Appendix D

HED Toxicity Profile for Warfarin

(From the 1991 Warfarin RED)

A. Human Health Assessment

1. Toxicology Data Base

This section discusses data available to the Agency for the toxicological evaluation of warfarin and and its sodium salt. All generic toxicology data requirements are satisfied.

Warfarin, a synthetic analogue of Vitamin K, functions as an antivitamin. Warfarin is a member of the coumarin family of chemicals of blood anticoagulants. The sodium salt of warfarin is used as an anticoagulant in the treatment of humans with hypercoagulation problems. The toxicity, mechanism of action, and treatment of overdoses of warfarin are part of the basic training of physicians. The Agency has based its determinations relative to human safety in this document on this body of human evidence and experience.

There is a delay of 12 to 72 hours between the ingestion of a single toxic dose of warfarin and the appearance of the toxic effects (hypocoagulation). The length of this delay is dependent on the normal half-life of the Vitamin K-dependent coagulation factors and is not significantly decreased by administering larger doses of warfarin. The mechanism of action explains the occurrence of toxic effects from daily ingestion of small doses of warfarin.

Warfarin toxicity is manifested in an increase in prothrombin and partial thromboplastin times and a decrease in the Vitamin K-dependent clotting factors, II, VII, IX, and X. Bleeding time, clot retraction, platelet counts, thrombin time, and euglobulin lysis times are usually normal. Signs of toxicity include cutaneous bleeding, hematuria, melena or hematochezia, hematoses, uterine bleeding in women, epistaxis, and gingival bleeding. Death follows excessive external or internal bleeding.

The high toxicity of technical warfarin clearly places it in Toxicity Category I. Because of the physical chemistry of warfarin, dermal and inhalation toxicity are not significant. Human experience with administration of warfarin by both oral and injection routes has produced no reports of allergic or sensitization problems.

Warfarin has clearly been established as a human teratogen at clinical doses. Birth defects have been observed as a result of exposure to coumarin anticoagulants during any trimester of pregnancy. Coumarin derivative use or abuse in pregnant women results in one-sixth of pregnancies ending in abortion or stillbirth. As stated previously, warfarin's toxicity, and mechanism of action in humans are well established. But the concentration of warfarin contained in bait material in products registered for homeowner use is low (0.025 to 1.0% active ingredient). Therefore, there is little potential for human toxicity from a single ingestion of treated bait from these products. Based on the availability and completeness of human information and the registered use patterns of warfarin, additional toxicology studies are not required.

Many incidents or suspected incidents of human exposure to anticoagulant rodenticides are reported annually to poison control centers. However, accidental ingestions of warfarin seldom result in life-threatening or disabling symptoms that can be attributed directly to warfarin, and there does not appear to be any evidence of significant health effects from single ingestions of warfarin.

The exact number of annual pet exposure incidents or suspected incidents that result from the use of warfarin against commensal rodents is unknown but many incidents are reported annually. Dog incidents account for most of the reported nontarget animal exposures. Deaths occur in some pet exposure incidents involving warfarin.

These reported human and pet poisoning incidents point to the need to require tamper-resistant bait stations when baits are applied in areas accessible to children and nontarget animals. Warfarin's use patterns do not trigger the data requirements for applicator or reentry exposure studies.

2. Dietary Exposure

Currently, there are no tolerances or exemptions from the requirement of tolerances for residues of warfarin in or on food/feed items. When the Registration Standard for warfarin was issued in August 1981, no residue chemistry data were required because none of the Federally registered uses was regarded as a food/feed use. Since that time the guidelines for residue chemistry have been issued. The Agency has subsequently determined that the use of tracking powder formulations in agricultural premises and in commercial, industrial, and institutional sites have the potential to contaminate food/feed products from rodents, insects and human tracking residues from treated areas.

The registrants of tracking powder formulations are required either to place additional use restrictions on their product labeling to reduce the likelihood of food or feed contamination, or to develop data to demonstrate whether warfarin can contaminate food/feed products from the currently registered use (refer to the residue chemistry data requirement tables). If a registrant elects to retain the current label with no additional restrictions and the required residue data confirm that warfarin can be transferred to food/feed products, appropriate food/feed additive regulations, supported by a full complement of toxicology and residue chemistry data, will be required. These data requirements can be avoided by the registrants of tracking powders if their product labels are modified to limit the use of tracking powders to areas where food contamination is unlikely.

There are no Codex Maximum Residue Levels for residues of warfarin in or on food/feed items.