

US EPA ARCHIVE DOCUMENT

11/30/72 Chemistry Br.

ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D. C. 20460

DEC 1 1972

Date: November 30, 1972

Reply to  
Attn of:

Subject: PP #2F1230; Chlorothalonil, Daconil, amendment of 10-16-72.

To: Mr. Lee TerBush, Acting Chief  
Coordination Branch  
Registration Division

Pesticide Petition No. 2F1230

*Crummey*  
*note comments* ~~*Beauch*~~  
*Quick*  
*Cox*  
Diamond Shamrock  
Cleveland, Ohio  
*File: PPA 2F1230*

Petitioner submits label revisions reflecting grazing restrictions and revised section F in response to reject letter of L. TerBush, 6/22/72. The revised section F purposes the following changes:

- 1) Drops tolerance for lima and snap bean vines.
- 2) Increases tolerance in snap beans from 5 to 15 ppm.
- 3) Reduces tolerance in meat and milk from 0.2 ppm to 0.14 ppm.
- 4) Proposes a tolerance of 0.3 ppm in peanut hulls.

New toxicity data are submitted and include LD<sub>50</sub> determinations for the 4-OH metabolite (DAC 3701 4-hydroxy-2,5,6-trichloroisophthalonitrile) in the dog and rat.

Dog LD<sub>50</sub> (oral) for the 4-OH metabolite: ca. 100 mg/kg.

Rat LD<sub>50</sub> (oral for the metabolite) = 332 mg/kg.

CB has found favorably for the revisions with these exceptions:

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- ✓ 1) The proposed feeding restriction against feeding bean vines and hay is not practical;
- 2) The reduced tolerance for meat and milk should be 0.15 ppm rather than 0.14; moreover, it is remotely possible that, on rare occasions, this tolerance level in milk could be exceeded slightly for a day or two from feeding residue - bearing bean vines and hay (memo of W.S. Cox, 11/29/72).

RECOMMENDATIONS

- 1) TB finds that the grazing restrictions are not of toxicological concern. —?
- 2) We have no objection to the proposal to drop lima and snap bean vines.
- 3) The increase in tolerance for snap beans is acceptable to TB since only very small amounts of Daconil would be added to the total dietary by such increase (see memo of D.L. Ritter, 6-14-72).
- 4) The proposal to reduce the milk and meat tolerances from 0.2 ppm to 0.14 ppm of Daconil and its 4-OH metabolite (CB suggested level is 0.15 ppm, see Cox review) is not acceptable to TB since the safety of such a level is not supported by the data so far in hand. Mr. TerBush in his letter of 6-22-72 indicated TB's concern with the lack of demonstrated safety of the 4-OH metabolite and requested that a three-generation reproduction study using the 4-OH metabolite (in rats preferably) be submitted. In conference with petitioners (memo of conference, L. TerBush, 7-18-72) Dr. Clara Williams said that 0.15 ppm in milk was not a "negligible residue", and indicated that even for a negligible tolerance, two 90-day studies with the metabolite using different species would be required. ←

In her review of 4-15-71, PP #1F1024, Dr. Williams determined that growth depression and reduced weaning weights of pups in a three-generation rat reproduction study of dams fed Daconil may have been due to ingestion of the dam's food by the pups, since exchange nursing failed to implicate the presence of Daconil in the dam's milk. Furthermore, residues of Daconil per se were not found in cow's milk (memo of W.S. Cox, PP #1F1024, 1-6-71). In light of the finding of significant amounts of 4-OH metabolite in cow's milk, it is entirely possible that the toxic reaction noted in these pups was due to its presence in the dam's milk.

Previously submitted metabolism studies<sup>1</sup> demonstrated that no appreciable amounts of the metabolite are formed in the dog and rat at levels fed up to 30,000 ppm for 2 years, since there is virtually none in the urine or in the kidneys or livers. Thus, petitioner's argument that exposure to the parent compound per se reflects considerable exposure to the 4-OH metabolite is invalid. The 4-OH metabolite is a minor metabolite of Daconil in rats and dogs.

<sup>1</sup> See the Wolfe and Stallard storage study in section D of PP #9F0743 for details.

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- 5) Mr. Cox raises the issue of occasionally exceeding the tolerance in meat and milk resulting from feeding animal feeds bearing excessive residues (see his comment under deficiency 1 in the 11-29-72 review).

*(see CB item 2 page 1 of this memo)*

TB is of the opinion that to permit such occasional excesses would set a dangerous precedent, even though the chances are remote that such excesses will in fact occur. With Daconil, and especially its 4-OH metabolite in milk, in light of the lack of safety data noted in (4) above, we could not agree to such occasional excesses.

*\* ✓*

Therefore, in keeping with our previously stated requirements, TB will need the following studies using the 4-OH metabolite, (DAC 3701):

- a) A three-generation reproduction study (preferably in rats). Only the first litter need be included. The original parent-breeders should remain on test diet for the duration of the entire study in order to provide data on long-term toxicity of this metabolite.
- b) A ninety day feeding study in a different species.
- c) Resolution of the question of pathological data on Daconil itself as indicated by Dr. Williams in the 7-18-72 conference.

*David L. Ritter per [signature]*

David L. Ritter, Pharmacologist  
Toxicology Branch  
Registration Division

DLRitter/km 11-30-72

R/D Init: CH Williams 11-30-72

cc: Division Reading File  
Branch Reading File  
Chemistry Branch  
Ecological Effects Branch  
PP #2F1230

Init: C.H. Williams *CHW*  
*12/1/72*

*and dilution in return. Furthermore, TB has just  
file into consideration the fact that most milk  
is computed before injection.*

*\* Note: This does not really reflect the correct situation, since there would be a label restriction which if observed would preclude higher residues. Also TB has already set the precedent of accepting the risks of occasional exposure to unsafe levels of residues, for example, norgestrel bromides in milk*