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OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Metalaxyl Registration Standard

TO: Lois Rossi, PM Team #21
Registration Division (TS-767)

THRU: Amy Rispin, Chief
Science Integration Staff
Hazard Evaluation Division (TS-769)

Carol L. Monroe for

Introduction

Metalaxyl (N-(2,6-dimethyl phenyl)-N-(methoxyacetyl)-alanine methyl ester) is a systemic fungicide registered for soil and/or foliar application on a wide variety of terrestrial food and non-food crops. When the Guidance Document for Metalaxyl was issued on December, 1981, final Pesticide Assessment Guidelines were not in place. As a result, many of the conclusions made in the original Standard concerning the adequacy of data submitted in support of registrations are not consistent with current policy. Hence, in several cases, we have made new requests for data and, in other cases, data requested were either not submitted or were found to be inadequate. The present document, therefore, cannot be considered final in the strict sense of the word.

The original reviews of a chronic rat and a mouse oncogenicity study indicated apparent dose-related oncogenic effects by metalaxyl. While this gave rise to regulatory concern, subsequent reevaluation of the histopathology and other aspects of the study led the Toxicology Branch Peer Review Committee to conclude that the results of these studies were negative, even though the Maximum Tolerated Dose (MTD) may not have been tested. Further testing is not warranted because: the doses tested were high enough to produce toxicity in the liver, metalaxyl is not structurally related to known oncogens, and available mutagenicity studies indicate no potential genotoxic activity. Adequate evidence thus provides no basis for further concern over the oncogenicity of metalaxyl.

It was also recognized that certain degradates of metalaxyl (see attachment for chemical structures) were highly persistent and both leachable and susceptible to systemic uptake by some plants. Consequently, EPA required ground water monitoring and, for wheat, a tolerance for inadvertent residues was established. These general issues, however, have not been fully resolved and are addressed below.

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Toxicology Summary

Results of adequate tests do not indicate that metalaxyl is oncogenic, mutagenic, or teratogenic. Chronic feeding studies in rats and dogs produced only minor toxicological effects on the liver with an NOEL of 6.25 mg/kg/day in the dog. This provides an ADI of 0.063 mg/kg/day. Acute toxicity is low (Toxicity Category III) for the oral and dermal routes of exposure but an inhalation study is required if the technical grade material is in a respirable form. Additional studies are also needed for general metabolism.

Residue Chemistry

Since HED has no information that metalaxyl is registered for use on leafy vegetable grouping, the group tolerances of 0.1 ppm for various leafy vegetables appear inappropriate and should be revoked.

The nature of the residues in animals is inadequately understood. Metabolism studies are needed in ruminants and in poultry.

A tolerance reassessment can not be completed because the adequacy of the tolerances in animal products can not be determined without the above metabolism studies. We do have a valid ADI and the TMRC for published and pending tolerances is 39% or less of that value for the various subgroups. Therefore, the present inadequacies of the data do not give rise to imminent concerns.

Environmental Fate Issues

Rotational Crop Studies indicate that some crops will take up metalaxyl residues of concern when planted 12 months or more after treatment of a prior crop. Confined studies are needed to identify all residues of concern plus field tests to determine the need for additional inadvertent tolerances. As an interim measure, a 12-month rotational crop interval should be required for all crops for which tolerances have not been established.

Ground Water Monitoring studies were required early in the registration process for metalaxyl. While the subsequent submissions were judged to be sufficient at the time, these studies need to be reviewed again by current standards. An addendum to this memo will clarify the need for additional monitoring and use of a Ground Water Advisory.

Ecological Effects

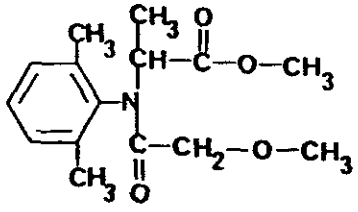
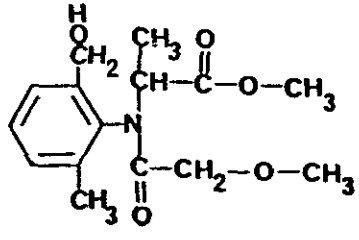
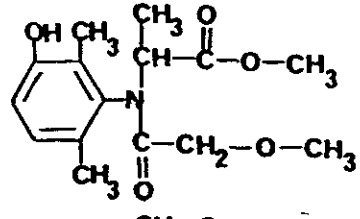
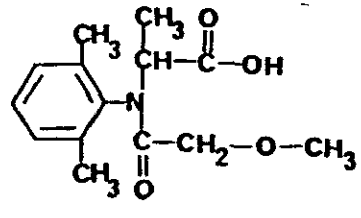
Based on available toxicity studies, no adverse effects to either endangered or non-endangered avian, mammalian, or fresh water aquatic species are expected from currently registered uses of metalaxyl. However, further testing is required on marine/estuarine species and honeybees.

The other identified data gaps do not appear likely to cause regulatory concern at this time.

Kyle Barbehenn
Biologist
Science Integration Staff

cc: A. Barton
Branch Chiefs
O. Gutenson
S. Simko
W. Hazel
R. Gardner

Table 1. Metalaxyl and its metabolites in plants and animals.

Code	Structure	Chemical Name	Common Name/ Abbreviation	Found in:	Reference (MRID)
I		N-(2,6-dimethylphenyl)-N-(methoxyacetyl)-alanine methyl ester	Metalaxyl, CGA-48988	lettuce foliage grapes and grape leaves potato tubers and foliage potato foliage	00114379, 00071610. 00071607, 00071606. 00071603, 00071604. 00071609.
II		N-[2-(hydroxymethyl)-6-methylphenyl]-N-(methoxyacetyl)-alanine methyl ester	CGA-94689	lettuce foliage[a] grapes and grape leaves[a] potato tubers and foliage[a] potato foliage	00114379, 00071610, 00071680. 00071607, 00071606. 00071603, 00071604. 00071609.
III		N-(3-hydroxy-2,6-dimethylphenyl)-N-(methoxyacetyl)-alanine methyl ester	CGA-100255	lettuce foliage[a] grapes and grape leaves[a] potato tubers and foliage[a]	00114379, 00071610, 00071680. 00071607, 00071606. 00071603, 00071604.
IV		N-(2,6-dimethylphenyl)-N-(methoxyacetyl)-alanine	CGA-62826	lettuce foliage[a] grapes and grape leaves[a] potato tubers potato foliage	00114379, 00071610. 00071607, 00071606. 00071603, 00071604. 00071609, 00071604.

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