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Pesticides

EPA

Metalaxyl

N-(2,6-Dimethylphenyl)-N-(methoxyacetyl) alanine methyl ester

Pesticide Registration Standard

METALAXYL

PESTICIDE REGISTRATION STANDARD

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Chapter 1
HOW TO REGISTER UNDER A REGISTRATION STANDARD

Organization of the Standard

This first chapter explains the purpose of a Registration Standard and summarizes the legal principles involved in registering or re-registering under a Standard. The second chapter sets forth the requirements that must be met to obtain or retain registration for products covered by this particular Registration Standard. In the remaining chapters, the Agency reviews the available data by scientific discipline, discusses the Agency's concerns with the identified potential hazards, and logically develops the conditions and requirements that would reduce those hazards to acceptable levels.

Purpose of the Standard

Section 3 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) provides that "no person in any State may distribute, sell, offer for sale, hold for sale, ship, deliver for shipment, or receive (and having so received) deliver or offer to deliver, to any person any pesticide which is not registered with the Administrator [of EPA]." To approve the registration of a pesticide, the Administrator must find, pursuant to Section 3(c)(5) that:

> "(A) its composition is such as to warrant the proposed claims for it;
> (B) its labeling and other material required to be submitted comply with the requirements of this Act;
> (C) it will perform its intended function without unreasonable adverse effects on the environment; and
> (D) when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment."

In making these findings, the Agency reviews a wide range of data which registrants are required to submit, and assesses the risks and benefits associated with the use of

the proposed pesticide. But the established approach to making these findings has been found to be defective on two counts:

First, EPA and its predecessor agency, the United States Department of Agriculture (USDA), routinely reviewed registration applications on a 'product by product' basis, evaluating each product-specific application somewhat independently. In the review of products containing similar components, there was little opportunity for a retrospective review of the full range of pertinent data available in Agency files and in the public literature. Thus the 'product by product' approach was often inefficient and sometimes resulted in inconsistent or incomplete regulatory judgements.

Second, over the years, as a result of inevitable and continuing advances in scientific knowledge, methodology, and policy, the data base for many pesticides came to be considered inadequate by current scientific and regulatory standards. Given the long history of pesticide regulation in several agencies, it is even likely that materials may have been lost from the data files. When EPA issued new requirements for registration in 1975 (40 CFR 162) and proposed new guidelines for hazard testing in 1978 (43 FR 29686, July 10, 1978 and 43 FR 37336, August 2, 1978), many products that had already been registered for years were being sold and used without the same assurances of human and environmental safety as was being required for new products. Because of this inconsistency, Congress directed EPA to re-register all previously registered products, so as to bring their registrations and their data bases into compliance with current requirements [See FIFRA Section 3(g)].

Facing the enormous job of re-reviewing and calling-in new data for the approximately 35,000 current registrations, and realizing the inefficiencies of the 'product by product' approach, the Agency decided that a new, more effective method of review was needed.

A new review procedure has been developed. Under it, EPA publishes documents called Registration Standards, each of which discusses a particular pesticide active ingredient. Each Registration Standard summarizes all the data available to the Agency on a particular active ingredient and its current uses, and sets forth the Agency's comprehensive position on the conditions and requirements for registration of all existing and future products which contain that active ingredient. These conditions and requirements, all of which must be met to obtain or retain full registration or re-registration under Section 3(c)(5) of FIFRA, include the submission of needed scientific data which the Agency

does not now have, compliance with standards of toxicity, composition, labeling, and packaging, and satisfaction of the data compensation provisions of FIFRA Section 3(c)(1)(D).

The Standard will also serve as a tool for product classification. As part of the registration of a pesticide product, EPA may classify each product for "general use" or "restricted use" [FIFRA Section 3(d)]. A pesticide is classified for "restricted use" when some special regulatory restriction is needed to ensure against unreasonable adverse effects to man or the environment. Many such risks of unreasonable adverse effects can be lessened if expressly-designed label precautions are strictly followed. Thus the special regulatory restriction for a "restricted use" pesticide is usually a requirement that it be applied only by, or under the supervision of, an applicator who has been certified by the State or Federal government as being competent to use pesticides safely, responsibly, and in accordance with label directions. A restricted-use pesticide can have other regulatory restrictions [40 CFR 162.11(c)(5)] instead of, or in addition to, the certified applicator requirement. These other regulatory restrictions may include such actions as seasonal or regional limitations on use, or a requirement for the monitoring of residue levels after use. A pesticide classified for "general use," or not classified at all, is available for use by any individual who is in compliance with State or local regulations. The Registration Standard review compares information about potential adverse effects of specific uses of the pesticide with risk criteria listed in 40 CFR 162.11(c), and thereby determines whether a product needs to be classifed for "restricted use." If the Standard does classify a pesticide for "restricted use," this determination is stated in the second chapter.

Requirement to Re-register Under the Standard

FIFRA Section 3(g), as amended in 1978, directs EPA to re-register all currently registered products as expeditiously as possible. Congress also agreed that re-registration should be accomplished by the use of Registration Standards.

Each registrant of a currently registered product to which this Standard applies, and who wishes to continue to sell or distribute his product in commerce, must apply for re-registration. His application must contain proposed labeling that complies with this Standard.

EPA will issue a notice of intent to cancel the registration of any currently registered product to which this Standard applies if the registrant fails to comply with the procedures for re-registration set forth in the Guidance Package which accompanies this Standard.

"Product Specific" Data and "Generic" Data

In the course of developing this Standard, EPA has determined the types of data needed for evaluation of the properties and effects of products to which the Standard applies, in the disciplinary areas of Product Chemistry, Environmental Fate, Toxicology, Residue Chemistry, and Ecological Effects. These determinations are based primarily on the data Guidelines proposed in 1978 (43 FR 29686, July 10, 1978, and 43 FR 37336, August 2, 1978), as applied to the use patterns of the products to which this Standard applies. Where it appeared that data from a normally applicable Guidelines requirement was actually unnecessary to evaluate these products, the Standard indicates that the requirement has been waived. On the other hand, in some cases studies not required by the Guidelines may be needed because of the particular composition or use pattern of products the Standard covers; if so, the Standard explains the Agency's reasoning. Data guidelines have not yet been proposed for the Residue Chemistry discipline but the requirements for such data have been in effect for some time and are, the Agency believes, relatively familiar to registrants. Data which we have found are needed to evaluate the registrability of some products covered by the Standard may not be needed for the evaluation of other products, depending upon the composition, formulation type, and intended uses of the product in question. The Standard states which data requirements apply to which product categories. (See the second chapter). The various kinds of data normally required for registration of a pesticide product can be divided into two basic groups:

(A) data that is "product specific," i.e., data that relates only to to the properties or effects of a product with a particular composition (or a group of products with closely similar composition); and

(B) "generic" data that pertains to the properties or effects of a particular ingredient, and thus is relevant to an evaluation of risks and benefits of all products containing that ingredient (or all such products having a certain use pattern), regardless of any such product's unique composition.

The Agency requires certain "product specific" data for each product to characterize the product's particular composition and physical/chemical properties (Product Chemistry), and to characterize the product's acute toxicity (which is a function of its total composition). The applicant for registration or re-registration of any product, whether

it is a manufacturing-use or end-use product, and without regard to its intended use pattern, must submit or cite enough of this kind of data to allow EPA to evaluate the product. For such purposes, "product specific" data on any product other than the applicant's is irrelevant, unless the other product is closely similar in composition to the applicant's. (Where it has been found practicable to group similar products for purposes of evaluating, with a single set of tests, all products in the group, the Standard so indicates). "Product specific" data on the efficacy of particular end-use products is also required where the exact formulation may affect efficacy and where failure of efficacy could cause public health problems.

All other data needed to evaluate pesticide products concerns the properties or effects of a particular ingredient of products (normally a pesticidally active ingredient, but in some cases a pesticidally inactive, "inert," ingredient). Some data in this "generic" category are required to evaluate the properties and effects of all products containing that ingredient [e.g., the acute LD-50 of the active ingredient in its technical or purer grade; see proposed 40 CFR 163.81-1(a), 43 FR 37355].

Other "generic" data are required to evaluate all products which both contain a particular ingredient and are intended for certain uses (see, e.g., proposed 40 CFR 163.82-1, 43 FR 37363, which requires subchronic oral testing of the active ingredient with respect to certain use patterns only). Where a particular data requirement is use-pattern dependent, it will apply to each end-use product which is to be labeled for that use pattern (except where such end-use product is formulated from a registered manufacturing-use product permitting such formulations) and to each manufacturing-use product with labeling that allows it to be used to make end-use products with that use pattern. Thus, for example, a subchronic oral dosing study is needed to evaluate the safety of any manufacturing-use product that legally could be used to make an end-use, food-crop pesticide. But if an end-use product's label specified it was for use only in ways that involved no food/feed exposure and no repeated human exposure, the subchronic oral dosing study would not be required to evaluate the product's safety; and if a manufacturing-use product's label states that the product is for use only in making end-use products not involving food/feed use or repeated human exposure, the subchronic oral study would not be relevant to the evaluation of the manufacturing-use product either.

If a registrant of a currently registered manufacturing-use or end-use product wishes to avoid the costs of data compensation [under FIFRA Section 3(c)(1)(D)] or data generation [under Section 3(c)(2)(B)] for "generic" data that is required only with respect to some use patterns, he may elect to delete those use patterns from his labeling at the time he re-registers his product. An applicant for registration of a new product under this Standard may similarly request approval of only certain use patterns.

Data Compensation Requirements under FIFRA 3(c)(1)(D)

Under FIFRA Section 3(c)(1)(D), an applicant for registration, re-registration, or amended registration must offer to pay compensation for certain existing data the Agency has used in developing the Registration Standard. The data for which compensation must be offered is all data which is described by all the following criteria:

(1) the data were first submitted to EPA (or to its predecessor agencies, USDA or FDA), on or after January 1, 1970;

(2) the data were submitted to EPA (or USDA or FDA) by some other applicant or registrant in support of an application for an experimental use permit, an amendment adding a new use to a registration, or for re-registration, or to support or maintain in effect an existing registration;

(3) the data are relevant to the Agency's decision to register or re-register the applicant's product under the Registration Standard, taking into account the applicant's product's composition and intended use pattern(s);

(4) the data are determined by EPA to be valid and usable in reaching regulatory conclusions; and

(5) the data are not those for which the applicant has been exempted by FIFRA Section 3(c)(2)(D) from the duty to offer to pay compensation. (This exemption applies to the "generic" data concerning the safety of an active ingredient of the applicant's product, not to "product specific" data. The exemption is available only to applicants whose product is labeled for end-uses for which the active ingredient in question is present in the applicant's product because of his use of another registered product containing that active ingredient which he purchases from another producer).

An applicant for re-registration of an already registered product under this Standard, or for registration of a new product under this Standard, accordingly must determine which of the data used by EPA in developing the Standard must be the subject of an offer to pay compensation, and must submit with his application the appropriate statements evidencing his compliance with FIFRA Section 3(c)(1)(D).

An applicant would never be required to offer to pay for "product specific" data submitted by another firm. In many, if not in most cases, data which are specific to another firm's product will not suffice to allow EPA to evaluate the applicant's product, that is, will not be useful to the Agency in determining whether the applicant's product is registrable. There may be cases, however, where because of close similarities between the composition of two or more products, another firm's data may suffice to allow EPA to evaluate some or all of the "product specific" aspects of the applicant's product. In such a case, the applicant may choose to cite that data instead of submitting data from tests on his own product, and if he chooses that option, he would have to comply with the offer-to-pay requirements of Section 3(C)(1)(D)for that data.

Each applicant for registration or re-registration of a manufacturing-use product, and each applicant for registration or re-registration of an end-use product, who is not exempted by FIFRA Section 3(c)(2)(D), must comply with the Section 3(c)(1)(D) requirements with respect to each item of "generic" data that relates to his product's intended uses.

A detailed description of the procedures an applicant must follow in applying for re-registration (or new registration) under this Standard is found in the Guidance Package for this Standard.

Obtaining Data to Fill "Data Gaps"; FIFRA 3(c)(2)(B)

Some of the kinds of data EPA needs for its evaluation of the properties and effects of products to which this Standard applies have never been submitted to the Agency (or, if submitted, have been found to have deficiencies rendering them inadequate for making registrability decisions) and have not been located in the published literature search that EPA conducted as part of preparing this Standard. Such instances of missing but required data are referred to in the Standard as "data gaps".

FIFRA Section 3(c)(2)(B), added to FIFRA by the Congress in 1978 authorizes EPA to require registrants to whom a data requirement applies to generate (or otherwise produce)

data to fill such "gaps" and submit those data to EPA. EPA must allow a reasonably sufficient period for this to be accomplished.

If a registrant fails to take appropriate and timely steps to fill the data gaps identified by a Section 3(c)(2)(B) order, his product's registration may be suspended until the data are submitted. A mechanism is provided whereby two or more registrants may agree to share in the costs of producing data for which they are both responsible.

The Standard lists, in its summary second chapter, the "generic" data gaps and notes the classes of products to which these data gaps pertain. The Standard also points out that to be registrable under the Standard, a product must be supported by certain required "product specific" data. In some cases, the Agency may possess sufficient "product specific" data on one currently registered product, but may lack such data on another. Only those Standards which apply to a very small number of currently registered products will attempt to state definitively the "product specific" data gaps on a 'product by product' basis. (Although the Standard will in some cases note which data that EPA does possess would suffice to satisfy certain "product specific" data requirements for a category of products with closely similar composition characteristics.)

As part of the process of re-registering currently registered products, EPA will issue Section 3(c)(2)(B) directives requiring the registrants to take appropriate steps to fill all identified data gaps -- whether that data in question is "product specific" or "generic" -- in accordance with a schedule.

Persons who wish to obtain registrations for new products under this Standard will be required to submit (or cite) sufficient "product specific" data before their applications are approved. Upon registration, they will be required under Section 3(c)(2)(B) to take appropriate steps to submit data needed to fill "generic" data gaps. (We expect they will respond to this requirement by entering into cost-sharing agreements with other registrants who previously have been told they must furnish the data.) The Guidance Package for this Standard details the steps that must be taken by registrants to comply with Section 3(c)(2)(B).

Amendments to the Standard

Applications for registration which propose uses or formulations that are not presently covered by the Standard, or which present product compositions, product

chemistry data, hazard data, toxicity levels, or labeling that do not meet the requirements of the Standard, will automatically be considered by the Agency to be requests for amendments to the Standard. In response to such applications, the Agency may request additional data to support the proposed amendment to the Standard, or may deny the application for registration on the grounds that the proposed product would cause unreasonable adverse effects to the environment. In the former case, when additional data have been satisfactorily supplied, and providing that the data do not indicate the potential for unreasonable adverse effects, the Agency will than amend the Standard to cover the new registration.

Each Registration Standard is based upon all data and information available to the Agency's reviewers on a particular date prior to the publication date. This "cut-off" date is stated at the beginning of the second chapter. Any subsequent data submissions and any approved amendments will be incorporated into the Registration Standard by means of addenda, which are available for inspection at EPA in Washington, D.C., or copies of which may be requested from the Agency. When all the present "data gaps" have been filled and the submitted data have been reviewed, the Agency will revise the Registration Standard. Thereafter, when the Agency determines that the internally maintained addenda have significantly altered the conditions for registration under the Standard, the document will be updated and re-issued for publication.

While the Registration Standard discusses only the uses and hazards of products containing the designated active ingredient(s), the Agency is also concerned with the potential hazards of some inert ingredients and impurities. Independent of the development of any one Standard, the Agency has initiated the evaluation of some inert ingredients of concern in a specific product to which the Standard applies, these ingredients will be pointed out in the Guidance Package.

Chapter II

REGULATORY POSITION

A. Introduction

This chapter describes in detail the Agency's regulatory position on products which contain metalaxyl as the sole active ingredient. The regulatory position adopted by the Agency incorporates a number of considerations. Foremost among these considerations is an analysis of the registrability of products containing metalaxyl based on the risk criteria found in Section 162.11(a) of Title 40 of the U.S. Code of Federal Regulations. The Agency's determination is presented below, and the rationale for this decision follows the position.

In addition to the basic regulatory decision and rationale, this chapter includes the following: criteria for the registration of metalaxyl products under the Standard; acceptable ranges and limits for product composition, acute toxicity, and use pattern/application method; required labeling; tolerance reassessment.

The scientific basis for a decision presented in this chapter can be found by reading the various disciplinary chapters (Chapters IV- VIII) which provide summaries of available scientific data on metalaxyl. References to Agency guidelines for testing are provided when appropriate. In instances where the data requirements differ from the guideline requirements, the rationale is presented in the footnotes of the table.

B. Description of Chemical

Metalaxyl [N-(2,6-Dimethylphenyl)-N-(methoxyacetyl) alanine methyl ester] is a white to beige, odorless crystal. Metalaxyl is a fungicide, registered for use in tobacco, ornamentals, and turf. Currently there are no permanent tolerances for the use of metalaxyl on food or feed crops. However, use on a variety of field and vegetable crops may be anticipated. See Chapter V for additional information on use patterns.

Metalaxyl is the accepted common name for the chemical. It is also known under the trade or company names Ridomil®, Subdue®, Apron®, and "CGA 48988". The Chemical Abstracts Registry (CAS) number for metalaxyl is 57837-19-1 and the EPA Shaughnessy number is 113501.

Ciba-Geigy Corporation is the sole producer and registrant.

C. Regulatory Position for Products Containing Metalaxyl

Metalaxyl as described in this Standard may be registered for sale, distribution, reformulation, and use in the United States. Considering information available to the Agency from the open literature and provided by the registrant as of May 30, 1981 (excluding residue data for pending tolerances): the Agency finds that none of the risk criteria found in Section 162.11(a) of Title 40 of the U.S. Code of Federal Regulations were met or exceeded for metalaxyl.

The information available to the Agency at the time of the development of this Standard was adequate to indicate that for the use currently registered, metalaxyl should not cause unreasonable adverse effects when used in compliance with proper label directions and precautions. Metalaxyl products currently registered may be reregistered subject to the conditions imposed for data requirements or other requirements of this Standard. New products may be registered under this Standard, and are subject to the same requirements.

D. Regulatory Rationale

EPA is authorized to issue conditional registrations for new chemicals under certain special circumstances (FIFRA s. 3(c)(7)(c)). These include cases where the early registration is in the public interest and should not under proposed usage conditions cause unreasonable adverse effects on the environment. Metalaxyl was first registered for the formulation of fungicides in 1979 and for use in a formulated product on tobacco in 1980. This use was found to be in the public interest because large potential economic losses due to blue mold in the tobacco crop were anticipated in the 1980 growing season.

Metalaxyl was first registered for use on tobacco with several conditions. These conditions included submission or generation of data in several scientific disciplines, i.e.:

- groundwater and soil monitoring be conducted to assess whether the potential for metalaxyl to leach demonstrated by environmental fate data could contaminate groundwater;
- submission of a 96-hour fish LC_{50} for rainbow trout and bluegill using the emulsifiable concentrate (EC) formulation;
- submission of a 48-hour LC_{50} for aquatic invertebrates using the EC formulation;
- submission of an invertebrate life-cycle test using the technical chemical; and
- a 90-day subchronic inhalation study using the technical chemical in smoke (40 CFR 163.82-4)

The Agency has evaluated submitted data in the area of fish and wildlife and has found that under the proposed usage metalaxyl should not cause unreasonable adverse effects on the environment. Other data are still outstanding and a further assessment of effects of metalaxyl on man and the environment from the current use pattern will be made at the time of submission.

E. Criteria for Registration Under the Standard

To be subject to this Standard, metalaxyl products must meet the following conditions:

- contain metalaxyl as the sole active ingredient;
- be within acceptable standards of product composition;
- be within acute toxicity limits;
- be labeled for acceptable uses; and
- bear required labeling.

Manufacturing-use metalaxyl products must bear label directions for formulation into acceptable end-uses.

The applicant for registration or reregistration of metalaxyl products subject to the Standard must comply with all terms and conditions described in this Standard, including commitment to fill data gaps on a time schedule specified by the Agency and, and when applicable, offer to pay compensation to the extent required by 3(c)(1)(D) and 3(c)(2)(D) of the Federal Insecticide, Fungicide, and Rodenticide Act [FIFRA] as amended, 7 U.S.C. 136(c)(1)(D) and 136(c)(2)(D).

FIFRA s. 3(c)(1)(D)(i) provides special "exclusive use" protection for any pesticide product first registered after September 30, 1978, that contains an active ingredient not found in any previously-registered product. The active ingredient, metalaxyl, was first registered on June 12, 1979 for the formulation of fungicides (EPA reg. no. 100-601) by Ciba-Geigy Corporation. The period of "exclusive use" lasts for 10 years after the initial registration.

The Bibliography portion of this Standard indicates which data are subject to this "exclusive use" provision.

With respect to other data, FIFRA s. 3(c)(1)(D)(ii) provides that data submitted after December 31, 1969 to support an existing registration or for reregistration may not be used to support the registration of another applicant for 15 years following the date that the data were originally submitted unless the applicant has made an offer to pay compensation for that data.

F. Acceptable Ranges and Limits

1. Manufacturing-Use Metalaxyl

a. Product Composition Standards

To be covered under this Standard, manufacturing-use metalaxyl products must contain metalaxyl as the sole active ingredient. Manufacturing-use metalaxyl with any percentage of active ingredient is acceptable under this Standard (with appropriate certification of limits).

b. Acute Toxicity Limits

The Agency will consider registration of manufacturing-use products containing metalaxyl regardless of the toxicity category, provided that the labeling of such products bears appropriate precautionary statements.

c. Use Patterns

To be covered under this Standard, manufacturing-use metalaxyl products must be labeled for formulation into end-use fungicides which are intended for outdoor, nondomestic, terrestrial, nonfood applications.

Metalaxyl, as of May 30, 1981 was registered only for outdoor, non-domestic, terrestrial, non-food applications.

The Agency will consider changed and additional use patterns with appropriate submission and/or citation of data that supports the finding that metalaxyl does not cause unreasonable adverse effects on man and the environment.

The Agency will consider additional non-food (non-domestic) terrestrial outdoor uses of metalaxyl provided any required data are cited or submitted for the registration of the use and the use will not result in an unacceptable risk to applicators or users of the site. The Agency has a fairly complete data base on which to base an assessment of this category of use.

The Agency received petitions for tolerances of metalaxyl (including the 2,6-dimethylaniline moiety) in or on several raw agricultural commodities and in meat, milk, poultry, and eggs. The Agency also received a tolerance petition for feed additive tolerances. The Agency is considering these tolerances and will consider any additional proposed tolerances on food and feed crops provided that applicants for the

registration of the additional crop(s) submit a petition(s) proposing a tolerance level for each crop, supply appropriate residue data, and demonstrate that the establishments of the tolerance is adequate to protect public health. Applicants must also demonstrate that the additional food crop-use pattern(s) will not result in an unacceptable risk to applicators or to field workers.

The residue chemistry data base for the proposed food crop uses is in review. The food crop uses are not toxicologically supported without the submission of additional chronic toxicology data in the areas of chronic feeding/ oncogenicity and mutagenicity.

The Agency will consider metalaxyl products for domestic or residential use as defined in 40 CFR 162.3 and in 40 CFR 162.16. This use may require child resistant packaging or an exemption from child resistant packaging if proposed metalaxyl products demonstrate acute hazards as defined in 40 CFR 162.16(c)(2).

2. End-Use Metalaxyl - Emulsifiable Concentrate (EC)

a. Product Composition Standard

End-use metalaxyl products with any percentage of active ingredient are acceptable under this Standard with appropriate certification of limits.

Inert ingredients in food-use formulations must be cleared for such use under 40 CFR 180.1001. As of April 1, 1981, metalaxyl is not registered for a food use. However, an experimental use (with a temporary tolerance) exists for metalaxyl on potatoes. All inert ingredients in EC metalaxyl are cleared.

b. Acute Toxicity Limits

The Agency will consider registration of any end-use metalaxyl product under this Standard provided that it falls under acute toxicity categories acceptable for general use and bears appropriate precautionary labeling.

If a proposed end-use product is accepted for (general) domestic or residential use and it has established acute toxicity ratings of Category I for primary eye irritation or Categories I and II for acute oral toxicity, acute dermal toxicity, acute inhalation and/or primary dermal toxicity, the product may require child resistant packaging or an exemption from child resistant packaging.

c. Use Patterns and Application Methods

To be registered under this Standard, end-use products of metalaxyl must be labeled as fungicides for use on one or more of the following sites:

food uses	non-food uses
none as of 5/30/81	tobacco
	conifers
	ornamentals
	turf

The Agency finds that current dosage rates and application methods are acceptable under this Standard. These rates are summarized in Chapter V.

A rotational crop restriction or a rotational crop tolerance is required because metalaxyl residues have been demonstrated to be available to subsequent crops after the initial treatment with metalaxyl. All end-use metalaxyl products intended for agricultural use must bear labeling of the appropriate rotational crop restriction or a rotational crop tolerance must exist for the appropriate crops.

g. Required Labeling

All manufacturing-use and end-use metalaxyl products must bear appropriate labeling. The guidance package for this Standard contains specific information regarding label requirements.

1. Manufacturing-Use Products

a. Use Pattern Statements

All manufacturing-use metalaxyl products must list on the label the intended end-uses of formulated products produced from the manufacturing-use products. All metalaxyl labels must bear the following statement:

"For Formulation into End-Use Fungicides".

b. Precautionary Statements

The guidance package provides an updated list of all precautionary statements which must appear for this type of product.

2. End-Use Metalaxyl Products

The guidance package provides an updated list of all precautionary statements which must appear for this type of product.

A rotational crop restriction is supported by data and is required for end-use products intended for agricultural use. Under "directions for use" and "note to user", the following restriction must appear:

> "If replanting is necessary, tobacco may be replanted immediately. Do not make a second application of [metalaxyl product]. Tobacco corn or root crops may be planted during the fall following treatment provided they are plowed down and not used for food or feed. Other crops may be planted 18 months following application."

H. Tolerance Reassessment

A temporary tolerance of 0.05 ppm in or on potatoes has been established for metalaxyl in association with an experimental use permit (100-EUP-1). The Provisional Acceptable Daily Intake (PADI) is based on the 90-day subchronic oral rat study (Drake 1977, 0011) with a no-observed effect level (NOEL) of 250 ppm. The NOEL equates to 12.5 mg/kg/day.

A 2000-fold safety factor is used to calculate the PADI because the toxicity study on which it is based is a subchronic study.

$$\text{PADI} = \frac{12.5 \text{ mg/kg/day}}{2000} = 0.0062 \text{ mg/kg/day}$$

The maximum permissable intake (MPI) for a 60 kg person is 0.3750 mg/day. For potatoes the theoretical maximum residue contribution (TMRC) equals 0.0041 mg/day/1.5 kg based on the tolerance level of 0.05 and a food factor of 5.43. This equates to approximately 1.09% of the PADI.

Chapter III

DATA REQUIREMENTS AND DATA GAPS

Manufacturing-use Metalaxyl

Table 1, entitled Metalaxyl Generic Data Requirements, includes those data that pertain to the properties or effects of metalaxyl as an active ingredient. Thus, these data are relevant to an evaluation of the risks and benefits of all products containing metalaxyl. Providing data to fill indicated gaps is the primary responsibility of the manufacturing-use product registrant(s). Registrants of end-use products which are not exempted by FIFRA Section 3(c)(2)(D) are also responsible for the submission of these data. Applicants for the registration or reregistration of manufacturing-use metalaxyl products must acknowledge reliance on existing data which fill indicated data requirements under FIFRA 3(c)(1)(D). These data are listed under the column entitled Bibliographic Citation in this table.

CIBA-GEIGY, the sole registrant of metalaxyl products, is entitled to exclusive use of these data for a ten year period, starting on June 12, 1979 [FIFRA s. 3(c)(1)(D)(i)]. These data may not be used to support any application for registration without the written permission of CIBA-GEIGY.

Table 2, entitled Metalaxyl Product-Specific Data Requirements for Manufacturing-Use Products, includes those data that relate only to the properties or effects of a product with a specific composition. Thus, these data are required of each product to characterize the product's particular composition and physical/chemical properties, and acute toxicity. Providing data to fulfill these data requirements for a particular product is the responsibility of each applicant for the registration or reregistration of a manufacturing-use metalaxyl product. If the Agency has in its possession product-specific data which fulfill a data requirement for a particular product, this is indicated in the guidance package accompanying this Standard.

Applicants for the registration of new manufacturing-use metalaxyl products must submit all required product specific data or establish that the proposed product is substantially similar to another product for which the Agency has received acceptable product-specific data.

If the Agency has determined that one or more existing manufacturing-use metalaxyl products are substantially similar, then this, too, is indicated. Product-specific data need not be acknowledged under FIFRA 3(c)(1)(D) unless

the Agency or a registrant has established that a product is substantially similar to another product for which the Agency has received acceptable product-specific data. If this should occur, the registrant(s) of the former product(s) is required to acknowledge reliance on these data.

End-Use Products of Metalaxyl

Registrants of end-use metalaxyl products not exempted by FIFRA Section 3(c)(2)(D) are responsible for the submission of "generic" data described in Tables 1 and 2 of this Chapter, in addition to the product-specific data listed in Table 3.

Registrants of all end-use metalaxyl products are advised that if data are not generated to fill generic data requirements for the manufacturing-use product(s), these registrations will be suspended. If continued availability of the manufacturing-use product is desired, these data must be supplied.

Table 3, entitled Metalaxyl Product-Specific Data Requirements for End-Use Products, includes those data that relate only to the properties or effects of an end-use product with a specific composition.

Table 1

Metalaxyl Product-Chemistry (See Chapter IV)
Generic Data Requirements

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
163.61-8(1)	Color	Yes	Technical Grade	Yes	Ciba-Geigy Corp. 1978; 0160	No[1/]
163.61-8(2)	Odor	Yes	Technical Grade	Yes	Ciba-Geigy Corp. 1978; 0160	No[1/]
163.61-8(3)	Melting Point	Yes	Technical Grade	Yes	Ciba-Geigy Corp. 1978; 0160	No[1/]
163.61-8(4)	Solubility	Yes	Technical Grade	Yes	Ciba-Geigy Corp. 1978; 0160	No[1/]
163.61-8(5)	Stability	Yes	Technical Grade	Yes	Ciba-Geigy Corp. 1978; 0160	No[1/]
163.61-8(6)	Octanol/water partition coefficient	Yes	Technical Grade	No		Yes/6 months
163.61-8(7)	Physical State	Yes	Technical Grade	Yes	Ciba-Geigy Corp. 1978; 0160	No[1/]

1/ Provided that the technical material used is Ciba-Geigy metalaxyl.

Data requirements are current as of July 1981. Refer to Guidance Package for updated requirements.

Table 1 (Cont'd)

Metalaxyl Product Chemistry (See Chapter IV)
Generic Data Requirements

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
163.61-8(8)	Density or Specific Gravity	Yes	Technical Grade	Yes	Ciba Geigy Corp. 1978; 0160	No[1/]
163.61-8(9)	Boiling Point	No				
163.61-8(10)	Vapor Pressure	Yes	Technical Grade	Yes	Ciba Geigy Corp. 1978; 0160	No[1/]
163.61-8(11)	pH	Yes	Technical Grade	No		Yes/6 months

1/ Provided that the technical material used is Ciba-Geigy metalaxyl.

Data requirements are current as of July 1981. Refer to Guidance Package for updated requirements.

Table 1 (Cont'd)

Metalaxyl Environmental Fate (See Chapter V)
Generic Data Requirements

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
163.62-7(b)	Hydrolysis	Yes	Technical or Radio-labeled Analytical Grade	Yes	Burkhard 1976; 0076	No
163.62-7(c)	Photodegradation	Yes	Technical or Radio-labeled Analytical Grade	Yes	Burkhard 1979; 0100	No
163.62-8(b)	Aerobic soil metabolism	Yes	Technical or Radio-labeled Analytical Grade	Yes	Ellgehausen 1978; 0081	No
163.62-8(c)	Anaerobic soil metabolism	Yes	Technical or Radio-label Analytical Grade	Yes	Ellgehausen 1978; 0081	No
163.62-8(f)	Microbial metabolism				Ercegovich 1979; 0102	
	(2) effects of microbes on pesticides	Yes			Ercegovich, Bogus 1979;0103	Reserved[1/]
	(3) effects of pesticides on microbes	Yes			Ercegovich, Vallejo, Bogus 1979; 0104	Reserved[1/]

1/ The requirement for the submission of data is currently reserved pending the development of protocols by the Agency.

Data requirements are current as of July 1981. Refer to Guidance Package for updated requirements.

Table 1 (Cont'd)

Metalaxyl Environmental Fate (See Chapter V)
Generic Data Requirements

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
163.62-8(g)	Activated Sludge Metabolism	Yes	Technical or Radio-labeled Analytical Grade	-	Doebbler 1979; 0101 Gliniski 1978; 0105	Reserved[1/]
163.62-9(b)	Leaching	Yes[3/]	Technical or Radio-labeled Analytical Grade	Yes	Guth 1976; 0087 Guth 1978; 0089	No
163.62-9(c)	Volatility	Yes[2/]	Technical or Radio-labeled Analytical Grade	Yes	Burkhard 1977; 0077	No
163.62-9(d)	Adsorption/ desorption	Yes[3/]		Yes	Guth 1978; 0088	No
163.62-10(b)	Terrestrial field dissipation	Yes	Representative formulation	Yes	Elgehausen 1977; 0079 0080	No
	(2) ornamentals and turf uses	Yes			Elgehausen 1977; 0079, 0080	

1/ The requirement for the submission of data is currently being reserved pending the development of protocols by the Agency.
2/ Required on case-by-case basis for commercial greenhouse, orchard, or field/vegetable crop uses that involve significant exposure.
3/ Registrant would have the option of conducting either a leaching or an adsorption/desorption study for terrestrial field applications.

Data requirements are current as of July 1981. Refer to Guidance Package for updated requirements.

Table 1 (Cont'd)

Metalaxyl Environmental Fate (See Chapter V)
Generic Data Requirements

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
163.62-10(f)	Combination and tank mix field dissipation	Yes[1/]	EC or non-radio-labeled technical grade			No
163.62-11(b)	Accumulation in rotational crops	Yes	Radiolabeled Analytical Grade Followed by Formulation	Yes	Fischer, Cassidy 1979; 0084,0082 Foster, Fischer, Cassidy 1978; 0086 Hamilton, Fischer, Cassidy 1979; 0090, 0091 Ciba-Geigy Corp. 1979; 0129	No
163.62-11(d)	Fish accumulation	Yes[3/]	Technical or Radio-labeled Analytical Grade	Yes	Iadd, Wilson 1979; 0093 Iadd, Enos 1979; 0092	No
163.62-13	Disposal and storage	Yes				Reserved[2/]
	Groundwater Monitoring	Yes[4/]		No[5/]		Yes/24 months

1/ Data required on a case-by-case basis for EUP's containing more than one active ingredient, intended for use as a component in tank mixtures or customarily applied serially with another pesticide product.
2/ The requirement for the submission of data is currently reserved pending the development of protocols by the Agency.
3/ Required because metalaxyl is expected to leach in sandy soils and reach water.
4/ Required because of strong leaching proclivity and potential to reach groundwater.
5/ Studies in progress.

Data requirements are current as of July 1981. Refer to Guidance Package for updated requirements.

Table 1 (Cont'd)

Metalaxyl Toxicology (See Chapter VI)
Generic Data Requirements

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
163.81-1	Acute Oral Toxicity	Yes	Technical Grade	Yes	Sachsse, Bathe 1976; 0026	No
163.81-2	Acute Dermal Toxicity	Yes	Technical Grade	Yes	Sachsse, Ullmann 1976; 0029	No
163.82-1	Subchronic Oral Toxicity	Yes	Technical Grade	Yes	Drake 1977; 0011 Finn 1977; 0012 deWard et al., 1980; 0045	No No
163.82-2	Subchronic 21-day Dermal Toxicity	Yes[1/]	Technical Grade	Yes	Toxigenics 1980;0041	No
163.82-3	Subchronic 90-day Dermal Toxicity	No				
163.82-4	Subchronic Inhalation Toxicity	Yes[2/]	Technical Grade in Smoke	No[3/]	Coate 1980; 0037	Yes/12 months

1/ Required for use on turf.
2/ Required for metalaxyl use on tobacco (see also Residue Chemistry)
3/ Study in progress. Pilot study only in Agency files.

Data requirements are current as of July 1981. Refer to Guidance Package for updated requirements.

Table 1 (Cont'd)
Metalaxyl Toxicology (See Chapter VI)
Generic Data Requirements

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
163.83-1	Chronic Feeding[1/]	No[1/]	Technical Grade	-	Life Science Research 1980; 0043	No[3/]
163.83-2	Oncogenicity[1/]	No[1/]	Technical Grade	-	Life Science Research 1980; 0043	No[3/]
163.83-3	Teratogenicity	Yes	Technical Grade	Yes	Fritz 1978; 0014 Fritz 1978; 0042	No
163.83-4	Reproduction[1/]	No[1/]	Technical Grade	-	Cozens et al. 1980; 0044	No
163.84-2 through 4	Mutagenicity[1/]	No[1/]	Technical Grade	-	Arni, Muller 1978; 0001 Fritz 1978; 0013	No[4/]
163.85-1	Metabolism	Yes[2/]	Technical Grade	Yes	Hanbock 1977; 0015 Hanbock 1978; 0016	No

1/ Not required for currently registered nonfood uses of metalaxyl; required in order to set a permanent tolerance or grant an exemption for a tolerance for a food use or to support this use toxicologically. Petitions to set tolerances have been submitted to the Agency.
2/ Required to set temporary tolerance on potatoes.
3/ Pathology summary tables must be resubmitted to include number of organs examined for number of animal examine - to support a food-crop use.
4/ Additional multi-test evidence is required in order to toxicologically support a food use.

Data requirements are current as of July 1981. Refer to Guidance Package for uplated requirements.

Table 1 (Cont'd)

Metalaxyl Ecological Effects (See Chapter VIII)
Generic Data Requirements

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
163.71-1	Avian Single-Dose Oral LD_{50}	Yes	Technical Grade	Yes	Beavers, Fink 1977; 0051	No
163.71-2	Avian Dietary LC_{50}	Yes	Technical Grade	Yes	Beavers, Fink 1977; 0052; 0053 Sachsse, Ullmann, 1976, 0061	No
163.71-3	Mammalian Acute Toxicity	No				
163.71-4	Avian Reproduction	No				
163.71-5	Simulated and Actual Field Testing for Mammals and Birds	No				

Data requirements are current as of July 1981. Refer to Guidance Package for updated requirements.

Table I (Cont'd)

Metalaxyl Ecological Effects (See Chapter VIII)
Generic Data Requirements

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
163.72-1	Fish Acute LC_{50}	Yes	Technical Grade	Yes	Fratus, Buccafusco 1978; 0056 Sachsse, Bathe 1976; 0059 Fratus, Buccafusco 1978; 0055 McCann 1979; 0067	No
163.72-2	Acute Toxicity to Aquatic Invertebrates	Yes	Technical Grade	Yes	LeBlanc, Cary 1978; 0058 LeBlanc, Cary 1977; 0057 McCann 1979; 0068	No
163.72-3	Acute Toxicity to Estaurine and Marine Organisms	No				
163.72-4	Embryo-larvae and Life-cycle Studies of Fish and Aquatic Invertebrates	Yes[1/]	Technical Grade	Yes	E.G. & G Bionomics 1980; 0062, 0063	No
163.72-5	Aquatic Organism Toxicity and Residue Studies	No				
163.72-6	Simulated or Actual Field Testing for Aquatic Organisms	No				

1/ An aquatic invertebrate life-cyle test (preferably Daphnia magna) is required because of metalaxyl's proposed use pattern, potential volume of use, persistence and mobility.

Data requirements are current as of July 1981. Refer to Guidance Package for uplated requirements.

Table 1 (Cont'd)

Metalaxyl Ecologcial Effects (See Chapter VIII)
Generic Data Requirements

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
Phytoxicity[1/]						
163.122-1	Target Area Phytotoxicity	Yes	EC	No		Yes/24 months[2/]
163.122-1	Aquatic Macrophytes	Yes	Technical Grade	No		Yes/24 months[2/]
163.122-2	Algae	Yes	Technical Grade	No		Yes/24 months[2/]

1/ Guidelines proposed November 1980.
2/ From date of implementation of Subpart J.

Data requirements are current as of July 1981. Refer to Guidance Package for updated requirements.

Table 1 (Cont'd)

Metalaxyl Ecological Effects (See Chapter VIII)
Generic Data Requirements for Emulsifiable Concentrate (EC) Products

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
163.72-1	Fish Acute LC_{50}	Yes[1/]	EC	Yes	McCann 1979; 0064, 0065	No
163.72-2	Acute Toxicity to Aquatic Invertebrates	Yes[1/]	EC	Yes	McCann 1979; 0068	No

1/ Data required for formulation because of differential toxicity between technical and formulation.

Data requirements are current as of July 1981. Refer to Guidance Package for updated requirements.

Table I (Cont'd)

Metalaxyl Residue Chemistry (See Chapter VII)
Generic Data Requirements for Manufacturing-Use Products

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
	Uptake, Distribution, and Metabolism in Plants	Yes	Radiolabeled Analytical Grade	Yes	Gross 1977; 0132 Fischer, Cassidy 1978; 0099 Foster, Fischer, Cassidy 1978; 0086	No[1/]
	Metabolism in Animals	Yes	Radiolabeled Analytical Grade	Yes	Fischer, Foster, Cassidy 1978; 0131 Hamlock 1977, 1978; 0015, 0016 Seim 1978, 0143	No[1,2/]
	Analytical Methods	Yes		Yes	Balasubramanian, Nixon 1978; 0117 Balasubramanian, Ross, 1978; 0120	No[1/]
	Nature of Residue in Tobacco	Yes	Radiolabeled Analytical Grade	Yes	Honeycutt, Cassidy 1978; 0106 Honeycutt, Fischer, Cassidy 1979; 0136	No

1/ Data sufficient to satisfy requirements for temporary tolerance only.
2/ For any future permanent tolerance request or expansion of the experimental use program, large animal feeding studies and tolerance proposals for residues in meat, milk, poultry, and eggs are required.

Data requirements are current as of July 1981. Refer to Guidance Package for uplated requirements.

Table 1 (Cont'd)
Metalaxyl Residue Chemistry (See Chapter VII)
Generic Data Requirements for Manufacturing-Use Products

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
					Ciba-Geigy Corp. 1978; 0127 Honeycutt, Szolics, Simoneaux, Cassidy 1979; 0139	
	Nature of Residue in Cigarette Smoke	Yes	Radiolabeled technical grade in cigarettes	Yes	Honeycutt, Szolics, Cassidy 1978; 0137	No
	Pyrolysis Products	Yes	Radiolabeled technical grade in cigarettes	Yes	Honeycutt, Szolics, Cassidy 1978; 0137	No
	Residue Data					
	Field Tobacco	Yes	Typical Formulation	Yes	Ciba-Geigy Corp. 1978; 0128	No
	Potatoes	Yes	Typical Formulation	Yes	Ciba-Geigy Corp. 1978; 0126	No[1/]
	Meat, Milk, Poultry and Eggs	Yes[2/]				
	Storage Stability	Yes		No		Yes/12 months

1/ Data sufficient to satisfy requirements for temporary tolerance only.
2/ For any future permanent tolerance request or expansion of the experimental use program, large animal feeding studies and tolerance proposals for residues in meat, milk, poultry, and eggs are required.

Data requirements are current as of July 1981. Refer to Guidance Package for updated requirements.

Table 2
Product Chemistry (See Chapter IV)
Metalaxyl Product-Specific Data Requirements for Manufacturing-Use Products

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or Totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
163.61-3	Product Identity and Disclosure of Ingredients	Yes	MUP	Yes	Ciba-Geigy Corp. 1978; 0160	No
163.61-4	Description of Manufacturing Process	Yes	MUP	Yes[1/]	Ciba-Geigy Corp. 1978; 0160	No
163.61-5	Discussion of Formation of Unint. Ingredients.	Yes	MUP	No		Yes/6 months
163.61-6	Declaration and Certification of Ingredient Limits	Yes	MUP	Yes	Ciba-Geigy Corp. 1978; 0160	No
163.61-7	Product Analytical Methods and Data	Yes	MUP	Yes[2/]	Ciba-Geigy Corp. 1978; 0160	No
163.61-8(7)	Physical State	Yes	MUP	Yes	Ciba-Geigy Corp. 1978; 0160	No
163.61-8(8)	Density or Specific Gravity	Yes	MUP	Yes	Ciba-Geigy Corp. 1978; 0160	No
163.61(10)	Vapor Pressure	Yes	MUP	Yes	Ciba-Geigy Corp. 1978; 0160	No
163.61-8(11)	pH	Yes	MUP	No		Yes/6 months
163.61-8(12)	Storage Stability	Yes	MUP	No		Yes/6 months

1/ The discussion should include side reactions and factors such as temperature and reactant impurities. Consideration should also be given to the quality control methods.
2/ Quantitative procedures will be needed for the unintentional impurities if such impurities are present in the product.

Data requirements are current as of July 1981. Refer to Guidance Package for updated requirements.

Table 2 (Cont'd)

Product Chemistry (See Chapter IV)
Metalaxyl Product-Specific Data Requirements for Manufacturing-Use Products

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
163.61-8(13)	Flammability	Yes	MUP	No		Yes/6 months
163.61-8(14)	Oxidizing or Reducing Action	Yes	MUP	No		Yes/6 months
163.61-8(15)	Explosiveness	Yes	MUP	No		Yes/6 months
163.61-8(18)	Corrosion Characteristics	Yes	MUP	No		Yes/6 months

Data requirements are current as of July 1981. Refer to Guidance Package for updated requirements.

Toxicology (See Chapter VI)
Metalaxyl Product-Specific Data Requirements for Manufacturing-Use Products

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
163.81-1	Acute Oral Toxicity	Yes*	MUP***	Yes	Sachsse, Bathe 1976; 0026	No
163.81-2	Acute Dermal Toxicity	Yes*	MUP***	Yes	Sachsse, Ullmann 1976; 0023	No
163.81-3	Acute Inhalation Toxicity	Yes	MUP***	No		No 1/
163.81-4	Primary Eye Irritation	Yes**	MUP***	Yes	Sachsse, Ullmann 1976; 0031	No
163.81-5	Primary Dermal Irritation	Yes	MUP***	Yes	Sachsse, Ullmann 1976; 0032	No
163.81-6	Dermal Sensitization	Yes	MUP***	Yes	Sachsse, Ullamn 1976; 0033	No

* Technical metalaxyl and the manufacturing-use product have been determined to be the same. These requirements may be filled by data required in Table 1 entitled: "Metalaxyl Toxicology Generic Data Requirements for Manufacturing-Use Products".

** A demonstration of pH between 1 and 3 or 12 and 14 or a demonstration of dermal irritability will be sufficient to categorize a product as an ocular irritant and additional testing will not be required.

*** Required for each manufacturing-use product or substantially similar product.

1/ A determination is first required whether MUP metalaxyl produces a respirable vapor and/or 20% or more of the aerodynamic equivalent of the product is composed of particulates not larger than 10 microns in diameter.

Data requirements are current as of July 1981. Refer to Guidance Package for updated requirements.

Table 3
Product Chemistry (See Chapter IV)
Metalaxyl Product-Specific Data Requirements for End-Use Products

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
Emulsifiable Concentrate (EC) Formulations[1/]						
163.61-3	Product Identity and Disclosure of Ingredients	Yes	EC	Yes	Ciba-Geigy Corp. 1976; 0161	No
163.61-4	Description of Manufacturing Process	Yes	EC	Yes	Ciba-Geigy Corp. 1976; 0161	No
163.61-6	Declaration and Certification of Ingredient Limits	Yes	EC	Yes	Ciba-Geigy Corp. 1978; 0161	No
163.61-7	Product Analytical Methods	Yes	EC	Yes	Ciba-Geigy Corp. 1978; 0161	No
163.61-8(1)	Color	Yes	EC	No		Yes/6 months
163.61-8(2)	Odor	Yes	EC	No		Yes/6 months
163.61-8(7)	Physical State	Yes	EC	No		Yes/6 months
163.61-8(8)	Density or Specific Gravity	Yes	EC	Yes	Ciba-Geigy Corp. 1978; 0161	No
163.61-8(9)	Boiling Point	Yes	EC	Yes	Ciba-Geigy Corp. 1978; 0161	No
163.61-8(10)	Vapor Pressure	Yes	EC	Yes	Ciba-Geigy Corp. 1978; 0161	No

1/ Data exist for Registration No. 100-607 (Ridomil 2E)

Data requirements are current as of July 1981. Refer to Guidance Package for updated requirements.

Table 3 (Cont'd)

Product Chemistry (See Chapter IV)
Product-Specific Data Requirements for End-Use Products

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
163.61-8(11)	pH	Yes	EC	Yes	Ciba-Geigy Corp. 1978; 0161	No
163.61-8(12)	Storage Stability	Yes	EC	Yes	Ciba-Geigy Corp. 1978; 0161	No
163.61-8(13)	Flammability	Yes	EC	No		Yes/6 months
163.61-8(14)	Oxidizing or Reducing Action	Yes	EC	Yes	Ciba-Geigy Corp. 1978; 0161	No
163.61-8(15)	Explosiveness	Yes	EC	No		Yes/6 months
163.61-8(16)	Miscibility	Yes	EC	Yes	Ciba-Geigy Corp. 1978; 0161	No
163.61-8(17)	Viscosity	Yes	EC	Yes	Ciba-Geigy Corp. 1978; 0161	No
163.61-8(18)	Corrosion Characteristics	Yes	EC	Yes	Ciba-Geigy Corp. 1978; 0161	No

Data requirements are current as of July 1981. Refer to Guidance Package for updated requirements.

Table 3 (Cont'd)
Toxicology (See Chapter VI)
Product-Specific Data Requirements for End-Use Products

Guidelines Citation	Name of Test	Are Data Required	Composition	Does EPA Have Data to Partially or totally Satisfy this Requirement	Bibliographic Citation	Must Additional Data be Submitted under FIFRA 3(c)(2)(B)? If so, months allowed for submission from published date of standard
Emulsifiable Concentrate (EC) Formulations						
163.81-1	Acute Oral Toxicity	Yes[1/]	Each product[1/]	Yes	Kapp, Piccirillo 1978; 0018	No
163.81-2	Acute Dermal Toxicity	Yes[1/]	Each product[1/]	Yes	Kapp, Piccirillo 1978; 0017	No
163.81-3	Acute Inhalation Toxicity	Yes[1/]	Each product[1/]	Partial[2/]	Piccirillo 1978;0021	No[2/]
163.81-4	Primary Eye Irritation	Yes[1/]	Each product[1/]	Yes	Piccirillo 1978l; 0020	No
163.81-5	Primry Dermal Irritation	Yes[1/]	Each product[1/]	Yes	Kapp, Piccirillo 1978; 0019	No
163.81-6	Dermal Sensitization	Yes[1/]	Each product[1/]	Yes[3/]		No

1/ For the purposes of acute toxicology testing 27.8% metalaxyl EC is substantially similar to 25.1% metalaxyl EC.
2/ A determination of whether EC metalaxyl causes a respirable vapor and/or 20% or more of the aerodynamic equivalent of the formulated product (as registered or under conditions of use) is composed of particulates not larger than 10 microns in diameter is required; additional data is not presently required.
3/ Data on technical shows little dermal sensitization and may be extrapolated to EC.

Data requirements are current as of July 1981. Refer to Guidance Package for updated requirements.

Chapter IV

PRODUCT CHEMISTRY

Manufacturing-Use Metalaxyl

- Introduction
- Chemical Identity
- Manufacturing Processes
- Formation of Unintentional Ingredients
- Active Ingredient Limits in Pesticide Products
- Product Analytical Methods and Data
- Physical and Chemical Properties

Emulsifiable Concentrate (EC) Metalaxyl

- Manufacturing Processes
- Active Ingredient Limits in Pesticide Products
- Product Analytical Methods and Data
- Physical and Chemical Properties

Introduction

FIFRA 3(c)(2)(A) requires the Agency to establish guidelines for registering pesticides in the United States. The Agency requires registrants to provide quantitative data on all added ingredients, active and inert.

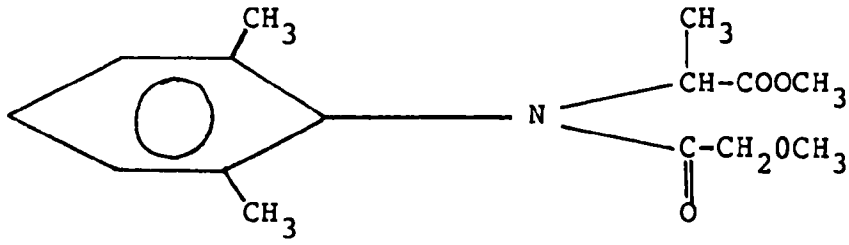
To establish the composition of products proposed for registration, the Agency requires data and information not only on the manufacturing and formulation processes but also a discussion on the formation of manufacturing impurities and other product ingredients, intentional and unintentional. Furthermore, to assure that the composition of the product as marketed will not vary from the composition evaluated at the time of registration, applicants are required to submit a statement certifying upper and lower composition limits for the added ingredients, or upper limits only for some unintentional ingredients. Subpart D of the Proposed Guidelines (43 FR 29696, July 10, 1978) suggests specific precision limits for ingredients based on the percentage of ingredient and the standard deviation of the analytical method.

In addition to the data on product composition, the Agency guidelines also require data to establish the physical and chemical properties of both the pesticide active ingredient and its formulations. For example, data are needed concerning the identity and physical state of the active ingredient

such as melting and boiling point data, ambient vapor pressure and solubility. Data are also required on the properties of the formulated product to establish labeling cautions e.g., flammability, corrosiveness or pesticide storage stability. The Agency uses these data to characterize each pesticide and to determine its environmental and health hazards.

Chemical Identity

"Metalaxyl" is the common name accepted by the American National Standards Institute (ANSI) for the chemical N-(2,6-Dimethylphenyl)-N-(methoxyacetyl)-alanine methyl ester.



Ciba-Geigy Corporation, presently the sole manufacturer of metalaxyl in the United States, has assigned metalaxyl the experimental number "CGA-48988" (for the active ingredient), and the trade names Ridomil®, Subdue®, and Apron®. The Chemical Abstracts Registry (CAS) number for metalaxyl is 57837-19-1 and the EPA Shaughnessy number is 113501. The common name, metalaxyl, will be used throughout this standard in lieu of other chemical or trade names.

Manufacturing Process

A manufacturing process for technical metalaxyl has been submitted to the Agency. (Ciba-Geigy Corporation 1978; 0160). Because this type of information is considered to be confidential business information, a discussion of the specific procedures, equipment and manufacturing conditions required for commercial production of metalaxyl cannot be published in this standard. The manufacturing process as submitted by Ciba-Geigy Corporation and the identification of impurities are detailed separately in the Confidential Appendix for internal Agency use.

The discussion of the manufacturing process should be more thorough and cover the factors related to the amounts of the toxicologically significant components and impurities present in the technical product. In addition to the basic reactions, the discussion should consider side reactions and factors such as temperature and reactant impurities.

Formation of Unintentional Ingredients

Additional information is needed concerning the toxicologically significant components and impurities. Quantitative procedures are needed for the unintentional impurities, nitrosamines for example, if such impurities are present.

Active Ingredient Limits in Pesticide Products

The components of technical metalaxyl have been identified (Ciba-Geigy Corporation 1978, 0160). This is confidential business information and cannot be listed here but is listed separately in the Confidential Appendix. Clarifying information is needed on some components. These components are listed in the Confidential Appendix. Technical metalaxyl contains approximately 90% active ingredient.

Product Analytical Methods and Data

An analytical method for the determination of technical metalaxyl, its related compounds, and impurities in the technical product, has been submitted to the Agency. A description may be found in the Confidential Appendix (Heinrichs 1978, 0164).

A description is not found in this standard but is detailed separately in the Confidential Appendix.

Validation data are needed to establish the reliability of this method. Analytical results are needed for five or more samples of the technical product which are representative of the manufacturing process.

Physical and Chemical Properties (Ciba-Geigy Corp. 1978, 0160)

Technical

Color: White to beige

Odor: Odorless

Physical State: Crystalline

Solubility: Water - 00.7%
Methanol - 65.0%
Benzene - 55.0%
Hexane - 00.9%
Isopropanol - 27.0%
Methylene Chloride - 75.0%

Stability: Stable up to 300° C; slight exothermic reaction up to 450°C

Melting Point: 71-72°C

Vapor Pressure: 2.2×10^{-6} Torr at 20°C

Density: 1.21 g/cm^3 at 20°C

Hydrolysis Rate:

Temperature	pH	Half-life, days
20°	1	>200
	9	115
	10	12
50°	5	>200
	7	>200

Dissociation Constant: No measurable dissociation

Molecular Weight: 279.34

Emulsifiable Concentrate (EC) Metalaxyl

Manufacturing Processes

A manufacturing process for EC metalaxyl has been submitted to the Agency (Ciba-Geigy Corp. 1978, 0161). This is confidential business information and is detailed separately in the Confidential Appendix.

Composition of EC Metalaxyl

The components of a formulation of EC metalaxyl have been identified in Ciba-Geigy Corp. 1978 (0161) and in the confidential statement of formula supplied to the Agency.

Product Analytical Methods

An analytical method that determines metalaxyl in formulations has also been submitted and a description may be found in the Confidential Appendix (Heinrichs 1978, 0166). This method is adequate for the formulated product. If the method of technical metalaxyl is validated by data then this method would be suitable for enforcement purposes.

Physical and Chemical Properties (Ciba-Geigy Corp. 1978; 0161)

Miscibility: Forms stable emulsion in water

pH (10% solution): 3-6; 3 is irritating to the eyes and skin, 6 is noncorrosive

Boiling Point: 155 ± 5°C

Flash Point (TCC): 92°F, typical or 33.3°C

Specific Gravity: 1.01, typical

Viscosity: 2.31 ± 0.05, typical (Cannon Fenske Viscometer)

Vapor Pressure: 3mm Hg at 20°C, typical

Explosive Characteristics: None reported

Corrosion Hazard: Not corrosive to tin or steel

Oxidizing/Reducing Potential: None

Weight a.i./gallon: 2 lb a.i./gal, typically or 239 gm/L

Storage Stability:	Temp.	Time	Assay(%)	Decomposition
	-	Original	24.9	-
	50°	4 weeks	25.3	0
		8 weeks	25.8	0
		24 weeks	25.5	0

Chapter V

ENVIRONMENTAL FATE

Use Summary

Environmental Fate - Manufacturing-Use Metalaxyl

- Hydrolysis
- Photodegradation
- Soil Metabolism
- Microbial Metabolism
- Leaching, Adsoprtion/Desorption
- Volatilization
- Field Dissipation
- Fish Accumulation
- Rotational Crop Accumulation
- Potential for Groundwater Contamination
- Groundwater Monitoring
- Analytical Methods

Labeling Restriction -- Rotational Crops

Use Summary

Metalaxyl is federally registered as a preplant soil incorporated systemic fungicide on tobacco, (1) for use in the field before transplanting for control of black shank (*Phylophthora parasitica* var. *Nicotianae*) and Blue Mold (*Ceronospora tabacina*) on all types of tobacco, and (2) for use in tobacco plant beds for control of blue mold and damping-off (*Phythium* spp.).

Metalaxyl is also federally registered as a soil or foliar treatment on ornamentals, conifers and turf to control damping off and blight, caused by Pythium spp. and Phytophthora diseases such as root and crown rot.

Metalaxyl is formulated as an emulsifiable concentrate (EC) containing 25.11% active ingredient and known under the trade names of Ridomil® and Subdue®.

Application is made once a season, before planting, by spray tank broadcast and incorporated in the top two to four inches of soil prior to transplant. Registered application rates are listed in Table 1.

A special local needs registration exists in Florida for use of metalaxyl on non-bearing citrus. Emergency exemptions have been granted for use of metalaxyl on potatoes in Maine and hops in Idaho, Oregon, and Washington. An experimental use permit has been approved by the Agency for use of metalaxyl on potatoes (1979-1981; renewed 1981-1983).

Potential sites of use include: nonbearing citrus, cottonseed, soybeans, wheat and certain vegetable crops.

TABLE 1: Registered Application Rates - Metalaxyl

FORMULATION	SITE	PEST/DISEASE	TYPE OF APPLICATION	RATE RANGE
25.11% EC	Tobacco	Black Shank Blue Mold Pythium (damping off)	Broadcast Incorporated in top 2-4 inches of soil	1/2 - 1 gal/acre 1.5 gal if disease levels >60%
	Tobacco Plant Bed	Blue Mold Pythium (damping off)		1 qt/acre in 50 gals. of water
				Pennsylvania only 2 qts/acre in 50 gals. of water
	Field Planted Tobacco Flue cured Tobacco	Blue Mold Black Shank		1-2 qts/acre 2-4 qts/acre
	Burley	Blue Mold Black Shank		2 qts/acre 4-6 qts/acre

Subdue 2E Metalaxyl

Formulation: 25.11% EC

Site	Pest or Disease	Type of Application	Rate Range
Foliage Plants	Pythium	Soil Drench	
Aglaonema	Phytophthora	Soil depth 4 inches or less	0.4-1.2 fl. ozs. with 100 gals of water to 800 sq. ft.
Aphelandra			
Dieffenbachia			
Peperomia			
Philodendron		Soil depth of more than 4 inches	0.4-1.2 fl. ozs. with 100 gals of water to 400-600 sq. ft.
Pothos			
Schefflera			
		Soil mix	0.1-0.4 fl. oz. with each cu. yd. of soil mixture
Azalea	Phytophthora (root and crown rot)	Soil Drench Soil depth 4 inches or less	1.2-4.0 fl. ozs. with 100 gals of H_2O to 800 sq. ft.
		Soil depth of more than 4 inches	1.2-4.0 fl. ozs. with 100 gals of H_2O to 400-600 sq. ft.
	Phytophthora (shoot blight)	Foliar Spray	1.2-2.4 fl. ozs. with 100 gals of H_2O. Spray to runoff.

Subdue 2E Metalaxyl

Formulation: 25.11% EC

Site	Pest or Disease	Type of Application	Rate Range
Bedding Plants Ageratum Aster Carnation Chrysanthemum Coleus Geranium Impatients Marigold Pansy Salvia Snapdragon Verbena Vinca Zinnia	Pythium Phytophthora	Soil Drench at seeding	0.25-0.5 fl. oz. with 100 gals of H_2O to 800 sq. ft.
		At transplanting	0.5-2.0 fl. oz. with 100 gals of H_2O to 800 sq. ft.
		Soil mix at seeding and at transplanting	0.1-0.2 fl. oz. with each cu. yd. of soil mix.
Flowers African violet Carnation Chrysanthenum Geranium Poinsettia	Pythium Phytophthora	Soil Drench Soil depth 4 inches or less	0.5.2.0 fl. ozs. with 100 gals of H_2O to 800 sq. ft.
		Soil depth of more than 4 inches	0.5-2.0 fl. ozs. with 100 gals of H_2O to 400-600 sq. ft.

Subdue 2E Metalaxyl

Formulation: 25.11% EC

Site	Pest or Disease	Type of Application	Rate Range
Woody Ornamentals Other than Azalea			
Acuba japonica Andromeda Arborvitae Ceanothus Ilex Pinus thumbergii Savin Juniper Tam Juniper Shore juniper Pittosporum Rhododendron	Pythium Phytophthora	Soil Drench Soil depth 4 inches or less	1.0-4.0 fl. ozs. with 100 gals of H_2O to 800 sq. ft.
		Soil depth of more than 4 inches	1.0-4.0 fl. ozs. with 100 gals of H_2O to 400-600 sq. ft.
Conifers	Phytophthora	Broadcast spray Seedbeds and Plug Plantings 2-0 transplants* [*2 yr. old seedling newly transplanted]	2-1/2 pts in 50 gals of H_2O per acre 5 pts in 50 gals of H_2O per acre
Turf	Pythium Blight	Broadcast spray Established turf	1-2 fl. ozs. in 3-5 gals of H_2O per 1,000 sq. ft.
	Pythium Damping Off and Pythium Blight	Newly seeded areas	1-2 fl. ozs. in 5-10 gals of H_2O per 1,000 sq. ft.

Environmental Fate - Manufacturing-Use Metalaxyl

Hydrolysis

Metalaxyl appears to be resistant to hydrolysis under "normal" environmental conditions (pH, temperature). Under test conditions, at pH 5, 7, and 9 and at 20-30°C, the half-life of metalaxyl is greater than 4 weeks.

The half-life varies from 5 hours to 5 days at pH 9-10 at 50-70°C. The half-life of the parent compound is 12 days in 0.1 NHCl at 70°C. Under prolonged or exaggerated conditions significant hydrolysis does occur. One degradation product [N-2,6-dimethyl phenyl-N-(2-methoxyacetyl) alanine (CGA-62826)] was found (Burkhard 1976, 0076).

Photodegradation

Metalaxyl is also stable to soil surface photolysis under conditions likely to be found in the environment. In a study by Burkhard (1978, 0078), the results showed that there was no difference between covered and exposed soil samples, following ^{14}C analysis and gas liquid chromatographic (GLC) analysis of extracts from test soils.

However, metalaxyl does photodegrade in water. A half-life of 1 week was reported for metalaxyl in water following exposure to sunlight. Degradation products include: N-(2,6-dimethylphenyl)-N-methoxy acetyl)-alanine (CGA-62826) (5%), 4 unidentified polar compounds (totaling 17%), and some volatile compounds (12%). Aqueous photolysis in the presence of photosensitizers greatly accelerates photodegradation of metalaxyl, to a half-life of 1 hour (Burkhard 1979, 0100).

Soil Metabolism

Ellgehausen (1978, 0081) studied the fate of metalaxyl in soil under aerobic; aerobic/anerobic; and sterile/aerobic conditions. In soil under aerobic conditions, metalaxyl degrades with a half-life of about 7 weeks. The only major soil degradation product was CGA-62826. The CGA-62826 then breaks down to non-extractable material and CO_2. Under anaerobic soil conditions, metalaxyl degrades with a half-life of about 9 weeks with CGA-62826 being the major product but persisting longer than the 7 weeks under aerobic conditions. Extractable metalaxyl declined approximately 3% from 31 days after treatment to 89 days after treatment. This indicates soil microbes contribute to its breakdown under non-sterile conditions.

Microbial Metabolism

At current use rates, metalaxyl will not affect soil microbe growth, metabolism of cellulose, protein, starch, or nitrification (Ercegovich 1979, 0102; Ercegovich, Bogus 1979, 0103; Ercegovich, Vallejo, Bogus 1979, 0104).

Two studies (Doebbler 1979, 0101; Glinski 1978, 0105) investigated the effects of metalaxyl on the activated sludge process. The studies have only been reviewed by the Agency for adverse effects on the environment. Metalaxyl is essentially unchanged by the treatment process, and will be discharged from the treatment plant with the effluent. In the study by Glinski (1978, 0105), levels of 50 and 100 mg metalaxyl per liter inhibited the breakdown of organic carbon. This mechanism allows metalaxyl to build up and pass unchanged through the system in the effluent.

Leaching, Adsorption/Desorption

Metalaxyl and its aged soil residues are readily leached in sandy soils, low in organic matter (Guth 1976, 0087, Guth 1978, 0089). Metalaxyl leaches less as the soil increases in organic matter content.

Guth (1978, 0089) studied the leaching characteristics of aged ^{14}C-metalaxyl residues in two soils, sand and silty loam. After 30 days of aerobic aging, 97.4% and 99.2% of the activity was extractable from the sandy and silt loam soils respectively. The results after leaching are (in % of applied ^{14}C-metalaxyl):

soil	% remaining soil	eluate
sandy	16.1.	79.2
silty loam	34.9	48.7

About 70% of the activity remaining in the soil was extracted with methanol and water. Of the metalaxyl found in the eluate of the sandy soil, 56% was parent metalaxyl, 31% was the major degradation product, CGA-62826, 1% was an unknown polar metabolite, and 12% was unaccounted. In the eluate of the silty loam soil, 70% was parent metalaxyl, 18% was CGA-62826, 1% was an unknown polar metabolite and 11% was unaccounted.

Soil adsorption of metalaxyl is minor (Guth 1978, 0088). This is supported by the leaching results which show metalaxyl to be a strong leacher.

Volatilization

The volatilization rate is directly proportional to the initial soil concentration of metalaxyl, the soil temperature, and the air flow rate across the soil surface. It is inversely proportional to greater soil adsorption capacities. Under typical use conditions, less than 0.5% of the applied metalaxyl would be lost due to volatilization (Burkhard 1977, 0077).

Field Dissipation

Under field conditions, the fate of metalaxyl in soil is similar to that under lab conditions except for the shorter half-life of two weeks under field conditions. The major soil degradation product formed was CGA-62826. CGA-62826 breaks down to nonextractable material and CO_2. The soil metabolism of metalaxyl was studied in the field by Ellgehausen (1977, 0079, 0080), Fischer and Cassidy (1978, 0099; and Foster, Fischer, Cassidy (1978, 0086).

Long term field dissipation studies were established at several locations under normal conditions to determine the persistence of metalaxyl after application to potatoes and tobacco (Ciba-Geigy Corporation 1980, 0125, 0149, 0141). The additional data cannot be fully interpreted because of flaws in the study. However, these data do not add new information about the field dissipation of metalaxyl.

Fish Accumulation

Exposure of fish to the parent compound or soil aged residues will not result in accumulation values above 10X in the whole fish (Ladd, Wilson 1979, 0093). During 14 days of depuration, 80% and more of the accumulated residues will be discharged (Ladd, Enos 1979, 0092). Tests indicate little, if any, potential for bioaccumulation. Hydrolysis data, which shows the parent compound to be stable under conditions of this experiment, support the conclusion that fish were exposed to unchanged parent metalaxyl during the exposure period.

Rotational Crop Accumulation

The amount of metalaxyl taken up by several field crops after a period of time subsequent to application of metalaxyl has been studied. Crops that were studied include spring oats, corn, lettuce, soybeans, sugarbeets, potatoes, and wheat. Amount of metalaxyl remaining in the soil and

available to crops was characterized (ratio of organic soluble material to non-extractable). Crops were planted from 33 weeks to 36 weeks after the last of six applications of 14C-metalaxyl at 0.4 lb ai/acre at 14-day intervals except for wheat which was planted immediately afer the same rate and intervals of application.

For spring oats, the highest total ^{14}C-metalaxyl levels (0.33 ppm) were found during the early periods of sampling in the whole plant and declined to 0.21 ppm at 11 weeks of growth. At 33 weeks after the last application when spring oats was planted, the soil residues were in the ratio of 7:10 organic extractable to non-extractable. This ratio changed over the next 11 weeks to 1:4 (Fischer, Cassidy, 1979; 0084).

Corn will not take up ^{14}C-metalaxyl residues in excess of 0.06 ppm in any plant part during growth through maturity. At planting (35 weeks after the last application of metalaxyl), the soil residues were in the ratio of 1:1 organic extractable to non-extractable. This ratio changed over the 21 weeks of the study to 1:12 (Fischer, Cassidy 1979; 0082).

Lettuce takes up ^{14}C-metalaxyl residues. Highest total of ^{14}C levels (0.11 ppm) were found during the early periods of sampling and declined to 0.06 ppm at 9 weeks of growth. These levels were found in the whole plant. The soil residues at planting 33 weeks after the last metalaxyl application were in the ratio 4:5 organic extractable to nonextractable. This ratio changed over the next 11 weeks to 1:6 (Fischer, Cassidy 1978; 0083).

Soybeans will take up ^{14}C-metalaxyl residues at levels of 0.2 to 0.8 ppm (calculated as parent compound). Most of the activity remains extractable from the plant during all stages of plant growth. At planting which was 36 weeks after the last application of metalaxyl, the soil residues were in the ratio of 1:1 organic extractable to non-extractable. This ratio changed over the next 20 weeks to 1:7. The parent compound at levels of 0.2 to 0.3 ppm persist in the soil for more than a year after multiple applications (Hamilton, Fischer, Cassidy 1979; 0090).

Sugarbeets will take up ^{14}C-residues at levels of 0.16 ppm at 6 weeks growth, but this level will drop to 0.02 ppm at 20 weeks, and will probably be even lower at maturity. The soil residues when the sugarbeets were planted at 33 weeks after the last application of metalaxyl were in the ratio of 3:4 organic extractable to non-extractable. This ratio changed over the next 20 weeks to 1:7. The parent compound will also persist in the soil at levels of 0.2 - 0.3 ppm for more than a year after multiple applications (Hamilton, Fischer, Cassidy 1979; 0091).

Wheat planted immediately after a series of applications of ^{14}C-metalaxyl results in ^{14}C residues being taken up by wheat at all stages of growth (Fischer, Cassidy 1978; 0085). Highest total residue levels (3.97 ppm) are found during the early periods of growth when the plants would be subjected to fall grazing. The activity in the soil changes from primarily organic soluble to primarily non-extractable during the 43 weeks post-application. This study does not serve as a rotational crop study since there was not at least a 30-day period between the final application of metalaxyl and planting.

Soil samples were taken periodically when potatoes were tested with metalaxyl(Foster, Fischer, Cassidy, 1978; 0086). The analyses of post-treatment soil samples showed the balance of ^{14}C-activity to change from a ratio of organic extractable to non-extractable of 10:1 after the second treatment to 35:1 after the sixth treatment. Characterization of the soil activity two weeks after the last treatment showed 68.7% to be parent compound and 19.8% to be CGA-62826 [(N-(2,6-dimethylphenyl)-N-methoxyacetyl) alanine]. These results show that soil degradation of parent metalaxyl is evident but a half-life cannot be calculated because of the repeat applications. The soil activity is primarily in the form of parent compound and CGA-62826.

Rotational crop studies (Ciba-Geigy Corporation 1979, 0129) were conducted applying metalaxyl at 0.5 lb to 1.0 lb ai/acre six times to potatoes and then planting winter wheat, corn, sugarbeets, soybeans and ryegrass as rotational crops. In addition, metalaxyl was applied as a preplant incorporated broadcast to tobacco at 3 and 6 lb. ai/acre. Soybeans, corn, and sweet potatoes were planted as rotational crops.

Winter wheat was planted as a rotational crop and early forage, spring forage, harvest straw and grain were analyzed for total metalaxyl residues. Winter wheat planted in rotation to metalaxyl treated potatoes will pick-up metalaxyl residues containing the 2,6-dimethyl aniline moiety even when the wheat is planted 13-1/2 months after the last treatment. Higher residue levels are taken up by wheat planted before the 13-1/2 months.

Field corn was planted as a rotational crop after metalaxyl treated potatoes. Silage stage forage, fodder, and grain were analyzed for total metalaxyl residues. Corn will take up 0.2 ppm metalaxyl residues at 5 weeks growth but at 9 weeks, the grain is found to contain less than 0.05 ppm.

Sugarbeets were planted as a rotational crop and early forage, late forage and roots were analyzed for total metalaxyl residues. Sugarbeets, planted 10 months after 6 applications of metalaxyl do not pick up detectable residues (0.05 ppm) in the roots when harvested at 4 months. However, the forage does contain residues.

Forage of soybeans planted as a rotational crop after potatoes was analyzed for total metalaxyl residues. Soybeans, planted 10 months after application of metalaxyl, picked up residues in the forage when harvested at one month's growth.

Metalaxyl was applied at 0.5 lb ai/acre to potatoes and rye grass was planted as a rotational crop. Rye grass forage was analyzed. Rye, planted 2-1/2 weeks after the last metalaxyl application to potatoes and harvested at one month's growth (forage stage) picked up detectable residues. It is not known whether residues available for pick up by rotational crops will be different due to a single 3 lb ai/acre application or 6 biweekly 0.5 lb ai/acre applications as in these studies.

Soybeans were planted as a rotational crop after a single preplant incorporated broadcast application of tobacco at either 3 or 6 lb ai/acre. Forage, fodder and bean samples were anlayzed for total metalaxyl residues. Soybeans, planted 13 months after application of metalaxyl and harvested at 1-1/2 and 5 months growth picked up residues. In another rotational planting of soybeans, 13-1/2 months after application of metalaxyl to tobacco, immature forage, fodder and grain samples were analyzed for metalaxyl total residues. This analysis shows that soybeans harvested at 2 and 4-1/2 months growth picked up residues.

Corn was also grown as a rotational crop after metalaxyl treated tobacco. Silage stage forage, fodder, and grain samples were analyzed for total residues. Corn, planted 12 months after a single preplant incorporated application of metalaxyl and harvested at 2 and 5 months of growth did not pick up detectable residues of metalaxyl at either treatment rate.

Sweet potatoes were planted as a rotational crop after metalaxyl treated tobacco and early forage, mature roots, and tops were analyzed for metalaxyl total residues. Sweet potatoes, planted 13 months after a single application of metalaxyl showed no detectable residues picked up by the roots or tops at 6 months growth. At 3 months growth (the early forage state), residues were detected. The maximum label rate for tobacco is 3 lb ai/acre. All rotational studies using metalaxyl treated tobacco had treatment rates of 3.0 and 6.0 lbs ai/acre.

The rotational crop data support a rotational crop restriction of one application of metalaxyl per season. If replanting is necessary a second application of metalaxyl should not be made.

The data also supports planting small grain cover crops provided they are plowed down and not used for food or feed purposes. If corn is planted, the label must carry the restriction of not to be planted until 12 months following treatment. The restriction on planting root crops should allow planting of the root crops sugar beets and sweet potatoes at 12 months following treatment. The 12-month restriction on rotating to sugarbeets and sweet potatoes may be extended to all root crops with the submission of rotational carrot data showing no detectable residues when planted 12 months following treatment. Other crops may be planted 18 months following treatment.

Potential for Groundwater Contamination

Metalaxyl and its soil aged residues readily leach in loamy and silty soils low in organic matter. Leaching is especially strong in sandy soils, posing possible groundwater contamination problems . Hydrolysis in groundwater has little effect on the degradation of metalaxyl, but microbes would degrade it. Under the influence of soil microbes, parent material will decline steadily while total amounts of degradation product CGA-62826 and non-extractable material will increase.

Time	%parent(Metalaxyl)	%CGA-62826	%non-extractable
1 mo.	60	30	6
3 mo.	19	48	20
6 mo.	5	33	37
12 mo.	<2	23	38

Therefore, several factors, such as how fast leaching occurs, amount of rainfall, presence of soil microbes and depth of the water table will determine the relative amounts of metalaxyl and its degradation products reaching groundwater. If groundwater contamination is shown, long term toxicological testing, similar to that required for a food-crop use, may be required.

Groundwater Monitoring

Groundwater monitoring studies were being conducted in Maryland and Florida as a condition of registration. Data provided to the Agency so far, showed no detectable metalaxyl residues in soil samples below 18 inches from the surface. Similarly, well water analysis showed no

detectable residues in any of the analyzed samples. Soil and water analyses were performed at 30 day intervals for 219 days following treatment.

The data discussed above were generated from studies conducted on tobacco farms in Florida and Maryland. Additional monitoring, from a site in Indian River, Florida, has been terminated. The Agency is considering the need to require additional monitoring.

Analytical Methods

Ciba-Geigy method no. A6-323 determines the residues of metalaxyl and its acid metabolite in soil. Treated soil is extracted with 50% aqueous methanol which is then made basic with NaOH. The parent compound is removed from this by extraction with dichloromethane which is then cleaned up and subjected to gas chromatographic (GC) analysis with a flame ionization detector. Residues of the acidic metabolite CGA-62826 [N-(2,6-dimethylphenyl)-N-(2-methoxyacetyl) alanine] are removed from the basified solution by acidification with HCl and partitioning with dichloromethane which is evaporated to dryness and reacted with diazomethane which converts the acid metabolite via methylation to the parent compound which is cleaned up and detected as parent compound (Nixon 1978, 0096).

This method has been validated (Balasubramanian et al. 1978, 0071). The percent of recoveries of the parent compound and the acid metabolite from soils fortified in the range of 0.05 - 10.0 ppm averaged 97 $\pm$ 14 and 104 $\pm$ 11, respectively.

Labeling Restriction -- Rotational Crop Statement

"If replanting is necessary, tobacco may be replanted immediately. Tobacco, corn or root crops may be planted the year following treatment. Small grain cover crops may be planted during the fall following treatment provided they are plowed down and not used for food or feed. Other crops may be planted 18 months following application."

Chapter VI

TOXICOLOGY

Toxicology - Manufacturing-Use Metalaxyl

- Acute Toxicity
- Subchronic Toxicity
  - Subchronic Oral Toxicity
  - Subchronic Dermal Toxicity
  - Subchronic Inhalation Toxicity
- Chronic Toxicity
  - Mutagenicity
  - Teratology
  - Reproduction
  - Chronic Feeding
  - Oncogenicity
- Metabolism

Toxicology - Emulsifiable Concentrate (EC) Metalaxyl
- Acute Toxicity

Toxicology - Manufacturing-Use Metalaxyl

Acute Toxicity

The acute oral LD50 of technical metalaxyl in rats is 669 mg/kg which suggests a moderate acute oral hazard to human beings (Sachsse, Bathe 1976; 0026). In rabbits, the acute dermal LD50 of technical metalaxyl is greater than 6000 mg/kg (Sachsse, Ullmann 1976; 0029) while the acute dermal LD50 in rats is greater than 3,170 mg/kg (Sachsse, Bathe 1976; 0023). This suggests a moderate acute dermal hazard to humans.

Technical metalaxyl is irritating to rabbit eyes (Sachsse, Ullmann 1976; 0031). Corneal involvement was noted which completely cleared 3 days after treatment. Technical metalaxyl has a low potential for primary dermal irritation in human beings. It was a mild irritant when applied to rabbit skin (Sachsse, Ullman 1976; 0032). In guinea pigs, technical metalaxyl demonstrated no skin sensitization (Sachsse, Ullmann 1976; 0033).

Based on the toxicity categories in 40 CFR 162.10 technical metalaxyl is a category III chemical for eye irritation, acute oral and acute dermal hazards. Technical metalaxyl, per se, is considered to pose little or no hazard based on the acute testing. Technical metalaxyl has a low hazard potential as a skin irritant and may be placed in category IV.

Subchronic Toxicity

Subchronic Oral Toxicity

Two three-month dietary studies were conducted using technical metalaxyl. The rat was the test species in one study (Drake 1977; 0011) and in the other study, the dog (Finn 1977; 0012).

In the rat 90-day dietary study, four groups totaling 180 rats received dosages of 50, 250, and 1250 ppm of 99% technical metalaxyl while one group served as an untreated control group. Two groups consisted of 25 male and 25 female rats each and 2 groups of 20 males and 20 females each. Effects included minimal cellular hypertrophy in parenchymal cells of five female rats receiving the highest dose. No other changes attributed to treatment were observed. The "No-Observed Effect Level" (NOEL) was 250 ppm based on effects of minimal cellular hypertrophy in the highest dose group. This study is adequate to assess the subchronic oral toxicity of technical metalaxyl in the rodent (Drake 1977; 0011).

Technical metalaxyl was administered to 3 male and 3 female dogs in two groups at 50 or 250 ppm while 4 male and 4 female dogs were treated at 1250 ppm and another group of 4 males and 4 females served as controls. No mortality or changes in animal behavior were observed. Any macroscopic findings were not treatment related. Microscopic examination revealed no dose related necropsy or other findings. Blood chemistry, hematology, and urine analysis; and ophalmoscopy examinations indicated no treatment related findings. The NOEL was 250 ppm. This is supplementary data because too few animals (3/sex) were used (Finn 1977; 0012).

In addition, a six-month oral toxicity study was conducted with technical metalaxyl in the dog (deWard et al., 1981, 0045). Fifty-six dogs (28 males and 28 females), six to eight months old were randomly assigned to four treatment groups. These treatment groups consisted of:

Group I (control) with 8 males and 8 females;
Group II (50 ppm) with 6 males and 6 females;
Group III (250 ppm) with 6 males and 6 females; and
Group IV (1,000 ppm) with 8 males and 8 females.

Two males and two females, each from Group I and IV were randomly selected as recovery dogs.

No dosage-related trends were noted in daily observations. No statistically significant differences were observed in: (1) body weights or weight gains; (2) weekly feed consumption; (3) hematology parameters; or (4) clinical chemistry parameters. No abnormalities or changes were observed in the ophthalmic examinations and the Schirmer tear test results conducted at the predose and terminal examinations. Semi-monthly urinalysis parameters were all within normal limits and no dosage related trends were detected.

Red blood cell count, hematocrit, and hemoglobin count were significantly decreased for Group IV males compared with control males at 60, 90, and 180 days. However, all values were within normal limits and no clinical signs of anemia were observed.

The most consistent clinical chemistry findings were in alkaline phosphatase levels. Alkaline phosphatase levels in Group IV (1000 ppm) male and female dogs were significantly higher than in controls at 120, 150, and 180 day bleedings.

The liver/brain weight ratios of Group IV females dosed at 1000 ppm were significantly increased compared with the control. Absolute liver weights and liver/body weight ratios of female and male dogs showed a trend of increased liver weight with increased dosage. These trends were not statistically signficant in either sex. No other trends were detected in organ weights or ratios.

No treatment-related lesions were seen at gross necropsy and during histopathological examination of the tissues.

The NOEL is considered to be 250 ppm in the diet of dogs for six months. The lowest effect level (LEL) is 1000 ppm and the effects consisted of increased alkaline phosphatase and liver/brain weight ratio.

This study is acceptable as a subchronic oral study in a nonrodent.

Subchronic Dermal Toxicity

In the 21-day dermal study (Toxigenics 1980, 0041), the powdered test material was applied under impervious binders to the abraded and intact (clipped free of hair) skin of rabbits. One half of each group and sex consisted of rabbits with abraded skin. A control group plus three test groups were employed. Each group consisted of 10 female and 10 male rabbits. The dosages used were 10, 100, 1000 mg/kg. The NOEL for the study is 1000 mg/kg/day.

All animals except one in the 100 mg/kg group, survived the study. No significant differences, when compared with the controls were observed for food consumption, body weight, hematology, clinical chemistry, or organ weight ratios. The pathologic studies did not show any lesions that can be attributed to the application of the test material. Nor is there any pathologic evidence that the test material influenced the development or severity of the spontaneous infections and degenerative lesions exhibited by the rabbits.

This study meets the requirements of an acceptable 21-day dermal subacute study.

Subchronic Inhalation Toxicity

A 90-day smoke inhalation study is required if pesticide residues in the smoke of treated tobacco are greater than .1 ppm. Therefore, this subchronic inhalation study is required for metalaxyl's use on tobacco. (See also the Residue Chemistry, Chapter VII). Also, a metabolite of concern of metalaxyl, 2.6-dimethylaniline is a pyrolysis product of metalaxyl.

In a preliminary study (Coate 1980, 0037), rats, in four groups of 10 male and 10 female rats each, were each exposed to the smoke from 16 cigarettes per day. Three groups received exposures to smoke from tobacco treated with metalaxyl technical in weight proportions of 130, 3,900 and 13,000 ppm. One group was exposed to smoke from untreated tobacco. The results indicate little or no toxic impact from exposures to metalaxyl-spiked cigarette smoke. There were no differences in pharmacotoxic signs observed and there were no biologically meaningful hematology or serum chemistry differences except slightly lowered calcium in metalaxyl treated female groups versus the control group that was dose-related. There were no meaningful organ or organ/body weight differences nor remarkable gross pathology differences.

Although exposed to about 40 minutes of a 64-fold range of non-pyrolyzed technical metalaxyl and an undetermined amount and range of its pyrolysis product, no important toxicological effects have been seen to result. The NOEL is the high-dose group (13,000 ppm of technical metalaxyl). This study suffices as a range finding study for the 90-day smoke inhalation study.

A 90-day smoke inhalation test is in progress; a report will be submitted in the summer of 1981.

Mutagenicity

The following studies represent only the minimun requirements for data on the potential heritable effects of metalaxyl.

1. A mamalian in-vitro point mutation test.

2. A sensitive sub-mammalian point mutation test. (Bacteria, fungi, insect).

3. A primary DNA damage test (i.e. sister chromatid exchange or unscheduled DNA synthesis).

4. A mammalian in-vitro cytogenetics test. If this test suggests a positive result, a dominant lethal or heritable translocation test may be required.

After results from these test systems and other toxicology disciplines have been considered, additional testing may be required to further characterize or quantify the potential genetic risks.

Although the Agency's mutagenic testing requirements are not final, the standards for these tests should be based on the principles set forth therein (FR 43, NO. 163, Tuesday, August 22, 1978). Protocols and choices of test systems should be accompanied by a scientific rationale. Substitutions of test systems for those listed above will be considered after discussion with the Agency.

The requirements should be considered an interim guide and not final Agency policy.

The mutagenic potential of metalaxyl was studied by Arni and Muller (1978, 0001) and Fritz (1978, 0013). In Arni and Muller, a salmonella/mammalian microsomal mutation study, the technical chemical at 25, 75, 225, 675, and 2025 ug/ 0.1 ml was tested with and without mammalian microsomal activation to detect point mutations. The test strains were TA 1535, TA 1537, TA 98, and TA 100. Metalaxyl was not mutagenic in this study.

A mouse dominant lethal study using the technical chemical was performed to evaluate cytotoxic or mutagenic effects on male germinal cells (Fritz 1978; 0013). Single doses of 65 or 195 mg/kg were administered to groups of 20 male mice per group. Each treated male was placed in a cage with 2 untreated females for 8 weeks to span the period of spermatozoon development. The data on mating ratios, the number of implantations, and embryonic deaths were comparable in all groups. No adverse toxicity was seen in treated males. However, one male in the 195 mg/kg group died. No evidence of test chemical mutagenicity was observed.

Guerzoni and Mattioli (1979, 0501) studied the mutagenic activity of new fungicides including Ridomil. Two microbiological tests were conducted: (1) a mitotic gene conversion with Saccharomyces cerevisiae (D4), and (2) a genetic forward mutation with Schizosaccharomyces pombe (P1). Reported results in this summary stated that Ridomil showed no mutagenic activity. This study has not been reviewed by the Agency.

Teratology

Fritz (1978, 0014) tested rats for teratogenic or embryotoxic effects of technical metalaxyl. Technical metalaxyl was administered by intubation at 20, 60, and 120 mg/kg body weight to groups of 25 rat dams from day 6 through 15 of gestation. A fourth group of 25 pregnant rats served as controls. Ratios of implantations and resorptions were comparable in treatment groups to control groups. Sex ratios of live fetuses from treatment groups to control group were unchanged. No malformations were found in the fetuses nor were the average weights of the fetuses of the treated groups significantly different from the control group. This study shows that technical metalaxyl is not teratogenic in rats at doses up to 120 mg/kg and suffices to assess the teratogenic potential of metalaxyl in rodents.

Chinchilla rabbits were given oral doses by intubation of technical metalaxyl of 5, 10, and 20 mg/kg from Day 6 through Day 18 of pregnancy (Fritz, 1978, 0042). Metalaxyl technical was not considered teratogenic in rabbits at gavage does up to 20 mg/kg. The no-observed effect level (NOEL) for fetotoxicity is 20 mg/kg.

Study results concluded that during the period of treatment, food consumption was found to be slightly reduced at the 10 mg/kg dose and markedly reduced at the 20 mg/kg dose. In addition the average body weight gain appeared to be slightly reduced in both of these dose groups. However, the mean numbers of corpora lutea and/or implantations were comparable for all groups. The rates of embryo and/or fetolethality (resorptions) were not significantly altered when compared with the control group. The sex ratios were comparable for all groups. The average weights of the live fetuses were comparable for all groups.

This study suffices to assess the teratogenic effects in nonrodents.

Reproduction

To assess the effects of metalaxyl on reproduction over 3 generations, four groups of SPF rats of the Crl: COBS (SD)BR strain were selected (Cozens et al. 1980, 0044). The groups each consisted of 25 male and 25 female rats and were dosed at 50, 250, and 1250 ppm of technical metalaxyl while one group served as control. Throughout the three generations, there were no consistent dosage effects on adult animals in respect to signs of reaction, mortalities, food consumption, water consumption, body weight change, food conversion ratios, mating performance, pregnancy rate, duration of gestation or findings at terminal autopsy.

Data obtained from the teratology sacrifices of parent females and first generation females did not indicate any adverse effect resulting from the administration of technical metalaxyl with respect to:

(a) mean litter parameters (as assessed by pre- and post-implantation loss, litter size, litter and mean fetal weights); or

(b) embryonic and fetal development (as assessed by the incidence of major malformations, minor anomalies and skeletal variants).

The NOEL for reproductive parameters and teratologic parameters is considered to be 1250 ppm.

Chronic Feeding and Oncogencity

Data are not required for currently registered non-food uses of metalaxyl. Data are required to set a permanent tolerance or to grant an exemption from a tolerance.

The 2-year rat feeding study (Life Sciences Research 1980, 0043) cannot be fully evaluated at this time. In the submitted report, the non-neoplastic microscopic pathology summary tables and the neoplastic summary tables list only the number of animals examined and not the number of various organs examined for the number of animals examined. As reported, every organ designated for every animal tested was examined microscopically. The individual animal pathology sheets do not demonstrate this.

These pathology summary tables must be resubmitted to include the number of organs examined for the number of animals examined. In addition, the determination of the maximum tolerated dose (MTD) for the study must be detailed.

Metabolism

In the first study with rats (Hambock 1977, 0015) the excreta and tissue distribution of ^{14}C-metalaxyl was studied. Male amd female rats were dosed with ^{14}C-metalaxyl at 0.5 or 25 mg/kg. The excreta and expired CO_2 were collected for analysis at 24-hour intervals. After six days, the rats were sacrificed and the radioactivity in various tissues was measured.

By the sixth day, almost all the administered radioactivity was excreted in the urine and feces for both levels. The amount of $^{14}CO_2$ expired was insignificant. Pooled urine (0-24 hours) for male and female was analyzed by thin-layer chromatography (TLC) and numerous metabolites were found in urine. No parent metalaxyl was detected in these samples. The residual radioactivity in all the tissues and organs was very low except in the liver, which contained from 0.002-0.004 ppm for 0.5 mg/kg dose rate and 0.146-0.255 for 25 mg/kg dose rate.

The second study (Hambock 1978, 0016) was carried out to isolate and identify the metabolites. Sixteen female rats were dosed orally with 27.9 mg/kg of ^{14}C-metalaxyl and the urine and feces were collected for 48 hours. The urine contained 63.5% of the administered dose and the feces, 32.8%. The analysis of urine extracts showed the same patterns as those reported from the previous study. The radioactivity in the urine was fractionated. In 0-48 hour urine, 62.1% of the metabolites were in the form of glucuronic acid conjugates as shown by aglycone released by p-glucuronidase incubation. At least 10 aglycones were released by enzyme treatment. It was noted that metalaxyl is readily absorbed, degraded and excreted by rats. The degradation of metalaxyl in the rat proceeds primarily via (1) methyl ester hydrolysis (2) N-dealkylation (3) methyl ester linkage (4) 2-(6)-methyl oxidation and subsequent formation of conjugates with glucuronic acid.

Toxicology - Emulsifiable Concentrate (EC) Metalaxyl

Acute Toxicity

The acute oral LD50 in male and female albino rats of 23.5% emulsifiable concentrate (EC) metalaxyl is 1889.5 mg/kg of bodyweight which suggests a moderate acute oral hazard to human beings (Kapp, Piccirillo 1978; 0018). This corresponds to toxicity category III. The acute dermal LD50 of this formulation in rabbits is 3,571.5 mg/kg of body weight (Kapp, Piccirillo 1978; 0017). This suggests a moderate acute dermal hazard to humans and corresponds to toxicity category III.

This formulation is irritating to rabbit eyes causing corneal opacity and conjunctival irritation persisting through 7 days (Piccirillo 1978; 0020). Corneal opacity persisted in two rabbits through termination on Day 14. Conjunctival irritation, consisting of redness, chemesis and discharge persisted through Day 14 in one animal. This corresponds to category I, but the study was not continued through 21 days to determine the irreversible nature of the corneal involvement or irritation. This formulation has a low potential for primary dermal irritation. It was a very slight irritant when applied to rabbit skin (kapp, Piccirillo 1978; 0019). This corresponds to category III.

An acute aersol inhalations study in 6 male and 6 female albino rats was conducted to determine the level of toxicity of this formulation after exposure for four hours. The nominal concentration of the test material generated in the exposure chamber was calculated to be 3.38 mg/L of air. No adverse effects were noted during the 4-hour exposure period or during the succeding 14-day observation period. The Agency finds this test to be supplemented because the LC_{50} was not determined. However for the purposes of precautionary labeling, the product could be placed in category III.

A second modified formulation containing approximately the same amount of active ingredient (24.9%) as the material tested is substantially similar. The Agency has determined with available information that this formulation should reflect approximately the same acute toxicity profile as the material tested. Additional testing of this second EC formulation is not required at this time.

Chapter VII

RESIDUE CHEMISTRY

Manufacturing-use Metalaxyl

Introduction

As discussed in the Use Summary (see Chapter IV), metalaxyl was federally registered in 1980 for use on tobacco. The Agency considers use of a pesticide on tobacco a non-food use and does not require a tolerance or an exemption from a tolerance. However, data are needed to assess the exposure of human beings to residual products upon the consumption of tobacco. Depending on the amount of residues, such data include the nature of residue in tobacco and cigarette smoke; and identification of pyrolysis products; and field residue data.

EPA sets tolerances for pesticides used on growing crops. The use of these pesticides will result in residues remaining in or on food or feed. In addition to its tobacco use, an experimental use permit (EUP) was submitted to the Agency for use of metalaxyl on potatoes. In association with this EUP (100-EUP-1), a temporary tolerance for this food use was granted by the Agency. The temporary tolerance in or on the raw agricultural commodity potatoes was set at 0.05 ppm. Residue chemistry data for the proposed use of metalaxyl on potatoes are discussed in this chapter. Additional data

would be needed for the Agency to grant permanent tolerances on potatoes. Additional tolerances would be required in order to register a product for uses on other raw agricultural commodities, including seed treatments, that may result in residues in food and feed. Appropriate chronic toxicology information is also necessary before a permanent tolerance is set.

Other uses of metalaxyl include turf, conifers, non-bearing citrus (Florida only) and ornamentals. These uses do not require a tolerance or an exemption from a tolerance.

Uptake, Distribution, and Metabolism in Plants

Potatoes

Available data indicate that metalaxyl (CGA-48988) is absorbed into the potato plant (leaves and stems) and is extensively metabolized. Little translocation of residues occurs from the stems to the potato tubers. Because of the low level of residues in the tubers, the fate of the compound in potatoes is adequately defined. The parent compound is the residue of concern.

In a study conducted near Basle, Switzerland (Gross 1977, 0132), eight-week old potato plants were sprayed until runoff with phenyl-^{14}C-metalaxyl at a rate equivalent to 0.18 lb ai/acre. The treatments were repeated 4 times at 10 day intervals. Mature plants with tubers were harvested for analysis five weeks after the last treatment. The plants were fractionated into tubers, leaves, stems and roots and the distribution of radioactivity was determined. About 1.5% of the total amount of radioactivity applied occured in the plants at the time of harvest. The rest of the radioactivity was lost, partly due to drift during the application and partly due to volatilization from the leaf surface. More than 90% of the plant radioactivity was present in the shoots and was found to consist mainly of polar acidic compounds. One of these was identified as N-(2,6-dimethyl phenyl)-N(-methoxyacetyl)-alanine (CGA-62826). Only 2.7% of the radioactivity was in the form of the unchanged fungicide. The tubers contained 0.02 ppm metalaxyl equivalents indicating little translocation of the activity from the foliage to the tubers. The radioactivity consisted exclusively of polar metabolites. It was also noted that neither metalaxyl nor its degradation products were taken by the tubers directly from the soil.

Another study (Fischer, Cassidy 1978; 0099) was carried out in New York State. White potatoes grown in field plots were treated with 3 foliar applications of phenyl-^{14}C-metalaxyl. The first application was made six weeks after plant emergence at the rate of 1.1 lb ai/ acre (3X of the maximum proposed rate of application). Subsequent applications were made at the same rate at 28 day intervals. Plant samples (tubers and stalks) were taken immediately before and after each treatment and at tuber maturity (18 weeks). It was determined that the level of radioactivity in stalks decreased about 80% within 4 weeks after each spraying. The level of radioactivity in the tubers decreased from 2.47 ppm at the first treatment, when they were small roots to 0.14 ppm at the time of harvest. It appears that the high levels in the tubers are due to contamination with radioactive soil. Partition characterization of the extractable radioactivity in the tubers and stalks indicate that potatoes can metabolize ^{14}C-metalaxyl extensively, especially in the tubers. Characterization of the radioactive metabolites in mature stalks showed that 2.7% could be accounted for as parent ^{14}C-metalaxyl and 11.4% as metabolite, CGA-62826. At maturity most of the radioactivity in the stalks was soluble in organic solvents. Thus, a large fraction of the metabolites appears not to be conjugated with natural products.

An additional study (Foster, Fischer, Cassidy 1978; 0086) was also carried out in New York State. White potatoes grown in field plots were treated with 6 foliar applications of phenyl-^{14}C-metalaxyl. The first application at 0.4 lb ai/acre was made six weeks after plant emergence. Subsequent applications at the same rate were made at 14 day intervals. Only tuber samples were studied. These tubers were weighed and the levels of radioactivity ranged from <.003 to 0.094 ppm, metalaxyl equivalents. This range is probably due to contamination with treated soil or translocation of ^{14}C-metalaxyl. Because of low levels, no further characterization of the radioactive components was attempted.

Tobacco

See the Nature of Residue in Tobacco in this chapter.

Animal Metabolism

Goat

A lactating goat was administered phenyl-^{14}C-metalaxyl by capsule at a level of 7.00 ppm in the feed for 10 consecutive days (Seim 1978, 0143; Fischer, Foster, Cassidy

1978, 0131). Urine, feces, milk and expired CO_2 and volatiles were collected daily for analysis. Blood was collected every second day and on the day of sacrifice. One day after the last dose, the goat was sacrificed and various organs and tissues were sampled. Most of the administered radioactivity was excreted by the time the goat was sacrificed, 93.9% in urine, 11.6% in feces and <.002% in expired volatiles and CO_2. Levels of radioactivity in tissues at sacrifice, expressed as ppm equivalent to ^{14}C-metalaxyl, were all below 0.05 ppm except the liver with 0.057 ppm. The radioactivity in milk ranged from 0.003 ppm equivalent to ^{14}C-metalaxyl on the first five days to 0.008 ppm on the seventh day, the last day of milk production. However, the quantity of radioactivity excreted as ng equivalent to ^{14}C-metalaxyl per day remained relatively constant during the first seven days. Therefore, a true plateau was reached on the first day at 0.003 ppm.

Characterization of the urine radioactivity by liquid partioning, thin layer chromatography (TLC), and electrophoresis show the components to be highly polar and all had organic acid properties. The overall TLC portions of the metabolites are similar in rats and goats treated with metalaxyl. The only glycosidic enzyme to hydrolyse the urine complex was glusulase.

Rat

[See the discussion of the rat metabolism studies (Hambock 1977, 1978; 0015, 0016) in the Toxicology Chapter VI.]

For the purpose of temporary tolerances, the above studies adequately define the metabolism of metalaxyl (CGA-48988) in animals. For any future permanent tolerance request or expansion of the experimental use program, additional metabolism data are needed on a goat or large ruminant animal (cow) with identification of the residues in milk and tissues.

Analytical Methods

The Agency requires the submission of, or reference to, validated analytical methods suitable for obtaining data on the nature and amount of pesticide residues resulting from the proposed use. One method must be suitable for tolerance enforcement. The regulatory method for determination of a pesticide in raw agricultural commodities must be capable of measuring the total toxic residue from the pesticide.

One analytical method, Ciba-Ceigy Method AG-325 (Balasubramanian, Nixon 1978, 0117) determines the parent compound (metalaxyl, CGA-48988) in potato tubers and field tobacco. Only the parent compound required analysis in potatoes because of the extremely low level of residues and the lack of definite characterization of metabolites.

The method employs methanol extraction, partitioning into dichloromethane and then hexane and cleanup on an alumina column. The purified residue is then taken up into acetone and quantitated by gas chromatograph (GC) using an alkali flame detector.

The lower limit of detection of this method is 0.05 ppm for potatoes and 1.0 ppm for tobacco.

This method is adequate for determination of residues of parent metalaxyl and is adequate for the determination of the proposed tolerance in potatoes.

Available data indicate that the method is very specific and no interferences will result from 66 out of 74 compounds having tolerances on potatoes. The remaining 8 compounds were not available for testing at that time and could not definitely be excluded on the basis of their structure (Balasubramanian, Ross 1978, 0119).

Although characterization of radioactive metabolites in tubers could not be achieved because of low residue levels, CGA-62826 (N-(2,6-dimethyl phenyl)-N-(methoxyacetyl)alanine) was found in leaves and stalks. Thus, CGA-62826 is considered as a possible metabolite of metalaxyl which can be present in tubers. To test this possibility, field samples of potatoes exhibiting the highest residues of metalaxyl were analyzed for CGA-62826 (Ciba-Geigy Corp. 1978, 0126).

In this procedure potato tubers are extracted with aqueous methanol and extracts concentrated according to methodology in AG 325. The concentrated extract is diluted with water, acidified and metalaxyl and CGA-62826 are partitioned into dichoromethane. The CGA-62826 is then extracted from the dichloromethane solution into aqueous sodium hydroxide, leaving parent metalaxyl in the organic phase. The aqueous phase is acidified and the CGA-62826 is partitioned into a second dichloromethane fraction. This organic phase is evaporated to dryness and the resulting material is reacted with diazomethane. After evaporation of the solvent, residues of CGA-62826, which are converted to metalaxyl by a methylation reaction, are cleaned up and detected in the same manner as parent metalaxyl in analytical method AG 325.

The above methods for analysis of metalaxyl and CGA-62826 for potatoes have not been evaluated in EPA laboratories. This must be done before the establishment of any permanent tolerance.

Method AG-330 (Balasubramanian, Ross 1978; 0120) determines total residues as 2,6-dimethylaniline (DMA). Residues are extracted with methanol-water, then a measured aliquot is evaporated and refluxed overnight with phosphoric acid in the presence of cobalt chloride. After reflux, the solution is made alkaline and the DMA steam distilled, derivatized with trichloroacetyl chloride, cleaned up on an alumina column and analyzed by gas chromatograph using alkali flame ionization detector in nitrogen-specific mode. The limit of detection for residues in tobacco is 1.0 ppm (in metalaxyl equivalents).

Compounds containing oxidized forms of DMA were not detected satisfactorily, but six standard compounds related to known metabolic products (containing DMA moiety) are shown to give satisfactory recoveries (85 to 104%).

Twelve fortification studies using green and cured, bright and burley samples fortified with 1 to 500 ppm parent compound gave recoveries of 65 to 87% (avg. 72%).

Analyses of tobacco leaves treated with ^{14}C-labeled metalaxyl show that from 36%to 68% of extractable radio-activity was detected with this method.

A comparison of parent and total residues (determined as DMA) in green and cured field-treated (either 50W or 2E formulation) gives total-to-parent ratios of 2.0 to 4.7, averaging 3.5.

This method is adequate for determination of total residues of metalaxyl (as DMA) in tobacco.

Nature of Residue in Tobacco

The nature of the residue for both cured and uncured tobacco has been studied. The component residue profiles of uncured bright and burley tobaccos are not significantly different. Residues were characterized as either non-extracted, organic (soluble in chloroform or methanol) or polar (soluble in water). A decline in extractability was noted in the cured tobaccos and is presumed to be an effect of curing.

In a greenhouse metabolism study (Honeycutt, Cassidy 1978, 0106), bright and burley tobacco were transplanted into a Georgia-sandy-loam soil. For the bright tobacco, radiolabelled phenyl-^{14}C-metalaxyl was added to the transplant water at an amount approximating either 0.25 lb. or 0.50 lb ai/acre. The phenyl-^{14}C-metalaxyl application to the burley tobacco was incorporated into the soil at approximately 6.0 lb ai/acre. The resulting residues present in the leaf fall into the three groups described above.

Residues of ^{14}C-metalaxyl *per se* average 42.5 ppm in the cured tobaccos. Total ^{14}C-metalaxyl residues are about 155 ppm. A standard cigarette prepared with either 10% or 40% of ^{14}C-labeled tobacco would be expected to contain total residues of ^{14}C-metalaxyl of 17 to 68 ug. Cigarettes (1g) prepared with greenhouse-grown ^{14}C labeled tobacco contained 19 ug (10% blend) and 82.2 ug (regular blend) when made with bright tobacco and 68.7 ug (regular blend) when made with burley.

Based on the field residue studies (Ciba-Geigy Corp. 1978, 0127) 1.0 gm cigarettes prepared with bright tobacco treated with 3.0 and 6.0 lb metalaxyl per acre contain residues of metalaxyl *per se* of 31 and 68 ug, and total residues of about 100 and 250 ug.

Another study concerns uptake and balance of labeled-metalaxyl in field-grown bright tobacco (Honeycutt, Fischer, Cassidy 1979; 0136). The soil was treated with 3 lb ai/acre ring-labeled metalaxyl applied before planting. Residue levels were considerably lower than in greenhouse-grown tobacco, presumably due to decreased availability of metalaxyl because of soil binding, and were also lower than in field-grown burley tobacco.

Residue levels increased about threefold on curing. For example, residues in 9 week-old leaves were 6.7 ppm for green leaves and 21.5 ppm cured leaves. Cured bottom leaves contained higher levels (21.5 ppm) than did cured top leaves (7.3 ppm).

Balance data showed a decrease in organic radioactive solubles from 49.1% at 5 weeks to 31.0% at 16 weeks and an increase in aqueous soluble metabolites from 43.0% at 5 weeks to 61.5% at 16 weeks. These changes occur more rapidly in field grown tobacco than in greenhouse tobacco.

Nonextractable radioactivity was low before curing, but rose to 10-20% upon curing. Aqueous soluble polar metabolites are higher in middle and upper cured leaves than in lower ones, which suggests that age decreases the amount of polar metabolites.

Additionally, it was found that labeled metalaxyl is transferred from treated to untreated leaves during curing. The amount of transfer occurring is expected to be a function of temperature and air flow rate in the curing ovens.

Seven major unknown polar metabolites in field cured tobacco each comprised more than 1% of the total radioactivity in the leaf. Minor unknown metabolites (17) were each less than 1% and no more than 10% of the total. No parent metalaxyl was found. The TLC patterns are qualitatively similar to greenhouse-grown bright and burley tobacco. Apparently metabolism occurs faster under field conditions than in the greenhouse.

In a greenhouse study, bright tobacco slips were treated by a transplant water procedure of 0.5 lb ai/acre with ring-labeled metalaxyl, and the mature top leaves were harvested and cured after 19 weeks (Honeycurr, Szolics, Simoneaus, Cassidy 1979, 0139). Residue levels were 93.7 ppm. Previous studies at 12 weeks showed that polar metabolites could be converted to nine aglycones, six of which corresponded to unconjugated metabolites. Four of those aglycones have now been identified primarily by GLC/MS, GLC/Fourier Transform IR and two dimensional TLC. Collectively, these and the parent compound account for 61% of the radioactivity in the leaf.

Based on the data, soil residues of metalaxyl are picked up and extensively metabolized. The major pathway appears to be conversion of a metalaxyl ring methyl group to methoxy group and conjugation of metalaxyl with glucose through this methoxy group. A second and minor pathway is a conjugation with glucose through the alanine carboxyl group of the metalaxyl metabolite, CGA-62826.

Nature of the Residue in Cigarette Smoke

Honeycutt, Szolics, and Cassidy (1978, 0137) studied the nature of metalaxyl residue in cigarette smoke. Four batches of radiolabelled cigarettes were prepared according to an accepted standard. Two batches were prepared with blended bright tobacco using regular bright tobacco and either 4% or 40% ^{14}C-bright tobacco. Two batches were similarly blended with regular 14-C-burley tobacco. The greenhouse-grown ^{14}C-tobaccos from the metabolism study (Cassidy, Ross 1978, 0123) were used in these cigarettes.

The two types of tobacco have similar residue profiles. In view of this only the smoke profile of the bright tobacco is summarized in Table VII-1. The only components identified were 2,6-dimethylanaline (DMA) and metalaxyl per se. Approximately half of the ^{14}C-activity present in these cigarettes remained in the ash or butts, or was trapped as 14-C carbon dioxide in the smoke. The sidestream smoke contained 75% of the radioactivity, while 25% was in the mainstream smoke.

There are differences between greenhouse and field-grown tobacco that significantly affect the smoking characteristics of the tobacco. The differences were negligible for the batches containing 4% radiolabelled greenhouse tobacco but were significant for the regular blend cigarettes containing 40% greenhouse tobacco. This is shown by the distribution of the tar residues (TPM-volatiles). The vapor phase (VP) volatiles are the smoke residues that would probably be inhaled through a cigarette filter.

The blend bright (4%) ^{14}C cigarettes were the source for these metalaxyl residues. They were the only residues characterized by GLC. The regular blend (40%) ^{14}C-metalaxyl residue for co-chromatographic characterization by 2 dimensional thin layer chromatography (2D-TLC) and high performance liquid chromatography (HPLC).

The reported ^{14}C-carbon dioxide (26.7%) and the calculated ^{14}C-metalaxyl remaining in the ash and butt (2.7% and 20%) were also determined with these cigarettes.

TABLE VII-1: Summary of the Residue Data for Cigarette Smoke

	TPM-Volatiles 44%		VP-Volatiles 6%	
Component(s)	MS(28%)	SS(16%)	MS(036%)	SS(4.74%)
Metalaxyl	7.5	5.2	0.07	0.38
2,6-DMA	0.7	2.2	<0.01	0.90
Polar (3)	2.0	2.2	-	-
Organic (4)	4.2	3.9	-	-
Other (22)	-	-	0.15 (6)	0.42 (22)
Total	14.4%	13.5	0.13%	1.60%
% of the volatiles recoverd	63%		34%	

About 100 micrograms is the total metalaxyl residue expected in cigarettes prepared with bright tobacco treated with 3.0 lb of metalaxyl per acre. For such cigarettes, the percentage

of residues in Table VII-1 are also equivalent to the microgram quantities of the components in the smoke. Similarly, for cigarettes prepared entirely with bright or burley tobacco treated at the maximum rate (6.0 lb. ai/acre) the microgram quantities of residues expected are factors of 2.5 and .23 respectively. These factors indicate that metalaxyl residues per se average about 27.5% of the total residue. These factors are based on the reported maximum residues of metalaxyl per se which were reported in the field studies and data from Table VII-1.

The nature of metalaxyl residue in cigarette smoke is adequately understood.

Pyrolysis Products

Pyrolysis and distillation products of metalaxyl tobacco metabolites into smoke as a result of the smoking process were identified. One organic component and 2,6-DMA are definitely pyrolysis products (Honeycutt, Szolics, Cassidy 1978; 0137). They are not found as components of the cured tobacco, but were smoke components. Three organic components in cured tobacco and smoke are probably distillation components.

Unlabelled pyrolysis products were not determined. The possibility of these components is indicated by the large proportion of ^{14}C-carbon dioxide in the smoke.

The characterization of the pyrolysis products of metalaxyl and its metabolites is marginally adequate.

Residue Data

Field Tobacco

Residue tests were conducted in North Carolina, Virginia, Tennessee, Maryland, and Georgia (Ciba-Geigy Corp. 1978, 0128). Bright or burley tobacco was grown and harvested according to the cultural practice of the respective areas. The reported residues vary considerably.

Test plots at all locations were treated with a 50% wettable powder (WP) formulation at rates of either 3.0 lb. or 6.0 lb. of metalaxyl per acre. In order to obtain a metalaxyl emulsifiable concentrate (EC) formulation, crossover data, plots in Maryland were also treated with at the same rates. Differences between the formulations did not significantly affect the metalaxyl residue in tobacco. Growing conditions, e.g. greenhouse vs. field do affect the residue profile.

Only metalaxyl residues per se were determined by the method of Balasubramanian and Nixon (1978, 0117). Residues in lower, uncured leaves at 12 weeks (84 days) treatment-to-harvest interval were up to 3.5 ppm in bright tobacco treated the the 3.0 lb. ai/acre rate. At the 6.0 lb. ai/acre rate, residues in bright tobacco at the same intervals ranged up to 9.2 ppm. However, residues in uncured composited burley leaves at 109 days preharvest interval (PHI) were <1.0 ppm.

Residue in lower, cured bright leaves at 84 days preharvest intervals with a 3.0 lb. ai/acre treatment rate ranged from 3 - 31 ppm. At 6.0 lb. ai/acre residues ranged from 4.6 - 68 ppm. In cured composited burley leaves at 109 days PHI, residues were 6.3 ppm at 6.0 lb. ai/acre treatment rate.

Additional residue reports (Ciba-Geigy Corp. 1978, 0127) contain results analyzed for total metalaxyl residues which are detected as derivatives of 2,5-dimethylaniline (DMA). These studies were conducted at the same locations as the ones for which metalaxyl per se were reported. Total residues in lower green (uncured) leaves ranged from 1.2-25 ppm at 3.0 lb ai/acre to 2.0-35 ppm at 6.0 lb ai/acre. Residues in composited green leaves (upper, middle and lower) from one study were <1.0 ppm from treatment with either 3.0 or 6.0 lb. ai/acre. These results were analyzed by the method of Balasubramanian and Ross (1978, 0120).

In the cured tobaccos, the lower leaves of bright tobacco at 84 days before harvest contained 7.9 to 83 ppm (at 3.0 lb ai/acre). At 6.0 ai/acre the values ranged from 15-179 ppm. Middle leaves of bright tobacco at 122 days contained 8.6 to 16 ppm metalaxyl and 8.1 to 50 ppm from treatment with 3.0 and 6.0 lb. ai/acre respectively. Upper bright leaves at 154 days PHI contained 6.0 to 12 ppm and 8.1 to 45 ppm from treatment (3.0 and 6.0 lb. ai/acre). Composited burley leaves at 109 days PHI contained <1.0 to 6.1 and 1.5 to 21 ppm and composited bright leaves contained 44 to 49 ppm (13 ppm parent metalaxyl) and 199 to 228 ppm (53 ppm parent). All samples were treated with either the EC formulation or a WP formulation.

Maximum residues in cigarettes are calculated using the tobacco with the highest residue levels which were 83 ppm (residues determined as DMA) in lower cured leaves. From the tobacco metabolism studies, the average ratio of radio-labelled metalaxyl recovered as DMA total amount of radio-labelled present was 55%. Therefore, the maximum level of metalaxyl and all metabolites is estimated to be 151 ppm or 151 ug per 1 g standard cigarette of which 38 ug would be in the mainstream smoke and likely be inhaled by a smoker.

Potatoes

Residue tests were conducted in 1977 and 1978 in 4 states, New York, Washington, Iowa, and Florida (Ciba-Geigy Corp. 1978, 0126). Metalaxyl was applied as a 50% WP formulation at rates of 0.5 and 1.0 lb. ai/acre. These rates are 1.33 and 2.67 times the maximum proposed rate of application.

A total of six foliar applications were made at approximately 2 week intervals. An additional test was conducted in Florida in 1978 using a metalaxyl 2E formulation to obtain crossover data. Potato tubers from three of these studies using the 50% WP at 0.5 lb ai/acre contained no detectable residues (<0.05 ppm) of metalaxyl at a 1 day PHI. Results from tests in New York and Iowa showed residues at levels of 0.07 to 0.18 ppm. At the 1.0 lb. ai/acre treatment rate, the residues ranged from <0.05 ppm to 0.23 ppm.

At the 7 day PHI, the tubers from plots sprayed at the 0.5 lb. ai/acre rate contained no detectable residues (<0.05 ppm). The tubers sprayed at 1.0 lb. ai/acre contained residues ranging from 0.08 to 0.99 ppm.

Potato tuber samples, at both PHI's treated at 1.0 lb. ai/acre and containing residues over 0.2 ppm of parent metalaxyl (CGA-48988) were further analyzed for residues of the metabolite, CGA-62826. No detectable residues (calculated as parent metalaxyl) were found.

The results of residue tests in Florida with a metalaxyl EC formulation show that this formulation will not result in residues greater than those resulting from the use of the 50% WP formulation.

Available data are adequate to show that the residues of metalaxyl in potato tubers from the proposed experimental use will not exceed the proposed temporary tolerance of 0.05 ppm.

Meat, Milk, Poultry and Eggs

The metabolism studies on goat and rat show that metalaxyl is rapidly metabolized and effectively excreted. Neither animal retained significant quantities of metalaxyl or its metabolites in the tissue and milk. Similar metabolites are present in both goats and rats, so the metabolic pathways are applicable to both animals.

If potatoes are part of the daily diet of feed animals, the percentage of the diet may approach 50%. The results from a three level meat and milk study are not available but the results of the goat study may be extrapolated to cattle.

The radiotracer feeding studies on a goat at 7 ppm in the diet show that the plateau residue level in milk was 0.003 ppm (Fischer, Foster, Cassidy 1978; 0131). Since the temporary tolerance is 0.05 ppm, the feeding level is 280 times the maximum calculated feeding level of 0.025 ppm. By extrapolation from the results of the goat study, the maximum residue expected in milk is $\frac{.003}{280}$=.00001 ppm (0.01 ppb).

A similar extrapolation with the higher residue found in goat tissues (0.057 ppm in the liver) shows that the maximum residue expected is $\frac{.057}{280}$ = .0002 ppm.

A temporary tolerance for meat and milk is not required for this experimental use permit on potatoes because the feeding of potatoes for cattle is not a common practice under current economic conditions and the maximum calculated values are extremely low.

For any future permanent tolerance request or an expansion of the experimental use program for food crops, large animal feeding studies and tolerance proposals for residues in meat, milk, poultry, and eggs are required.

Formulated Metalaxyl

Required Labeling

Tobacco

A second EC application of metalaxyl is not permitted for one year and then only for tobacco.

Chapter VIII

ECOLOGICAL EFFECTS

Ecological Effects -- Manufacturing-Use Metalaxyl
  Non-target Wildlife
    Birds
    Fish
    Invertebrates
    Aquatic Life-Cycle Studies

Ecological Effects -- Emulsifiable Concentrate Metalaxyl
  Aquatic Organisms

Ecological Effects - Manufacturing-Use Metalaxyl

Non-target Wildlife

Birds

Manufacturing-use metalaxyl is practically non-toxic to birds. The acute oral LD50 of technical metalaxyl to the mallard duck is 1,466 mg/kg (Beavers, Fink 1977; 0051). An eight-day dietary study on the mallard duck (technical metalaxyl) yielded an LC50 greater than 10,000 ppm (Beavers, Fink 1977; 0053). A bobwhite quail dietary study using technical metalaxyl also resulted in an LC50 value greater than 10,000 ppm (Beavers, Fink 1977; 0052).

Another 8-day dietary study conducted by Sachsse and Ullmann (1976, 0061) on the Japanese quail also yielded values over 10,000 ppm. This test is classified by the Agency as supplemental because the Japanese quail is not a recommended species.

Fish

Manufacturing-use metalaxyl is practically non-toxic to fish. Two 96-hour LC50 studies using technical metalaxyl on a coldwater fish (rainbow trout) yielded LC50's greater than 100 ppm (Fratus, Buccafusco 1978, 0056; Sachsse, Bathe 1976, 0059). McCann (1979, 0067) reports an LC50 value of 132 ppm for rainbow trout.

In a warmwater fish (bluegill sunfish), two studies also yielded 96-hour LC50 values greater than 100 ppm for technical metalaxyl (Fratus, Buccafusco 1978, 0055; Sachsse, Bathe 1976, 0059). An additional study on blue gills yielded a similar LC50 value of 139 ppm (McCann 1979, 0067).

Additional values of greater than 100 ppm were also reported in the catfish, carp, and guppy for technical metalaxyl (Sachsse, Bathe 1976, 0059). These data provide only supplemental information because the fish used in the test are not acceptable test species.

Sachsse and Bathe (1976, 0059) provides only supplemental data because of several additional deficiencies in the study including: (1) the loading factor was excessive; (2) an LC50 value was not established (3) test vessels were aerated for the trout; (4) tests were conducted at lower than normal temperatures or over a fluctuating temperature range; and (5) numbers of fish tested or the numbers of concentrations were not adequate for the carp, catfish, and bluegill.

Invertebrates

LeBlanc and Cary (1978, 0058) reported a 48-hour LC50 value of 28 ppm for technical metalaxyl on aquatic invertebrates (Daphnia magna). This corresponds to slight toxicity in aquatic invertebrates. McCann (0068) reports an LC50 of 121 ppm. A 48-hour LC50 value of 29.3 ppm was found in a previous study that was judged supplemental in part due to the use of combined data from separate tests. (Le Blanc 1977, 0057).

Embryo-larvae and Life-cycle Studies

An aquatic laboratory life-cycle test was conducted with Daphnia magna as the test species. The test substance was technical metalaxyl of 90.1% purity. The minimum threshold concentration or the minimum toxicant concentration to elicit an adverse response is greater than 1.2 mg/l and less than 2.7 mg/l (E.G. and G. Bionomics 1980, 0062).

An embryo-larvae study using the fathead minnow (Pimephales promelas) was conducted with technical metalaxyl of 90.1% purity. The minimum threshold concentration to minnow eggs and fry is greater than 9.1 mg/l. That is, active ingredient levels as high as 9.1 mg/l had no adverse effects on percent of eggs hatched, survival, or growth of fry. (E.G. and G. Bionomics 1980, 0063).

Ecological Effects - Emulsifiable Concentrate (EC) Metalaxyl

Aquatic Organisms

Aquatic bioassays indicate differential toxicity of different formulations of metalaxyl. This is apparently due to inert ingredients. Therefore, prior to any registration of a new formulation, the Agency will consider the need for aquatic bioassays on that formulation.

Formulated EC metalaxyl (27.9% a.i.) yielded 96-hour LC50 values in bluegill and rainbow trout of 27 ppm and 18.4 ppm respectively based on the EC formulation (McCann 1979; 0064, 0065). A 48-hour LC50 of 12.5 ppm based on this formulation was found for Daphnia magna (McCann 1979, 0066). These values indicate that EC metalaxyl is slightly toxic to aquatic species.

IX. CASE BIBLIOGRAPHY

Guide to Use of This Bibliography

1. Content of Bibliography. This bibliography contains citations of all the studies reviewed by EPA in arriving at the positions and conclusions stated elsewhere in this standard. Primary sources for studies in this bibliography have been the body of data submitted to EPA and its predecessor agencies in support of past regulatory decisions, and the published technical literature.

2. Units of Entry. The unit of entry in this bibliography is called a "study". In the case of published materials, this corresponds closely to an article. In the case of unpublished materials submitted to the Agency, the Agency has sought to identify documents at a level parallel to a published article from within the typically larger volumes in which they were submitted. The resulting "studies" generally have a distinct title (or at least a single subject), can stand alone for purposes of review, and can be described with a conventional bibliographic citation. The Agency has attempted also to unite basic documents and commentaries upon them, treating them as a single study.

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(4) Volume Identification. The final element in the trailing parenthesis identifies the EPA accession number of the volume in which the original submission of the study appears. The six-digit accession number follows the symbol 'CDL', standing for "Company Data Library". This accession number is in turn followed by an alphabetic suffix which shows the relative position of the study within the volume. For example, within accession number 123456, the first study would be 123456-A; the second, 123456-B; the 26th, 123456-Z; and the 27th,123456-AA.

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CASE BIBLIOGRAPHY

Section 1: Citations Considered to be Part of the Data Base Supporting Registrations Under the Standard, and therefore entitled to Exclusive Use Provision of FIFRA.

GS-0081:

:0001 Arni, P.; Muller, D. (1978) Salmonella/Mammalian-Microsome Mutagencity Test with CGA-48988--Test for Mutagenic Properties in Bacteria: Experiment No. 78-2514. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy Ltd., Basle, Switzerland; CDL:234428-K)

:0117 Balasubramanian, K.; Nixon, W. (1978) Gas Chromatographic Residue Determination of CGA-48988 in Crop Samples: Method AG-325. (Unpublished study received October 31, 1979 under 100-607 prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:241243-D)

:0071 Balasubramanian, K.; Nixon, W; Ross, J. (1978) Validation of Analytical Method AG-323 for the Determination of Residues of CGA-48988 and its Acid Metabolite CGA-62826 in Soil: ABR-78048. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:234438-B)

:0120 Balasubramanian, K; Ross, J. (1978) The Determination of CGA-48988 and its Metabolities in Tobacco as 2.6-Dimethylaniline using Phosphoric Acid Reflux: Method AG-330 dated November 7, 1978. (Unpublished study received October 31, 1979 under 100-607 prepared by Ciba-Geigy Corp. Greensboro, N.C., CDL:241246-D)

:0119 Balasubramanian, K.; Ross, J. (1978) Specificity of Analytical Method AG-325 for the Determination of Residues of CGA-48988 in Potatoes: ABR:78052. (Unpublished study received September 5, 1978 under 100-EUP-1, 8G2121 submitted by Ciba-Geigy Corp., Greensboro, N.C., CDL: 097389-C)

:0121 Balasubramanian, K.; Ross, J. (1979) Specificity of Analytical Method AG-330 for the Determination of Total Residues of CGA-48988 in Potatoes: ABR:79013. (Unpublished study received October 31, 1979 under 100-607 prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL: 241243-C)

:0051 Beavers, J.; Fink, R. (1977) Acute Oral LD_{50}-Mallard Duck CGA-48988 Technical, Final Report. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Wildlife International Ltd. for Ciba-Geigy Corporation, Greensboro, N.C., CDL:234439-D)

:0052 Beavers, J.; Fink, R. (1977) Eight-day Dietary LC_{50}-Bobwhite Quail CGA-48988 Technical, Final Report: Project No. 108-147. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Wildlife International Ltd. for Ciba-Geigy Corp., Greensboro, N.C., CDL:234439-F)

:0053 Beavers, J.; Fink, R. (1977) Eight-day Dietary LC_{50}-Mallard Duck, CGA-48988, Final Report: Project No. 108-148. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Wildlife International Ltd. for Ciba-Geigy Corp., Greensboro, N.C., CDL:234439-H)

:0076 Burkhard, N. (1976) Hydrolysis of CGA-48988 under Laboratory Conditions: AC 2.52, Project Report 26/76. (Unpublished Study received July 13 1978 under 100-EUP-62; preapred by Ciba-Geigy Ltd., Basle, Switzerland, CDL:234438-C)

:0077 Burkhard, N. (1977) Volatilization of CGA-48988 from Soil Under Laboratory Conditions: AC 2.52, Project Report 29/77. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy Ltd., Basle, Switzerland; CDL:234438-D)

:0100 Burkhard, N. (1978) Photolysis of CGA-48988 (Ridomil®, in Aqueous Solution under Artifical Sunlight Conditions: AC 2.52, Project Report 12/79. (Unpublished study received April 26, 1979 under 100-600; prepared by Ciba-Geigy Corp. Greensboro, N.C.; CDL:238231-F)

:0078 Burkhard, N. (1978) Photolysis of CGA-48988 (Ridomil® on Soil Surfaces under Artificial Sunlight Conditions: AC 2.52, Project Report 09/78. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy Ltd., Basle, Switzerland; CDL:234438-E)

:0160 Ciba-Geigy Corporation (1978) Ciba-Geigy Technical CGA-48988--Product Chemistry Information. (Unpublished study received July 13, 1978 under 100-EUP-63; CDL:234427-A)

:0161 Ciba-Geigy Corporation (1978) CGA-48988 2EC--Product Chemistry Information. (Unpublished study received July 13, 1978 under 100-EUP-63; CDL:234427-A)

:0126 Ciba-Geigy Corporation (1978) Residue Reports of CGA-48988 on Potatoes. (Unpublished study that includes AG-A 4903, AG-A 4903 2nd Rept., AG-A 4935, AG-A 4936, AG-A 4936 2nd Rept., AG-A 4937, AG-A 4937 I-III 2nd Rept., AG-A 4977, AG-A 4977 2nd Rept., AG-A 4978, AG-A 4978 2nd Rept., AG-A 4979, AG-A 4979 2nd Rept., AG-A 4998, AG-A 4998 I-II, 2nd Rept., AG-A 6038, AG-A 6038 2nd Rept., 3rd Rept., 4th Rept., 5th Rept., AG-A 6039, AG-A 6039 2nd Rept. received September 5, 1978 under 100-EUP-1, 8G2121 submitted by Ciba-Geigy Corp., Greensboro, N.C., CDL:097389-A)

:0127 Ciba-Geigy Corporation (1978) Residue Reports - Metalaxyl Total Analyses. (Unpublished study that includes NC AG-A 4732 II, IV 2nd Rept., VA AG-A 4778 II, III 2nd Rept., TN AG-A 4785 III 2nd Rept., MD AG-A 4789 II, III 2nd Rept., GA AG-A 4799 2nd Rept., received October 31, 1979 under 100-607; CDL:241246-B)

:0128 Ciba-Geigy Corporation (1978) Residue Reports Tobacco - Metalaxyl Parent Analyses. (Unpublished study that includes NC AG-A 4732 II, IV; VA AG-A 4778 II, III; TN AG-A 4785 III; MD AG-A 4789 II, III; GA AG-A 4799, received October 31, 1979 under 100-607; CDL:241246-A)

:0129 Ciba-Geigy Corporation (1979) Residue Reports--Rotational Studies. (Unpublished study that includes [NY] AG-A 5027 I, II, III A; AG-A 5118 I, IIA; AG-A 5119 I, II; AG-A 5131; [NC] AG-A 5146 I, II; AG-A 5209 I, II; AG-A 5210 I, II; AG-A 5211 I, II; AG-A 5342 received October 31, 1979 under 100-607; CDL:241243)

:0107 Ciba-Geigy Corporation (1980) Interim Report: Fourth Metalaxyl Ground Water Monitoring Project Status Report, Tobacco-Suwanee County, Florida and the Tobacco Experimental Farm, MD. (Unpublished study received November 14, 1980 under 100-607 prepared by Ciba-Geigy Corp., Greensboro, N.C.; CDL:273743-A)

:0037 Coate, W. (1980) Final Report: Subacute Inhalation Toxicity Study in Rats, CGA-48988 (Metalaxyl)--Spiked Cigarettes: Project No. 483-187. (Unpublished study received April 29, 1980 under 100-607 prepared by Hazleton Laboratories America for Ciba-Geigy Corp., Greensboro, N.C.; CDL:242398)

:0044 Cozens et al. (1980) Rat reproduction study (Unpublished study received 1981; prepared by Huntington Research Centre for Ciba-Geigy Corp., Greensboro, N.C.; CDL: 070015)

:0045 deWard et al. (1980) Subchronic oral toxicity in dogs (Unpublished study received 1981; prepared by Elars Bioresearch Laboratories Inc., for Ciba-Geigy Corp., Greensboro, N.C.; CDL: 070016)

:0101 Doebbler, G. (1979) Investigation of the Metabolism by Activated Sludge of the Compound CGA-48988: 11506-96. (Unpublished study received April 26, 1979 under 100-600; prepared by Union Carbide Environmental Services, submitted by Ciba-Geigy Corp., Greensboro, N.C., CDL:238231-G)

:0011 Drake, J. (1977) Three-Months Dietary Study in Rats with Compound CGA-48988. (Unpublished study received July 13, 1978 under 100-EUP-62 prepared by Geigy Pharmaceuticals, Wilmslow, Cheshire for Ciba-Geigy Ltd., Basle, Switzerland; CDL:234428-H)

:0062 E.G. and G. Bionomics (1980) Metalaxyl life cycle test- Daphnia magna (Unpublished study received Jan. 1981 under 100-607 prepared for Ciba-Geigy Corp., Greensboro, N.C.; CDL: 244183)

:0063 E.G. and G. Bionomics (1980) Metalaxyl embryolarvae test-Fathead minnow (Unpublished study received Jan. 1981 under 100-607 prepared for Ciba Geigy Corp., Greensboro, N.C.; CDL: 244183)

:0079 Ellgehausen, H. (1977) Distribution and Degradation of CGA-48988 Ridomil® in a Field Soil: AC 2.52. Project Report 55/77. (Unpublished study received July 13, 1978 under 100-EUP-62 prepared by Ciba-Geigy Ltd., Basle, Switzerland; CDL:234438-F)

:0080 Ellgehausen, H. (1977) Distribution of the Non-Extractable Radioactivity between Different Soil Organic Matter Fractions of a Field Soil Treated with ^{14}C-Labeled CGA-48988: Project Report 56/77, Addendum to Project Report 55/77. (Unpublished study received July 13, 1978 under 100-EUP-62 prepared by Ciba-Geigy Ltd., Basle, Switzerland, CDL:234438-G)

:0081 Ellgehausen, H. (1978) Degradation of CGA-48988 Ridomil® in Soil Under Aerobic, Aerobic/Anaerobic and Sterile/Aerobic Conditions: AC 2.52, Project Report 08/78. (Unpublished study received July 13, 1978 under 100-EUP-62 prepared by Ciba-Geigy Ltd., Basle, Switzerland, CDL: 234438-H)

:0102 Ercegovich, C. (1979?) The Effects of N-(2,6-Dimethylphenyl)-N-(Methoxyacetyl)-Alanine Methyl Ester on Soil Microorganisms. (Unpublished study received April 26, 1979 under 100-600 prepared by Penn. State University; submitted by Ciba-Geigy Corp., Greensboro, N.C., CDL:238231-J)

:0103 Ercegovich, C.; Bogus, E. (1979?) Effects of [N-(2,6-dimethylphenyl)-N-(methoxyacetyl)-alanine methyl ester] (CGA-48988) on the Degradation of ^{14}C-cellulose, ^{14}C-protein, and ^{14}C-starch in Soil. (Unpublished study received April 26, 1979 under 100-600 prepared by Penn. State University, submitted by Ciba-Geigy Corp., Greensboro, N.C., CDL:238231-K)

:0104 Ercegovich, C.; Vallejo, R., Bogus, E. (1979?) The Effects of 5,25, and 125 ppm of CGA-48988 [N-(2,6-Dimethylphenyl)-N-(Methoxyacetyl)-Alanine methyl ester on Soil Nitrification. (Unpublished study received April 26, 1979 under 100-600 prepared by Penn. State University, submitted by Ciba-Geigy Corp., Greensboro, N.C., CDL: 238231-L)

:0012 Finn, J. (1977) CGA-48988 Ninety-one Day Dietary Toxicity Study in Beagle Dogs: Report No. 653/38014. (Unpublished study received July 13,1978 under 100-EUP-62 prepared by Hazleton Laboratories Europe Ltd. for Ciba-Geigy Ltd., Basle, Switzerland; CDL:234428-I)

:0099 Fischer, W.; Cassidy, J. (1978) Balance annd Metabolism of Ø-^{14}C-CGA-48988 in Potatoes: Report ABR-78001. (Unpublished study received July 13, 1978 under 100-EUP-62 prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:234438-I)

:0083 Fischer, W.; Cassidy, J. (1978) Uptake and Characterization of Ø-^{14}C-CGA-48988 and its Soil Metabolites in Rotation Lettuce: ABR-78078. (Unpublished study received October 31, 1979 under 100-607 prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:241243-G)

:0085 Fischer, W.; Cassidy, J. (1978) Uptake and Characterization of Ø-^{14}C - CGA-48988 and its Soil Metabolites in Rotation Winter Wheat: ABR-78077. (Unpublished study received October 31, 1979 under 100-607 prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:241243-F)

:0082 Fischer, W.; Cassidy, J. (1979) Uptake and Characterization of Ø-^{14}C-CGA-48988 and its Soil Metabolites in Field Rotation Corn: ABR-79004. (Unpublished study received October 31, 1979 under 100-607 prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:241243-I)

:0084 Fischer, W.; Cassidy, J. (1979) Uptake annd Characterization of Ø-^{14}C-CGA-48988 and its Soil Metabolites in Field Rotation Spring Oats: ABR-79002. (Unpublished study received October 31, 1979 under 100-607; prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:241243-H)

:0131 Fischer, W.; Foster, R., Cassidy, J. (1978) Balance and Metabolism of Ø-^{14}C-CGA-48988 in a Lactating Goat: ABR-78046. (Unpublished study received September 5, 1978 under 100-EUP-1, 3G2121; prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:097388-D)

:0086 Foster, R.; Fischer, W., Cassidy, J. (1978) Uptake of Ø-^{14}C-CGA-48988 in Potatoes Grown in a Field Plot-Preparation of Rotational Plots: ABR-78013. (Unpublished study received October 31, 1979 under 100-607 prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL: 241243-J)

:0055 Fratus, G.; Buccafusco, R. (1978) Acute Toxicity of CGA-48988 Technical to Bluegill (Lepomis macrochirus): Report # BW-78-12-381. (Unpublished study received January 25, 1979 under 100-601, prepared by EG & G Bionomics Laboratory for Ciba-Geigy Corp., Greensboro, N.C., CDL:236854-A)

:0056 Fratus, G.; Buccafusco, R. (1978) Acute Toxicity of CGA-48988 Technical to Rainbow Trout (Salmo gairdneri): Report # BW-78-12-376. (Unpublished study received January 25, 1979 under 100-601, prepared by EG & G Bionomics Laboratory for Ciba-Geigy Corp., Greensboro, N.C., CDL:236854-B)

:0013 Fritz, H. (1978) Dominant Lethal Study-CGA 48988 Tech. Mouse -- Test for Cytotoxic or Mutagenic Effects on Male Germinal Cells: Experiment No. 327761. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy Ltd., Basle, Switzertland, CDL:234428-L)

:0014 Fritz, H. (1978) Reproduction Study CGA-48988 Tech. Rat Seg. II--Test for Teratogenic or Embryotoxic Effects: Experiment No. 227716. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy Ltd., Basle, Switzerland; CDL:234428-J)

:0105 Glinski, D. (1978) Effects of CGA-48988 on the Performance of the Activated Sludge Process. (Unpublished study received April 26, 1979 under 100-600 prepared by Union Carbide Environmental Services, submitted by Ciba-Geigy Corp., Greensboro, N.C., CDL:238231-0)

:0132 Gross, D. (1977) Metabolism of CGA-48988 in Field Grown Potato Plants: AC 2.52, Project Report 30/77. (Unpublished study received September 5, 1978 under 100-EUP-1, 8G 2121; prepared by Ciba-Geigy Ltd., Basle, Switzerland; CDL:097388-C)

:0087 Guth, J. (1976) Leaching Model Study with the Fungicide CGA-48988 in Four Standard Soils: Project Report 30/76. (Unpublished study received July 13, 1978 under 100-EUP-62 prepared by Ciba-Geigy Ltd., Basle, Switzerland; CDL:234438-K)

:0088 Guth, J. (1978) Adsorption and Desorption of CGA-48938 (Ridomil® in Various Soil Types: Project Report 35/78. (Unpublished study received July 13, 1978 under 100-EUP-62 prepared by Ciba-Geigy Ltd., Basle, Switzerland; CDL:234438-M)

:0089 Guth, J. (1978) Leaching Characteristics of Aged ^{14}C-CGA-48988 (Ridomil® Residues in Two Standard Soils; Project Report 33/78. (Unpublished study received July 13, 1978 under 100-EUP-62 prepared by Ciba-Geigy Ltd., Basle, Switzerland; CDL:234438-L)

:0015 Hambock, H. (1977) Distribution, Degradation and Excretion of CGA-48988 in the Rat: AC 2.52, Project Report 18/77. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy Ltd., Basle, Switzerland; CDL:234431-E)

:0016 Hambock, H. (1978) Metabolism of CGA-48988 in the Rat: AC 2.52, Project Report 26/78. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy Ltd., Basle, Switzerland; CDL: 234431-F)

:0090 Hamilton, T. Fischer; W., Cassidy, J. (1979) Uptake of Ø-^{14}C-CGA-48988 and its Soil Metabolites in Field Rotation Soybeans: ABR-79003. (Unpublished study received October 31, 1979 under 100-607 prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:241243-K)

:0091 Hamilton, T.; Fischer, W.; Cassidy, J. (1979) Uptake and characterization of Ø-^{14}C-CGA-48988 and its Soil Metabolites in Field Rotation Sugarbeets: ABR-79005. (Unpublished study received October 31, 1979 under 100-607 prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:241243-L)

:0166 Heinrichs, L. (1978) Analysis of CGA-48988 in Formulations by Gas Chromatography: Method No. PA-173-T. (Unpublished study received July 13, 1978 under 100-EUP-63; prepared by Ciba-Geigy Corp., Greensboro, N.C.; CDL:234427-A)

:0164 Heinrichs, L. (1978) Analysis of CGA-48988 Technical and Related Impurities by Gas Chromatography: Methods PA-172-T and PA-173-T. (Unpublished study received July 13, 1978 under 100-EUP-63; prepared by Ciba-Geigy Corporation, Greensboro, N.C., CDL:234427-A)

:0106 Honeycutt, R.; Cassidy, J. (1978) Uptake and Balance of ^{14}C-CGA-48988 and its Metabolities in Greenhouse Grown Bright and Burley Tobacco: ABR-78036. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL: 234438-N)

:0136 Honeycutt, R.; Fischer, W., Cassidy, J. (1979) Uptake and Balance of Ø-^{14}C-CGA-48988 and its Metabolites in Field Grown Bright Tobacco: ABR-79100. (Unpublished study received October 31, 1979 under 100-607 prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:241245-B)

:0137 Honeycutt, R.; Szolics, I., Cassidy, J. (1978) Balance and Characterization of Pyrolysis Products of Ø-^{14}C-CGA-48988 and its Metabolites in Cigarettes containing Bright and Burley Tobacco treated with Ø-^{14}C-CGA-48988: ABR-78040. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:234431-B)

:0139 Honeycutt, R.; Szolics, I., Simoneaux, B., Cassidy, J. (1979) Identification of the Major Aglycones of Ø-^{14}C-CGA-48988 Conjugated Metabolites in Cured Greenhouse Grown Bright Tobacco: ABR-79003. (Unpublished study received October 31, 1979 under 100-607 prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:241245-A)

:0017 Kapp, R.; Piccirillo, V. (1978) Acute Dermal Toxicity Study in Rabbits, CGA-48988 2EC, Final Report: Project No. 483-149. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Hazleton Laboratories America, Inc. for Ciba-Geigy Corp., Greensboro, N.C., CDL:234429-C)

:0018 Kapp, R.; Piccirillo, V. (1978) Acute Oral Toxicity Study in Male and Female Albino Rats, CGA-48988 2EC, Final Report: Project No. 483-148. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Hazleton Laboratories America, Inc. for Ciba-Geigy Corp., Greensboro, N.C., CDL:234429-B)

:0019 Kapp, R.; Piccirillo, V. (1978) Primary Skin Irritation Study in Rabbits, CGA-48988 2EC, Final Report: Project No. 483-151. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Hazleton Laboratories America, Inc. for Ciba-Geigy Corp., Greensboro, N.C., CDL:234429-E)

:0092 Ladd, S.; Enos, J. (1979) Kinetics of Ø-^{14}C-CGA-48988 in a Model Aquatic Ecosystem: Report #BW-78-10-328. (Unpublished study received April 26, 1979 under 100-600; prepared by EG&G, Bionomics for Ciba-Geigy Corp.; Greensboro, N.C.; CDL:238232-G).

:0093 Ladd, S.; Wilson, W. (1979) Accumulation and Elimination of ^{14}C-Residues by Bluegill Sunfish (Lepomis macrochirus) Exposed to Ø-^{14}C-CGA-48988. Report #BW-78-10-328. (Unpublished study received April 26, 1979 under 100-600; preapred by EG&G, Bionomics for Ciba-Geigy Corp., Greensboro, N.C.; CDL:238232-E)

:0057 LeBlanc, G. (1977) Acute Toxicity of CGA-48988 Technical to the Water Flea (Daphnia magna). (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by EG&G, Bionomics for Ciba-Geigy Corporation, Greensboro, N.C.; CDL:234439-C)

:0058 LeBlanc, G.; Cary, G. (1978) Acute Toxicity of CGA-48988 to the Water Flea (Daphnia magna): Report #BW 78-12-364. (Unpublished study received Jan. 25, 1979 under 100-601, prepared by EG&G Bionomics Laboratory for Ciba-Geigy Corp., Greensboro, N.C.; CDL:236854-C)

:0043 Life Science Research (1980) CGA-48988 Toxicity and Carcinogenicity in Dietary Administration to Rats for 105 Weeks. (Unpublished report prepared by Life Science Research, Suffolk, England, submitted by Ciba-Geigy Corp., Greensboro, N.C.; CDL:241771-A)

:0067 McCann (1979) Acute LC50 of metalaxyl in rainbow trout and bluegill sunfish (Unpublished study prepared by EPA Laboratories, Beltsville, Maryland)

:0068 McCann (1979) 48-hour LC50 in Daphnia magna (Unpublished study prepared by EPA Laboratories, Beltsville, Maryland)

:0064 McCann (1979) 96-hour LC50 in bluegill sunfish of E.C. metalaxyl (Unpublished study prepared by EPA Laboratories, Beltsville, Maryland)

:0065 McCann (1979) 96-hour LC50 in rainbow trout of E.C. metalaxyl (Unpublished study prepared by EPA Laboratories, Beltsville, Maryland)

:0096 Nixon, W. (1978) Gas Chromatographic Method for the Determination of Residues of CGA-48988 and its Acid Metabolite CGA-62826 in Soil: Method AG-323. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy Corp., Greensboro, N.C.; CDL:234438-O)

:0108 Nixon, W. (1980) Protocol: Ridomil Mobility Study—Fort Pierce Research Station, Florida. (Unpublished study received November 14, 1980 under 100-607 prepared by Ciba-Geigy Corp., Greensboro, N.C.; CDL:243743-B)

:0020 Piccirillo, V. (1978) Acute Eye Irritation Study in Rabbits, CGA-48988 2EC, Final Report: Project No. 483-150. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Hazleton Laboratories America, Inc. for Ciba-Geigy Corp., Greensboro, N.C.; CDL:234429-D)

:0021 Piccirillo, V. (1978) Acute Inhalation Toxicity Study in Rats, CGA-48988 2EC, Final Report: Project No. 483-152. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Hazleton Laboratories America, Inc. for Ciba-Geigy Corp., Greensboro, N.C.; CDL:234429-F)

:0023 Sachsse, K.; Bathe, R. (1976) Acute Dermal LD_{50} in the Rat of Technical CGA-48988: Project No. Siss 5388. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy Ltd., Basle, Switzerland; CDL:234428-D)

:0026 Sachsse, K; Bathe, R. (1976) Acute Oral LD_{50} in the Rat of Technical CGA-48988: Project No. Siss 5388. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy, Ltd., Basle, Switzerland; CDL:234428-B)

:0059 Sachsse, K.; Bathe, R. (1976) Acute Toxicity to Rainbow Trout, Carp, Catfish, Bluegill and Guppy of Technical CGA-48988: Project No. Siss 5388. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy Ltd., Basle, Switzerland; CDL:234439-B)

:0029 Sachsse, K.; Ullmann, L. (1976) Acute Dermal LD_{50} in the Rabbit of Technical CGA-48988: Project No. 408378, Siss 6547. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy, Ltd., Basle, Switzerland; CDL:234439-L)

:0061 Sachsse, K., Ullmann, L. (1976) Eight-day Feeding Toxicity in the Japanese Quail of Technical CGA-48988: Project No. Siss 5388. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy, Ltd.; Basle, Switzerland; CDL:234439-G)

:0031 Sachsse, K., Ullmann, L. (1976) Eye Irritation in the Rabbit of Technical CGA-48988: Project No. 5388. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy, Ltd., Basle, Switzerland; CDL:234428-F)

:0032 Sachsse, K., Ullmann, L. (1976) Eye Irritation in the Rabbit after Single Application of Technical CGA-48988: Project No. 5388. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy, Ltd., Basle, Switzerland; CDL:234428-E)

:0033 Sachsse, K.; Ullmann, L. (1976) Skin Sensitizing (Contact Allergenic) Effect in Guinea Pigs of Technical CGA-48988: Project No. Siss 5388. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy, Ltd., Basle, Switzerland; CDL:234428-G)

:0143 Seim, V. (1978) Biological Report for the Metabolism of Ø-^{14}C-CGA-48988 in a Lactating Goat: BIOL-78002. (Unpublished study received Sept. 5, 1978 under 100-EUP-1, 8G2121; prepared by Ciba-Geigy Corp.; Vero Beach, Fla.; CDL:097388-E)

:0041 Toxigenics (1980) Metalaxyl 21-day dermal toxicity test (Unpublished study received Jan. 1981 under 100-607; submitted by Ciba Geigy Corp., Greensboro, N.C.; CDL: 244182)

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CASE BIBLIOGRAPHY

Section 2: Citations Examined and Judged to be Citations Inappropriate for Use in Developing the Standard

GS-0081:

:0116 Balasubramanian, K.; Nixon, W. (1978) The Determination of CGA-48988 and its Metabolites in Tobacco as 2,6-Dimethylaniline using Phosphoric Acid Reflux. Method AG-330. (Unpublished study received October 31, 1979 under 100-607 prepared by Ciba-Geigy Corp., Greensboro, N.C.; CDL:241243-E)

:0118 Balasubramanian, K.; Nixon, W; Ross, J. (1978) Validation of Method AG-325 for the Determination of CGA-48988 Residues in Tobacco: ABR-78039. (Unpublished study received July 13, 1978 under 100-EUP-62 prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:234432-B)

:0122 Balasubramanian, K.; Ross, J. (1979) Validation of Method AG-330 for the Determination of CGA-48988 and its Metabolites containing the 2,6-Dimethylaniline Common Moiety in Tobacco: ABR-79016. (Unpublished study received October 31, 1979 under 100-607; prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:241246-C)

:0074 Ballantine, L. (1979) CGA-48988: Environmental Impact Statement--Summary of Environmental Chemistry Information: ABR-79041. (Unpublished report received October 31, 1979 under 100-607 prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:241243-B)

:0075 Ballantine, L. (1979) Rotational Crop Data Submitted in Support of Conditional Registration for Ridomil (Metalaxyl) Use on Tobacco: ABR-79099. (Unpublished study received October 31, 1979 under 100-607 prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:241243-A)

:0072 Ballantine, L.; Fischer, W. (1978) Environmental Investigations Protocol, ^{14}C-Fish Residue Bioaccumulation Study Soil-Water-Fish Model Aquatic Ecosystem. (Unpublished study received April 26, 1979 under 100-600; prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL: 238232-H)

:0073 Ballantine, L.; Fisher, W. (1978) Environmental Investigations Protocol; Flow-Through ^{14}C-Fish Residue Accumulation Study. (Unpublished study received April 26, 1979 under 100-600 prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:238232-F)

:0002 Bathe R. (1978) Acute Oral LD_{50} in the Rat of CGA-48988 35 WP (A-6038 A): 785188 GU 2.1. (Unpublished study received August 30, 1979 under 100-608; prepared by Ciba-Geigy Ltd., Basle, Switzerland; CDL:241049-B)

:0003 Cannelongo, B. (1978) Rabbit Eye Irritation, CGA-48988 2E-G: Project No. 973-78. (Unpublished study received March 1979 under 100-EUP-63; prepared by Stillmeadow, Inc. for Ciba-Geigy Corp., Greensboro, N.C., CDL:237807-D)

:0004 Cannelongo, B. (1978) Rabbit Primary Skin Irritation, CGA-48988 2E-G: Project No. 974-78. (Unpublished study received March 1979 under 100-EUP-63; prepared by Stillmeadow, Inc. for Ciba-Geigy Corp., Greensboro, N.C.; CDL:237807-E)

:0005 Cannelongo, B. (1979) Rabbit Acute Dermal Toxicity, CGA-48988 2E-G: Project No. 972-78. (Unpublished study received March 1979 under 100-EUP-63; prepared by Stillmeadow, Inc. for Ciba-Geigy Corp., Greensboro, N.C., CDL:237807-C)

:0123 Cassidy, J.; Ross, J. (1978) Summary of Section D CGA-48988--Tobacco; Results of Tests on the Amounts and Nature of Residues in Tobacco and its Smoke: ABR-78045. (Unpublished report received July 13, 1978 under 100-EUP-62 prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL: 234430)

:0124 Cassidy, J.; Ross, J. (1979) Summary of Section D, Metalaxyl (CGA-48988) - Tobacco--Results of Tests on the Amounts and Nature of Metalaxyl Residues in Tobacco and its Smoke: ABR-79103. (Unpublished study received October 31, 1979 under 100-607; prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:241244)

:0141 Ciba-Geigy Corporation (1977) Residues in Soil--CGA-48988 50W Applied to Tobacco. (Unpublished study that includes AG-A 4604 I, II, III, IV, V, VI-A received April 26, 1979 under 100-600; prepared by North Carolina State Univ. Tobacco Research Station, Reidsville, N.C. for Ciba-Geigy Corp., Greensboro, N.C.; CDL:238232-J)

:0162 Ciba-Geigy Corporation (1978) CGA-48988 5W Chemical Data. (Unpublished study received September 5, 1978 under 100-600; CDL: 235063-A)

:0006 Ciba-Geigy Corporation (1978) Full Reports of Investigations made with respect to the Safety of Pesticide CGA-48988 (Ridiomil 2E--Summary of Acute Toxicology Information. (Unpublished study received July 13, 1978 under 100-EUP-62; CDL:234429-A)

:0007 Ciba-Geigy Corporation (1978) Full Reports of Investigations Made with Respect to the Safety of the Pesticide CGA-48988 Technical--Summary of Toxicology Information. (Unpublished report received July 13, 1978 under 100-EUP-62; CDL:234428-A)

:0054 Ciba-Geigy Corporation (1978) Reports of Investigations Made with Respect to the Safety of CGA-48988 Technical to Representative Wildlife Species--Environmental Safety Summary. (Unpublished report received July 13, 1978 under 100-EUP-62; CDL:234439-A)

:0125 Ciba-Geigy Corporation (1978) Residues in Soil-Soil Dissipation. (Unpublished study that includes AG-A 4813 I, II, III, IV received April 26, 1979 under 100-600; CDL:238232-L)

:0149 Ciba-Geigy Corporation (1978) Residues in Soil--CGA-48988 50W Applied to Tobacco. (Unpublished study that includes AG-A 4604 VII received April 26, 1979 under 100-600 prepared by North Carolina State Univ. Tobacco Research Station, Reidsville, N.C.; CDL:238232-K)

:0163 Ciba-Geigy Corporation (1979) Apron 35 SD; Chemical Data Section. (Unpublished study received August 30, 1979 under 100-608; CDL-241048)

:0008 Ciba-Geigy Corporation (1979) Full Reports of Investigations made with Respect to the Safety of Pesticide Ridomil (CGA-48988) 2E-G--Summary of Acute Toxicology Information. (Unpublished study received March 1979 under 100-EUP-63; CDL:237807-A)

:0009 Ciba-Geigy Corporation (1979) Summary-Reports on Investigations Made with Respect to the Safety of the Pesticide CGA-48988 Ridomil 35 SD (Apron 35 SD). (Unpublished study received August 30, 1979 under 100-608; CDL: 241049-A)

:0010 Coate, W. (1978) Revised Final Report Four-Hour Acute Inhalation Toxicity in Rats CGA-48988 2E-C: Project No. 483-167. (Unpublished study received March 1979 under 100-EUP-63; prepared by Hazleton Laboratories America, Inc. for Ciba-Geigy Corp. Greensboro, N.C., CDL: 237807-F)

:0038 Elm Farm Laboratories (1979) CGA-48988--Potential Oncogenicity in Dietary Administration to Mice for a Period of 104 weeks: Summary 0-92 Weeks. (Unpublished report prepared by Elm Farm Laboratories, Life Science Research, Suffolk, England, submitted by Ciba-Geigy Corp., Greensboro, N.C.; CDL:241771-B)

:0133 Hermes, P. (1972) Biphasic Extraction of Radioactive Metabolites from Treated Biological Material: Method AG-214 dated August 15, 1972. (Unpublished study received September 5, 1978 under 100-EUP-1, 8G 2121; prepared by Ciba-Geigy Corp., Ardsley, NY; CDL:097390-A)

:0134 Hermes, P. (1973) Radioassay of ^{14}C in Biological Materials by Combustion using the Harvey Biological Material Oxidizer (BMO): Method AG-252 dated August 8, 1973. (Unpublished study received September 5, 1978 under 100-EUP-1, 8G2121 prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:097390-D)

:0138 Honeycutt, R.; Simoneaux, B., Szolics, I., Cassidy, J. (1978) Characterization of Polar Metabolites of Ø-^{14}C-CGA-48988 in Greenhouse Grown Bright Tobacco: ABR-78044. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy Corp., Greensboro, N.C., CDL:234431-C)

:0165 Hoppe, T. (1978) Chemical Hazards Testing -- Drying, Grinding and Thermal Stability of CGA-48988-5W: CHT Ref: 62-78-09. (Unpublished study received September 5, 1978 under 100-600; prepared by Ciba-Geigy Corp., Toms River, N.J.; CDL:235063-B)

:0040 Huntingdon Research Centre (1979) Summary of CGA-48988--Multigeneration [Reproduction] Study: Test No. 77 0023. (Unpublished report prepared by Huntingdon Research Centre, Huntingdon, England; submitted by Ciba-Geigy Corp., Greensboro, N.C.; CDL:241771-C)

:0094 Laskowski, D. (1979) Effects of Pesticides on Soil Microorganisms. (Unpublished study received April 26, 1979 under 100-600; prepared by Residue/Environmental/Metabolism Research, Agricultural Products Dept., Dow Chemical U.S.A. Midland, MI; presented at Weed Science Society Annual Meeting, San Francisco, 1979; CDL:238232-I)

:0147 Martin, G.; Boka, G.; Secrest, W.; Ryskiewich, D. (1978) Potassium Hydroxide Fusion of CGA-48988 Derivatives and Treated Biological Samples: ABR-78047. (Unpublished study received Oct. 31, 1979 under 100-607, prepared by Ciba-Geigy Corp., Greensboro, N.C.; CDL:241247-B)

:0095 Newby, L. (1978) CGA-48988: Environmental Impact Statement: ABR-78054. (Unpublished study received July 13, 1978 under 100-EUP-62 prepared by Ciba-Geigy Corp., Greensboro, N.C.; CDL:234438-A)

:0148 Ramsteiner, K. (1978) Status Report: Method Development of CGA-48988, January 1, 1978 -- Mass Spectrometric Fragmentation of CGA-48988, Its Metabolites and/or Reference Compounds. (Unpublished report received Oct. 31, 1979 under 100-607 submitted by Ciba-Geigy Corp., Greensboro, N.C.; CDL:241247-C)

:0140 Roger, J. (19??) Radioassay of $C^{14}O_2$ by Acid Neutralization and Subsequent Counting by Liquid Scintillation: Method AG-250 supercedes AG-112. (Unpublished study received Sept. 5, 1978 under 100-EUP-1, 8G2121 prepared by Ciba-Geigy Corp., Greensboro, N.C.; CDL:097390-C)

:0022 Sabol, R. (1979) Rat Acute Oral Toxicity, CGA-48988 2E-G: Project No. 971-78. (Unpublished study received March 1979 under 100-EUP-63; prepared by Stillmeadow, Inc. for Ciba-Geigy Corp., Greensboro, N.C.; CDL:237807-B)

:0024 Sachsse, K.; Bathe, R. (1976) Acute Intraperitoneal LD_{50} in the Rat of Technical CGA-48988: Project No. Siss 5388. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy, Ltd., Basle, Switzerland; CDL:234429-G)

:0025 Sachsse, K.; Bathe, R. (1976) Acute Oral LD_{50} in the Mouse of Technical CGA-48988: Project No. Siss 5388. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy, Ltd., Basle, Switzerland; CDL:234439-J)

:0027 Sachsse, K.; Bathe, R. (1977) Acute Dermal LD_{50} in the Rat of CGA-48988 WP 50 (A-55150A): Siss 5907 PH 2.635. (Unpublished study received Aug. 30, 1979 under 100-608; prepared by Ciba-Geigy, Ltd., Basle, Switzerland; CDL:241049-D)

:0028 Sachsse, K.; Bathe, R. (1977) Acute Oral LD_{50} in the Rat of CGA-48988 WP 50 (A-5514 A): Siss 5907 PH 2.635. (Unpublished study received Aug. 30, 1979 under 100-608; prepared by Ciba-Geigy, Ltd., Basle, Switzerland; CDL:241049-C)

:0060 Sachsse, K., Ullmann, L. (1976) Acute Oral LD_{50} in the Japanese Quail of Technical CGA-48988: Project No. Siss 5388. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy, Ltd.; Basle, Switzerland; CDL:234439-E)

:0030 Sachsse, K., Ullmann, L. (1976) Acute Oral LD_{50} in the Rabbit of Technical CGA-48988: Project No. Siss 5388. (Unpublished study received July 13, 1978 under 100-EUP-62; prepared by Ciba-Geigy, Ltd., Basle, Switzerland; CDL:234439-K)

:0034 Sachsse, K., Ullmann, L. (1977) Acute Dust Inhalation Toxicity in the Rat of CGA-48988 WP 50 (A-55140A): Siss 5907 PH 2.635. (Unpublished study received Aug. 30, 1979 under 100-608; prepared by Ciba-Geigy, Ltd., Basle, Switzerland; CDL:241049-E)

:0035 Sachsse, K.; Ullmann, L. (1977) Eye Irritation in the Rabbit of CGA-48988 WP 50 (A-55140A): Siss 5907 PH 2.635. (Unpublished study received Aug. 30, 1979 under 100-608; prepared by Ciba-Geigy, Ltd., Basle, Switzerland; CDL:241049-F)

:0036 Sachsse, K.; Ullmann, L. (1977) Skin Irritation in the Rabbit after Single Application of CGA 48988 WP 50. (A-55140A): Siss 5907 PH 2.635. (Unpublished study received Aug. 30, 1979 under 100-608; prepared by Ciba-Geigy, Ltd., Basle, Switzerland; CDL:241049-G)

:0142 Secrest, W.; Honeycutt, R. (1977) Material Balance Determination on Cigarettes Containing Tobacco with ^{14}C Compounds: Method AG-318 dated September 9, 1977. (Unpublished study received July 13, 1978 under 100-EUP-62 submitted by Ciba-Geigy, Corp., Greensboro, N.C.; CDL:234433-G)

:0144 Seim, V. (1978) Biological Report for the Metabolism of Ø-^{14}C-CGA-48988 in Greenhouse Grown Tobacco When Applied as a Drench to Bright Tobacco and Preplant Incorporated to Burley Tobacco: BIOL-78003. (Unpublished study received July 13, 1978 under 100-EUP-62;prepared by Ciba-Geigy Corp.; Vero Beach, Fla.; CDL:234431-D)

:0097 Simoneaux, B.; Hermes, P. (1973) Extraction of CGA-10832 Residues from Soil: Method AG-254 dated August 10, 1973 supercedes AG-219. (Unpublished study received Sept. 5, 1978 under 100-EUP-1, 8G2121 prepared by Ciba-Geigy Corp.; Ardsley, NY; CDL:097390-E)

:0098 Simoneaux, B.; Roger, J. (1972) Blending of Soils and Homogenization of Biological Materials for Radioassay and Extraction: Method AG-223 dated Oct. 5, 1972. (Unpublished study received Sept. 5, 1978 under 100-EUP-1, 8G2121 prepared by Ciba-Geigy, Corp., Ardsley, NY; CDL:097390-B)

:0145 Thomas, R.; Hermes, P. (19??) High Voltage Electrophoresis for Characterization of Charged Radioactive Metabolites: Method AG-300. (Unpublished study received Sept. 5, 1978 under 100-EUP-1, 8G2121 prepared by Ciba-Geigy Corp.; Ardsley, NY; CDL:097390-G)

:0146 Wolf, M.; Sumner, D. (1974) Statistical Methods in the Measurement of Radioactivity: Method AG-276 dated Jan. 1, 1974. (Unpublished study received Sept. 5, 1978 under 100-EUP-1, 8G2121 prepared by Ciba-Geigy, Corp.; Ardsley, NY; CDL:097390-F)