

File: PP# 1F1024

January 6, 1971

AF 25-202

PP #1F1024: Daconil on various raw agricultural commodities.
Evaluation of analytical methods and residue data.

Division of Regulations and Petitions Control
and Division of Toxicology

Diamond Shamrock Chemical Company proposes that the following tolerances be established for residues of the fungicide tetrachloroisophthalonitrile (Daconil 2787) and its metabolite 4-hydroxy-trichloroisophthalonitrile (DAC 3701):

- 20 ppm on peanut vine hay, sugar beet tops, and sweet corn forage. ✓
- 15 ppm on celery.
- 5 ppm on snap beans, broccoli, brussels sprouts, cabbage, carrots, cauliflower, cucumbers, melons, pumpkins, squash (winter and summer), and tomatoes.
- 1 ppm on lima beans (pods removed) and sweet corn (kernels plus cob with husks removed).
- 0.1 ppm on peanuts and sugar beets (negligible residues).

A tolerance of 0.1 ppm for residues of Daconil and its hydroxy metabolite in or on potatoes (PP #9F0743) has previously been established. A proposal (PP #7F0599) for tolerances for most of the crops considered in the present petition was withdrawn due to inadequacies in the data for plant metabolism and analytical methodology.

Conclusions

1. The metabolism of Daconil by plants has not been adequately delineated.
2. There is an adequate method available for enforcement of tolerances as the parent compound.
- 3(a). Based on conclusion 1, we are unable to conclude that the proposed tolerances are appropriate.
 - (b). In the cases of snap beans and peanuts, the proposed tolerances appear to be inadequate even for residues of Daconil per se.
 - (c). The data for celery, lima beans, sugar beet roots and tops, and sweet corn forage are too meager for us to give an opinion as to the adequacy of the proposed tolerances even for Daconil per se.

4. Daconil per se has no tendency to store in meat or milk. However, the hydroxy-metabolite is stored in meat, fat, and milk. The available data do not permit us to conclude whether residues of the hydroxy-metabolite in meat and milk are derived from the ingestion of the parent or the hydroxy-metabolite.

5. In view of the unresolved questions concerning the metabolism of Daconil in soil, we are unable to derive any conclusions as to the persistence of Daconil metabolites in soil. Daconil per se degrades rapidly in soils.

Recommendation

Due to the conclusions outlined above, we recommend against the proposed tolerances.

The PRD, USDA (in their opinion on residues, 11/5/70) has listed 16 deficiencies which must be resolved before they can give a final opinion. The two major questions deal with the metabolism of Daconil and the need for validation data (especially for macerated samples). The remaining fourteen deal with individual crops and the need for additional residue data and in the case of celery, a more appropriate tolerance level.

In addition to the deficiencies cited by PRD, USDA, we will need the following:

(a) Data reflecting the presence or absence of benzamide derivatives of Daconil in plants since we would expect that, particularly in soil, such metabolite(s) would be intermediate between Daconil and its hydroxy-metabolite and the chloro-benzoic acid metabolites postulated by PRD, USDA.

(b) Data reflecting the presence or absence in plants of conjugates of hydroxy-Daconil and of metabolites of chloro-benzoic acid or those derived from benzamide.

(c) If data obtained in (a) and (b) indicate that additional toxic metabolites do occur in plants, we will need adequately validated methods of analyses for their residues.

(d) A successful method tryout (in our hands) for residues of the hydroxy-metabolite on at least two representative crops.

(e) A more appropriate tolerance for lima beans. The proposed tolerance is for lima beans (pods removed). Since the raw agricultural commodity is lima beans in pods, the tolerance should be proposed for that item. Additional residue data will be needed for both lima beans (in pods) and lima bean vines with adequate geographical representation and reflecting residues at the proposed PHI. Also, since the petitioner apparently contemplates the feed uses of the vines, he should propose an appropriate tolerance for this item.

(f) The petitioner has made no provision for restrictions on the feed uses of snap bean vines nor has he proposed a tolerance for this feed item. Consequently, we will need to know the petitioner's intent in this regard.

(g) Since corn forage (used for silage) is a major feed item, we will need data for residues of the hydroxy-metabolite and conjugates thereof on corn silage processed from treated corn forage. This is necessary because data in the subject petition indicates that Daconil is degraded by microbial organisms to the hydroxy-metabolite. We would expect a similar effect during ensilage. Also, the grower has no control over sweet corn cannery waste and a possible alternative would be to have the use restricted to sweet corn produced for the fresh vegetable market only.

(h) Since the farmer or dairy operator cannot predict accurately when a milk animal will freshen and since the milk-out study shows that it may be several weeks (after removal from treated feed) before residues of hydroxy-metabolite are not detected in milk, more appropriate restrictions against uses of treated feed items for dairy animals may be necessary.

(i) The available data do not permit us to conclude that the proposed 30-day preslaughter withdrawal period is adequate to insure the absence of residues of hydroxy-Daconil in the tissues or fat of meat animals. In the absence of data reflecting the rate of decline, a longer withdrawal period, if practical, may be required. This will also depend upon the findings relating to additional toxic metabolites as well as on the data requested in item (j) below.

(j) We need additional data as to the tendency of Daconil to transfer to meat and milk as the hydroxy-metabolite. Reserve samples from the Daconil feeding study, if available, should be analyzed for the hydroxy-metabolite. As indicated above, other metabolites may also be a problem.

(k) If the required metabolism data do indicate that other toxic metabolite(s) of Daconil occur in plants, and if the petitioner intends that the feed items be used for feed or forage, we will need additional feeding studies for these metabolite(s).

(l) Some additional data may be required on the persistence of Daconil metabolites in soil since the available data indicate that at 45 days (end of ^{14}C -study), about one-third of the activity was represented by an unidentified metabolite and "unextractable activity." Particular attention should be given to determine if benzamide derivatives are part of this unidentified material and if they have a tendency to persist. This data will not be required if the data obtained in (a) and (b) resolve our questions as to the nature of terminal residues. We will need

some assurance that technical Daconil is essentially free of hexachlorobenzene, which is present as a manufacturing impurity in appreciable amounts in the related pesticide Dacthal.

Detailed Considerations

Formulation

Daconil is formulated as a 75% w.p. (trade name Bravo 75). The technical product is 95.6-98.5% pure. The impurities consist of [REDACTED]

All of the inerts are cleared under Section 120.1001.

We note that Dacthal, a related chemical, has been found to contain appreciable amounts of hexachlorobenzene as a manufacturing impurity. Information furnished on the manufacturing process for Daconil does not permit us to conclude whether this impurity could occur in technical Daconil.

Proposed Uses

Generally, Daconil is used as needed (usually at weekly intervals) as a post-emergence spray. PHIs of zero to 14 days are to be observed.

The label imposes a restriction against the feeding of treated crops to lactating dairy animals and provides a 30-day withdrawal period for livestock to be slaughtered. (We do not consider these restrictions practical; see "Residues in Meat and Milk.")

Due to the number of crops involved, details of the proposed uses are outlined for individual crops under "Residue Data" below. However, we note here that in all cases Daconil is to be diluted with sufficient water to obtain adequate coverage.

Nature of the Residue

Daconil is resistant to degradation by moderately alkaline or acidic aqueous media and by UV radiation. Limited data for celery show that field washing of treated celery reduces zero-day deposits by about 50% but that aged (14-day) residues are only reduced slightly.

Soils and plants can degrade Daconil to the 4-hydroxy metabolite. In soils, Daconil is rapidly degraded and at 1½ months, the hydroxy-metabolite is the principal acetone-extractable residue (ca. 70% of the total) with no parent compound present and ca. 20% not extractable. On plants such

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as peanut and lima bean foliage, up to about 10% of the residues are the hydroxy-metabolite. However, sugar beet tops were found to be free of this metabolite and this was true of most of the crops for which residue data are available. (We have no data for residues of hydroxy-Daconil on corn forage.)

A microbiological study involving bacteria obtained from soil shows that an aqueous culture rapidly degrades Daconil to the hydroxy-metabolite.

The available ¹⁴C studies on plants are qualitative in nature and involved immature plants under greenhouse conditions. These data (presented in PP #7F0599) indicate that foliar deposits do not translocate and that there is no uptake from roots to the aerial plant parts. Based on the above data and residue data presented in PP #9F0743, we concluded that, for potatoes, the terminal residues of concern are Daconil per se and insignificant amounts of the hydroxy metabolite.

However, the PRD, USDA has raised the question of other possible metabolites; i.e., the chlorobenzoic acid derivatives of Daconil and their hydroxy metabolites. We note that Daconil is related to dichlobenil which contains one CN group and two Cl atoms, whereas Daconil contains two CN groups and four Cl atoms. Since, in soil, dichlobenil is known to degrade to its benzamide, we believe that Daconil in soil could also form the benzamides of the parent compound and the hydroxy-metabolite.

Also, it is distinctly possible that the hydroxy-metabolite(s) of Daconil could form conjugates in the plants and in previous studies, there was no attempt to determine conjugated metabolites.

Consequently, we conclude that the fate of Daconil in plants and soils has not been adequately delineated.

For the fate of Daconil in animals, see below under "Residues in Meat and Milk."

Method of Analysis

This subject was last discussed in our review of PP #9F0743 (memo of A. R. Rathman, 7/14/70) wherein it was concluded that the petitioner's methods for residues of Daconil and DAC 3701 were adequate for enforcement of the proposed tolerance for potatoes. (Only the method for the parent compound has been tried out in FDA laboratories; since no detectable residues of DAC 3701 were found on harvested potatoes, no method tryout was recommended for the determination of the metabolite.)

The petitioner's methods are sensitive to at least 0.05 ppm of each compound. However, crop blanks are quite variable--from <0.02 ppm in potatoes to 0.35 ppm in peanut hulls. Recoveries are generally good (>80%).

Until a method tryout for DAC 3701 has been successfully completed, we find the available methods adequate only for Daconil per se. Also, we need to evaluate the validation data requested by PRD.

Residue Data

Most of the residue data (for parent compound only) were reviewed in PP #7F0599 (memo of B. Malone, 8/28/67).

Due to (1) the unresolved questions as to the nature and magnitude of unidentified metabolites of Daconil and (2) the numerous deficiencies cited by the PRD, USDA, we will be brief in our comments concerning the residue data.

It should be understood that our comments below on the adequacy of the proposed tolerances are based on the residue values for Daconil as reported by the petitioner.

Celery

Use 0.75 to 2.25 lbs act/A. The lower rates are to be used on a 3 to 5 day schedule and the higher rates on a 7 day schedule. Start applications when transplants are set in the fields. Do not apply within 7 days of harvest. Remove residues by stripping, trimming, and washing. (Note: There is also a use of up to 1.875 lbs act/A on celery seed beds to be applied twice weekly or as needed to maintain control.) Start applications shortly after emergence.

Data presented in PP # 7F0599 show that residues at 7 days after last treatment on field trimmed and washed celery (following 26 applications of 2.5 lbs act/A) would not exceed 10 ppm.

However, the PRD, USDA indicates that the practice of field washing of celery may be limited to Florida. Consequently, harvested celery in other areas could have considerable higher residues, i.e., of the order of 25 ppm. We defer to the PRD, USDA as to the practicality of the label warning concerning field trimming and washing.

Data in the subject petition are rather limited and do not permit us to estimate the tolerance level needed even for Daconil per se.

Lima Beans

(The proposed tolerance is for lima beans without pods.)

Use 1.5 lbs act/A. Begin applications at early bloom stage or when disease first threatens and repeat at 7 day intervals or as necessary to maintain control. Do not apply within 7 days of harvest. Do not feed treated vines to livestock within 30 days of slaughter or to lactating dairy animals.

Only one study (Tennessee) reflects residues of both parent and the hydroxy-metabolite on lima bean foliage. This study involved four applications of 1.5 lbs act/A and the samples were taken 3 days after the last treatment. Residues of the parent were 52 ppm and those of the hydroxy-metabolite were 1.0 ppm. Residue values for shelled lima beans presented previously (for the parent) were 0.4 ppm (max.) at 0 days. The petitioner is proposing a tolerance for shelled lima beans. Since the raw agricultural commodity is lima beans in pods, the tolerance should be proposed for that item.

We will need additional data for lima beans in pods and lima bean vines with more geographical representation and a more nearly representative number of applications and at times near the proposed PHI.

It is to be noted that, while the petitioner has proposed tolerances for other feed items, he has not proposed a tolerance for lima bean vines. The petitioner should clarify his intent in this regard.

Snap Beans

Use 2.25 lbs act/A. Apply at early bloom stage or when disease first threatens and repeat at weekly intervals. Do not apply within 7 days of harvest. (No restriction is provided against the feed use of vines.)

The only available residue data on snap beans were those presented in PP #7F0599 and involved surface stripping of samples. The two studies indicate that residues might exceed the tolerance.

We will need additional residue data for snap beans and snap bean vines and reflecting the extraction of macerated samples.

The petitioner has made no provisions for restrictions against the feed use of snap bean vines. Suitable feeding restrictions will be necessary. Likewise, a tolerance may be necessary for snap bean vines and hay.

Broccoli, Brussels Sprouts, Cabbage, and Cauliflower

Use 1.125 to 2.0 lbs act/A according to disease conditions. Begin applications after transplants are set in field or shortly after emergence of field seeded crops. Repeat at 7 to 10-day intervals as necessary to maintain control.

The available residue data (a total of 5 studies on broccoli, brussels sprouts, and cabbage) indicate that combined residues of Daconil and the hydroxy-metabolite will not exceed the proposed 5 ppm tolerance level.

Carrots

Use 1.125 to 1.5 lbs act/A. Start applications when disease threatens and repeat at 7 to 10-day intervals or as necessary to maintain control.

Data presented in PP #7F0599 and the subject petition indicate that there is little buildup of residues of Daconil or DAC 3701 on the carrot root, the maximum being of the order of 0.5 ppm.

Melons (Cantaloupes, Honeydews, Muskmelons, and Watermelons), Squash and Pumpkins

Use 1.125 lbs act/A to 2.25 lbs act/A. Begin applications when plants are in first true leaf stage or when conditions are favorable for disease conditions. Repeat at 7-day intervals. Under severe disease conditions, shorten spray intervals.

Data presented in PP #7F0599 indicate that maximum residues of Daconil on cucumbers will be <3 ppm, on squash, muskmelons, and honeydew melons will be <2 ppm, and on cantaloupes and watermelons will be <1 ppm.

Data in the current petition tend to confirm the above findings, except that the data indicate that cantaloupes will also have residues of up to 2 ppm.

Residues of DAC 3701 are negligible (<0.1 ppm).

Tomatoes

Use 1.125 to 2.25 lbs act/A. Begin applications when disease threatens and repeat at 7 to 10-day intervals. Under severe conditions, shorten spray intervals.

Residue data indicate that the proposed tolerance is adequate to cover maximum residues of Daconil per se at zero day resulting from the proposed use.

Residue data in the current petition tend to confirm the above opinion. For DAC 3701, the data indicate that only trace residues (≤ 0.1 ppm) of the metabolite are to be expected.

Sweet Corn and Sweet Corn Forage

Use 1.125 to 1.5 lbs act/A. Begin applications when conditions favor disease development and repeat at 4 to 7-day intervals or as required to maintain control. Do not apply within 14 days of harvest. Do not feed treated forage to livestock within 30 days of slaughter or to lactating dairy animals.

The limited available residue data (with one exception) are for sweet corn (kernels plus cob with husks removed). These indicate residues of Daconil on sweet corn per se would be <0.2 ppm.

We will need additional residue data including data for ensiled corn forage which would be expected to have higher residues of the hydroxy-metabolite.

Since the grower has no control over the disposition of sweet corn cannery waste, the proposed use will have to be limited to corn produced for the fresh vegetable market.

Peanuts

Use 0.75 to 1.125 lbs act/A. Start applications when disease first appears and repeat at 10 to 14-day intervals or as necessary to maintain control. Do not apply within 14 days of harvest. Do not feed vine hay to livestock within 30 days of slaughter or to lactating dairy animals.

Only a few of the studies reflect the proposed 14-day PHI, with most PHIs exceeding 1 month. As to the human food, shelled peanuts, this is probably a "no residue" situation as in the case of potatoes. However, crop blanks are erratic and quite high compared to the proposed tolerance (i.e., up to 0.22 ppm). For this reason, the proposed tolerance for peanuts is inadequate.

The petitioner's data for peanut hay and hulls also are deficient in that few samples were analyzed at or near the proposed PHIs.

The few pertinent data indicate that appreciable residues of Daconil and measurable residues of DAC 3701 would be present in or on peanut vine hay but not on the hulls (a minor feed item--maximum of 5% of the diet).

Sugar Beets, Roots and Tops

Use 1.125 to 1.5 lbs act/A. Begin applications when disease threatens and repeat at 10 to 14-day intervals or as necessary to maintain control. Do not apply within 14 days of harvest. Do not feed treated tops to livestock within 30 days of slaughter or to lactating dairy animals.

The available residue data are deficient in that there is only one study with a PHI of 14 days; all the others involve PHIs of 25 days ✓ or longer. Also, there are no residue data for DAC 3701 at the proposed PHI and only one value (at a longer PHI) for the tops and two values for the roots. We do not consider the available data to be adequate.

Residues in Meat and Milk

Small animal feeding studies (presented in PP #7F0599) show that Daconil per se is excreted largely unchanged by rats and dogs. Only small amounts of activity ($<0.5\%$) were detected in tissues or expired CO_2 when ^{14}C -Daconil was fed. "Cold" feeding studies at very high levels (1,500 to 30,000 ppm) to dogs showed trace residues of DAC-3701 in kidney and liver but none in other tissues (PP #9F0743).

In a milkout study reported in the current petition, cold Daconil was fed to lactating cows for 30 days at rates of 25, 75, and 250 ppm in the total diet. By a method sensitive to 0.02 ppm, ca. 5% of the milk samples in the 30-day study showed apparent residues of 0.03 or 0.04 ppm but these were scattered among the test groups. No tests were made for the hydroxy-metabolite; however, two other postulated metabolites were looked for and were found to be absent. The petitioner had previously established that these two metabolites are not present in crop residues. In the second study, lactating cows were again fed Daconil (30 days) at the above rates, but with 0.2, 0.6, and 2.0 ppm of the hydroxy-metabolite added respectively. In this study, dose-responsive residues of the hydroxy-metabolite were found in the milk with maxima ranging from 0.30 ppm at the low level to 1.34 ppm at the high level. Residues of Daconil per se were not detectable (<0.05 ppm).

As to residues transferring to meat, the second cow feeding study (above) shows that, in cattle sacrificed at 30 days, detectable residues of the hydroxy-metabolite transfer to all tissues at feeding levels of 0.6 ppm or higher (only kidney showed finite residues at the 0.2 ppm feeding level). These residues are dose responsive and tend to be higher in the transport and excretory organs (liver and kidney). After a 32-day withdrawal period, the remaining animals showed no detectable residues (≤ 0.03 ppm) in the fat or any tissue.

We conclude that Daconil per se has no tendency to transfer to milk, but the hydroxy-metabolite is stored in meat, fat, and milk.

The petitioner's label bears a restriction: "Do not feed treated crops to lactating dairy animals." We consider this restriction impractical since the farmer cannot predict accurately when a milk animal will freshen and the data indicate that it may be several weeks after withdrawal from feed dosed with the hydroxy-metabolite before residues are non-detectable. Thus, the restriction where practical should be extended to all dairy animals.

The petitioner, by a label restriction, has attempted to render this a Category 3 situation with respect to meat. This restriction involves a 30-day (preslaughter) withdrawal period. However, for reasons explained below, we cannot be certain that this restriction will ensure the absence of residues of the hydroxy-metabolite in fat, meat, and meat byproducts.

Our rationale for this conclusion is as follows:

1. The available data reflect only residues in tissues at the end of the 30-day feeding study and at the end of the 32-day withdrawal period. There are no intermediate data to reflect the rate of decline of such residues.
2. Control values, particularly for DAC 3701, in the liver and kidney are erratic; this also applies to a lesser extent to blanks in muscle and fat. Consequently, there is some question as to the validity of the "zero" residues at the end of the 32-day withdrawal period.
3. The grower has no control over the disposition of certain feed items which could contribute residues to meat animals. These include sweet corn cannery waste, peanuts, peanut meal and peanut hulls. However, only the cannery waste is likely to have significant residues of the hydroxy-metabolite which appears to be the metabolite of interest.
4. When sweet corn forage is ensiled, it undergoes a fermentation process. Thus, even though DAC 3701 residues on harvested corn forage would be expected to be rather low, we could reasonably expect Daconil residues to convert under bacterial activity to DAC 3701. The same situation may apply to "ensiled sugar beet tops."

Overall, we conclude that the available data do not permit us to categorize the proposed uses with respect to Section 120.6(a) insofar as meat and milk are concerned. In addition, the available data do not permit us to conclude whether residues transferring to meat or milk are derived from the metabolite or the parent compound. We are asking for additional data to clarify this question.

For "Poultry and Eggs," see below under "Other Considerations."

Soil Persistence

In PP #9F0743 (memo of A. Rathman, 10/9/68), we concluded that Daconil per se has little tendency to persist in soil. Also, we pointed out that the hydroxy-metabolite (DAC 3701) has a half life of over 7 months and we recommended that the PRD, USDA be consulted as to whether a label warning should be required with respect to rotation of crops. (Subsequently, PRD found no warning to be needed.)

As pointed out under "Nature of the Residue," the hydroxy-metabolite is the principal extractable residue in soils. However, in soil laboratory studies (see PP #7F0599), approximately 30% of the activity of applied ¹⁴C-Daconil existed (at 46 days) as unidentified metabolites.

Due to the above data and to the unresolved questions of unidentified metabolites (as benzoic acids or benzamides), we are unable to conclude at this time that residues of Daconil are non-persistent.

Other Considerations

Since the petitioner contemplates the foraging of some crops and due to the number of treatments permitted in conjunction with relatively short PHIs, we initially had some concern over the possibility of residues resulting in fat and meat via dermal exposure.

In this regard, the two crops of most concern are sweet corn and peanuts. In the first case, we conclude that it would be most unlikely that the farmer would allow meat or dairy animals to forage sweet corn since the crop would be much too valuable.

In the case of peanuts, we note that Morrison ("Feeds and Feeding") states that up to one-third of all peanuts grown are used for "hogging down." However, it is now our understanding (from Mr. James E. Thigpen, ASCS, USDA) that this practice dropped off rapidly after World War II. To the best of available knowledge, it is practiced, if at all, only on the fringes of the peanut belt in Florida.

Consequently, we conclude that there is little likelihood of residues occurring via dermal exposure from the proposed uses particularly in conjunction with the proposed 30-day PHI.

As to poultry, the only feed items involved are pelleted sugar beet tops (5% of the diet) and peanut meal (20% of the diet). The available data indicate that residues on these items will consist of the parent compound only. Based on the available feeding studies which involve greatly exaggerated feeding rates, we conclude that there will be no problem of residues transferring to poultry and eggs.

Daconil, as its hydroxy-metabolite, is ^{theoretically} a precursor of a dioxin moiety. Due to the route of synthesis of the parent compound [REDACTED], we have no

concern as to dioxins being present in the technical material. As to residues producing dioxins, our concern here is limited to oilseed crops and in this petition peanuts are our only concern. However, the data show that there is no likelihood of finite residues of the hydroxy-metabolite in peanuts. Consequently, we conclude that there is no problem of dioxins in connection with the proposed use. (Note: Should the metabolism data required above indicate that residues of the conjugated hydroxy-metabolite do occur in peanuts, we would then consider this to be a problem.)

The only established tolerance is expressed in terms of "2,4,5,6-tetrachloroisophthalonitrile and its metabolite 4-hydroxy-2,5,6-trichloroisophthalonitrile." The accepted nomenclature for these compounds is as follows: "tetrachloroisophthalonitrile and its metabolite 4-hydroxy-trichloroisophthalonitrile." When additional tolerances are established, they should be expressed in the latter form.

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RD/I - JWolff, JGCummings