Jennifer C. Coley, Ph.D., Chemist, ECD, HED (79-709)

Product Manager No.17 (T.R. Cox), Insecticide-Residience Branch, RD (79-707), and HED (79-709)

TSD: Richard D. Schmitt, Acting Chief, Residue Chemistry Branch, HED (79-709)

This amendent 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 "forage".

Petitioner's Response to No. 1: The petitioner has replaced the word "forage" with "forage" 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. 2: 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-monoxyhexyloxalkyl 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. 2: The petitioner has declared that the nature of the residue in plants has been elucidated in their temporary tolerance petition for permethrin on a variety of crops, submitted December 14, 1979. Let indicate that the cis and trans isomers of 3-monoxyhexyloxalkyl alcohol are the major metabolites of permethrin and that 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.

[BEST AVAILABLE COPY]
Comments/Conclusions No. 25: We disagree with the petitioner's conception that PCA and 3-PBA are present in relatively small amounts compared to the parent compound. On the contrary, for example, the below tabulated metabolic data on sorghum show that the metabolites, PCA and 3-PBA, could indeed be present in large quantities even compared to the parent compound:

<table>
<thead>
<tr>
<th>Compounds</th>
<th>1st-Day</th>
<th>30-Day</th>
<th>60-Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permethrin</td>
<td>64.1</td>
<td>36.2</td>
<td>19.4</td>
</tr>
<tr>
<td>PCA</td>
<td>9.2</td>
<td>14.4</td>
<td>17.5</td>
</tr>
<tr>
<td>3-PBA</td>
<td>0.5</td>
<td>9.6</td>
<td>10.5</td>
</tr>
<tr>
<td>Ester metabolites</td>
<td>6.5</td>
<td>1.7</td>
<td>1.1</td>
</tr>
<tr>
<td>Acid metabolites</td>
<td>1.3</td>
<td>1.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Alcohol metabolites</td>
<td>6.0</td>
<td>10.3</td>
<td>15.2</td>
</tr>
<tr>
<td>Polar residues</td>
<td>5.7</td>
<td>15.4</td>
<td>16.4</td>
</tr>
<tr>
<td>Non-extractable residues</td>
<td>5.2</td>
<td>12.9</td>
<td>17.0</td>
</tr>
</tbody>
</table>

Average % of Applied Intervals

In the above, at 14, 30 and 60 day intervals, the parent compound accounted for 64.1, 36 and 19.4% of the total activity. At the same intervals, PCA + 3-PBA accounted for 17.7, 26 and 28% of the total activity. Thus, these metabolites, PCA and 3-PBA, must be included in the tolerance regulations for permethrin in plant commodities (see also our Comments/Conclusions No. 26 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 "14C studies" have shown the ratio of cis/trans permethrin isomers to change from 43/57 to 70/30 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. 26: The petitioner submitted residue data for permethrin, PCA 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; these data were also submitted for soybean foliage. ICI argues that extremely low levels of PCA and trans and cis-3-PBA do not warrant their inclusion in the tolerance expression for permethrin.
Contents/Conclusions No. 21: With reference to celery, it is our opinion that the levels of 3-PBA and \( \alpha, \gamma \)-DCVA are not extremely low. For example, celery samples collected at Belle Glade, Florida gave the following results:

<table>
<thead>
<tr>
<th></th>
<th>DCVA</th>
<th>DCVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Permethrin</td>
<td>3-PBA</td>
<td>3-PBA</td>
</tr>
<tr>
<td>3-T-1-Week</td>
<td>3-T-1-Week</td>
<td></td>
</tr>
<tr>
<td>Found, ppm</td>
<td>1.9</td>
<td>1.35</td>
</tr>
<tr>
<td>% of total residue</td>
<td>76</td>
<td>64</td>
</tr>
<tr>
<td>% of proposed tolerance</td>
<td>63</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>25</td>
</tr>
</tbody>
</table>

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 lab laboratory has validated the methodology for the metabolites (see also Deficiency 5a), 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 (PMB 2159 and PMB 2161) that residues in seeds ranged from 0.01 to 0.05 ppm, in foliage from 1.04 to 15.03 ppm and in hay from 1.14 to 29.86 ppm. We were not concerned with the high levels of residues in soybean foliage and hay since we found the label restriction prohibiting the seeding 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 0.14-0.05 ppm permethrin, 0.1 ppm DCVA and 0.05 ppm 3-PBA. The sensitivities for the involved procedures are claimed as 0.1 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 (0.15 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 metabolite residues, DCVA and 3-PBA, calculated as parent. Section F needs to be revised.

Deficiency No. 22: The nature of the residue in milks is adequately documented. The tolerance regulations for milk, poultry and eggs should be revised to include cis- and trans- 3-(2,2-dichlorovinyl)-1,2-dimethylcyclopropane carboxylic acid, 3-phenoxymethyl alcohol, and 3-phenoxybenzonic 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 Prop. 29,
independently from that of tomatoes; the new proposed label does not
contain a use for tomatoes. Second, the petitioner has stated that the
use of permethrin on celery grown only in the state of Florida. Reference
15 of Prop. 29 is offered for our consideration. This reference, a
letter written by Mr. George M. Talbert, 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 0.004%, 0.003%, 0.0055% and 0.0025
ppm in goat, butterfat, poultry and eggs (yolk) tissues, respectively.

ICI concluded that for celery and soybeans alone there is no need to
revisit 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 permethrin
tolerances are established on a national basis. Therefore, we look for
additional residue data (parent+37% 3-PBA) on celery grown in California
and Michigan in order to ensure 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 produce).
However, we must remind the petitioner that a permethrin use has already
been approved for the plant commodities, cottonseed, 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 (β-naphtha, 3-PBA and 3-phenoxynbenzoic 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 controls were fortified with
permethrin at levels ranging from 0.05 to 10 ppm, and recoveries ranged
from 76 to 100%.
Deficiency No. 2b: No judgment with regards to adequate analytical methodology can be made until such time as the deficiencies in the metabolite 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. 2b: 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-PHA, calculated as parent. The petitioner has submitted methodology for the determination of DCVA and 3-PHA in plant commodities. We will submit this methodology to our method trial unit (CSUSA, BBFSU, EPA). The tryout will be conducted on soybeans and celery. After receiving the "initial methodology" for DCVA, 3-PHA and 3-methoxybenzoic 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 "initial methodology" for the metabolites in animal commodities will be contingent upon successful EPA method trials. Deficiency No. 3b has not been resolved.

Deficiency No. 4b: 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. 4b: 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 EPA 540/3-79 for residue data (parent compound) that reflect analyses on untrimmed celery samples. In the present submission, metabolite residue values for celery grown in Florida range from 0.10 to 0.3 ppm for DCVA and from 0.12 to 0.3 ppm for 3-PHA (PM=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-PHA) on celery grown in California and Michigan would be sufficient. We will 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. 22: No judgment with respect to levels of residues of pentachlorophenol and/or conjugated metabolites to be expected in soybeans can be made until the analytical information requested above is submitted. Residues of pentachlorophenol would not be expected to exceed 0.1 ppm in soybeans under this use.

Petitioner's Response No. 42: The requested residue data for the metabolites, pentachlorophenol and 3-PCA, in/on soybeans are submitted within the present amendment.

Comments/Conclusions No. 44: We have previously said in Comments/Conclusions No. 39 that from the proposed use the expected residues of pentachlorophenol (0.05 ppm pentachlorophenol + <0.1 ppm DCVA + <0.05 ppm 3-PHA) on soybeans should not exceed a total 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-PHA metabolites are included.

Deficiency No. 45: The soybean processing study was found to be deficient in that: 1. The beans did not contain 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. 46: Within this amendment, the petitioner has submitted another soybean fractionation study. Fifty kg of harvested soybeans (with hulls) were fortified with 50 mg of Asphus 2A. 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.

Pentachlorophenol control values of <0.05 ppm were reported for refined oil and soapstock; all of the remaining fractions had pentachlorophenol control values of <0.1 ppm. DCVA control values of <0.1, <0.1, <0.1 and 0.0 ppm were reported for soybeans, hulls, meal and soapstock, respectively. No 3-PHA values for any of the fortified or unfortified fractions were reported because the chromatographic peak of this derivative coeluted with a large and non-reproducible interference peak. Pentachlorophenol and DCVA residue values for the fortified samples are given below:

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Pentachlorophenol ppm</th>
<th>DCVA, ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>with hulls</td>
<td>without hulls</td>
</tr>
<tr>
<td>Soybeans</td>
<td>0.35</td>
<td>0.37</td>
</tr>
<tr>
<td>Hulls</td>
<td>-</td>
<td>0.13</td>
</tr>
<tr>
<td>Meal</td>
<td>0.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Crude oil</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Refined oil</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Soapstock</td>
<td>&lt;0.05</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Analyses of cottonseed, hulls and meal samples certified with 0.67, 1.43 and 0.17 ppm DCHA, respectively, gave recoveries values of 94%, 96% and 76%.

Concentrations/Conclusions: No. 44: The fractionation study is inadequate in that the cottonseed meal were fortified only with non-steroidal metabolites were not a part of the fortification mixture. Therefore, the reported DCHA values are meaningless. For this study, fortification of a field treated cotton sample would have been more appropriate. The fractionation study needs to be revised; revision data should contain values for parathion, DCHA and 3-CBA. Deficiency No. 45 has not been resolved.

Deficiency No. 45: Since we concluded above that the metabolites cis- and trans-1-(2-chlorophenyl)-2-methylpropionyl acetate and 1-methyl-2-chloroethyl alcohol should be included in the tolerance regulations, we will need additional revision data for these non-steroidal forms of these metabolites in order to determine what levels are to be expected in cottonseed meal and cottonseed meal. In addition, a revision study using cottonseed containing non-steroidal pesticide residue of cotton seed and/or conjugated metabolites may be needed. If the additional revision data shows that, generally, the combined level of metabolite and/or nitrogen of 40 Brassicae in cottonseed or cottonseed meal is needed. It appears that higher tolerance levels for cottonseed meal and cottonseed may be needed when metabolites are included in the regulations.

Petitioner's Comments No. 44: IC is deferring a response on this time: Cottonseed have been deleted in the revised Section E.

Concentrations/Conclusions: No. 44: This deficiency is not at this time.

Deficiency No. 45: The food-additive tolerance for parathion in cottonseed has not been revised. Since cottonseed in this toxic bi-product are considered to be covered under a tolerance for each of these crops. This tolerance proposal should be withdrawn.

Petitioner's Comments No. 45: The proposal has been withdrawn.

Concentrations/Conclusions: No. 46: The deficiency is not at this time.

Deficiency No. 50: No final judgment can be made with respect to the levels of residues of parathion 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 section studies for cattle and chickens using parathion metabolites may be needed.

Petitioner's Comments No. 50: To be acted to on the above proposal.
Conclusions/Conclusions No. 5a: First, we refer the petitioner to the above
Conclusions/Conclusions No. 4a and 5a. Second, the petitioner should be
informed that the feeding study was carried out in a satisfactory manner,
but it was unfortunate that no analysis for the crystallized metabolites were
reported. The TLC studies clearly showed that the animal tissues
contained appreciable amounts of the metabolites, DCVA, 3-PHA and
3-phenoxypybenzoic 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-PHA and 3-phenoxypybenzoic acid) calculated as parent.

Deficiency No. 5a has not been resolved.

Deficiency No. 5b: The tolerance on milk should be proposed as X ppa in
milk fat reflecting Y ppa 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 extension. Within the present
amendment, ICI's revised Section F deletes all proposed tolerances for
animal products, tomatoes and tomato products.

Conclusions/Conclusions No. 5b: We refer the petitioner to the above
Conclusions/Conclusions nos. 2a, 2b, 4c and 5a. For plant commodities, a
revised Section F should include the parent compound plus the DCVA and
3-PHA metabolites. For future permethrin tolerances on animal
commodities, the revised Section F should include the parent compound plus
DCVA, 3-PHA and 3-phenoxypybenzoic 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.

Conclusions/Conclusions No. 6: This is a TOX question and RCB 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 Conclusions/Conclusions 2a, 2b, 2c, 2b, 2b, 4a, 4b, 4c, 5a, 5b
and 6. The petitioner should be so informed.