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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Partial Response (December 15, 1987) by Centre International d'Etudes du Lindane (CIEL) to Data Gap 171-4 [Magnitude of Residue in Animals (Dairy Cattle Meat and Milk)] as Identified in the Residue Chemistry Chapter of the September 30, 1985 Lindane Registration Standard (RCB No. 4037) - MRID Nos. 406605-00 and 406605-05

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and

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THRU: Charles L. Trichilo, Ph.D., Chief
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The law firm of McKenna, Conner, & Cuneo has submitted a partial response to Residue Chemistry (158.125) data gaps cited in the Lindane Registration Standard

(September 30, 1985) on behalf of its client, CIEL, the Centre International d'Etudes du Lindane [Rhone-Poulenc, Inc.; Celamerck GmbH & Company, KG and its U.S. affiliates, E.M. Industries Inc.; and Inquinosa (Qimocos de Noroeste SA Industries)]. The submission consists of a letter of transmittal dated June 9, 1988 from Charles A. O'Connor III of McKenna, Conner & Cuneo to Mr. George T. LaRocca, Product Manager 15, EPA/RD, listing four Magnitude of the Residue studies and a Freezer Storage Stability study including a complete study titled "Lindane Tissue and Milk Residue Study in Dairy Cows" conducted by Agrisearch Inc., Frederick, MD 21701, Project No. 1508 dated December 15, 1987.

In the transmittal letter, the registrant has expressed his concern regarding the results obtained from some of the Magnitude of the Residue studies as follows:

> Two of the above studies, specifically the residue studies in sheep and in dairy cows, indicate residues that exceed current tolerances. Accordingly, these studies possibly fall within the scope of FIFRA 6(a)(2), as described in EPA's 1985 FEDERAL REGISTER notice; 50 Fed. Reg. 38,115 (1985). We would like to discuss these findings with EPA in order to determine whether additional studies are in order, or whether revisions to the existing tolerances must be made.

Summary of Remaining Data Gaps Related to 171-4 - Magnitude of the Residue - Meat, Meat Byproducts, Fat, and Milk (Dairy Cattle)

Data gap 171-4 (Magnitude of the Residue - Meat and Milk - Dairy Cattle is not yet fulfilled.

- The spray and dip treatments impose no limit to the number of applications which can be made to livestock (cattle). A revised label is required which specifies the number of applications permitted and the interval between applications to cattle. The treatment rate should be supported by adequate residue data. This is a data gap.

- The nature of the residue in animals is not adequately understood. If animal metabolism studies reveal the presence of other residues of toxicological concern besides lindane per se, residue data will also be required for these residues.

- Available residue data from the submitted dairy cattle feeding/dipping study do not support the tolerance of 7 ppm for residues of lindane per se in the fat of dairy cattle. The data also indicated the need for lindane tolerances in the meat and meat byproducts (kidney, heart, and liver) and milk of dairy cattle. Appropriate meat (including meat byproducts) and milk tolerances for dairy cattle will also need to be established when the nature of the residue (ruminants) has been adequately delineated by the registrant.

Recommendations

DEB recommends that the registrant secure and retain his reserve tissue and milk samples obtained from the dairy cattle feeding/dipping study in the event that possible future reanalysis by appropriate analytical methodology to determine additional residues (metabolites) of toxicological concern is warranted based upon his satisfaction of DEB's and TB's response to all remaining deficiencies cited in DEB's C. Deyrup March 24, 1988 memorandum re: Lindane Data Gap 171-4 (Nature of the Residue in Livestock Ruminants). (Note: If the reserved samples are stored too long, they may not be supported by the present storage stability data. In this case, a new cattle feeding study would be needed.)

When all remaining 171-4 data gaps relative to magnitude of the residue in dairy cattle meat, meat byproducts, fat, and milk and ruminant metabolism have been satisfied the registrant should then repropose fat and establish meat, meat byproducts, and milk tolerances for dairy cattle to reflect both the nature and magnitude of the total toxic residues resulting from all proposed uses of lindane.

DEB also recommends that the registrant respond to all of DEB's comments/conclusions outlined below.

The data gaps associated with magnitude of the residue in dairy cattle meat, meat byproducts, fat, and milk after reviewing the present submission are discussed in detail under DEB's Comments/Conclusions below.

DEB's Comments/Conclusions Re: Magnitude of the Residue: Dairy Cattle Meat, Meat Byproducts, Fat, and Milk

1. In conjunction with the submitted dairy cattle feeding/dipping study, DEB reiterates the following

data gap in the Lindane Registration Standard (September 30, 1985):

> The spray and dip treatments impose no limit to the number of applications which can be made to livestock. A revised label is required which specifies the number of applications permitted and the interval between applications. The treatment rate should be supported by adequate residue data. This is a data gap.

The submitted dairy cattle feeding/dipping study employed two dipping treatments at a 1-week interval with a preslaughter interval of less than 1 day. If this treatment schedule supports the registrant's proposed use then the revised labels requested by DEB in the Lindane Registration Standard should also reflect this treatment schedule.

2. A frozen storage stability study for lindane residues in poultry and cattle (covering 2 through 9 or 12 months) has been submitted in a separate submission (see DEB's review of August 23, 1988). In the subject dairy cattle feeding and dipping study, tissue and organ samples were stored at -15 degrees C for 4 to 4 1/2 months and milk samples at -15 degrees C for 1 to 3 months. DEB concludes that the results of the registrant's currently submitted lindane storage stability data in milk (lindane recoveries of 87 and 90 percent from 1 or 5 ppm fortified controls stored at-15 degrees C for 2 and 9 months, respectively) and the preceding storage stability study for both animal tissues and milk support the residue data obtained for the parent compound lindane in the current study.

3. DEB concurs with the registrant that a consistent linear concentration dependence on lindane feeding levels and tissue and organ residue levels was observed. DEB does not concur with the registrant's statement, however, that there appears (with the exception of kidney) to be no increases in tissue or organ residue levels in cows that were dosed orally and dipped, over those that were only orally dosed. For example, DEB calculates that average lindane residue levels in both dairy cattle kidney and fat samples increased approximately 2X in animals exposed both (1X) orally and dermally as compared

to animals exposed (1X) orally only, which represents 0.7 and 21.6 ppm in the kidney and fat, respectively.

4. DEB concurs with the registrant that essentially a linear concentration dependence between lindane oral dose levels and the lindane residue levels found in milk was observed with residues plateauing at ca. 0.5 ppm (1X) approximately 7 days of treatment.

   Based on the submitted data DEB also calculates the ratio of lindane in milk/feed to be 2.7, 2.1, and 2.6 percent, respectively, at the 1X, 3X, and 10X feeding levels.

5. DEB has calculated that maximum lindane residue levels in milk increased approximately 3.6X to 1.37 and 1.26 ppm at study days 21 and 28, respectively, for animals exposed both (1X) orally and dermally as compared to animals exposed (1X) orally only.

6. DEB concludes that the current 7 ppm tolerance for residues of lindane per se in fat of dairy cattle is inadequate to support lindane residues (ca. 12 ppm) resulting from a 20 ppm (1X) feeding level or oral exposure only. Based on the results of these same 1X feeding levels, tolerances for lindane per se would also need to be proposed by the registrant for meat (muscle, ca. 1 ppm) and meat byproducts (kidney, ca. 0.5 ppm; heart, ca. 1.25 ppm; and liver, ca. 0.1 ppm). Provided the current lindane label is retained and revised to permit two dairy cattle dipping treatments at a 1-week interval followed by no preslaughter interval, then the tolerances proposed by the registrant for lindane per se reflecting oral exposure only in fat, meat (muscle), and meat byproducts (kidney and heart) will need to be increased by a factor of approximately 2X, 2X, 3X, and 2X, respectively.

7. Tolerances for residues of lindane per se in milk are needed to support maximum lindane residues (ca. 0.5 ppm) resulting from a 20 ppm (1X) feeding level or oral exposure only. Provided the current lindane label is retained and revised to permit two dairy cattle dipping treatments at a 1-week interval followed by no preslaughter interval, then the tolerance proposed by the registrant for lindane per se

in milk reflecting oral exposure only will need to be increased by a factor of approximately 3.6X.

8. DEB, however, cannot at the present time, arrive at any final conclusion regarding the adequacy of the submitted dairy cattle feeding/dipping study to establish appropriate animal commodity tolerances until all remaining deficiencies [see DEB's C. Deyrup March 24, 1988 memorandum re: Lindane Data Gap Section 171-4 (Nature of the Residue in Livestock Ruminants)] have been adequately addressed by the registrant, including the identity of unidentified ^{14}C residues in goat liver and kidney which are of concern to TB (see TB's J. Doherty May 19, 1988 memorandum re: Lindane: TB's Response to DEB Inquiry Concerning More Adequate Identification of Lindane Residues in Goat Liver and Kidney). If these ^{14}C residues (metabolites) once identified are then determined by TB to be of toxicological concern, then they would also need to be included in future tolerance expressions for animal commodities. Accordingly, the registrant should now secure and retain his reserve animal commodity samples obtained from the dairy cattle feeding/dipping study for possible future reanalysis by appropriate analytical methodology to determine these additional residues (metabolites) of toxicological concern (Note: If the reserved samples are stored too long, they may not be supported by the present storage stability data).

   An updated section of Table A containing the pertinent data requirements addressed in this submission is attached to this review.

Detailed Considerations

Pertinent data gaps cited in the Registration Standard will be restated below followed by CIEL's response.

158.125 Residue Chemistry

171-4 - Magnitude of the Residue - Meat (Includes Meat, Fat, and Meat Byproducts)

The following additional data are required:

- Available residue data do not support the tolerance of 7 ppm for residues of lindane in the fat from

cattle, goats, horses, and sheep and 4 ppm in the fat from hogs because much of the data were generated by questionable or unspecified methods and most of the studies did not specify the conditions under which the samples were stored or give the duration of the storage period before analysis. Residue data using adequate methodology must be submitted for residues of lindane in animal fat resulting from the various methods of application and at appropriate dosages. Unless the requested animal metabolism studies establish the absence or radioactive residues in other tissues, residue data on meat and meat byproducts are needed in order to establish tolerances on these commodities for residues of parent lindane. If animal metabolism studies reveal the presence of other residues of toxicological concern besides parent lindane, residue data will also be required for these residues.

- The results of previous studies indicating the presence of lindane residues in cattle fat following spray application of 0.075% lindane but not after application of 0.03% lindane need to be verified. The spray and dip treatments impose no limit to the number of applications permitted and the interval between applications. A revised label is required which specifies the number of applications permitted and the interval between applications. The treatment rate should be supported by adequate residue data. Preslaughter intervals of 30 days are imposed following spray treatment and 60 days following dip treatment. Preslaughter intervals greater than 3 days are not practical since animals may not be sent to slaughter over an extended period of time, and, if sold, the pesticidal history of the animals may not be known to the new owner. Residue data reflecting preslaughter intervals of 3 days or less are required for spray and dip applications.

- No tolerance has been established for residues of lindane in milk. Available residue data on the 3% pressurized spray for the spot treatment of screwworms indicate that lindane residues are detected in milk up to 29 days after a second treatment and 24 days after a single treatment. A tolerance for lindane residues in milk will have to be established unless revised labeling is submitted for this type of product that prohibits use on lactating dairy animals. Dairy cattle and dairy goats may be exposed to lindane by several direct or indirect methods;

therefore, a tolerance level for lindane residues in milk, based on adequate residue data, must be proposed. This proposed tolerance should be high enough to include residues arising from ingestion as well as dermal treatments applicable to dairy cattle and goats (i.e., pressurized spray treatment and animal sponge treatment, dust treatment, and dust bag, back rubber or rubbing post applications). Alternatively, labeling bearing restrictions against any method of application to lactating dairy animals (cattle and goats) should be submitted. However, since it is not possible for the Agency to estimate the lindane dietary burden imposed upon livestock until the required residue data on crops and feed items have been submitted and reviewed, a tolerance for residues of lindane in milk may have to be established based upon dietary intake, even if all direct applications were prohibited. Labeling for all lindane end-use products with directions for use on livestock premises or farm buildings must bear a prohibition against application in dairy barns.

CIEL's Response

The registrant has submitted a dairy cattle feeding/dipping study in which lindane residues only were determined in tissues and milk following both oral and dermal dosing with lindane.

Partial Summary of Study

". . . Thirteen milking Holstein cows were acclimated to the Agrisearch facilities for two weeks during which time the cows were shown to be healthy and in good milk production. The cows were assigned to the four groups (4 cows/treatment group plus 1 control) to provide comparable milk production between groups. Dose levels were 0 ppm, 20 ppm, 60 ppm, and 200 ppm. The daily dose was given to each cow by gelatin capsule after the am milking. Milk subsamples were collected for analysis on days 0, 1, 3, 7, 14, 21, 25, and 28. The pm milk was kept separate from the following am milk. Three cows from each treatment group were run through a dip tank containing Prentox 20% EC at a lindane concentration of approximately 0.06% a.i. on days 21 and 28 of the study period. Tissue samples were taken from each cow after sacrifice by exsanguination. All samples were immediately frozen on dry ice and analyzed for lindane residues by validated AOAC Multiresidue GLC methodology with electron capture detection . . . ."

Sample Collection and Preparation

". . . Each cow was milked twice daily at approximately 5:00 am and at 4:30 pm. A single milk pail milker was assigned to the cows in each dose level to eliminate cross contamination between dose groups. Milk production records (lbs) were maintained for each milking during the acclimation and dosing periods.

"Milk samples (one 1 liter sample and one 0.5 liter sample) were taken from each cow on dose days 0 (before dosing), 1, 3, 7, 14, 21, 25, and 28. Milk samples from each cow were taken from the pm milking and from the following am milking and were frozen separately. All milk samples were stored frozen at -15 degrees C prior to analysis.

"Necropsy was performed after sacrifice by exsanguination at the Mt. Airy Locker plant, Mt. Airy, Maryland. Animals were sacrificed in sequence from control to low dose to mid dose to high dose cows to minimize potential contamination between animals. The non-dip animals were necropsied first for the cows within a dose group. Sacrifices occurred 20 hours after administering the 28 day doses. The following tissues were excised, placed on dry ice, and stored frozen at -15 degrees C (by group) until analysis: liver, kidneys, heart, composite of leg and loin muscle, and a composite of omental and peripheral fat.

"Samples were stored frozen at -15 degrees C until analysis. Milk samples were stored from 30 to 79 days and tissue and organ samples were stored 120 to 142 days. Dose check samples were stored from 137 to 203 days prior to analysis.

"All milk subsamples were allowed to thaw and were homogenized by shaking, where 10 or 20 g aliquots were taken for analysis. All tissue and organ samples were ground on dry ice using a Hobart food chopper or Wiley Mill. Ground tissue samples were placed in the freezer until all dry ice had sublimed, where 10 g samples were weighed out for analysis . . . ."

Sample Analysis/Validation

For each animal, results of analysis for lindane residues in the five analyzed tissues (liver, heart, kidney, muscle, and fat) and milk obtained at each sampling and at each dose level were summarized by the registrant. None of the reported residue values were corrected for controls or for average recovery values.

The overall recovery of lindane from fresh spiked control samples that were carried through the laboratory with treated samples averaged 88.8 percent for milk (0.001 to 10.0 ppm spikes) and 103.2 percent for tissue and organs (0.01 to 20.0 ppm spike).

DEB's Comments/Conclusions re: Conduct of Study

The overall conduct of the registrant's submitted dairy cattle feeding/dipping study generally conforms to the suggestions made by DEB in a meeting with the registrant following the issuance of the September 30, 1985 Lindane Registration Standard (see February 10, 1986 memorandum of R. Perfetti). In that memorandum RCB (DEB) suggested the following relative to the animal feeding studies:

6. In the case of feeding studies, three animals at three dose levels should be used.

7. The animals in the feeding studies above should receive both oral and dermal medications with lindane. The dermal treatments should reflect maximum concentrations and the maximum number of dips expected in actual use.

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9. Dipping of the animals will suffice for requirements for experiments with other forms of treatment.

10. As far as the oral doses are concerned, the levels for the lowest dose could be calculated from theoretical dry-down factors for grape and apple pomace.

11. In the dip/oral dosing experiments it will be acceptable to perform the last dip of the animals, then continue to feed them labeled lindane for 3 days, and finally sacrifice them within 24 hours of the last oral dose (within 3 days of the last dip).

The aforementioned suggestions were reemphasized in part by DEB (RCB) in its C. Deyrup March 24, 1986 protocol review

re: a lindane dermal application metabolism study, as follows:

"RCB agrees that the dip application would represent the worst case for dermal application and recommends that the dip application would be adequate for the purpose of assessing the levels of residues arising in animal commodities from dermal treatment.

"The registrant proposes to sacrifice the animals 48 hours after the second application. Generally, RCB recommends that animals be sacrificed within 24 hours after the last treatment. Several studies cited by the Lindane Registration Standard indicate that higher residue levels of lindane in milk were observed 24 hours after spraying than 48 hours after spraying. Therefore, the registrant will need to slaughter his animals 24 hours after treatment, instead of 48 hours after treatment."

In regard to Item 10 of the February 10, 1986 R. Perfetti memorandum, the registrant's calculated level for the lowest dietary dose was based on theoretical dry-down factors for apples, grapes, and tomatoes since these commodities appear to contribute the most to the dietary burden of lindane. These values were calculated for the dairy cattle diet as follows:

RAC	Tolerance (ppm)	Dry-Down Factor (Pomace)	ppm in Pomace	Percent in Diet (Dairy Cattle)	Lindane in Diet (ppm) (Dairy Cattle)
Apple	1.0	8	8	25	2.0
Grape	1.0	4.3	4.3	20	0.86
Tomato	3.0	20	60	25	15.0
					17.86

1X feeding level or dairy cattle = 20 ppm since exposure of beef cattle from same dietary sources = 20.29 ppm.

Since it is unlikely that dairy cattle would receive a ration consisting of all pomace, DEB concludes that the calculated dietary exposure for dairy cattle would represent a theoretical worst-case situation.

In regard to Item 11 of the R. Perfetti February 10, 1986 memorandum, animals were not fed for 3 days beyond the last dipping treatment and then sacrificed within 24 hours of the last oral dose. In the submitted experiment all animals were

sacrificed within 20 hours of the last dose and/or dipping treatment. DEB has no objection to the protocol utilized in the submitted study, although it deviates somewhat from the original protocol suggested by DEB.

In conjunction with the submitted dairy cattle feeding/dipping study, DEB reiterates the following data gap cited in the Lindane Registration Standard (September 30, 1985):

> 2) The spray and dip treatments impose no limit to the number of applications which can be made to livestock. A revised label is required which specifies the number of applications permitted and the interval between applications. The treatment rate should be supported by adequate residue data. This is a data gap.

The submitted dairy cattle feeding/dipping study employed two dipping treatments at a 1-week interval with a preslaughter interval of less than 1 day. If this treatment schedule supports the registrant's proposed use then the revised labels requested by DEB in the Lindane Registration Standard should also reflect this treatment schedule.

Results of Tissue Residue Analysis in Dairy Cattle Using Lindane

All tissue and organ samples were stored frozen at -15 degrees C for 120 to 142 days from time of animal slaughter to time of analysis.

Lindane residue values discussed below were not corrected for control tissue background or average recovery values of concurrently fortified controls which were respectively reported for liver, heart, kidney, muscle, and fat as (0.009 ppm/102.3%); (0.005 ppm/106.0%); (0.012 ppm/103.0%); (0.007 ppm/91.7%); and (0.005 ppm/113.0%).

Representative gas chromotograms were submitted for only treated fat and liver samples.

Lindane residues were reported in dairy cattle tissues as a result of all treatments and treatment levels as follows:

1. Feeding (Oral Exposure)

   Liver

   Residues at the 20 ppm (1X), 60 ppm (3X), and 200 ppm (10X) feeding levels were 0.10, 0.19, and 0.72 ppm, respectively.

   Heart

   Residues at the 1X, 3X, and 10X feeding levels were 1.23, 1.56, and 10.3 ppm, respectively.

   Kidney

   Residues at the 1X, 3X, and 10X feeding levels were 0.34, 1.07, and 4.57 ppm, respectively.

   Muscle

   Residues at the 1X, 3X, and 10X feeding levels were 0.97, 1.80, and 8.75 ppm, respectively.

   Fat

   Residues at the 1X, 3X, and 10X feeding levels were 11.9, 20.2, and 158.1 ppm, respectively.

2. Feeding and Dipping (Oral and Dermal Exposure)

   Liver

   Total maximum (average) residues following two dipping treatments at a 1-week interval with simultaneous feeding at the 20 ppm (1X), 60 ppm (3X), and 200 ppm (10X) levels were 0.12 (0.09); 0.23 (0.14); and 1.15 (0.74) ppm, respectively.

   Heart

   Total maximum (average) residues following dipping treatments and feeding at the 1X, 3X, and 10X levels were 2.70 (1.65); 2.99 (2.05); and 11.21 (7.92) ppm, respectively.

Kidney

Total maximum (average) residues following dipping treatments and feeding at the 1X, 3X, and 10X levels were 1.06 (0.70); 1.51 (1.24); and 10.10 (8.62) ppm, respectively.

Muscle

Total maximum (average) residues following dipping treatments and feeding at the 1X, 3X, and 10X levels were 1.33 (1.10); 2.32 (1.76); and 5.73 (4.85) ppm, respectively.

Fat

Total maximum (average) residues following dipping treatments and feeding at the 1X, 3X, and 10X levels were 24.3 (21.6); 47.8 (41.6); and 158.0 (133.1) ppm, respectively.

		Total (Average) Lindane Residues (ppm) Resulting From:	
Matrix	Feeding Level	Feeding	Feeding and Dipping
Fat	1X	11.9	21.6
	3X	20.2	41.6
	10X	158.1	133.1
Muscle	1X	0.97	1.10
	3X	1.80	1.76
	10X	8.75	4.85
Kidney	1X	0.34	0.70
	3X	1.07	1.24
	10X	4.57	8.62
Heart	1X	1.23	1.65
	3X	1.56	2.05
	10X	10.3	7.92
Liver	1X	0.10	0.09
	3X	0.19	0.14
	10X	0.72	0.74

The registrant summarizes the reported lindane residue data in dairy cattle tissue as follows:

> There appeared to be no increases in tissue or organ residue levels in the cows that were dosed orally and dipped, over those that were only orally dosed. The only exception was that kidney residue levels were consistently higher for the dipped cows at all dose levels. In general, fat and fatty tissues contained the highest residues, and the liver contained the lowest residues (< 1.7 ppm for the 200 ppm dose level animals). There was a consistent relationship between lindane dose level (oral) and tissue and organ residue levels . . .

Results of Milk Residue Analysis in Dairy Cattle Using Lindane

All milk samples were stored frozen at -15 degrees C for 30 to 79 days from collection to time of analysis. The registrant has provided validation data indicating milk storage recoveries at -15 degrees C of (75-96%) X = 87 percent at 64 days and (83-98%) X = 90 percent at 265 days. All milk samples were fortified with lindane at either 1 or 5 ppm. Representative gas chromatograms were submitted for treated milk samples.

1. Feeding (Oral Exposure)

   Total lindane residues in milk at the 20, 60, and 200 ppm feeding level and at 7, 14, 21, 25, and 28 days of treatment were (0.47, 1.08, 5.20), (0.17, 0.75, 3.12), (0.19, 1.02, 7.08), (0.31, 1.19, 5.49), and (1.10, 1.90, 10.81 ppm), respectively. Control values were all reported as < 0.001 ppm and sample recoveries were (48.0-142.0%) X = 88.8 percent.

2. Feeding and Dipping (Oral and Dermal Exposure)

   Total maximum (average) lindane residues in milk following two dipping treatments at a 1-week interval (days 21 and 28) at a 20, 60, and 200 ppm feeding

level and sampled at 1, 3, 7, 14, 21, 25, 28, and 29 days of treatment were as follows:

	Lindane Residue Levels in Milk (ppm)		
Study Day	1X (20 ppm)	3X (60 ppm)	10X (200 ppm
1	0.18 (0.11)	0.81 (0.69)	2.92 (2.58)
3	0.36 (0.25)	1.67 (1.46)	6.11 (4.09)
7	0.50 (0.38)	3.05 (1.82)	4.46 (3.53)
14	0.38 (0.24)	1.79 (1.31)	3.12 (3.03)
21*	1.37 (1.12)	5.49 (4.41)	10.17 (10.10)
25	0.35 (0.32)	1.96 (1.16)	6.76 (5.89)
28*	1.26 (1.10)	3.23 (2.55)	16.97 (14.97)
29	0.68 (0.59)	4.75 (2.99)	12.71 (9.59)

*Cows dipped approximately 12 hours prior to milk collection on these days.

The registrant summarizes the reported lindane residue data in dairy cattle milk as follows:

> Lindane residue levels in milk appeared to be at a plateau level by day seven for all cows . . . . However, immediately after the cows were dipped in the 0.06% a.i. lindane solution, residue levels in milk increased substantially. The milking on day 25, three days post dip, returned to the levels measured prior to dipping the animals. . . Cows that were orally dosed and not dipped showed an increase in milk residue . . . immediately after the other cows were dipped, apparently due to common housing of the cows. However, the increase was much lower than found in the cows that were actually dipped. There was a good relationship between lindane oral dose levels and the lindane residue levels found in milk . . . .

DEB's Comments/Conclusions re: Results of Study

1. Tissue Residues

DEB concurs with the registrant that a consistent linear concentration dependence on lindane feeding level and tissue and organ residue levels was observed. DEB does not concur with the registrant's statement, however, that there appeared (with the

exception of kidney) to be no increase in tissue or organ residue levels in cows that were dosed orally and dipped over those that were only orally dosed. For example, DEB calculates that average lindane residue levels in both dairy cattle kidney and fat samples increased approximately 2X in animals exposed both (1X) orally and dermally as compared to animals exposed (1X) orally only, which represents 0.70 and 21.6 pm in the kidney and fat, respectively.

2. Milk

DEB concurs with the registrant that essentially a linear concentration dependence between lindane oral dose levels and the lindane residue levels found in milk was observed with residues plateauing at ca. 0.5 ppm (1X) at approximately 7 days of treatment.

Based on the submitted data, DEB calculates the ratio of lindane in milk/feed to be 2.7, 2.1, and 2.6 percent, respectively, at the 1X, 3X, and 10X feeding levels. Saha, J.G., Res. Rev. 26, 86-126 (1969), as cited in the Residue Chemistry Chapter of the September 30, 1985 Lindane Registration Standard, reported the ratio of lindane residue levels in milk to ppm residue in the feed as 0.04 to 1.

As reported by the registrant, dipping of cows in a 0.06-percent ai lindane solution substantially increased lindane residue levels in milk as compared to nondipped animals. Three days postdipping, residue levels in milk generally declined to predip (14-day) levels at the 1X feeding level. For example, following each dip (+ 12 hours) maximum lindane residue levels in milk increased approximately 3.6X to 1.37 and 1.26 ppm at study days 21 and 28, respectively.

3. Tolerance Considerations

DEB concludes that the registrant has provided storage stability data (see DEB's review of August 23, 1988) that support the residue data obtained for the parent compound lindane.

DEB concludes that the current 7 ppm tolerance for residues of lindane per se in fat of dairy cattle is inadequate to support lindane residues (ca. 12 ppm) resulting from a 20 ppm (1X) feeding level or oral exposure only. Based on the results of these same 1X

feeding levels, tolerances for lindane per se would also need to be proposed by the registrant for meat (muscle, ca. 1 ppm) and meat byproducts (kidney, ca. 0.5 ppm heart ca. 1.25 ppm and liver, ca. 0.1 ppm). Provided the current lindane label is retained and revised to permit two dairy cattle dipping treatments at a 1-week interval followed by no preslaughter interval, then the tolerances proposed by the registrant for lindane per se reflecting oral exposure only in fat, meat (muscle), and meat byproducts (kidney and heart), will need to be increased by a factor of approximately 2X, 2X, 3X, and 2X, respectively.

Tolerances for residues of lindane per se in milk are needed to support maximum lindane residues (ca. 0.5 ppm) resulting from a 20 ppm (1X) feeding level or oral exposure only. Provided the current lindane label is retained and revised to permit two dairy cattle dipping treatments at a 1-week interval followed by no preslaughter interval, then the tolerance proposed by the registrant for lindane per se in milk reflecting oral exposure only will need to be increased by a factor of approximately 3.6X.

DEB, however, cannot at the present time, arrive at any final conclusion regarding the adequacy of the submitted dairy cattle feeding/dipping study to establish appropriate animal commodity tolerances until all remaining deficiencies [see DEB's C. Deyrup March 24, 1988 memorandum re: Lindane Data Gap Section 171-4 (Nature of the Residue in Livestock Ruminants)] have been adequately addressed by the registrant including the identity of identified ^{14}C residues in goat liver and kidney which are of concern to TB (see TB's J. Doherty May 19, 1988 memorandum re: Lindane: TB's Response to DEB Inquiry Concerning More Adequate Identification of Lindane Residues in Goat Liver and Kidney). If these ^{14}C residues (metabolites), once identified, are then determined by TB to be of toxicological concern, then they would also need to be included in future tolerance expressions for animal commodities. Accordingly, the registrant should now secure and retain his reserve animal commodity samples obtained from the dairy cattle feeding/dipping study for possible future reanalysis by appropriate analytical methodology to determine these additional residues (metabolites) of toxicological concern (Note: If the

reserved samples are stored too long, they may not be supported by the present storage stability data).

Attachment

cc: Reviewer (M. Kovacs), TOX, Registration Standard (Lindane), RF, SF (Lindane), Circulation (7), E. Eldredge (ISB/PMSD), A. Rispin - EFCD

TS-769C:DEB:M. Kovacs:CM#2:Rm 810:557-7689:Typist KENCO, edited by:vg:9/19/88

RDI:J.H. Onley - 9/13/88:R.D. Schmitt - 9/13/88

Attachment
[DEB #4037; MRID Nos. 406605-00 and -05]

Table A
Generic Data Requirements for Lindane

Data Requirements	Composition[1/]	Does EPA Have Data to Satisfy This Requirement?	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?	Timeframe For Data Submission[2/]
158.125 Residue Chemistry					
171-4 - Magnitude of the Residue - Residue Studies [8,9,10/] (cont'd)					
- Meat (includes meat, fat, and meat byproducts)	TGAI and Plant Metabolites	Partially	00045126 00088165 00089592 00101478 00118724 00118725 MRID No. 406605-05	Yes[108/]	18 Months
- Milk	TGAI and Plant Metabolites	Partially	00104441 00025685 00075989 00088048 00118722 00118723 00118725 00118739 00098785 GS0315009 GS0315010 MRID No. 406605-05	Yes[109/]	18 Months
- Poultry and Eggs	TGAI and Plant Metabolites	No	-	Yes[110/]	18 Months

158.125 Residue Chemistry Footnotes (cont'd)

106/A food additive tolerance will not be necessary for refined sunflower oil from second generation sunflower seed, if it is established that sunflower oil is always deodorized and/or hydrogenated during the refining process. It has been shown that residues of lindane do not survive the hydrogenation or deodorization step in the refinement of oil. If the required plant metabolism studies indicate the presence of other residues besides parent, and if significant levels of these metabolites are found in second generation sunflower seed, then a processing study will be required to determine if these residues concentrate in processed commodities.

107/The use of lindane on tobacco does not require a tolerance or an exemption from tolerance, but data are needed to assess the exposure to residues resulting from the use of lindane. There are no lindane residue data on tobacco which reflect the present uses. Residue data from field trials in Kentucky/Virginia/Tennessee, and Georgia/North Carolina/South Carolina are required. Residue data reflecting application of the EC formulations should be included, as residues would be expected to be higher from that type of formulation. Since tobacco plants can be subjected to both foliar and transplant water treatment, residue data reflecting both foliar and transplant treatment at the maximum application rates are needed. If use is limited to foliar or transplant treatment (rather than both), revised labeling with this restriction must be submitted. A residue profile on tobacco smoke is also required. If residues of 0.1 ppm or more are found on green freshly harvested tobacco, pyrolysis products from the active ingredient must be characterized. The total number of foliar applications and the interval between application should be specified in a revised label.

108/ALL METHODS OF APPLICATION TO LIVESTOCK

Available residue data do not support the tolerance of 7 ppm for residues of lindane in the fat from cattle, goats, horses, and sheep and 4 ppm in the fat from hogs because much of the data were generated by questionable or unspecified methods and most of the studies did not specify the conditions under which the samples were stored or give the duration of the storage period before analysis. Residue data using adequate methodology must be submitted for residues of lindane in animal fat resulting from the various methods of application and at appropriate dosages. Unless the requested animal metabolism studies establish the absence or presence of other residues of toxicological concern besides parent lindane, residue data will also be required for these residues.

SPRAYS AND DIPS

The results of previous studies indicating the presence of lindane residues in cattle fat following spray application of 0.075% lindane but not after application of 0.03% lindane need to be verified. The spray and dip treatments impose no limit to the number of applications which can be made to livestock. A revised label treatment rate should be supported by adequate residue data. Preslaughter intervals of 30 days are imposed following spray treatment and 60 days following dip treatment. Preslaughter intervals greater than 3 days are not practical since animals may be sent to slaughter over an extended period of time, and, if sold, the pesticidal history of the animals may not be known to the new owner. Residue data reflecting preslaughter intervals of 3 days or less are required for spray and dip applications.

158.125 Residue Chemistry Footnotes (cont'd)

The current use permits the spraying and dipping of hogs. No residue data are available for the dipping of hogs, but some of the available data on cattle indicate that residues resulting from dipping could be higher than from spray treatment. Residue data reflecting analyses of fat tissue from hogs which have been dipped at the maximum application rate are required.

Available data indicate that unshorn lambs have much higher residues in the fat after dipping than shorn sheep. More residue data on unshorn lambs and sheep reflecting the maximum treatment rate are required to support the tolerance.

Since dips and sprays may be formulated with toxaphene, labeling must include the more stringent precautions and restrictions associated with each of the pesticide components involved in a combination product.

PRESSURIZED SPRAYS

No residue data are available for the residue levels of lindane in livestock fat following spot treatment for screwworms with the 3% lindane pressurized spray. No preslaughter interval is imposed following pressurized spray application. Residue data reflecting use of the 3% pressurized lindane spray are required to support the tolerance. Fat samples reflecting various preslaughter intervals (including a 0-day preslaughter interval) should be analyzed so that the buildup and decay of lindane residues as a function of time after treatment can be evaluated. The number of 3% lindane pressurized spray applications for the spot treatment of screwworm-infested livestock is not specified. Revised label is required which specifies the number of applications permitted. The treatment rate should be supported by adequate residue data.

SPONGE TREATMENT

Although there are no residue data for animal sponge treatment, the requested residue data for the use of the pressurized spray treatment for the spot treatment of screw-worms would cover residues arising from this application. The total number of application for this use should be specified in a revised label. In order to extrapolate from the requested residue data on the 3% lindane pressurized spray, the dosage for the animal sponge treatment in terms of percent lindane is required.