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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Mancozeb (014504)
Rohm and Haas Response to Registration Standard
Rohm and Haas letter of 7/2/87 (90 day response)
Rohm and Haas letter of 7/6/87 (Response to Product
Chemistry Data Gaps)
Rohm and Haas letter of 7/6/87 (Response to Residue/
Metabolism Data Gaps)
EPA Reg. No. 707-78
[MRID Nos. 402583-00 and -01, RCB No. 2725]

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THRU: Edward Zager, Section Head
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TO: Lois Rossi, PM #21
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Rohm and Haas has submitted a response to the Product Chemistry and Residue Chemistry portions of the Mancozeb Registration Standard. The Product Chemistry response will be discussed by W. Hazel in his upcoming review (W. Hazel, personal communication, 1/5/88), and will not be discussed here further. (See review of RCB No. 2937). This review will not discuss all of the Rohm and Haas response to the Registration Standard. RCB was requested to review the Rohm and Haas response so that RD could respond to a recent letter from the registrant. Additional portions of the Rohm and Haas response will be discussed in an update of this review.

Mancozeb is a coordination product of zinc ion and maneb (manganese zinc ethylenebisdithiocarbamate). Tolerances have been established for residues of mancozeb on a number of raw agricultural commodities including kidney and liver at 0.5 ppm (40 CFR 180.176). Tolerances for mancozeb are calculated as zineb equivalents. An interim tolerance for residues of mancozeb in potatoes is found in 40 CFR 180.319. Food and feed additive

tolerances have been established for several processed commodities (21 CFR 193.460 and 21 CFR 561.410). One tolerance petition for residues of mancozeb in lettuce, peppers, and beans is in reject status (PP#3F2949, M. Kovacs, 12/10/87, RCB No. 2654).

The Product and Residue Chemistry chapters for the Mancozeb Registration Standard were completed on 9/10/86. An update was completed on 1/27/87. The Mancozeb Registration Standard (Guidance Package) was issued in April, 1987. EPA has also announced the initiation of a Special Review of the ethylene bisdithiocarbamate pesticides (EBDCs), including mancozeb (52 FR 27172, 7/17/87). An earlier Special Review (then called RPAR) of the EBDC fungicides was initiated in 1977 and concluded in 1982 with the EBDC pesticides being returned to the registration process, subject to certain conditions. Several Data Call In Notices have been issued for Product and Residue Chemistry data. Dietary exposure (Residue Chemistry) and Product Chemistry data were required by a 10/19/84 DCI, including plant and livestock metabolism data, crop residue data, and data on conversion/reduction/concentration of mancozeb and its metabolites and degradation products, especially ethylene thiourea (ETU). Additional Residue chemistry data were required by a 4/30/85 DCI (livestock feeding studies). Data received in response to these Data Call In notices were reviewed in the preparation of the Registration Standard.

CONCLUSIONS

The purpose of this interim review is to enable Registration Division to respond to the registrant's recent letter. Our review of the registrant's submission is not complete. However, the registrant needs to know our conclusions on the need for additional plant metabolism data.

1. Labeling changes are still needed. The registrant must propose a maximum number of applications per season or a maximum seasonal rate for each crop. The submitted residue data must reflect this proposed maximum rate.

2. Since Rohm and Haas has indicated that they will not support dust formulations, all registrations for dust formulations should be cancelled.

3a. Additional plant metabolism data are needed. Although our review of the plant metabolism information submitted by Rohm and Haas is not complete, we are able to make the following statement.

Even if the metabolism studies on sugar beet tops and wheat are later considered to be valid studies, additional metabolism data will be needed on tomatoes and possibly apples. Although

not specifically stated in the Registration Standard, metabolism studies on a pome fruit and on a fruiting vegetable crop were needed because of the large amount of mancozeb use on these types of crops. The three crops chosen by Rohm and Haas for metabolism studies each account for less than 2 % of mancozeb use. Additionally, wheat and soybean samples were not taken at short enough intervals after the final treatment to be considered representative of the use on apples and tomatoes. The first wheat and soybean samples were taken over 45 days after the last treatment. The Registration Standard specifically states the need for sampling intervals through at least 21 days. Several sampling intervals are needed. Tomatoes should be initially sampled no later than five days after the last treatment, with additional sampling intervals up to at least 21 days after the last treatment.

A waiver from the requirement of additional metabolism studies is not appropriate.

3b. No comment can be made regarding the registrant's discussion of animal metabolism data at this time. The requirement for additional metabolism data on apples may be waived if the metabolism of mancozeb on tomatoes is similar to the metabolism on other crops.

4a. The registrant should be informed of the following data requirement in 3(c)2(B) format. This requirement was listed in the text of the Registration Standard, but not in the data tables.

An enforcement method is needed which is capable of distinguishing between/among the different EBDC fungicides, and other contaminants that degrade to CS₂.

The registrant has requested a waiver from the requirement of a specific analytical method. A waiver of the requirement for enforcement methodology which distinguishes between the different EBDC fungicides is not appropriate. The Agency needs to be able to distinguish between the different EBDC fungicides for enforcement purposes. While analysis for the metal cations might not distinguish mancozeb residues from other EBDC residues or from naturally occurring metal cations, other types of analysis may be possible.

4b. The requirement for data on PAM Multiresidue Methods I, II, III, and IV remains outstanding. A theoretical discussion based on the chemical structure of mancozeb and its metabolites and degradates discussing why the parent, metabolites, and degradates would not be recovered by PAM Multiresidue methods I, II, III, and IV may be sufficient.

4c. If the requested data regarding the nature of the residue in plants and animals reveal additional metabolites of toxicological concern, additional analytical methods for data collection and enforcement may be required.

5. Storage stability data. The registrant is correct in stating that the fortified storage stability studies they have submitted are adequate to show that mancozeb is stable in frozen storage for up to 12 months and that ETU is stable in frozen storage for up to 6 months. However, storage intervals and conditions of sample storage from harvest until analysis were not available for the residue data reviewed for the Registration Standard. Any data submitted for which the frozen storage interval is longer than 12 or 6 months for mancozeb or ETU, respectively, are not valid.

Weathered storage stability studies will not be required if all samples were analyzed within 12 months of harvest for mancozeb and within 6 months for ETU, and were stored frozen from harvest until analysis. If any samples were stored longer than 12 months and 6 months, then both weathered and fortified storage stability data are needed.

Fortified storage stability protocols for livestock feeding studies and crops will be reviewed separately (See RCB No. 3203).

6. Residue and processing data. We have no objection to Rohm and Haas not supporting the dust formulations providing all registrations for dust formulations are cancelled.

7. Ground vs. aerial data. The summary table submitted to compare ground and aerial applications does not clearly state from which study each data point was obtained, and therefore cannot be further evaluated. However, all previously submitted data were reviewed for the Registration Standard and the requirement for both ground and aerial data was made after considering all previously submitted data. We reiterate that residue data are needed for both ground and aerial applications. The registrant might consider conducting a bridging study to satisfy this requirement. A bridging study would involve side by side residue field trials for at least one crop in each crop group. Separate side by side tests would be needed for several diverse locations for each crop.

RECOMMENDATIONS

We recommend that the registrant be informed of our conclusions, and advised to submit the required data. The registrant should also be informed that our review of their discussions of previously submitted plant and animal metabolism

data is not complete at this time. Additional review of those portions of their submission will follow at a later date. Although our review of their discussion of previously submitted metabolism data is not complete, we are able to determine that additional plant metabolism data are necessary, as discussed in Conclusion 3a. The registrant should be provided with a complete copy of our review.

Detailed Considerations

We will discuss the registrant's 90 day response, followed by the response to the Registration Standard data gaps. The registrant's response to the plant and animal metabolism data gaps cannot be fully discussed at this time.

Rohm and Haas 90 day response

Rohm and Haas indicates that they are submitting new residue data for both ground and aerial applications, and a discussion of previously submitted data on plant metabolism, poultry metabolism, and storage stability. These data are included with the Rohm and Haas submission of 7/2/87. Rohm and Haas is submitting a request for a waiver of the requirement for a specific analytical method for residues. The table included in their submission also indicates that they are requesting a waiver from the requirement of plant metabolism studies. These waiver requests are included in the Rohm and Haas submission of 7/6/87.

Data to be submitted in the future include residue data on crops, processing studies, and animal feeding studies. Residue data for only the 80 WP formulation will be submitted. The dust formulations will not be supported.

RCB Comment

Our discussion of the Rohm and Haas submission of 7/6/87 follows. We have no objection to the deletion of residue data for the dust formulations, provided that all dust formulations of mancozeb are cancelled.

Rohm and Haas response to data gaps

Deficiency 1 - Labeling

The registrant must propose a maximum number of applications per season or a maximum seasonal rate for each crop. The submitted residue data must reflect this proposed maximum rate.

Registrant Response

None. No revised labeling was included in this submission.

RCB Comment

This deficiency remains outstanding. Additional labeling changes may be required when the required residue data are submitted and reviewed.

Deficiency 2 - Tolerance Reassessment

Data gaps exist for plant and animal metabolism and storage stability. Thus any conclusions made at this time regarding the adequacy of existing tolerances are subject to change. Tolerances for animal commodities will not be assessed until the requested animal metabolism studies are completed and reviewed.

Established tolerances for residues of mancozeb in/on wheat, barley, oat, and rye processed products are tentatively considered adequate, but will be reassessed when residue data on wheat are submitted.

Insufficient data are available to ascertain the adequacy of the established tolerances for residues of mancozeb in/on apples, asparagus, bananas, carrots, celery, corn (fresh), corn fodder and forage, corn grain, cottonseed, cranberries, cucumbers, grapes, melons, onions, papayas, peanuts, peanut vines and hay, pears, potatoes, sugar beet roots and tops, summer squash, tomatoes, wheat grain, and wheat straw.

Although insufficient data are available to ascertain the adequacy of established tolerances for residues of mancozeb in/on barley grain and straw, crabapples, oat grain and straw, quinces, and rye grain and straw, no residue data are required for these commodities, since the necessary residue data will be translated from the crops listed in the previous paragraph.

Processing studies are required for corn, cottonseed, peanuts, potatoes, and sugar beets. Tolerances may be required for processed commodities of these crops.

Tolerance proposals and residue data are required for barley forage, barley hay, corn silage, oat forage, oat hay, peanut hulls, rye forage, wheat forage, and wheat hay. Alternatively, feeding restrictions may be

proposed for all these except corn silage and peanut hulls.

Food/feed additive tolerances must be proposed for dry apple pomace, grape pomace (wet and dry), grape juice, and raisin waste.

Tolerance proposals and/or residue data are required reflecting seed or propagation stock treatment of flax, pineapple, rice, safflower, and sorghum.

Registrant Response

None. No tolerance proposals were included in this submission.

RCB Comment

This deficiency remains outstanding.

Deficiency 3a - Nature of the Residue - Plants

Data depicting the uptake, distribution, and metabolism of mancozeb in pome fruit and fruiting vegetable crops following foliar applications must be submitted. Sampling intervals through at least 21 days must be included. The identities and quantities of residues in or on mature plant parts must be determined in order to elucidate the terminal residues. Residue identities must be confirmed by a method such as GC, HPLC and/or mass spectroscopy. Data reflecting solvent extraction efficiency of mancozeb residues must also be presented. Representative samples from these tests must also be analyzed by enforcement methods to ascertain that these methods are capable of determining all metabolites of concern.

(From text of Residue Chemistry Chapter and addendum, not in Registration Standard Tables.) The metabolism of mancozeb is adequately understood for soybeans, but not for wheat. Over 70% of the ¹⁴C activity in soybeans was characterized, and almost 100 % of the activity in soybean pods was characterized. The sugar beet metabolism study was adequate for sugar beet roots, because 59% of the activity in roots was characterized as either EBDC metabolites or natural products. However, only 32% of the activity in sugar beet tops was characterized.

Previously Submitted Data

Metabolism studies on soybeans, sugar beets, and wheat have been submitted previously and were discussed in the Residue Chemistry Chapter of the Mancozeb Registration Standard or Addendum 1.

Registrant Response

Rohm and Haas submitted additional information on metabolism in sugarbeets and wheat, consisting of a letter clarifying previously submitted studies. The registrant requests a waiver from the requirement of additional plant metabolism data in tomatoes and apples.

RCB Comment

The additional information submitted by Rohm and Haas will not be discussed at this time. However, even if the metabolism studies on sugar beet tops and wheat are considered to be valid studies, additional metabolism data will be needed on tomatoes and possibly apples. Although not specifically stated in the Registration Standard, metabolism studies on a pome fruit and on a fruiting vegetable crop were needed because of the large amount of mancozeb use on these types of crops. The three crops chosen by Rohm and Haas for metabolism studies each account for less than 2 % of mancozeb use. Additionally, wheat and soybean samples were not taken at short enough intervals after the final treatment to be considered representative of the use on apples and tomatoes. The first wheat and soybean samples were taken over 45 days after the last treatment. The Registration Standard specifically states the need for sampling intervals through at least 21 days. Several sampling intervals are needed. Tomatoes should be initially sampled no later than five days after the last treatment, with additional sampling intervals up to at least 21 days after the last treatment.

Thus, a waiver from the requirement of additional metabolism data on apples and tomatoes is not justified. The requirement for additional metabolism data on apples may be waived if the metabolism of mancozeb on tomatoes is similar to the metabolism of mancozeb on other crops. This deficiency remains outstanding. Review of the additional information submitted by the registrant regarding the sugar beet and wheat metabolism studies will continue.

Deficiency 3b - Nature of the Residue - livestock

Metabolism studies utilizing poultry are required. Animals must be dosed for three days with [14C] mancozeb at a level sufficient to make residue identification and quantification possible. Eggs must be collected twice daily during the dosing period. Animals must be sacrificed within 24 hours of the final

dose. The distribution and characterization of residues must be determined in eggs, liver, kidney, muscle, and fat. Precautions must be taken to minimize EBDC degradation during analysis steps due to the presence of water, methanol, and atmospheric oxygen. Samples from the studies requested above should also be analyzed using current enforcement methods to ascertain the validity of these methods. Upon receipt of the requested data, the need for, and nature of, tolerances for residues in animal products will be determined.

Registrant Response

Rohm and Haas submitted a letter clarifying previously submitted studies.

RCB Comment

No comment can be made regarding the registrant's submission on this topic at this time. Review of the additional information will continue and will be reported on at a later time.

Deficiency 4 - Residue Analytical Method

Deficiency 4a - Enforcement Analytical Method

(This requirement was listed in the text, but not in the tables. It should be sent to the registrant in 3(c)2(b) format.

An enforcement method is needed which is capable of distinguishing between/among the different EBDC fungicides.

Registrant Response

Rohm and Haas requested a waiver from the requirement of enforcement methodology which distinguishes between the different EBDC pesticides. They state that the current method measures CS₂ evolution and applies to all EBDC fungicides. The EBDC fungicides differ chemically only by the metal cation associated with the ethylenebisdithiocarbamate moiety. A specific method would require specific analysis based on the metal cations, which also occur naturally in the crop matrix. It is not possible to distinguish metal cations due to residues from naturally occurring metals. Therefore, this requirement should be waived.

RCB Comment

A waiver of the requirement for enforcement methodology which distinguishes between the different EBDC fungicides is not appropriate. The Agency needs to be able to distinguish between the different EBDC fungicides for enforcement purposes. While

analysis for the metal cations may not distinguish mancozeb residues from other EBDC residues or from naturally occurring metal cations, other types of analysis may be possible. Additionally, an enforcement method is needed to distinguish between/among other contaminants which degrade to CS₂.

Deficiency 4b - Multiresidue Methodology

Residues of ethylenethiourea (ETU) and mancozeb, per se, in/on crop samples must be subjected to analysis by the multiresidue methods published as an addendum to Subdivision O. Protocols for methods I, II, III, and IV are available from NTIS under Order No. PB86 203734/AS.

Registrant Response

Rohm and Haas did not respond to the requirement for data on the FDA Multiresidue methods.

RCB Comment

The requirement for data on PAM Multiresidue Methods I, II, III, and IV remains outstanding. A statement that mancozeb and its metabolites and degradates are not recovered by PAM Multiresidue methods I, II, III, and IV would be sufficient, assuming that the statement is true.

Deficiency 4c - Analytical Methodology - Additional metabolites

If the requested data regarding the nature of the residue in plants and animals reveal additional metabolites of toxicological concern, additional analytical methods for data collection and enforcement may be required.

Registrant Response

None.

RCB Comment

No response is needed from the registrant at this time.

Deficiency 5 - Storage Stability

Available storage stability data are adequate to demonstrate that mancozeb is stable in/on frozen plant samples for up to 12 months and ETU is stable for up to 6 months in frozen plant samples.

To support crop residue data, storage stability studies must be conducted on both weathered samples

(mancozeb) and fortified frozen samples (mancozeb, metabolites and ETU) of one representative crop from each crop grouping (40 CFR 180.34) on which registered uses of mancozeb exist. Analyses of each crop must be conducted over a time period that includes the time interval that the raw agricultural commodity is held in frozen storage prior to the crop residue analysis. To support residue data on processed commodities, fortified storage stability data are required for all processing studies submitted to the Agency. Analyses must be conducted over a time period that includes the frozen storage of the raw agricultural commodity prior to processing and each processed commodity prior to the residue analysis. Protocols for these studies must be submitted to and approved by the Agency prior to initiating the studies.

(a) Storage stability data using weathered samples. Data are required on the parent compound, mancozeb, in which crop samples field treated with a typical end use product are frozen immediately upon harvesting. The integrity of the samples must be maintained by freezing. The samples must be analyzed for mancozeb on the day they arrive at the analytical laboratory, and then stored frozen and analyzed periodically for mancozeb during the time intervals specified in the Agency approved protocol.

(b) Storage stability data using fortified samples. Data are required on mancozeb, ETU, and metabolites in which a group of untreated samples of raw agricultural commodities and processed crops are fortified (spiked) with only mancozeb pure active ingredient, another group of samples is fortified with only ETU, and other groups are fortified individually with each additional metabolite. Immediately after fortification, the samples fortified with mancozeb must be analyzed for mancozeb and ETU; samples fortified with ETU must be analyzed for only ETU; and samples fortified with other metabolites must be analyzed for only the metabolite with which the sample was fortified. Sample integrity must be maintained by freezing, and analyses for mancozeb, ETU, and metabolites must be conducted periodically during the time intervals specified in the Agency approved protocol.

(c) Storage stability data for livestock/poultry feeding studies. If cattle and poultry feeding studies are required (see Registration Standard Guidance Package, Data Table footnotes 71 and 72), fortified storage stability studies will be required on all animal commodities (i.e., tissues, milk and eggs) for

which residue data are submitted to the Agency. Analyses must be conducted over a time period that includes the time interval that each commodity is held in frozen storage prior to residue analyses.

(These deficiencies were in the text and not in the Guidance Package Table Footnotes.)

All requested residue data must be accompanied by data regarding storage intervals and conditions of sample storage from harvest until analysis.

If metabolism studies reveal the presence of other metabolites of concern, then storage stability studies must be conducted on these additional metabolites for the length of time the samples were stored.

Registrant Response

Rohm and Haas claims that the storage stability studies they have submitted are adequate. They claim that weathered residue storage stability studies are not needed. Rohm and Haas states that they will provide harvest to analysis intervals for each crop analysis, along with sample storage conditions.

Fortified storage stability protocols for livestock and poultry tissues and crop samples have recently been submitted. (See RCB No. 3203.)

RCB Comment

The registrant is correct in stating that the fortified storage stability studies they have submitted are adequate to show that mancozeb is stable in frozen storage for up to 12 months and that ETU is stable in frozen storage for up to 6 months. However, storage intervals and conditions of sample storage from harvest until analysis were not available for the residue data reviewed for the Registration Standard. Thus, any data submitted for which the frozen storage interval is longer than 12 or 6 months for mancozeb or ETU, respectively, are not valid.

Weathered storage stability studies will not be required if all samples were analyzed within 12 months of harvest for mancozeb and within 6 months for ETU, and were stored frozen from harvest until analysis. If any samples were stored longer than 12 months and 6 months, then both weathered and fortified storage stability data are needed.

Fortified storage stability protocols for livestock feeding studies and crops will be reviewed separately (See RCB No. 3203).

Deficiency 6- Residue and Processing Data

Detailed deficiencies will not be listed here. These deficiencies list treatment rates and number of treatments, and required geographical representation for wettable powder and dust formulations. Data for both ground and aerial applications are required.

Registrant Response

Rohm and Haas will conduct additional trials with the 80WP formulation, but will not conduct residue trials with the dust formulation. Regarding ground vs. aerial applications, Rohm and Haas submitted a summary table of previously submitted data and stated that residue levels were similar for both types of applications, and therefore, only one type of application should be sufficient for future residue field trials.

RCB Comment

We have no objection to Rohm and Haas not supporting the dust formulations, providing all registrations for dust formulations are cancelled.

The summary table submitted to compare ground and aerial applications does not clearly state from which study each data point was obtained, and therefore cannot be further evaluated. However, all previously submitted data were reviewed for the Registration Standard and the requirement for both ground and aerial data was made after considering all previously submitted data. We reiterate that residue data are needed for both ground and aerial applications. The registrant might consider conducting a bridging study to satisfy this requirement. A bridging study would involve side by side residue field trials for at least one crop in each crop group. Separate side by side tests would be needed for several diverse locations for each crop.

cc:R.F., circu, S. Hummel, mancozeb S.R.F. (Hummel), mancozeb R.S.F. (Boodee), mancozeb S.F., V. Bael (SRB/RD), TOX, PMSD/ISB
RDI:EZ:04/18/88:RDS:04/19/88
TS-769:RCB:SVH:svh:RM810:CM#2:x77324:4/20/88