

Opinion of the Scientific Committee on Plants regarding the evaluation of warfarin in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market (Opinion expressed by the Scientific Committee on Plants on 6 June 2000) (SCP/WARFAR/002-Final)

1. TITLE

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

2. TERMS OF REFERENCE

In the context of the possible inclusion of warfarin in Annex I to Directive 91/414/EEC ¹, the Commission consulted the Scientific Committee on Plants (SCP) on the following question:

The Committee is requested to comment on the acceptability of using clinical data generated following repeated warfarin use as an anti-coagulant in human medicine for establishing an Acceptable Daily Intake (ADI) and an Acceptable Operator Exposure Level (AOEL).

3. BACKGROUND

Warfarin 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 report prepared by Ireland as Rapporteur Member State (RMS) and the recommendations of the ECCO ² Peer Review Programme.

In addition to its rodenticide uses warfarin is used as a human medicine. During its evaluation numerous major data gaps have been identified, particularly in the toxicological data package. These include studies on chronic toxicity, carcinogenicity and multigeneration. The SCP is requested to give its opinion on the need for these core study requirements for a plant protection product given the long history of the safe clinical use of warfarin.

4. OPINION OF THE COMMITTEE

4.1 Question

The Committee is requested to comment on the acceptability of using clinical data generated following repeated warfarin use as an anti-coagulant in human medicine for establishing an Acceptable Daily Intake (ADI) and an Acceptable Operator Exposure Limit (AOEL).

4.2 Opinion

The SCP is of the opinion that it is not necessary to allocate an ADI for warfarin. However, data available from the extensive clinical use of warfarin as an anticoagulant may confidently be expected to support the establishment of an ADI, should this be considered necessary. An AOEL can likewise be established based on human data, taking into account that in rats about 15% of the applied dose is absorbed through the skin.

4.3 Scientific background on which the opinion is based

The intended use of warfarin-based products as rodenticides does not result in any significant exposure of the general population. Furthermore, dietary intake is not a route of exposure resulting from the use of warfarin as a rodenticide since it is not intended to be applied to crops. Therefore, it does not appear necessary to establish an ADI.

Warfarin-based products are liquid concentrate (0.5%), powder (0.5%) or solid bait (0.05%). Worker exposure occurs during preparation of baits (from the liquid concentrate) and handling of the tracking powder or of the baits. Given the low volatility of warfarin, only dermal exposure may be relevant (percutaneous studies of ¹⁴C labelled warfarin in rats showed absorption of radioactivity applied to 14.4%), although inhalation cannot be totally excluded when handling the tracking powder.

Warfarin (a 4-hydroxycoumarin derivative) is an anticoagulant, which acts as a vitamin K antagonist. Its effect is related to inhibition of vitamin K epoxide-reductase which causes depletion of the reduced form of vitamin K. In turn, this causes inhibition of the synthesis of a number of blood coagulation factors which are synthesised in the liver via reduced vitamin K-dependent steps (4).

Warfarin is widely used in humans for both short-term (weeks-months) and long-term (years) oral anticoagulation therapy. The latter mainly in long-term (life-time) prevention of stroke in chronic atrial fibrillation, post-operative therapy after heart valve replacement and post-myocardial infarction therapy. Therapeutic doses prolong prothrombin time (as assessed by determining the International Normalised Ratio - INR) within defined ranges according to the pathological condition to be treated: doses vary between 2 and 10 mg/person/day (3).

A number of clinical trials have been conducted to assess both the efficacy and possible adverse effects of warfarin therapy. The most frequent adverse effects were bleeding episodes, which tend to decline if patient's INR is frequently monitored. In approximately 50 years of clinical use of this drug only a few cases of the so-called "Warfarin-induced skin necrosis" have been described. These cases typically occur in obese, middle-aged patients (usually female) who develop haemorrhagic lesions after about a week of treatment, generally in the extremities and in areas with subcutaneous fat. Other non-haemorrhagic adverse reaction are: ecchymosis and purpura in subjects with skin fragility, maculo-papular, vesiculous, or urticated rashes, and the "purple toes syndrome" probably due to cholesterol microemboli from atheromas of the aorta (2). There are also reports that patients with long-term anticoagulant (not warfarin) therapy have a reduced bone mass: this effect might be related to the fact that three vitamin K - dependent proteins are present in the bone but this effect does not appear to be associated with clinical consequences in developed organisms (4).

The administration of warfarin to women during the first trimester of pregnancy is associated with about 5% incidence of foetal anomalies known as "foetal warfarin syndrome" or "warfarin embryopathy". This is characterised by nasal hypoplasia, bone anomalies and bone-growth retardation which might be related to interference with vitamin-K dependent bone proteins. Administration of warfarin during the second or third trimester of pregnancy may lead to foetal loss and CNS ³ lesions associated with haemorrhage (2). A number of studies on reproduction have been performed in rodents with warfarin with and without the addition of vitamin K to prevent the anticoagulant effects. It was shown that, in fact, administration of vitamin K1 prevented the haemorrhagic syndrome whereas bone lesion, which are comparable to those observed in humans, were not prevented since extrahepatic vitamin K deficiency could not be corrected.

Long-term chronic/carcinogenicity studies are not available due to the difficulty in their performance given the high susceptibility of rodents, especially rats, to the anticoagulant effect of warfarin. Few limited epidemiological studies have been conducted in patients chronically treated with warfarin (or other anticoagulant) and no evidence of increased incidence of malignancies was observed (1). Genotoxicity studies showed some positive results **in vitro**, whereas **in vivo** studies were negative. Taken together, these data do not point to a carcinogenic risk associated with warfarin (or anticoagulant in general) exposure.

A number of acute poisoning incidences with anticoagulants have been reported in the literature, only a few deriving from occupational accidents. The worst cases were associated with anticoagulants different from warfarin. A specific therapy is available for these poisonings (vitamin K1).

5. REFERENCES

- (1) Annegers, J.F., Zacharski L.R. 1980. Cancer morbidity and mortality in previously anticoagulated patients. *Thrombosis Res.* 18: 399-403.
- (2) Gallerani M., Manfredini M., Moratelli R., Moratelli S. 1999. Non-haemorrhagic adverse reactions of oral anticoagulant therapy. *Int. J. Cardiol.* 49:1-7
- (3) Resh H, Pietschmann P, Krexner E, Willvonseder R. 1995. Decreased peripheral bone mineral content in patients under anticoagulant therapy with phenprocoumon. *Eur Heart J* 1991, 12:439-441.
- (4) WHO/IPCS Anticoagulant rodenticides. EHC 175, 1995, Geneva.

6. LISTE OF DOCUMENTS MADE AVAILABLE TO THE SCP

- (1) Terms of reference - Evaluation of warfarin in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market. (SCP/WARFAR/1/)
- (2) Terms of reference - Evaluation of warfarin in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market. (SCP/WARFAR/2/).
- (3) Warfarin: Report from Rapporteur Member State (Ireland) on the dossier.
- (4) Warfarin: draft review report for the active substance - doc. 7579/VI/98-rev.4 (SCP/WARFAR/4/).

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 expert Dr. A. Fait.

¹ OJ L 230, 19. 08. 1991, p. 1.

² European Community Co-ordination

³ Central nervous system