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EPN 51289 and EPN 515190. Permethrin on celery and soybeans. Amendment of March 7, 1980.

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This amendment replies to the Registration Division letter of 6/22/79 concerning the deficiencies noted in our review of 5/3/79. For convenience, these deficiencies are re-listed below in sequence. Each deficiency is followed by the petitioner's response and our comments/conclusions.

Deficiency No. 1: The term "forage" in the soybean feeding restriction should be changed to "fodder".

Petitioner's Response to No. 1: The petitioner has replaced the word "forage" with "fodder" on the proposed label. The petitioner has also deleted tomatoes from the proposed label and from the revised Section F.

Comments/Conclusions to No. 1: Deficiency No. 1 has been resolved.

Deficiency No. 2a: The nature of the residue in celery and soybeans is not adequately understood. In order to determine whether the metabolites *cis*- and *trans*- 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid and 3-phenoxybenzyl alcohol should be included in the tolerance regulations for these crops, we will need either residue data for free and/or conjugated metabolites in celery and soybeans or additional metabolism studies for these crops.

Petitioner's Response to No. 2a: The petitioner has declared that the nature of the residue in plants has been elucidated in ICI's temporary tolerance petition for permethrin on a variety of crops, submitted December 18, 1979. ICI indicated that 3-PBA and the *trans* and *cis* isomers of BPA are the major metabolites of permethrin, and these are present in relatively small amounts compared to the amount of parent compound. These metabolites are present as conjugated materials, and essentially no free metabolites have been detected.

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Comments/Conclusions No. 2a: We disagree with the petitioner's conception that DCVA and 3-PBA are present in relatively small amounts compared to the parent compound. On the contrary, for example, the below <sup>14</sup>C metabolic data on soybeans show that the metabolites, DCVA and 3-PBA, could indeed be present in large quantities when compared to the parent compound:

| <u>Compounds</u>         | <u>Average % of Applied Intervals</u> |               |               |
|--------------------------|---------------------------------------|---------------|---------------|
|                          | <u>14-Day</u>                         | <u>30-Day</u> | <u>60-Day</u> |
| Permethrin               | 64.1                                  | 34            | 19.4          |
| DCVA                     | 9.2                                   | 14.4          | 17.5          |
| 3-PBA                    | 0.5                                   | 9.6           | 10.5          |
| Ester metabolites        | 0                                     | 1.7           | 1.1           |
| Acid metabolites         | 1.3                                   | 1.7           | 2.9           |
| Alcohol metabolites      | 6.0                                   | 10.3          | 15.2          |
| Polar residues           | 5.7                                   | 15.4          | 16.4          |
| Non-extractable residues | 5.2                                   | 12.9          | 17.0          |

In the above, at 14, 30 and 60 day intervals, the parent compound accounted for 64.1, 34 and 19.4% of the total activity. At the same intervals, DCVA + 3-PBA accounted for 17.7, 24 and 28% of the total activity. Thus, these metabolites, DCVA and 3-PBA, must be included in the tolerance regulations for permethrin in plant commodities (see also our Comments/Conclusions #2b below). Section F needs to be revised.

The petitioner's statement that mostly conjugated materials, and essentially no free metabolites have been detected in plants greatly enhance the need for animal feeding studies; we shall discuss this later in our Comments/Conclusions No. 5a.

Finally, the pertinent "<sup>14</sup>C studies" have shown the ratio of cis/trans permethrin isomers to change from 40/60 to 60/40 as time increased. Generally, in the "field studies," the ratio of cis/trans isomers in/on plants became equal or high trans/low cis as time increased. The petitioner should explain the reason for these different isomeric patterns. Deficiency No. 2a is not resolved.

Deficiency No. 2b: Minimal residue data submitted for tomatoes indicate that the two metabolites named in 2a above should be included in the tolerance regulation for this commodity.

Petitioner's Response No. 2b: The petitioner submitted residue data for permethrin, DCVA and 3-PBA on celery from two locations in the state of Florida and on check and treated soybean samples from plots located in 4 different states; some data were also submitted for soybean foliage. ICI argue that extremely low levels of 3-PBA and trans- and cis- DCVA do not warrant their inclusion in the tolerance expression for permethrin.

Comments/Conclusions No. 2b: With reference to celery, it is our judgment that the levels of 3-PBA and trans, cis DCVA are not extremely low. For example, celery samples collected at Belle Glade, Florida gave the following results:

|                         | Permethrin |       | DCVA                | DCVA                |
|-------------------------|------------|-------|---------------------|---------------------|
|                         | 3-day      | 7-day | +<br>3-PBA<br>3-day | +<br>3-PBA<br>7-day |
| Found, ppm              | 1.9        | 1.35  | 0.6                 | 0.75                |
| % of total residue      | 76         | 64    | 24                  | 35                  |
| % of proposed tolerance | 63         | 45    | 20                  | 25                  |

Although, the above residue data for celery is limited (see also Deficiency 4a), there is enough to conclude that the metabolites (DCVA and 3-PBA) are a substantial part of the terminal residue. These metabolites (calculated as parent) must be included in the tolerance regulations for permethrin on plant commodities. Section F should be revised. After we have received more residue data on celery (see Deficiency 4a) and after our EPA laboratory has validated the methodology for the metabolites (see also Deficiency 5b), we will be able to draw a conclusion on the adequacy of the proposed tolerance on celery.

With reference to soybean products, we stated in our previous review (P22822009 and P22822010-0/3/79-Dr. R. Pericetti) that residues in beans ranged from <0.01 to 0.05 ppm, in foliage from 1.04 to 18.03 ppm and in hay from 1.14 to 29.84 ppm. We were not concerned with the high levels of residues in soybean foliage and hay since we found the label restriction prohibiting the feeding or grazing of soybean forage and fodder to be practical. Residue data for the metabolites on soybeans were lacking.

In the present submission, residues found in mature soybeans were <0.01-0.05 ppm permethrin, <0.1 ppm DCVA and <0.05 ppm 3-PBA. The sensitivities for the involved procedures are claimed as 0.01 ppm for permethrin, 0.1 ppm for DCVA and 0.05 ppm for 3-PBA. Based on these facts (residues found and claimed procedural sensitivities), we would not expect residues of permethrin (0.05 ppm permethrin + <0.1 ppm DCVA + <0.05 ppm 3-PBA) to exceed the proposed tolerance of 0.1 ppm on soybeans (beans only). However, the petitioner should be advised that this conclusion is contingent upon a successful EPA method trial for the metabolites and we still require that tolerance regulations for permethrin on "plant commodities" must include the parent compound, permethrin, plus the possible metabolic residues, DCVA and 3-PBA, calculated as parent. Section F needs to be revised.

Deficiency No. 2c: The nature of the residue in animals is adequately understood. The tolerance regulations for meat, milk, poultry and eggs should be revised to include cis- and trans- 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid, 3-phenoxybenzyl alcohol, and 3-phenoxybenzoic acid. Methodology for determining these metabolites (free and conjugated) is needed.

Petitioner's Response No. 2c: First, the petitioner has requested that the agency consider the review of soybeans and celery in P#052099 independently from that of tomatoes; the new proposed label does not contain a use for tomatoes. Second, the petitioner has again proposed the use of permethrin on celery grown only in the state of Florida. Reference IG of P#082029 is offered for our consideration. This reference, a letter written by Mr. George M. Talbott, General Manager of Florida Celery Exchange, indicates that in Florida neither celery nor celery by-products are fed to livestock or poultry. Third, by using mathematical calculations, the petitioner contends that treated soybeans and soybean hulls would cause terminal residues of 0.0008, 0.0034, 0.0055 and 0.0025 ppm in goat, butterfat, poultry and eggs (yolks) tissues, respectively.

ICI concluded that for celery and soybeans alone there is no need to revise the tolerance expression for permethrin or to provide analytical methods for permethrin metabolites in animal products. ICI requested that this requirement be deferred until such time that the use of permethrin on tomatoes is addressed.

Comments/Conclusions No. 2c: The petitioner has withdrawn the proposed use on tomatoes.

We cannot concur with the use of permethrin on celery in the state of Florida only (see also Comments/Conclusions No. 4a) because permanent tolerances are established on a national basis. Therefore, we look for additional residue data (parent+DCVA+3-PBA) on celery grown in California and Michigan in order to assure adequate geographical representation in the residue data.

Further, in order to address the deficiency at hand, the petitioner has provided calculations for permethrin on soybeans and soybean hulls and has asked for a deferred consideration for permethrin use on tomatoes which involved more significant residues (i.e., 75 ppm on tomato pomace). However, we must remind the petitioner that a permethrin use has already been approved for the plant commodity, cottonseeds, and proposed permethrin uses on fresh alfalfa, alfalfa hay, apples, dried apple pomace, broccoli, brussels sprouts, cauliflower, sweet corn, corn fodder and forage, lettuce, lettuce refuse, cabbage, cabbage refuse and potatoes are under review. Soybeans and/or soybean products in several combinations with the preceding plant commodities may be fed to animals. With such a wide variety of proposed uses, it is necessary that methodology for the metabolites (DCVA, 3-PBA and 3-phenoxybenzoic acid) in animal commodities be available, and the metabolites should be included in all future tolerance regulations for animal commodities.

Deficiency No. 2c has not been resolved.

Deficiency No. 3a: Raw validation data for parent compound in celery are needed.

Petitioner's Response No. 3a: ICI has submitted validation data for the parent compound in celery. Untreated samples were fortified with permethrin at levels ranging from 0.05 to 10 ppm, and recoveries ranged from 70 to 100%.

Comments/Conclusions No. 3a: We consider deficiency No. 3a to be resolved.

Deficiency No. 2b: No judgment with regards to adequate analytical methodology can be made until such time as the deficiencies in the metabolism of permethrin are resolved. It does appear however, that additional methodology for free and/or conjugated metabolites will be needed. This would include validation data, blank crop values, and possibly a second method trial.

Petitioner's Response No. 3b: No direct response is given. Referral is made to Petitioner's Response No. 2a.

Comments/Conclusions No. 3b: We concluded in Comments/Conclusions No. 2a that the proposed permethrin tolerance regulations on plant commodities should include the parent compound and the two metabolites, DCVA and 3-PBA, calculated as parent. The petitioner has submitted methodology for the determination of DCVA and 3-PBA in plant commodities. We will submit this methodology to our method trial unit (CSIS, RFSB, EPA). The tryout will be conducted on soybeans and celery. After receiving the "awaited methodology" for DCVA, 3-PBA and 3-oxobenzoic acid in animal commodities (meat, milk, meat by-products and fat), we will also submit that methodology to our EPA method trial unit. Final judgment on the adequacy of the present methodology for metabolites in plant commodities and the "awaited methodology" for the metabolites in animal commodities will be contingent upon successful EPA method trials. Deficiency No. 3b has not been resolved.

Deficiency No. 4a: Additional residue data on celery grown in California and Michigan are needed in order to assure adequate geographical representation in the residue data. These data should include analyses for free and/or conjugated metabolites of permethrin. These celery residue data should also reflect analyses of the celery with as little trimming as could ever be expected on the marketed commodity.

Petitioner's Response No. 4a: ICI has proposed to limit the use of permethrin on celery to Florida only. Therefore, no residue data from other celery growing areas were submitted. References are made to PH-827819 for residue data (parent compound) that reflect analyses on untrimmed celery samples. In the present submission, metabolite residue values for celery grown in Florida ranged from 0.16 to 0.3 ppm for DCVA and from 0.12 to 0.3 ppm for 3-PBA (PHI=3 days).

Comments/Conclusions No. 4a: We cannot concur with a limited permethrin use in the state of Florida only; the setting of "permanent tolerances" requires adequate geographical representation. At the very least, residue data (parent+DCVA+3-PBA) on celery grown in California and Michigan would be sufficient. We shall draw a conclusion on the adequacy of the proposed tolerance on celery after receiving the required residue data and the results from our method trial unit. Deficiency No. 4a has not been resolved.

Deficiency No. 4b: No judgment with respect to levels of residues of parent and free or conjugated metabolites to be expected in soybeans can be made until the additional information requested above is submitted. Residues of permethrin per se would not be expected to exceed 0.1 ppm in soybeans under this use.

Petitioner's Response No. 4b: The requested residue data for the metabolites, DCVA and 3-PBA, in/on soybeans are submitted within the present amendment.

Comments/Conclusions No. 4b: We have previously said in Comments/Conclusions No. 2b that from the proposed use the expected residues of permethrin (0.05 ppm permethrin + <0.1 ppm DCVA + <0.05 ppm 3-PBA) on soybeans should not exceed a tolerance of 0.1 ppm. This deficiency may be considered resolved providing that the methodology for the metabolites is found to be satisfactory by EPA's method trial unit and if Section F is revised whereas DCVA and 3-Pba metabolites are included.

Deficiency No. 4c: The soybean processing study was found to be deficient in that: 1. The beans did not contain high enough levels originally to accurately determine concentration factors in by-products; 2. Refined oil was not analyzed; and 3. No analyses for free and/or conjugated metabolites were performed. An additional processing study using soybeans containing appropriate residues at or near the tolerance level and reflecting analysis for parent and free and/or conjugated metabolites is needed. In addition, analysis of the refined oil should be performed.

Petitioner's Response No. 4c: Within this amendment, the petitioner has submitted another soybean fractionation study. Fifty kg of harvested soybeans (with hulls) were fortified with 50 mg of Ambush 2d. The fortified soybeans (with hulls) and 50 kg of unfortified soybeans (with hulls) were each divided into two 25 kg subsamples. One subsample of each (fortified and unfortified) was processed into hulls, solvent extracted meal, crude oil, refined bleached deodorized oil and soapstock. One of each subsample was also processed without first removing the hulls. Permethrin control values of <0.05 ppm were reported for refined oil and soapstock; all of the remaining fractions had permethrin control values of <0.01 ppm. DCVA control values of <0.1, <0.1, <0.1 and 0.3 ppm were reported for soybeans, hulls, meal and soapstock, respectively. No 3-PBA values for any of the fortified or unfortified fractions were reported because the chromatographic peak of this derivative coeluted with a large and nonreproducible interference peak. Permethrin and DCVA residue values for the fortified samples are given below:

| <u>Fraction</u> | <u>Permethrin ppm</u> |                      | <u>DCVA, ppm</u>  |                      |
|-----------------|-----------------------|----------------------|-------------------|----------------------|
|                 | <u>with hulls</u>     | <u>without hulls</u> | <u>with hulls</u> | <u>without hulls</u> |
| Soybeans        | 0.35                  | 0.37                 | <0.1              | <0.1                 |
| Hulls           | -                     | 0.53                 | -                 | <0.1                 |
| Meal            | 0.1                   | 0.63                 | <0.1              | <0.1                 |
| Crude oil       | 0.63                  | 0.63                 | -                 | -                    |
| Refined oil     | 0.82                  | 0.63                 | -                 | -                    |
| Soapstock       | <0.05                 | 0.05                 | <0.8              | <0.8                 |

Analyses of soybeans, hulls and seed samples fortified with 0.40, 1.00 and 0.17 ppm DCHA, respectively, gave recovery values of 86, 90 and 70%.

Comments/Conclusions No. 4c: The fractionation study is inadequate in that the soybean samples were fortified only with parent DCHA metabolites were not a part of the fortification mixture. Therefore, the reported DCHA values are meaningless. For this study, fortification of a field treated soybean (hull) sample would had been more appropriate. The fractionation study needs to be rerun; residue data should contain values for permethrin, DCHA and 3-DEA. Deficiency No. 4c has not been resolved.

Deficiency No. 4d: Since we concluded above that the metabolites *cis*- and *trans*-3-(1,2-dichlorovinyl)-1,2-dimethylcyclopropane carboxylic acid and 1-ethanoxycyclohexyl alcohol should be included in the tolerance regulations, we will need additional residue data for free and conjugated forms of these metabolites in order to determine what levels are to be expected in tomatoes and tomato by-products. An additional processing study using tomatoes containing appropriate residues of parent and free and/or conjugated metabolites may be needed. If the additional residue data shows that, generally, the combined level of metabolites comprise <1% of the total residue in tomatoes we conclude that no food-additive tolerance for tomato juice, puree, or catsup are needed. It appears that higher tolerance levels for tomatoes and dried tomato products will be needed when metabolites are included in the regulation.

Petitioner's Response No. 41: ICI is deferring a response on tomatoes at this time. Tomatoes have been deleted in the revised Section F.

Comments/Conclusions No. 41: This deficiency is met at this time.

Deficiency No. 4e: No food-additive tolerance for tomato pulp is needed since residues in this tomato by-product are considered to be covered under a tolerance for dried tomato products. This tolerance proposal should be withdrawn.

Petitioner's Response No. 4e: The proposal has been withdrawn.

Comments/Conclusions No. 4e: The deficiency is met at this time.

Deficiency No. 4f: No final judgment can be made with respect to the levels of residues of permethrin and metabolites to be expected in meat, milk, poultry and eggs until the additional information discussed above is submitted and reviewed. Depending on the outcome of these additional studies new feeding studies for cattle and chickens using permethrin metabolites may be needed.

Petitioner's Response No. 4f: He was asked to see the above responses.



Comments/Conclusions No. 5a: First, we refer the petitioner to the above Comments/Conclusions Nos. 2a and 2b. Second, the petitioner should be informed that the feeding study was carried out in a satisfactory manner, but it was unfortunate that no analyses for the proposed metabolites were reported. The <sup>14</sup>C studies clearly showed that the animal tissues contained appreciable amounts of the metabolites, DCVA, 3-PBA and 3-phenoxybenzoic acid. Without adequate feeding studies, any efforts to draw conclusions on the expected amounts of permethrin residues in meat, milk, poultry and eggs would be conjectural. Hence, new cattle and poultry feeding studies need to be carried out wherein the animal commodities/tissues are analyzed for the parent compound and the metabolites (DCVA, 3-PBA and 3-phenoxybenzoic acid) calculated as parent.

Deficiency No. 5a has not been resolved.

Deficiency No. 5b: The tolerance on milk should be proposed as X ppm in milk fat reflecting Y ppm in whole milk. Again, meat, milk, poultry and egg tolerances should be proposed in terms of parent and the metabolites listed in 2c above.

Petitioner's Response No. 5b: ICI argues that there is no need at this time to revise the current tolerance expression. Within the present amendment, ICI's revised Section F deletes all proposed tolerances for animal products, tomatoes and tomato products.

Comments/Conclusions No. 5b: We refer the petitioner to the above Comments/Conclusions Nos. 2a, 2b, 4c and 5a. For plant commodities, a revised Section F should include the parent compound plus the DCVA and 3-PBA metabolites. For future permethrin tolerances on animal commodities, the revised Section F should include the parent compound plus DCVA, 3-PBA and 3-phenoxybenzoic acid metabolites. All metabolites should be calculated as parent.

Deficiency No. 5b has not been resolved.

Deficiency No. 6: As indicated in the April 25, 1979 Federal Register publication which established tolerances for permethrin from use on cotton, the final judgment on the oncogenicity of this compound has not yet been made.

Petitioner's Response No. 6: The petitioner requests that this registration proceed on a conditional basis until a final judgment in this area has been made.

Comments/Conclusions No. 6: This is a TOX question and ECH defers the petitioner's conditional request on the oncogenicity of permethrin to TOX.

#### Recommendations

We recommend that the proposed tolerances not be established for the reasons given in Comments/Conclusions 2a, 2b, 2c, 3b, 4a, 4b, 4c, 5a, 5b and 6. The petitioner should be so informed.