# Opinion of the Scientific Committee on Plants CP regarding the evaluation of amitrole 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 6 June 2000) (SCP/AMITR/002-Final)

## 1. TITLE

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

## 2. TERMS OF REFERENCE

The Scientific Committee on Plants is requested to respond to the following questions 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.

1) Can the Committee confirm that the appropriate study for the estimation of the AOEL [2] is the dermal 28-day study? If not, which study would the Committee propose?

2) Can the Committee comment on the relevance for man of the thyroid tumors found in rodents?

## 3. BACKGROUND

Amitrole also known as aminotriazole is an existing active substance in the context of Directive 91/414/EEC concerning the placing of plant protection products on the market and is one of the active substances covered by the first stage of the work programme provided for under the Directive.

In order to prepare its opinion, the Scientific Committee on Plants had access to documentation comprising a monograph prepared by France as Rapporteur Member State (RMS) and the recommendations of the ECCO [3] Peer Review Programme.

Amitrole is a non-selective broad spectrum systemic herbicide mainly acting via the foliage but also with some activity through the roots. It is used on cultivated areas and for total weed control in non-cropping situations, such as, roadsides, railway lines and buildings. Rates of applications vary from 1.2 to 3.6 kg a.s./ha.

## 4. OPINION

### 4.1. Question 1

Can the Committee confirm that for amitrole, the appropriate study for the estimation of the AOEL is the dermal 28-day study? If not, which study would the Committee propose?

**Opinion**

Due to the toxicological properties of amitrole, the NOAEL [4] of 100 mg/kg bw/day observed in the dermal 28-day study in rats can be used for the derivation of AOEL, taking into consideration an estimated skin absorption rate of 0.1-1 %.

**Scientific background on which the opinion is based**

Amitrole has been subjected to extensive toxicological testing. The main resulting evidence can be summarised as follows:

> Oral absorption of amitrole in rats is fast, distribution is rapid without evidence of accumulation, metabolism is limited, and excretion is complete mainly through urine as unchanged compound. Blood levels of amitrole in rats are identical after 4 and 21 day administration indicating the absence of accumulation. The critical effect of amitrole in experimental animals consists of an anti-thyroid action due to blockage of thyroid peroxidase, decrease of thyroid hormone levels and the consequent stimulation of the thyroid by the pituitary gland. The fall in the level of thyroid circulating hormones in the dosed animals is considered to be a reliable and early indicator of such an effect. Consistent with its physico-chemical properties, absorption of amitrole through skin is very limited. A study in rats indicated that only 0.1% amitrole penetrates the skin **.** An **in vitro** study on human skin indicated dermal absorption varying from 0.5 to 3.5 %. A 15-day dermal toxicity study performed in 1984 in rabbits and a more recent 28-day dermal toxicity study in rats, performed according to the OECD Guideline n° 410, indicated a NOAEL of 100 mg/kg bw/day. The comparison of these NOAELs with the NOAEL of 1.5 mg/kg bw/day observed in an oral 28-day study in rats and with the NOAEL of 0.1 mg/kg bw/day observed in an oral 13-week study in male rats confirms that the ratio between skin and oral absorption is of about two to three orders of magnitude.

An overall evaluation of the results of the studies available in several species (rats, rabbits, mice, hamsters, dogs, monkeys and humans) indicates that:

> > oral short-term and long-term NOAELs in rats differ by only one order of magnitude; dermal short-term toxicity, when considering the rate of skin absorption, also provides a similar NOAEL; the NOAELs for the critical effect on thyroid in species other than the rat are either similar or greater; primates, including man, appear to be much less sensitive than rats to the critical thyroid effect.

**Conclusion.**

In order to derive the AOEL for amitrole, the NOAEL of 100 mg/kg bw/day observed in the dermal 28-day study in rats can be used. Estimating the skin absorption rate at around 0.1-1 %, such a NOAEL would provide an estimated no-effect absorption level of 0.1-1 mg/kg bw/day which is comparable to the NOAEL of 1.5 mg/kg bw/day observed in the oral 28-day

study in rats and the NOAEL of 0.1 mg/kg bw/day observed in the oral 13-week study in rats (estimated oral absorption rate: 100%).

### 4.2. Question 2

Can the Committee comment on the relevance for man of the thyroid tumors found in rodents?

### Opinion

The thyroid tumours found in rats after long-term amitrole treatment appear to be of little or no relevance for humans. The thyroid carcinogenic effect of amitrole appears to be mediated through thyroid-pituitary disruption to which humans are less sensitive than rodents.

### Scientific background on which the opinion is based

Amitrole has been shown to be goitrogenic in several species including mice, rats and hamsters and causes thyroid cancer in rats after prolonged exposure. Antithyroid effect of amitrole appears to be linked to its inhibition of thyroid peroxidase which is thought to catalyse both thyroglobulin iodination and tyrosine (3-monoiodotyrosine and 3,5-diiodotyrosine) coupling, leading to the formation of the thyroid hormones T4 (3,3,3',5'-tetraiodotyronine) and T3 (3,5,3'-triiodotyronine). Consequently, rats treated with amitrole have low serum T4 and T3 levels with a parallel increase in TSH [5] levels. In turn, high TSH levels cause increased thyroid weight and follicular cell number (with associated increased mitotic activity) which might progress towards malignancy. It should be pointed out that progression to malignancy can be, at least partially, halted by administration of thyroid hormones or surgical hypophysectomy, both procedures leading to reduced TSH levels (3, 4, 5).

It should also be noted that adult rats lack the thyroid hormone binding globulin, which is the specific high-affinity serum carrier protein present in humans. The absence of this carrier protein results in a greater proportion of free serum thyroid hormones, which is readily available to metabolism and excretion. Consequently, these hormones have a shorter half-life and the required accelerated production is driven by very high TSH levels. These levels are much higher in rats than in humans (6- to 60-fold) which renders rats more sensitive than humans to chemically induced thyroid-pituitary disruption (1, 2, 3).

Genotoxicity studies with amitrole gave negative results in most tests. Whether a potential genotoxicity might play a role in thyroid cancerogenesis after hypertrophic and hyperplastic stimulation remains to be ascertained. However, tumours in rats have been observed only after thyroid homeostasis disruption [6].

Conflicting data have been reported that relate to high TSH levels and thyroid cancer in humans. Pre-existing goitre or thyroid nodules seem related to increased thyroid cancer risk; however, an association between hypothyroidism and thyroid cancer has not been demonstrated. The only known human thyroid carcinogen is x-irradiation and no chemical has been identified as being carcinogenic to the human thyroid (1, 2, 3, 4).

In summary, humans appear to be less sensitive to thyroid disruption than rodents. Furthermore, rats show significant increases in thyroid cancer associated with thyroid - pituitary disruption while humans show little increase, if any.

In conclusion, since

> the thyroid carcinogenic effect of amitrole appears to be mediated through thyroid-pituitary disruption to which humans are less sensitive there does not seem to be a role for increased TSH in human thyroid carcinogenicity,

the thyroid tumours found in rats after long-term amitrole treatment appear to be of little or no relevance for humans.

## 5. REFERENCES


- (1) Capen CC, Dybing E, Rice JM, Wilbourn JD. Species differences in thyroid, kidney and urinary bladder carcinogenesis. IARC Scientific Publication No. 147. IARC, France, 1999.
- (2) Hill RN, Crisp TM, Hurley PM, Rosenthal SL, Singh DV. Risk assessment of thyroid follicular tumors. Env Health Perspect 1998, 106:447-457.
- (3) Hurley PM, Hill RN, Whiting RJ. Mode of carcinogenic action of pesticides inducing thyroid follicular tumors in rodents. Env Health Perspect 1998, 106:436-445.
- (4) WHO/IPCS. Amitrole. Environmental Health Criteria 158. Geneva, 1994
- (5) WHO/IPCS. Amitrole in: Pesticide residues in food - 1993. Geneva, 1994, pp. 3-37.


## 6. LISTE OF DOCUMENTS MADE AVAILABLE TO THE SCP

- (1) Terms of reference: Evaluation of amitrole in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market. (SCP/AMITR/1/).
- (2) Amitrole (aminotriazole): report from Rapporteur Member State (France) on the dossier.
- (3) Amitrole (aminotriazole): Evaluation table and comments to the table. Doc. 6840/VI/97-rev.1 (SCP/AMITR/3/)
- (4) Amitrole: operator exposure - Risk assessment using UK-POEM and German model - summary table. (SCP/AMITR/4)
- (5) Amitrole: draft review report for the active substance 6839/VI/97-rev.0 (SCP/AMITR/5/)

## 7. ACKNOWLEDGEMENTS


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**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 experts Dr. A. Fait; (Question 2) Professors C. L. Galli, J. Parry, R. Schulte-Hermann and Drs. J. Rice and P. Wester

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[1] OJ L 230, 19.08.1991, p.1.

[2] Acceptable Operator Exposure Level

[3] European Community Co-ordination

[4] No Observed Adverse Effect Level

[5] Thyroid stimulating hormone

[6] The Committee is aware that in view of some positive/equivocal or missing genotoxicity data the significance of tumors at sites other than the thyroid in amitrole-treated mice reported in older published studies will be re-evaluated by the International Agency for Research on Cancer (IARC) in the near future.