PMSD/ISB

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

AUG 29 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: ID No. 52904-C. Lindane Registration Standard Followup. Residues in Swine. MRID No. 406605-04. DEB No. 4038

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and
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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, and Cuneo has submitted a partial response to Residue Chemistry data gaps cited in the Lindane Registration Standard (9/30/85) on behalf of its client, CIEL, the Centre International d'Etudes du Lindane. The submission consists of a study entitled "Tissue Residue Study in Swine using Lindane".

Conclusions

1. DEB reserves its conclusion on the adequacy of this residue study at this time, since the nature of the residue in animals is not adequately understood. Much of the radioactive residue found in the animal metabolism studies has not been characterized. The Toxicology Branch has expressed concern for the unidentified residues in animal liver and kidney. Additional residue data on lindane metabolites present may be required.

2. Additional analytical methodology may be needed for the analysis of lindane metabolites. If this is the case, the registrant is cautioned on the use of rotary evaporation as a means of concentrating samples since previous experience has shown that some metabolites are lost in this concentrating step.

Recommendations

1. DEB recommends that the Registrant resolve those issues raised in DEB's 3/24/88 review of the animal (cattle) metabolism study.

2. DEB recommends that the Registrant be prepared to reanalyze his reserve samples (supportable by storage stability data) and/or carry out a new swine feeding study to quantify any lindane metabolites found to be of toxicological concern.

Detailed Considerations

Pertinent data gaps cited in the Registration Standard will be restated below, followed by CIEL's response and DEB's comments/conclusions.

Data Gap (see footnote 108, Guidance for Reregistration of Products Containing Lindane, September 1985)

Available residue data do not support the tolerance of 4 ppm in 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 of radioactive residues in other tissues, residue data on meat and meat by-products 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 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.

Registrant's Response to Data Gap

The registrant has conducted a study to determine the zero-day withdrawal residues of lindane (parent compound only) in swine tissue. The study was conducted for Centre International d'Etudes du Lindane (CIEL), by Southwest Bio-Labs, Las Crues, NM.

Eighteen swine (15 weeks old, and weighing 50-70 kg) were fed lindane via gel capsules for 28 days. Three groups of 6 animals each were treated at nominal levels of 7 ppm (1X), 21 ppm (3X), and 70 ppm (10X). Two additional animals served as controls for the experiment. The 1X level was calculated to provide the maximum expected pesticide exposure to animals via the diet (see memo of G.T. LaRocca to C.A. O'Conner, dated 9/3/86). Two male and two female animals at each exposure level were also dip treated on treatment days 21 and 28 with a 0.06% Lindane solution supplied from water dilution of a 20% emulsifiable concentrate of Prentox Lindane. Animals were sacrificed at approximately 6-10 hours after the last dose. Fat (composite), kidney, liver and muscle (composite) samples were collected and analyzed for lindane residues. All samples were frozen and maintained at -20^{O} C until further processed for residue analysis. Samples were stored for 6 months or less prior to analysis.

Tissue samples were analyzed by using the AOAC Multiresidue Method with slight modifications in the concentration and final volume steps to simplify analysis of the higher than normal residue levels found in this study. The method essentially involves the extraction of lindane from tissues by blending samples with acetonitrile in the presence of celite. The extracting solvent is separated from tissue by vacuum filtration. An aqueous salt solution is added to the acetonitrile extract and the lindane is partitioned into petroleum ether for further cleanup by open column Florisil chromatography. Lindane is eluted from the Florisil column with 6% ethyl ether in petroleum ether and concentrated by evaporation for quantitation by electron capture gas chromatography. Quantitation was achieved by retention time and peak height comparison to an external lindane reference standard. The claimed method sensitivity is about 0.02 ppm. When muscle and fat were fortified at the approximate levels of 0.1, 1.0 and 10.0 ppm, recoveries ranged from 69% to 118%. All control samples analyzed had no detectable residues (< 0.02 ppm). Table I. summarizes the results of the residue analyses.

Table I. Summary of Swine Residues by Tissue and Treatment

Group	Fat		Kidney		Liver		Muscle	
	D* (a)	NON-D** (b)	D (a)	NON-D (b)	D (a)	NON-D (b)	D (a)	NON-D (b)
1X	2.690	1.663	0.116	0.049	<0.02	<0.02	0.176	0.086
3X	7.715	5.632	0.336	0.209	0.058[C]	<0.02	0.519	0.242
10X	21.333	16.184	0.774	0.392	<0.02	<0.02	0.850	0.777

* Dipped
** Non-dipped

(a) Mean of four animals with three replicates per animal.
(b) Mean of two animals with three replicates per animal.
(c) Group contained one animal with unusually high values.

DEB's Comments/Conclusions

DEB cannot make a determination on the adequacy of this residue study at this time. The nature of the residue in animals is not adequately understood since much of the radioactive residues found in the animal (cattle) metabolism studies has not been identified (see memo of C. Deyrup, dated March 24, 1988), and we are not requiring that a swine metabolism study be done. The Toxicology Branch has expressed concern for the unidentified residues in animal liver and kidney, although the metabolites have not been specified (see memo of E. Budd, dated May 19, 1988). Additional residue data on metabolites levels present may be required, after the Registrant has resolved those issues relating to the cattle metabolism study.

Additional methodology may also be needed to analyze for metabolites. If this is the case, the registrant is cautioned on the use of rotary evaporation as a means of concentrating samples since previous experience shows that some metabolites are lost in this concentrating step.

Storage stability data submitted by the registrant supports lindane (parent compound) stability at freezing temperatures for at least 9 months (see memo of S.H. Willett, August 23, 1988).

Residue data supported by storage stability data maybe needed on lindane metabolites that are of toxicoligical concern. This may require reanalyses of reserve samples and/or carrying out a new swine feeding study.

cc: Lindane Reg. Std. File, W. Boodee, PMSD/ISB (E. Eldridge), RF, SHWillett, Circ., SF
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