non-extractable (up to 22%) residues in the sediment.

Acute toxicity of prosulfuron to *Daphnia magna* was determined to be > 120 mg/l (=48 h EC_{50}[5], but only one concentration was tested); the 21 day NOEC[6] was determined to be 148 mg/L. Acute toxicity tests were performed with several of the metabolites using *Daphnia magna* and the results are as follows:

Chemical	**Maximum % detected in various water-sediment studies**[7]	**48 h EC_{50} for *Daphnia magna* (mg/L)**
Prosulfuron	70	> 120
CGA 159902	51	74
CGA 300406	27	>100
CGA 349707 + M5	44	> 100 (for CGA 349707)
CGA 150829	11	16
CGA 325025	6	Not tested
CGA 325028	22	Not tested
'others' (include CGA325026, CGA325027, CGA325030, G28533, CGA188838)	Exact percentages not given in monograph, but G 28533 and CGA 325030 reached > 10%	Not tested

No chronic tests with *Daphnia magna* were performed with any of the metabolites. No test was performed with prosulfuron or any of its metabolites with a sediment-dwelling species.

The absence of chronic test was justified by the following arguments:

1. The chronic toxicity of prosulfuron to *Daphnia magna* is low.

2. Comparison of the acute toxicity of prosulfuron and its metabolites to *Daphnia magna* indicated that the metabolites were not more toxic than the parent compound.

3. Despite significant partitioning of prosulfuron and its metabolites to sediment, predicted concentrations in sediments resulting from agricultural usage of the parent are likely to be very low.

The Committee's response to these is as follows:

1. Toxicity to *Daphnia* is an inappropriate trigger for requiring a test with sediment-dwelling species (SCP, 2000). If aquatic sediments are likely to be exposed to an active substance or its metabolites, then the risk to sediment dwellers should be addressed.

2. Comparison of acute toxicity of prosulfuron and its metabolites is inadequate because:

[5] Median effective concentration.
[6] No Observed Effect Concentration.
[7] Monograph Volume 3, pp. 234-235. The percentages reported are from different studies which is the reason why the sum adds up to > 100%.

- the test of prosulfuron used only one concentration (i.e., > 120 vs. > 100 is not a helpful comparison),

- the test with the parent substance was conducted under flow-through conditions whereas the tests with the metabolites were conducted under static conditions,

- the toxicity of M5 was not tested, though the notifier provided indirect evidence that the toxicity of this metabolite is likely to be > 1 mg/l based on the results of the test with its precursor CGA 300406 (notifier assessment), and

- two of the metabolites are more toxic to Daphnia than prosulfuron (even though the former were tested under static conditions and the latter under flow through). Predicted sediment concentrations do appear to be low, however the Committee is concerned;

- because the metabolites appear to be persistent in sediments (after 1 year 43.3% of the applied parent radioactivity could be recovered as metabolites M5 + CGA 349707 in sediment-water systems with 15.4 % AR in the sediment phase) (notifier assessment), and

- given the degree of uncertainty in the predicted sediment concentrations (e.g., input to sediment via runoff has not been estimated).

As indicated above, the Committee noted that persistent metabolites other than M5 and CGA 349707 formed in significant quantities in sediment-water tests, yet the risks associated with these other metabolites do not appear to have been quantified (Monograph Volume 3, p. 270). The Committee's overall conclusion therefore is that the risks of the metabolites of prosulfuron to sediment-dwelling species have not been adequately assessed.

II. Question 2

The Committee is requested to comment on possible hormonal disruption effects on uterus and mammary glands in test animals and possible relevance to humans.

Opinion of the Committee:

The Committee concludes that the possibility that prosulfuron might have a mild oestrogenic effect at high doses in rats cannot be excluded. However, since this possible effect is observed in rats well above the NOAEL/LOAEL used for setting the ADI and AOEL and is not observed in other species, it is not considered relevant for human risk assessment of prosulfuron in the context of its intended uses.

Scientific background on which the opinion is based:

II.1 Introduction

Endocrine disrupting chemicals are by definition exogenous substances that cause adverse health effects in an intact organism, or its progeny, or in (sub)populations consequent to primary changes in endocrine function. It is theorised that these agents are responsible for reproductive abnormalities in humans, livestock and wildlife and for the

increased incidence of tumours occurring in endocrine responsive tissues (SCP, 1999). The complexity of hormonal interaction makes the evaluation of dose-response curves derived from toxicological data with endocrine disruptors difficult. The SCP has previously suggested (SCP, 1999) to add testing for more appropriate endpoints if a compound is suspected of being an endocrine disruptor. Since hormonal disruptors may promote the occurrence and development of tumours via proliferating effects, tumour incidences have to be registered.

II.2 Findings from prosulfuron studies

From the prosulfuron monograph the following data were considered:

1. The observations which could indicate an endocrine effect of prosulfuron came from the 2 year chronic toxicity/oncogenicity study with Crl:CD(SD)BR rats. These were the increased incidence of cystic uterine endometrial hyperplasia (52% incidence in controls versus 86% incidence in top dose females) and uterine horn dilatation (8% incidence in controls versus 18% in top dose females, i.e. 4000 ppm equal to 205.8 mg/kg bw/day) as well as the increased incidence of acinar atrophy of the mammary gland in top dose males (49% in controls versus 63% incidence at 4000 ppm equal to 160.9 mg/kg bw/day for males), indicating a possible oestrogenic effect of prosulfuron or its metabolites. This study also showed a slight increase in the incidence of testicular interstitial cell tumours in male rats (8.57% in the 2000 ppm group equal to 79.9 mg/kg bw/day for males versus 1.6% in the control group and a historical control range of 0% – 6.67%), and a small increase in the incidence of mammary gland adenocarcinomas in females at the same dose levels (26% at 2000 ppm equal to 95.7 mg/kg bw/day for females versus 17.5% in controls). However, when the increased survival of animals from these groups was considered, the changes were not significant. There was an apparent earlier onset of mammary gland adenocarcinomas in females, but no significance was obtained for this observation.

   In the carcinogenicity study with mice as well as in the one year dog study, possible endocrine effects were not observed.

2. No disturbances of the reproductive performance (precoital interval, mating index, parturition index, gestation length) were found during the two generation reproductive toxicity study in rats. There was a significant reduction of the pup body weight on lactation day 14 and 21 in the two highest dosage groups (2000 ppm equal to 119 mg/kg bw/day in males and 147 mg/kg bw/day in females and 4000 ppm equal to 245 mg/kg bw/day in males and 304 mg/kg bw/day in females). Maternal body weights for these two groups were also decreased.

3. Prosulfuron was reported not to be teratogenic in studies with rats and rabbits, although in rats a high incidence of skeletal malformations (extra rudimentary thoracic ribs, constricted thoracic vertebrae) was found in the top dose groups (200 and 400 mg/kg bw/day from gestational day 6 to 15). As reported for other members of this class of compounds an impaired ossification might have caused these alterations.

4. Prosulfuron did not exhibit genotoxic effects in various test systems (Ames test, mammalian gene mutation assay, cytogenetic test, autoradiographic DNA-repair test).

5. The critical target organ in animals was the liver and to a lesser degree the haematopoietic system. A reduction of body weight in both sexes was observed at relatively low doses in short term toxicity studies with rats, mice, and dogs. NOELs based upon these effects were used to establish ADI (NOEL 1.9 mg/kg bw/day) and AOEL (NOEL 5.9 mg/kg bw/day).

II.3 Conclusion

The Committee considers that the only observations that could indicate endocrine disruptive effects are the increased incidence of cystic uterine endometrial hyperplasia, uterine horn dilatation in females and acinar atrophy of the mammary glands in males at 4000 ppm (equal to 160.9 mg/kg bw/day for males and 205.8 mg/kg bw/day for females) in the 2 year dietary study in the rat. Data on reproduction do not indicate endocrine disrupting activity of prosulfuron at the highest dose tested of 4000 ppm (equal to 245 mg/kg bw/day in males and 304 mg/kg bw/day in females). Prenatal developmental toxicity studies do not show any effects to be related with endocrine disruption and no significant increased incidences of hormone related tumours were seen in carcinogenicity studies in rats. Moreover, short and long term studies in mice and dogs do not show any hormone related effect.

The Committee concludes that the possibility that prosulfuron might have a mild oestrogenic effect at high doses in rats cannot be excluded. However, since this possible effect is observed in rats well above the NOAEL/LOAEL used for setting the ADI and AOEL and is not observed in other species, it is not considered relevant for human risk assessment of prosulfuron in the context of its intended uses.

E. REFERENCES

SCP (1999) Opinion of the Scientific Committee on Plants on Endocrine disruption relevance 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 2 December 1999).
http://europa.eu.int/comm/food/fs/sc/scp/out55_en.html

SCP (2000). Opinion of the Scientific Committee on Plants regarding the Draft guidance document on relevant metabolites (Document SANCO/221/2000-Rev.2 of October 1999) (Opinion adopted by the Scientific Committee on Plants on 30 November 2000). http://europa.eu.int/comm/food/fs/sc/scp/out82_ppp_en.html

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