# Opinion of the Scientific Committee on Plants regarding the possible inclusion of Fenarimol in annex 1 of Directive 91/414/EEC concerning the placing of plant protection products on the market (SCP/FENARI/005-FINAL) - (Opinion adopted by the Scientific Committee on Plants on May 18, 1999)

## TERMS OF REFERENCE

The Commission referred the following two questions to the Scientific Committee on Plants in the context of its work programme to examine existing active substances pursuant to Article 8.2 of Directive 91/414/EEC [1] concerning the placing on the market of plant protection products.

1. How does the Scientific Committee for Plants interpret the multi-generation studies conducted in the guinea pigs and rats and in particular could the aromatase inhibition of fenarimol have effects which might have been overlooked in the evaluation conducted by the rapporteur Member State?

2. Do the toxicological studies submitted for this active substance permit a reliable ADI and AOEL to be established? If so, what ADI and AOEL is recommended by the Committee?

## BACKGROUND

Fenarimol is currently undergoing evaluation in the context of possible inclusion in Annex I to Directive 91/414/EEC. The Committee had been supplied with documentation comprising a dossier provided by Dow AgroSciences, a monograph prepared by the United Kingdom Authorities, the results of the ECCO Peer Review.

Fenarimol is a pyrimidin-5-yl benzhydrol systemic fungicide which has protective, curative and eradicative activity. It is authorised for use as a plant protection product on food and ornamental crops.

## OPINION OF THE COMMITTEE

### Question 1

**How does the Scientific Committee for Plants interpret the multi-generation studies conducted in the guinea pigs and rats and in particular could the aromatase inhibition of fenarimol have effects which might have been overlooked in the evaluation conducted by the rapporteur Member State?**

1. In single- and/or multi-generation studies with fenarimol reduced fertility was shown to be male mediated and only slightly reversible in rats. No treatment-related lesions have been observed in male and female reproductive organs and no effects on sperm morphology have been seen in rats. The histological techniques used have however been poorly reported and it

was considered that the effects of fenarimol on male fertility (especially possible effects on testes and sperm) had not been sufficiently demonstrated in rats.

The Committee considered the reduced fertility in male rats as an adverse effect which is due to a weak but effective inhibition of aromatase by fenarimol. It is known that this species and mice are dependent on aromatase-mediated oestrogen biosynthesis for the organisation and expression of male sexual behaviour. Since fenarimol and/or its metabolites are formed in the body and can cross the maternal/embryo-foetal barriers and the blood/milk barrier of rats, the (male) offspring can be exposed during important phases of sexual differentiation and this might therefore affect fertility.

In addition, dystocia, reduced live-born litter size and reduced post-partum survival occurred in rats exposed to fenarimol; some of these effects have also been seen in mice. These effects are female mediated and the latter effects were considered to be a consequence of substance-related parturition difficulties.

Data provided showed that fenarimol significantly attenuates the sharp decline in progesterone levels that normally occurs in rats over the last few days of pregnancy. This is the explanation for the effects of high dose levels of fenarimol on pregnancy duration and foetal or pup survival. It was noted that this effect of fenarimol is seen in particular in small rodents since these species react on a reduction in ovarian corpora lutea progesterone production as a trigger for the onset of labour. The aromatase inhibition by fenarimol and its specific effects as seen in small rodents is not relevant to the human species.

The two-generation guinea pig study with one dose level of fenarimol was carefully examined by the Committee. Following consideration of the published data on reproductive biology, it would have been preferable to use such study design rather than the rat multi-generation data as the basis for assessing the reproductive toxic risks of fenarimol. The same conclusion was made in the special overview from the notifier (4). However, the Committee was of the opinion that the data from the two-generation guinea pig study with one dose level of fenarimol could not override the data from the rat studies. It was appreciated that the guinea pig, by contrast resembles man in several important respects, especially the aspects discussed above. Indeed, it is open to discussion if the choice for guinea pigs would be preferable when designing safety evaluation studies with hormonally-active agents that have the potential to interfere with human reproductive development. However, this two-generation guinea pig study with fenarimol was judged more as a pilot study and hence the data were considered insufficient to solve the physiological differences between the rat model and the human in respect to sensitivity to the effects of fenarimol on aromatase inhibition.

It was concluded that although the guinea pig model seemed to be the model of choice for defining the level of risk for the human for the effect of aromatase inhibition, the data from this study do not permit an assessment that is quantitatively acceptable. This was mainly due to the insufficient design, such as lack of histopathology, absence of information on time to mating and lack of investigation of effects on the second generation, and the use of only one dose level of fenarimol. This dose level of fenarimol that was selected based on the dose level causing effects in rats, without further explanation on comparitive data..

**CONCLUSION**

- The SCP concluded that the effects of fenarimol on male fertility seen in rats had to be considered relevant for human risk assessment although man is less sensitive than rats to the effects of aromatase inhibition by fenarimol.

- The SCP also concluded that the effects of fenarimol on parturition in rats could be considered as not relevant for human risk assessment. It was further concluded that, apart from male-mediated reduced fertility and effects associated with delayed parturition, there was no convincing evidence for other adverse reproductive effects associated with aromatase inhibition by fenarimol.

**Question 2**

**Do the toxicological studies submitted for this active substance permit a reliable ADI [2] and AOEL [3] to be established? If so, what ADI and AOEL is recommended by the Committee?**

1. The Committee concluded that the single/multi-generation data submitted for this active substance permitted the setting of a reliable NOAEL [4] (relevant for human risk assessment) of 25 ppm (which can be considered equivalent to 2 mg/kg bw per day), based on reduced male fertility observed at 50 ppm and taking parturition effects in rats as not relevant to human risk assessment.

2. **ADI**

With the acceptance of the NOAEL of 25 ppm the ADI proposal of 0.01 mg/kg bw is supported. The ADI proposal of the rapporteur is based on the NOAEL of 1.3 mg/kg bw per day (25 ppm) in a chronic rat study. Such ADI of 0.01 mg/kg bw gives a margin of safety of 730 on the dose level of 130 ppm (7.3 mg/kg bw per day for males) at which severe effects of fertility were noted. This is acceptable because it is reasonable to conclude that humans are not more sensitive than rats to the aromatase-mediated reproductive effects of fenarimol.

**AOEL**

In general terms, an AOEL can be considered as the amount of active substance to which operators using the pesticide product, other workers and bystanders may be exposed without any adverse health effects. An AOEL is expressed in mg/kg bw per day. There is currently a debate within the EU about setting AOELs. An AOEL (based on oral studies) can be considered relevant for repeated exposure of operators. A systemic AOEL should be corrected for the amount of oral absorption but this is not necessary for fenarimol because oral absorption is extensive.

The proposal in the fenarimol monograph is as follows:

AOEL = 0.1 mg/kg bw per day based on NOAELs of 12.5 mg/kg bw per day (based on mild bile stasis in 12-month dog study) and 13 mg/kg bw per day (based on evidence of delayed foetal development in absence of maternal toxicity in rat developmental toxicity study).

The question is whether this proposal is acceptable because effects on fertility and parturition have been seen in rats at doses below 12.5 mg/kg bw per day. Since the fertility effects of fenarimol are considered relevant for human risk assessment and assuming that pregnant

operators/ workers/ bystanders and the developing foetus could be exposed during the stage in foetal development when male sexual differentiation and fertility is Â‘organisedÂ’, the relevant NOAEL from the rat multi-generation studies will be 25 ppm (which can be considered equivalent to 2 mg/kg bw per day).

The SCP considers that it is not appropriate to apply an additional safety factor to account for the severity of the fertility effects seen at 130 ppm. Accordingly, it is appropriate to apply a 100-fold safety factor to give an AOEL of 0.02 mg/kg bw per day.

## OVERALL CONCLUSION

- The SCP concluded that the effects of fenarimol on male fertility seen in rats had to be considered relevant for human risk assessment although man is less sensitive than rats to the effects of aromatase inhibition by fenarimol.

- The SCP also concluded that the effects of fenarimol on parturition in rats could be considered as not relevant for human risk assessment. It was further concluded that, apart from male-mediated reduced fertility and effects associated with delayed parturition, there was no convincing evidence for other adverse reproductive effects associated with aromatase inhibition by fenarimol.

- The toxicological studies submitted for fenarimol permit to establish a reliable ADI and AOEL. The SCP agrees with the proposed ADI of 0.01 mg/kg bw and suggests to adopt an AOEL of 0.02 mg/kg bw.

## ACKNOWLEDGEMENTS

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- 7. DowAgroSciences Â– Billington, R and Carey, E.W. 1997.
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[1] OJ No 230,19.8.1991, p.1 [2] Acceptable daily intake [3] Admissible operator exposure level [4] No observed adverse effect level