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

MAR 24 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Partial Response (7/21/87) by Centre International d'Etudes du Lindane (CIEL) to Data Gap §171-4 (Nature of the Residue in Livestock Ruminants) as Identified in the Residue Chemistry Chapter of the 9/30/85 Lindane Registration Standard. (RCB #3312) MRID No. 402713-02.

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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 (9/30/85) on behalf of its client, CIEL, the Centre International d'Etudes du Lindane [Rhone-Poulenc, Inc.; Celamerck GmbH & Co., KG and its US affiliate, E.M. Industries Inc.; and Inquinosa (Qimocos de Noroeste SA Industries)]. The submission consists of a cover letter from C.A. O'Connor (McKenna, Conner, and Cuneo) and a radiolabeled goat metabolism study, "Metabolism Study of ^{14}C-Lindane Fed or Topically applied to Lactating Goats."

Summary of Remaining Data Gaps, re: 171-4-Ruminant Metabolism

Data Gap 171-4 (Ruminant Metabolism) is not yet fulfilled.

- The registrant needs to verify the dosages used in the oral goat metabolism study, submit the raw radiometric data for all the various fractions, matrix samples, and identified metabolites, explain inconsistencies in some of the reported residue levels, confirm the identities of the residues found in the studies, and furnish additional chromatograms and recovery data for the expected metabolites from additional goat matrices.

- The nature of the residue is not adequately understood. Virtually none of the residues in the liver of the goat dosed at the 10X rate has been identified, even though the radioactivity residue level in this sample was almost 20 ppm lindane equivalents. Unless TOX is not concerned about unidentified residues in the liver and kidney of ruminants, the registrant will need to submit a more complete characterization of the TRR in these matrices. There is currently no way to detect residues of potential toxicological concern in liver, even when radioassay indicates that residue levels far exceed the established tolerance (7 ppm in goat fat; no tolerances for other ruminant tissues).

Recommendations

RCB recommends that the Registrant proceed with satisfying those requirements relating to the ruminant feeding study (see Footnotes 108 and 109 of the September 1985 Guidance for the Reregistration of Pesticide Products containing Lindane as the Active Ingredient) only after TOX has responded to RCB's deference (RCB's Comments/ Conclusions #5) below and after he has responded to all RCB's Comments/Conclusions outlined below.

The data gaps associated with ruminant metabolism are discussed in detail under RCB's Comments/Conclusions below.

RCB's Comments/Conclusions, re: Ruminant Metabolism

1. On page 3 of ADC Project #957A, the petitioner describes the treatment regimen as: "For each dose, an aliquot (goat 1, 100 ul; goat 2, 100 ul; goat 3, 797 ul) of the dosing solution equivalent to 50.2 mg lindane (20.1 ppm) for the 1X goats (2 goats) and 400 mg (200 ppm) for the 10X goat was added to a gelatin capsule... two-thirds filled with cornmeal." The goats were dosed twice daily (8 doses total). Assuming an intake of 2000-2500 g per day, it seems to RCB that this dosage is equivalent to a 2X rate, if each capsule contained 50.2 mg lindane, and the goats received 2 capsules daily. The petitioner will need to verify the dosages used in the oral metabolism study.

2. The petitioner needs to submit the raw radiometric data for all the various fractions, zones corresponding to identified metabolites, and matrix samples so that RCB can verify the % of the TRR which has been identified.

3. The registrant has identified 10 metabolites in goat tissues and milk. The identity of lindane and these metabolites should be confirmed (e.g., with GC/MS) so that TOX can determine whether any of the residues are of especial toxicological concern.

4. According to Table 15 (ADC Project 957C) 25.5% of the TRR in kidney was extractable with hexane, whereas 34.9% of the TRR was extractable according to Table 3 of the same project. The registrant will need to explain this difference.

5. The nature of the residue is not adequately understood. Only 4.5-7.0% of the TRR in kidney has been identified; virtually none (0.3-0.7% of the TRR) of the residues in the liver of the goat dosed at the 10X rate has been identified, even though the radioactivity residue level in this sample was almost 20 ppm lindane equivalents. Unless TOX is not concerned about unidentified residues in the liver and kidney of ruminants, the registrant will need to submit a more complete characterization of the TRR.

6. There is currently no way to detect residues of potential toxicological concern in liver, even when radioassay indicates that residue levels far exceed the established tolerance (7 ppm in goat fat; no tolerances in other ruminant tissues).

7. Only those residues partitioning into organic solvents were characterized, although a major portion of the TRR of liver and kidney remained in the aqueous phase. Radioactive residues in the aqueous phase also need to be identified.

8. GLC was used to identify tissue residues; in the case of liver, such a high background was obtained with control samples that any identifications based on this technique might be questionable. It seems to RCB that the use of GC/MS or thermospray/MS could be useful.

9. The petitioner has submitted recovery data of various metabolites from fat. Corresponding recovery data from muscle, kidney, liver, and milk should also be submitted.

10. Considering the complexity of the chromatograms submitted to demonstrate the presence of the metabolite 1,3,5-trichlorobenzene in liver, the petitioner will need to submit the corresponding chromatograms demonstrating the presence of lindane in the livers of 10X dosed goats and dermally treated goats and provide the recovery of lindane from liver.

11. The registrant relied upon GLC to identify residues because

the radioactivity was lost from the plates through volatilization. One audioradiograph of a liver extract and various standards was submitted, but the labels on the audioradiograph are indecipherable (Figure 1, Project ADC 957C). The registrant will need to submit a more clearly labeled audioradiograph and should specify whether the liver extract used had been subjected to hydrolysis or not. If any useful radiographs of hydrolyzed liver extracts were obtained, they should be submitted.

12. Ethereal extracts of milk were concentrated on a rotatory evaporator at ambient temperature. The petitioner has submitted data that indicate that the loss of activity in concentrating hexane fractions in Kuderna-Danish evaporators is minimal; corresponding data should be submitted for the rotatory evaporator step.

13. The total ^{14}C-residue levels reported in milk in Table 1 of Ref No. 87/BHL/349/AG (ASD No.:87/239-The Analysis of Milk from Goats Orally and Topically Dosed with Lindane from ADC Projects #957A and #957B) appear to differ from the residue levels reported in Table III (ADC Project #957A) and Table III (ADC Project #957B). For instance, the residue level in Sample No. 1x-02-07 is reported as 0.4788 ppm in ADC Project #957A and as 0.190 ppm in Ref No. 87/BHL/349/AG. The petitioner will need to explain the differences in residue levels reported for the same sample in different reports.

14. The registrant has submitted a review of metabolites identified in various animal studies, most of which used rats and has identified several residues in goat urine. RCB cannot extrapolate from these data to residues expected to arise in ruminant kidney and liver. Information in RCB's files indicate that metabolites detected in urine may not have been subjected to the influence of intestinal micro-organisms and that tissue may contain metabolites which are poorly degraded and may tend to accumulate. In fact, the submitted study indicates that residues do accumulate in liver; radioactive residues in liver were about 37-55 times higher in the liver than in muscle from goats fed lindane.

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

Note to PM: TOX should be informed that RCB is deferring to TOX on the need to identify residues concentrating in liver and kidney.

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: Nature of the residue (Metabolism)

Ruminants

The following additional data are required:

- "Animal metabolism studies are required to identify the residues of parent lindane and all metabolites in both a lactating ruminant (meat and milk) and poultry (meat and eggs). The lactating ruminant study must employ ^{14}C-labeled lindane with a feeding level high enough for identification of the radioactive residues in tissues and milk. The test animals must be dosed for at least 3 consecutive days at this level. Since lindane may also be applied as a livestock dip, the test animals must also be dipped in ^{14}C-labeled lindane, in order to reflect both modes of exposure. If the required plant metabolism studies result in the identification of a metabolite that is not found in animals, then an additional ruminant metabolism study that involves dosing with this metabolite will be required...."

CIEL's Response

The petitioner has submitted goat metabolism studies reflecting oral and dermal dosing of the animals.

Dermal Application Protocol

In its memo of 3/24/86, RCB had concluded that a patch or spray application could substitute for a study using a dip application (memo of C. Deyrup). Two studies were carried out. In the first study, the goat's back was shaved (area: approximately 90 sq. in.), and the ^{14}C-lindane 27.5% EC formulation was diluted with water and radioassayed. Two applications, one week apart, were administered to the shaved area; the dosages consisted of 113.3 mg per application. The petitioner explains that a typical dosage for a cow would be 1-2 gallons of a 0.06% lindane solution or 4.54 grams per dose. Since a goat weighs about 1/10 as much as a cow, the corresponding dose for a goat would be 0.45 g/dose. But since only about 1/4 of the animal will be treated, only 1/4 of the label dose, or 113.5 mg of lindane would be used for each application. The goat was slaughtered 48 hours after the second application.

The protocol of the second topical application study reflected RCB's suggestions that the goat be sacrificed within 24 hours of the second dose and that the application rate reflect at least a 1X rate (memo C. Deyrup, 6/12/86). For this study, the treatment area was about 272 sq. in. Instead of shaving the treatment area, the region was clipped so that a stubble about 1/8 inch long remained. The treatment consisted of two doses consisting of about 454 mg for

each dose. Two treatments were applied with a one week treatment interval.

The goats were milked morning and evening; the AM and PM samples were kept separate for analysis. A sample of milk from each goat was separated into skim milk and milkfat by centrifugation.

Urine and feces were also collected.

Because accountability of the administered dose was low for the 0.25X study (16.5%), in the second study, the goat was monitored for volatiles. After each of the doses, the goat was placed in an individual respiration chamber for 8 hours. About 0.1% of the air from the chamber was pumped through an oxidizer with two CO_2 collection traps. Less than 0.1% of the applied dose was recovered as volatiles; so in vitro hide studies were carried out. ^{14}C-Lindane was applied to the shaved skin from a freshly killed steer. The hide was placed on the bottom plate of a small desiccator maintained at 39°C so that the bottom of the hide was in contact with sterile physiological saline. The system was flushed with oxygen, and the effluent was passed through an oxidizer with two traps. The saline, hide, and trapped volatiles were radioassayed after 5, 8, and 24 hours. One run included an Amberlite XAD-2 trap.

Oral Dosing Protocol

The petitioner states, "For each dose, an aliquot (goat 1, 100 ul; goat 2, 100 ul; goat 3, 797 ul) of the dosing solution equivalent to 50.2 mg lindane (20.1 ppm) for the 1X goats (2 goats) and 400 mg (200 ppm) for the 10X goat was added to a gelatin capsule... two-thirds filled with cornmeal." The goats were dosed twice daily (8 doses total). The goats were milked twice daily; AM and PM samples were kept separate. An aliquot of milk from each goat was separated into skim milk and milkfat by centrifugation.

Feces and urine were also collected.

After the fifth dose, the 10X goat was placed in a respiration chamber for 10 hours. The 1X goats were placed in respiration chambers for 12 hours after the seventh dose. The effluent from each chamber was passed through two CO_2 collection traps containing oxidizer cocktail without prior oxidation. Only 0.7% of a single dose was recovered from the 10X goat, and 0.2 and 1.0% of a single dose were recovered from the two 1X goats.

An in vitro goat rumen study was conducted to determine the level of volatiles resulting from rumen metabolism. ^{14}C-Lindane (1.29 mg) was added to buffered rumen (100 ml rumen fluid) containing finely ground alfalfa cubes and dairy ration. Nitrogen was passed through the system to maintain anaerobic conditions, and the effluent was passed through an oxidizer before trapping of the resulting CO_2.

Preliminary in vitro studies using steer rumen had demonstrated that polyurethane foam, charcoal, ethylene glycol, XAD-4 or XAD-2 resin, Carbosieve, Carbotrap, 0.1 N KOH, and isooctane were ineffective at trapping the volatiles generated from rumen incubation of lindane. However, passing the effluent gas through an oxidizer and trapping of the resulting CO_2 yielded a total recovery of 67% of $^{14}CO_2$. Since combustion of the effluent gas was needed in order to efficiently determine the levels of the volatiles, identification of the volatiles was precluded.

Total Radioactive Residues

The recoveries of the administered dose from the goats are tabulated below. The data reflect dermal and oral dosing.

Sample	% Recovery of Total Dose				
	Goat 1	Goat 2	Goat 3	Goat 4	Goat 0
Milk	2.0	2.4	1.1	0.9	0.6
Urine	45.9	34.7	39.9	11.9	9.9
Feces	5.1	8.0	5.8	0.8	1.2
CO_2[1]	0.2	1.0	0.7	---	<0.1
Tissues	4.0	4.1	4.4	1.8	1.8
Gut contents	1.5	1.3	1.3	---	---
Hide	---	---	---	1.1	16.9
Total	58.7	51.5	53.2	16.5	30.4

[1] Extrapolating from the yield of CO_2 collected during the test interval

Goats 1 and 2 = 1X feeding rate
Goat 3 = 10X feeding rate
Goat 4 = 0.25X dermal rate
Goat 0 = 1X dermal rate

The petitioner argues that the low recoveries in the feeding study result from the formation of volatile metabolites. The steer and goat rumen studies resulted in recoveries of 67 and 55%, respectively, of the added ^{14}C-lindane as trapped CO_2 after combustion of volatiles in the effluent.

The registrant ascribes the poor recoveries of applied lindane in the in vitro hide experiments to leaks and absorption of volatile metabolites; almost all the activity found remained in the desiccator (9.9-27.4%). Lindane itself should have been recovered in the XAD-2 trap which was used in one run; therefore the registrant believes that the volatiles consisted of metabolites of lindane such as pentachlorocyclohexene. The registrant concludes that the low recoveries encountered in the topical studies were due to volatilization and points out that recoveries were lower in the study using a 48 hour pre-slaughter interval (16.5%) than in the study using a 24 hour pre-slaughter interval (30.4%).

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In the metabolism study, radioactive residues appeared to plateau in milk after about 2.5-3 days of feeding. The maximum levels of residues found in milk from the feeding study are given below.

Animal	Total radioactive residue (ppm) [day of highest level]
Goat 1 (1X)	0.396 [2.5]
Goat 2 (1X)	0.479 [2.5]
Goat 3 (10X)	3.192 [3.0]

The distribution of the total radioactive residue (TRR) between skim milk and milkfat is given below for the feeding study. In all three goats, 85-86% of the residues partitioned into the milkfat (based on a fat content of 4.1%).

Day of Dose	Animal	Sample	TRR in PPM
2.5	Goat 1 (1X)	Milkfat	6.317
	Goat 1	Skim milk	0.046
3.0	Goat 2 (1X)	Milkfat	7.612
	Goat 2	Skim milk	0.056
1.0	Goat 3 (10X)	Milkfat	48.892
	Goat 3	Skim milk	0.343

In the topically treated goats, residues tended to peak 0.5-1.5 days after treatment. In both goats, the maximum level after the second treatment exceeded the peak level after the first treatment. In the goat treated at the 0.25X rate, the peak levels occurred half a day after the first treatment (0.127 ppm) and one day after the second treatment (0.148 ppm). In the goat treated at the 1X rate, the peak levels occurred 1.5 days after the first treatment (0.610 ppm) and half a day after the second treatment (0.7453 ppm).

The distribution of the TRR between skim milk and milkfat is tabulated below. The data reflect residues after the second treatment.

Animal	Treatment Day	Sample	TRR in PPM
TOP 4 (0.25X)	7.5	Milkfat	4.178
TOP 4	7.5	Skim milk	0.028
TOP 0 (1.0X)	8.0	Milkfat	10.017
Top 0	8.0	Skim milk	0.060

In the topically treated goats, 86-87% of the TRR partitioned into the milkfat.

The various tissues were assayed by combustion analysis. The reported radioactive residue levels are tabulated below.

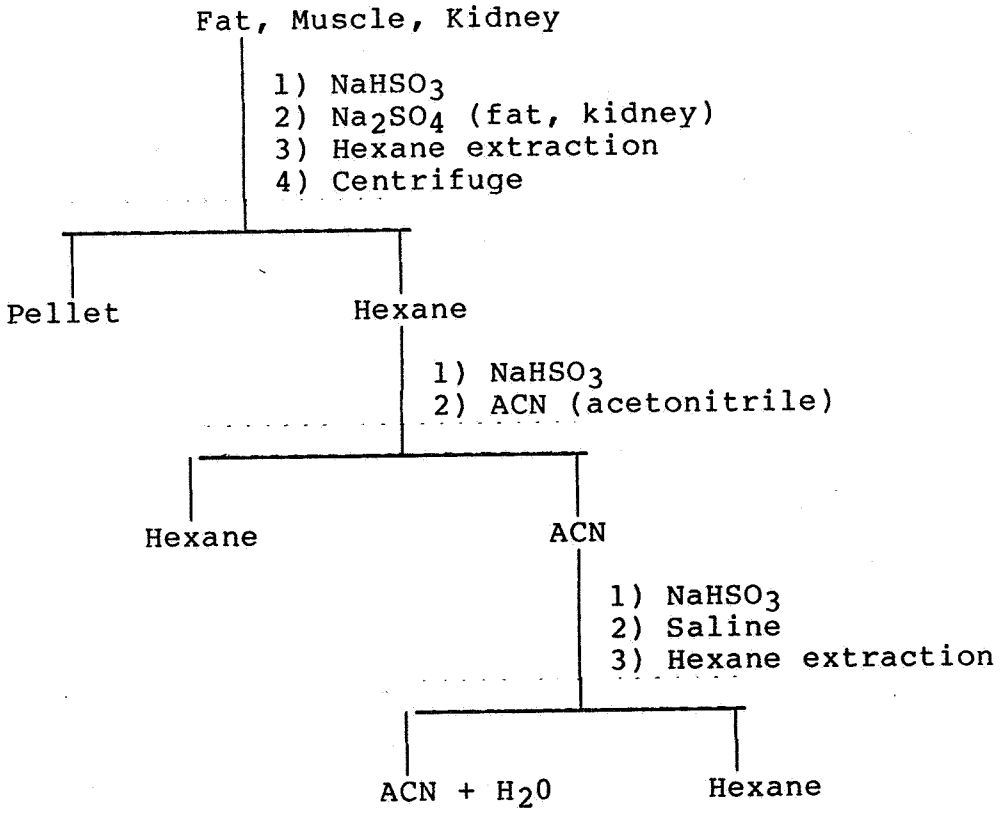
TRR in PPM in Goat Matrices

Matrix	Goat 1 OR-1X	Goat 2 OR-1X	Goat 3 OR-10X	Goat 4 TOP-0.25X	Goat 0 TOP-1X
Fat	2.596	4.618	36.784	1.19-1.66	6.07-6.99
Kidney	0.731	0.734	5.995	0.197	0.730
Liver	3.824	4.094	19.506	0.497	2.808
Hide	--	--	--	1.600	435.58
Muscle	0.086	0.074	0.528	0.037	0.238
Muscle under patch	--	--	--	0.113	0.380

Identification of Metabolites

Preliminary experiments had indicated that concentration on a rotatory evaporator led to loss of a great portion of the radioactivity through volatilization. Because of the loss of activity upon evaporation, every concentration step was conducted with Kuderna-Danish evaporators.

The following extraction scheme was used in extracting residues from fat, liver, and kidney tissues.



The final hexane extracts were concentrated with Kuderna-Danish evaporators, applied to Florisil columns, and eluted with various solvents.

Because a considerable amount of activity remained in the kidney sample pellets, they were further extracted with methanol:water (80:20), and the methanol was evaporated using a Kuderna-Danish evaporator. The remaining aqueous was acidified to 6N HCl by the addition of an equal amount of 12N HCl and extracted with ether. The acidic phase was refluxed for 8 hours and extracted with ether. A liquid/liquid extractor was then used to again extract the acidic phase with ether for at least 16 more hours.

Liver was extracted with MeOH/H_2O (80:20), and the extract was then subjected to the same extraction procedures as the kidney pellet extract described above.

The efficiency of the tissue extractions is given below.

	% TRR Extracted	
	Hexane	MeOH/H_2O 80:20
Muscle	99.9	108.0
Fat	122.1	116.9
Kidney	34.9	94.4
Liver	20.3	94.3

Preliminary experiments on liver had indicated that refluxing acid, sulfatase, and beta-glucuronidase released little activity from the initial aqueous extract. Attempts to extract activity from the aqueous liver extracts after hydrolysis are tabulated below.

EtOAc Extraction from	% of Aqueous Activity Extracted after: HCl Reflux	Beta-Glucuronidase	Sulfatase
pH 2	18.3	3.1	3.6
pH 7	3.7	0.7	0.8
pH 10	0.5	0.4	0.4

The petitioner has provided data on the radioactivity content of the final hexane extract before and after concentration; very little activity was lost by concentration in Kuderna-Danish evaporators (< 5%). Less than 10% of the TRR remained on the columns following chromatography of the final hexane extracts.

Only those residues partitioning into organic solvents were characterized. Although radioactive residues in muscle and fat partitioned into organic solvents, most of the radioactive residues in kidney and liver remained in the aqueous layer even after acid hydrolysis and liquid/liquid extraction. The % TRR from liver and kidney samples which was extractable into organic solvents and therefore available for characterization is given below.

% TRR in Organic Phase	Kidney Oral (10X)	Kidney Dermal	Liver Oral (10X)	Liver Dermal
% TRR eluted from Florisil	14.2	9.4, 15.7	--	--
% TRR freed by H_3O^+	19.7	46.6, 19.7	18.8	14.3, 12.6
Total available for identification	33.9	56, 35.4	18.8	14.3, 12.6

Methanol was added to the milk samples which were then extracted with ether/pet ether and centrifuged. The ether phase was concentrated on a rotatory evaporator at ambient temperature, since losses of radioactivity occurred with a water bath temperature of 35°C. The ethereal concentrates were chromatographed on a Florisil column. The remaining aqueous phase was acidified, refluxed for 16 hours, and extracted with ethyl acetate. The % TRR partitioning into organic solvents is tabulated below.

Sample	% TRR in Et_2O	% TRR in EtOAc after H_3O^+
Oral 1X	75.5-91.3	5.9-16.7
Oral 10X	84.0-89.1	6.8-7.5
Dermal 0.25X	87.7-90.5	8.2-11.0
Dermal 1.0X	94.8-95.2	4.1-4.7

Identification of Radioactive Residues

Lindane was determined by the Marsden method for determining lindane as well as by GLC of fractions following Florisil chromatography.

The animal metabolism of lindane has been extensively investigated, and many reports have been published. The petitioner has submitted a summary of some of these studies. By culling the literature, the petitioner selected 27 lindane metabolite standards. Identification of radioactive residues was carried out primarily with GLC, because activity tended to evaporate from TLC plates. In the analysis of tissues, only GLC was used. In the milk studies, GLC was used to quantitate lindane and 1,2,4-trichlorobenzene, and TLC was used to identify the other residues. Two-dimensional TLC was used to confirm the identity of 2,3,5-trichlorophenol and 2,3,4,5-tetrachlorophenol in the milk samples.

Lindane itself was the major residue identified in fat, muscle, and milk. However, in kidney, lindane accounted for only 4.5-7.0% of the TRR; the remainder of the TRR was unidentified. Even

though the liver residue content amounted to 19.5 ppm lindane equivalents for the 10X dosed goat, only 0.5% of the TRR consisted of lindane. Trace amounts of 1,3,5-trichlorobenzene may have been present in liver (<0.02 ppm); >99% of the TRR in liver was uncharacterized in the 10X dosed goat.

The metabolic profile of goat matrices is described in the table below.

Matrix	Goat 1 OR-1X	Goat 2 OR-1X	Goat 3 OR-10X	Goat 4 DERM-0.25X	Goat 0 DERM-1X
Fat					
TRR (ppm)	2.596	4.618	36.784	1.19-1.66	6.07-6.99
% TRR:					
lindane[1]	83.1	73.1	71.2	88.6	65.5
Tetrachlorobenzenes	1.5	0.9	0.8	ND	0.4
Hexachlorocyclohexene	0.7	0.4	0.4	0.7	0.4
1,2,4-trichlorobenzene	4.9	5.3	3.6	2.9	3.8
% TRR identified	90.2	79.7	76.0	92.2	70.1
Kidney					
TRR (ppm)	0.731	0.734	5.995	0.197	0.730
% TRR lindane[1]			4.5	6.5	7.0
% TRR identified			4.5	6.5	7.0
Muscle					
TRR (ppm)	0.086	0.074	0.528	0.037 0.113[2]	0.238 0.380[2]
% TRR lindane[1]	28.3	58.6	45.1	61.1 74.6[2]	60.8 68.9[2]
% TRR identified	28.3	58.6	45.1	61.1 74.6[2]	60.8 68.9[2]
Liver					
TRR (ppm)	3.824	4.094	19.506	0.497	2.808
% TRR:					
lindane[3]			0.2-0.6	9.7	1.7
1,3,5-trichlorobenzene			<0.1		
% TRR identified			<0.3-<0.7	9.7	1.7

[1] After Florisil chromatography
[2] Muscle under treated patch

[3] Lindane determined by Marsden procedure without Florisil chromatography

The methodology used to characterize the metabolic profiles of the various tissues led to recoveries of 64-83% for residues of lindane from muscle, kidney, and fat. The recovery of lindane from liver was not given. Residues of lindane in liver were determined by a method, which does not incorporate chromatography on Florisil (P.J. Marsden, J. Ag. Food Chem., 1986, 34, 795). Chromatograms reflecting the analysis of lindane in liver by the Marsden procedure were not submitted.

The petitioner has submitted the recoveries of 20 possible metabolites from fat. The recoveries of the metabolites (with the exception of of the recovery of pentachlorophenol and pentachlorobenzene) ranged from 63-177%. The recovery of pentachlorophenol from fat was 49.7%, and the recovery of pentachlorobenzene was 28.3%. Recoveries of metabolites from other matrices were not submitted.

The metabolic profile of residues in goat milk are outlined below.

	Contribution to % TRR									
Residue[a]	Goat 1 OR-1X		Goat 2 OR-1X		Goat 3 OR-10X		Goat 4 TOP-0.25X		Goat 0 TOP-1X	
Lindane	[b]64.7	[c]72.1	[b]73.8	[c]77.0	[b]71.5	[c]72.1	[b]108.6	[c]85.0	[b]90.0	[c]99.8
	[b]77.0	[c]77.0	[b]57.2	[c]55.0	[b]54.9	[c]59.1	[b]84.1	[c]84.1	[b]75.3	[c]85.3
1,2,4-TCB	[b] 9.0	[c]11.1	[b]0.0	[c]4.4	[b]6.0	[c]7.1	[b]0.0	[c]16.7	[b]14.9	[c]8.4
	[b]15.5	[c]17.7	[b]11.3	[c]16.7	[b]10.1	[c]16.7	[b]0.0	[c]13.2	[b]9.9	[c]14.4
2,4,5-TCP[d]	0.8		0.2		0.9		1.0		0.6	
	1.0		2.1		0.9		1.4		0.5	
4-CP[d]	0.2		0.3		0.2		0.2		0.1	
	0.2		0.5		0.2		0.3		0.1	
3,4-DCP[d]	0.3		0.5		0.4		0.5		0.3	
	0.4		0.9		0.4		0.6		0.2	
2,3,4,5-TeCP[d]	1.8		2.9		2.1		2.5		1.4	
	2.3		5.1		2.3		3.4		1.3	
2,3,5-TCP[d]	1.0		1.6		1.1		1.4		0.8	
	1.3		2.8		1.2		1.9		0.7	

[a] See Table at end of section for abbreviations
[b] Analysis based on GLC
[c] Analysis based on liquid scintillation counting (LSC)
[d] Analysis based on TLC with LSC

Based on GLC and TLC analyses, 70-114% of the TRR in milk has been accounted for; based on LSC and TLC analyses, 81-111% of the TRR in milk has been accounted for.

The activity of the milk fractions which would contain the phenolic residues accounted for 4-17% of the TRR. The petitioner believes that 6-8 phenols were hydrolytically liberated, but was able to identify only 5 of the phenols

Urine samples were hydrolyzed with hydrochloric acid, and then extracted with toluene and ethyl acetate. The organic extracts were cleaned up by chromatography on acidic alumina. Residues were identified by GLC following methylation with diazomethane.

The following residues were identified in urine: 2,5-or 2,5-DCP; 2,6-DCP; 2,3,5-TCP; 2,3,6-TCP; 2,4,5-TCP; 2,4,6-TCP; 2,3,4,5-TeCP, and 2,3,5,6- or 2,3,4,6-TeCP.

Therefore, the following residues have been identified in goat matrices:

Residue	Abbreviation	Matrix
Lindane		All matrices but urine
1,2,4-trichloro-benzene	1,2,4-TCB	Fat, milk
1,2,3,4-tetra-chlorobenzene	1,2,3,4-TeCB	Fat
Hexachlorocyclo-hexene	HCCH (ene)	Fat
1,2,3,5-tetra-chlorobenzene	1,2,3,5-TeCB	Fat
1,2,4,5-tetra-chlorobenzene	1,2,4,5-TeCB	Fat
2,3,4,5-tetra-chlorophenol	2,3,4,5-TeCP	Milk, urine
2,4,5-Tri-chlorophenol	2,4,5-TCP	Milk, urine
2,3,5-tri-chlorophenol	2,3,5-TCP	Milk, urine
3,4-dichloro-phenol	3,4-DCP	Milk
4-chlorophenol	4-CP	Milk
2,4- or 2,5- and 2,6-dichloro-phenol	2,4- or 2,5- and 2,6-DCP	Urine

Residue	Abbreviation	Matrix
2,3,6- and 2,4,6-trichlorophenol	2,3,6- and 2,4,6-TCP	Urine
2,3,5,6- or 2,3,4,6-tetra chlorophenol	2,3,5,6- or 2,3,4,6-TeCP	Urine

The petitioner concludes that the metabolism results generally are consistent with reports in the literature; i.e., the metabolism in animals is rapid and results in the formation of alcohols, phenols, benzenes, and conjugates of these compounds.

The petitioner has submitted a review of lindane animal metabolism studies. The review was prepared by Dr. Y.C. Berisford and G.M. Cowie of Scientific Consulting Services and Dr. R.A. White, Jr., of Research Testing & Development Corporation. Most of the studies were carried out on rats. In addition to the di-, tri-, and tetrachlorophenols and benzenes, pentachlorophenol was also reported to be a metabolite in warm-blooded animals.

cc: Lindane Reg. Std. File, W. Boodee, PMSD/ISB, RF, Reviewer-Deyrup, G. La Rocca-PM#15, Circu, Lindane Subject File
RDI: JHOnley:3/9/88:RDSchmitt:3/14/88
TS-769:RCB:CM#2:RM810:X7484:CDeyrup:cd:3/16/88

Residue	Abbreviation	Matrix
2,3,6- and 2,4,6-tri-chlorophenol	2,3,6- and 2,4,6-TCP	Urine
2,3,5,6- or 2,3,4,6-tetra chlorophenol	2,3,5,6- or 2,3,4,6-TeCP	Urine

The petitioner concludes that the metabolism results generally are consistent with reports in the literature; i.e., the metabolism in animals is rapid and results in the formation of alcohols, phenols, benzenes, and conjugates of these compounds.

The petitioner has submitted a review of lindane animal metabolism studies. The review was prepared by Dr. Y.C. Berisford and G.M. Cowie of Scientific Consulting Services and Dr. R.A. White, Jr., of Research Testing & Development Corporation. Most of the studies were carried out on rats. In addition to the di-, tri-, and tetra-chlorophenols and benzenes, pentachlorophenol was also reported to be a metabolite in warm-blooded animals.

Attachment 1: Updated Table A

cc (with Attachment): Lindane Reg. Std. File, W. Boodee, PMSD/ISB, RF, ReviewerDeyrup, G. La Rocca-PM#15, Circu, Lindane Subject File
RDI: JHOnley:3/9/88:RDSchmitt:3/14/88
TS-769:RCB:CM#2:RM810:X7484:CDeyrup:cd:3/16/88

TABLE A

Attachment 1

GENERIC DATA REQUIREMENTS FOR LINDANE

Data Requirement	Composition 1/	Does EPA Have Data To Satisfy This Requirement?	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA § 3(c)(2)(B) ?	Time Frame For Data 2/ Submission
§158.125 Residue Chemistry					
171-4 - Nature of Residue					
- Plants	PAIRA	Partially		Yes	24 Months
- Livestock	PAIRA and Plant Metabolites	Partially	402713-02	Yes	18 Months
171-4 - Residue Analytical Method					
- Plant and Animal Residues	TGAI and	Partially		Reserved	
171-4 - Storage Stability Data					
Animal commodities	PAI	No		Yes	18 Months
Plant commodities	PAI	No		Yes	48 Months
	Metabolites	No		Reserved	
171-4 - Magnitude of the Residue - Residue Studies					
- Crop Group #1 - Root and Tuber Vegetables					
o Crop 1 - Beets					
-- Crop field trials	TEP	No		Yes	48 Months