Opinion of the Scientific Committee on Plants regarding reproductive effects of Vinclozolin in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market (SCP/VINCLO/019-Final) - Opinion expressed by the SCP on 28 October 1999

TERMS OF REFERENCE

The Scientific Committee on Plants (SCP) is asked to consider the following questions:

1) Is there enough scientific evidence to support the assumption that reproductive effects observed in rats would not occur at significantly lower doses in humans i.e. that humans might be significantly more sensitive? In this respect the Committee is requested to comment particularly on the possible increased sensitivity of infants and children to these effects.

2) Are the reproductive effects of vinclozolin mediated via an acute or (sub-)chronic exposure response?

BACKGROUND

In the context of its work to establish maximum pesticide residue limits (MRLs) pursuant to the relevant Community legislation, the Commission invited the SCP to address the above mentioned questions. These questions have been addressed to the Committee in order to facilitate the estimation of an acceptable daily intake (ADI) and provide guidance on the nature of the appropriate dietary risk assessment applicable to vinclozolin.

Vinclozolin belongs to the dicarboximides group of fungicide and is fungitoxic against spore germination and mycelial growth. It is a contact fungicide with local systemic properties and controls infections caused by **Botrysis, Monilinia and Sclerotinia** in a wide range of fruit, vegetables, ornamentals and amenity turf.

OPINION OF THE COMMITTEE

Question 1a

Is there enough scientific evidence to support the assumption that reproductive effects observed in rats would not occur at significantly lower doses in humans i.e. that humans might be significantly more sensitive?

Answer 1a.

The Committee is satisfied that the notifier submitted sufficient data to establish that the mode of action by which the reproductive effects are mediated is through the competitive binding to androgen receptors. For obvious reasons the notifier could not present data from human studies relating to the substance. To overcome the problem data are available from a medicinal product, flutamide, used as an anti-androgen which acts through androgen receptor

binding. These data indicate that the activity of flutamide is comparable in humans and in rats. Hence, the different test animal species used (rats, mice and dogs) are considered valid and relevant models for chemicals with this mode of action. The results of these studies do not indicate that humans will be affected by such substances at significantly lower doses, i.e. there is no reason to expect that humans would be more sensitive to vinclozolin than rats.

Question 1b.

In this respect the Committee is requested to comment particularly on the possible increased sensitivity of infants and children to these effects.

Answer 1b.

The effects induced in rats by vinclozolin during the development period are irreversible. This contrasts with the situation in adult animals where the effects have been shown to be reversible. Furthermore, the effects occur at lower doses during development than in adults. In this context, the Committee concludes that the situation in humans would not be expected to be different from that seen in rats.

Question 2.

Are the reproductive effects of vinclozolin mediated via an acute or (sub-)chronic exposure response?

Answer 2.

In the area of developmental toxicity the following four main principles are of paramount importance: time of exposure, mode of action, genetics of the organism and the existence of a threshold dose. In the case of vinclozolin it is unlikely that a single dose would induce a developmental effect for the following reasons:

- a) the known mode of action of the substance;
- b) the fact that humans are not more sensitive than laboratory animal models; and
- c) the realistic level of a single exposure.

ACKNOWLEDGEMENTS

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

Professor M. Maroni (Chairman), and Committee Members Professor A. Silva Fernandes, Drs M-P Delcour, R. Hans, G. Speijers and invited experts Professors P. Peters and I. Chahoud and Dr O. Meyer.

REFERENCES

- 1. Dossier prepared by BASF in the context of the revaluation programme pursuant to Directive 91/414/EEC.
- 2. Monograph prepared by the French Authorities as Rapporteur Member State.

- 3. Review Report prepared by the Commission services of the Directorate-General for Agriculture and the recommendations of the ECCO Peer Review Programme
- 4. Summary document 6293/VI/99-rev3: vinclozolin Safety Assessment Â– Open Questions
- 5. Questions of clarifications sought by the SCP from the notifier BASF (Document SCP/VIMCLO/012 dated 28 June 1999).
- 6. Response of BASF dated 3 August 1999 to questions of clarifications from the SCP comprising three files and 30 studies).