

US EPA ARCHIVE DOCUMENT

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 20 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT : EPA Reg. No. 352-354. Benomyl; Protocol for Bound Liver Residues. Letter of February 11, 1986. No Accession Number. RCB No. 657.

FROM : Sami Malak, Ph.D., Chemist *Sami Malak*
Tolerance Petition Section III
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

THRU : Philip V. Errico, Section Head *Philip V. Errico*
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TO : Henry M. Jacoby, PM#21
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Registration Division (TS-767)

The petitioner, E. I. Du Pont de Nemours & Co., Inc., responded to our memo of October 18, 1985 concerning animal metabolism protocols and suggested certain modifications to the experimental design of protocol A. In our memo of 10/18/85, we discussed in detail two alternative protocols (A & B) for benomyl residues designed to answer the question of "plateau" level for bound residues in the liver. The question of bound residues was raised in connection with PP#6F1748 and was part of the Agency's 3(c)(2)(B) Data Call-In letter of May 14, 1985 and a meeting with company representatives on August 26, 1985 (see S. Malak's memo of meeting on benomyl, 8/29/85).

In our 8/29/85 memo, we concluded that protocol A may address the stated objectives in resolving the question of bound liver residues and suggested five modifications in the experimental design of protocol A. In their letter of 2/11/86, Du Pont seems to be in agreement with two of the suggested five modifications (#'2 & 5), however, they suggested certain revisions in the remaining three points (#'s 1, 3 & 4). Points of disagreement between the Agency and Du Pont are cited below, each followed by the petitioner's response and our comments.

Modification #1

The level of feeding of 50 ppm is approximately equivalent to an approximate 1X feeding level of 45 ppm. In addition to the 1X dose, a second set of goats may be fed an exaggerated dose of 10X (450 ppm).

Petitioner's response

One of the main points made in the October 18, 1985 memorandum was the conclusion that 45 ppm benomyl in feed items represented an approximate 1X feeding level. This estimate of a worst case exposure of dairy cattle was based on the following feed items described in the Agency's memorandum of August 15, 1984, from E. T. Haerberer to H. M. Jacoby:

<u>Feed Items</u>	<u>Tolerance (ppm)</u>	<u>Percent of diet</u>	<u>Calculated residues (ppm)</u>
Dehydrated grape pomace	125	20	25.0
Bean vine forage	50	37	18.5
Grains	0.2	43	0.1
			43.6

The petitioner has also submitted an argument that the hypothetical diet used by RCB to calculate the "Theoretical Maximum Dietary Intake (TMDI)" of benomyl is unreasonable. Du Pont has consulted with dairy scientists from Texas, Nebraska, Oklahoma, Kansas and Colorado and arrived at what they consider to be reasonable dairy cow diet. In their estimate, Du Pont listed 3 or 4 feed items with grains constituting 75-85% of the diet, roughage 8-15%, protein 5%, and minerals 2-5%. Of the four estimates, the highest TMDI was calculated at 0.2 ppm.

Du Pont concluded that with such low actual 1X level in real diets, it would be very difficult to run a meaningful study to determine bound liver residues. Even at the 10X (2.0 ppm) it would be difficult to obtain significant liver residues after any normal period of time. They added, however, that the proposed level of 50 ppm benomyl certainly represent an exaggerated dose (250X) and should furnish significant bound liver residues for measurement.

RCB's Comments

Of the four estimates on the "Theoretical Maximum Dietary Intake (TMDI)", Du Pont omitted two of the possible feed items with high benomyl residues. These are dehydrated grape pomace with a tolerance of 125 ppm and bean vine forage with a tolerance of 50 ppm.

In calculating the TMDI, the Agency follows established rules and guidelines that has been approved by Industry, Academia, Federal and State Agencies. In general, when calculating the TMDI, the Harris Guide and the Pesticide Assessment Guidelines, Subdivision O, are consulted. In so doing, the Agency is mainly interested in a "worst case ration" containing feed items with the highest tolerances since it is expected that such items could be included in the feed ration of livestock. Such factors as cost of feed, milk production, fat content, egg size or color, etc., that may call for an "ideal ration" are not appropriate parameters to include in a "worst case" estimate for tolerance setting purposes.

Consulting Morrison, F. B. (1957): Feed and Feeding, A Handbook for the Student and Stockman (The Morrison Publishing Company, N. Y. 1165 pp.) and assuming a dairy cow weighing 1400 pounds that is capable of producing 30 pounds of milk daily with a fat content of 4%, the recommended "ideal diet" for such cow would contain 2 pounds of hay and silage and 5.9 pounds of grain mixtures/100 pounds of live weight. The ration also calls for certain additional minerals composed of calcium, phosphorus and salts at 0.2 to 1.5% of the diet. When considerations are given to the registered uses of benomyl for which there are tolerances for r.a.c.'s under 40CFR§180.294, and feed additive tolerances under 40CFR§561.50, the following "Dietary Intake (DI)" was calculated:

Feed Items	Tolerance (ppm)	Percent of diet	DI (ppm)
Dehydrated grape pomace	125	12.5	15.625
Bean vine forage	50	12.5	6.250
Corn and/or soybeans	0.2	73.8	0.148
Minerals (Ca,P,Salts)	---	1.2	----

22.023

We note that the DI is approximately 0.5X the TMDI, whereas, it is 110X that of Du Pont's hypothetical diet. In this regard, we should point out that because of the many variables influencing the level of the TMDI, no two levels are expected to be equal. For example, RCB's previous assessment of 43.6 ppm of the TMDI for benomyl (E. T. Haeberer, 8/15/84), may be somewhat higher if one considers the recommended percentages in the diet for dried grape pomace and bean vine forage.

The following is the resulting estimate for a second TMDI for benomyl.

<u>Feed Items</u>	<u>Tolerance (ppm)</u>	<u>Percent of diet</u>	<u>TMDI (ppm)</u>
Dehydrated grape pomace	125	30	37.5
Bean vine forage	50	35	17.5
Corn and/or soybeans	0.2	35	0.07
			55.07

For the above reasons, it is our judgement that the petitioner's suggested revisions in the "Theoretical Maximum Dietary Intake (TMDI)" of approximately 45 ppm for benomyl is not adequately supported. Therefore, and for the purpose of the proposed experimental design, RCB does not contemplate further revisions in the suggested modifications stated in point #1 of S. Malak's memo of 10/18/85. It has been RCB's policy to recommend feeding levels at exaggerated rates to cover future tolerance requests of a pesticide applied to a raw agricultural commodity. In this case, the questions to be addressed are the determination of the "plateau" level of benomyl residues in beef liver and the subsequent depletion of residues once feeding has ceased. As long as these questions are appropriately addressed, RCB has no objections to running the feeding studies at levels less than 450 ppm, but equal to or greater than 45 ppm. Running the study at approximately 45 ppm should cover only the presently established tolerances. Future tolerance requests for benomyl on potential livestock feed items may necessitate additional studies of this type.

Modification #3

The experimental design should include two animals per time point for a total of six goats/dose level and controls.

Petitioner's Response

We agree that the experimental design should include two animals per time point for a total of six goats to be fed at the 50 ppm level. However, there is no need for control animals in a study of this type, since they would serve no purpose.

RCB's Comments

The petitioner seems to respond to two different issues: (a) Objections on the use of control animals, and (b) Affirmation on the use of a single dose level of 50 ppm. We will discuss each issue independently.

(a) Use of Control Animals

The Pesticide Assessment Guidelines, Subdivision O, does not recommend the use of control animals in studies dealing with elucidating the nature of residues in livestock. However, the experimental design of this protocol calls for elucidating the "plateau" level of benomyl bound liver residues. In the protocol for bound residues, we agreed on three time points at which a dosed and a control animal per time point are to be sacrificed for a total of six animals per dose level. Our objectives would be best addressed if a control animal is included per each time point. However, since the experimental technique calls for determining the level of bound radioactivity by combustion and LSC, we feel that at least one control animal should be included to provide a background count for all time points for a total of 7 animals for the entire experiment.

(b) Dosing Level

In our memo of October 18, 1985, we recommended the use of two dosing levels, a 1X and an exaggerated dose of 10X, equivalent to 50 and 450 ppm, respectively. The petitioner's response seems to affirm the 50 ppm dosing level and omitted any references on the use of higher dose level. RCB will have no objections to running the feeding studies at levels less than 450 ppm, but equal to or greater than 45 ppm. Completing this study at approximately 45 ppm should cover only the presently established tolerances. Future tolerance requests for benomyl on potential livestock feed items may necessitate additional studies to determine the "plateau level" of bound benomyl residues in beef liver.

Modification #4

Our objectives are best addressed using cattle rather than goats, since cattle liver is the commodity of concern to the Toxicologists. If the petitioner conducts this study with goats, they should be aware that a study using cattle may be necessary.

Petitioner's Response

We understand that the Agency could always insist that this study should be conducted using cattle rather than goats, but the scientific data available from studies run to date suggest that very similar results are obtained when goats or cattle are used. For example two goat studies run at feeding levels of 36 ppm and 88 ppm benomyl gave total liver residues of 3.8 ppm and 3.6 ppm respectively (EPA Accession No's 097791 and 099097 respectively). A corresponding study in cattle run at a feeding level of 50 ppm benomyl gave total liver residues of 4.1 ppm (EPA Accession No. 259638).

RCB's Comments

The petitioner's comments have been noted.

Conclusions

1. The petitioner's suggested revisions in the "Theoretical Maximum Dietary Intake (TMDI)" of approximately 45 ppm for benomyl is not adequately supported. Therefore, and for the purpose of the proposed experimental design, RCB does not contemplate further revisions in the suggested modifications stated in point #1 of S. Malak's memo of 10/18/85. It has been RCB's policy to recommend feeding levels at exaggerated rates to cover future tolerance requests of a pesticide applied to a raw agricultural commodity. In this case, the questions to be addressed are the determination of the "plateau" level of benomyl residues in beef liver and the subsequent depletion of residues once feeding has ceased. As long as these questions are appropriately addressed, RCB has no objections to running the feeding studies at levels less than 450 ppm, but equal to or greater than 45 ppm.
2. At least one control animal should be included for the purpose of providing a background count for a total of 7 animals for the entire experiment.
3. From the available data, it is obvious that benomyl residues in a dairy cow's liver was 4.12 ppm reflecting 1X dose and that in a goat's liver was 3.6 ppm reflecting 1.76X dose level. For this reason and because cattle rather than goats were the choice of the Toxicologists, we re-iterate our previous recommendation in that cattle rather than goats should be used in the proposed experiment. If the petitioner conducts this study with goats, they should be aware that a study using cattle may be necessary.

Other Comments

Conclusion #3 was discussed with Dr. Marion Copley of the Toxicology Branch.

cc: RF, Circu, S.Malak, SF (benomyl), PP#6F1748, TOX (Dr. Copley).
RDI:P.V.Errico:6/17/86:R.D.Schmitt:6/18/86
TS-769:RCB:CM#2:RM810:S.Malak:X-557-7330:3/20/86, revised 6/17,86.