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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJ: #8340-15. Evaluation of TPTH Analytical Methods.
[Acc.#258228 & 258332; RCB #1135]
MRID 142876 MRID 128877

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TO: H. Jacoby, PM Team #21
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Amer. Hoechst Corp. has submitted both product chemistry and residue chemistry data in response to the "data call-in" program for the Registration Standard on the fungicide triphenyltin hydroxide (TPTH). The registration guidance document for TPTH lists as a product chemistry gap and as a residue chemistry gap the following items from 40 CFR §58.120 and 40 CFR§58.125, respectively:

Guideline Number	Data Requirement	Test Material
62-3	Analytical Methods and Data for Enforcement of Limits	TGAI
171-4	Residue Analytical Method for Plant and Animal Residues	TGAI and metabolites

Included in these gaps was the requirement that analytical methodology for plant and animal residues be submitted which would be suitable for redefining TPTH tolerances and for enforcement purposes. The method(s) should determine the collective or separate residues of TPTH and its metabolites, di- and monophenyltin hydroxides (or oxides) in plants and in animal tissues. Also indicated in the TPTH PD-1, residue data for tetraphenyltin (TPT), TPTH and di- and monophenyltin metabolites in processed peanuts, potatoes and sugar beets are required. Thus for these processed products a validated method for TPT residues is also required.

The registrant has indicated with respect to plant residues that "since the mono- and diphenyltin metabolites were never

isolated in radiolabeled metabolism studies, there is no reason to include them as part of the residue tolerance". They agree with RCB that a method to determine TPTH and the mono and diphenyltin metabolites be required for animal tissues since the metabolites were identified in radiolabeled metabolism studies.

The decision to require analytical methodology for plant and animals for TPTH and di- and monophenyltin metabolites was based on the results of radiolabeled metabolism studies and the known chemistry of triphenyltin compounds. Metabolism studies in plants and animals suggest that translocation of residues of TPTH which does occur involves the breaking of the carbon-tin bond. In fact, the diphenyltin metabolites were identified in rice foliage while both di- and monophenyltin metabolites were identified in cattle (PP#eF2823, memo of 7/14/83). Based on these metabolism studies and the concern of Toxicology Branch with organotin moieties (10/28/83, memo of J. Doherty), we reiterate the necessity of analytical methodology for TPTH and di- and monophenyltin metabolites in plants as well as animal tissues.

The registrant should also be informed that the Registration Standard section discussing residue data on sugar beets reports that both di- and tetraphenyltin are likely conversion products in the drying process for wet pulp. We must reiterate the requirement for residue methodology for tetraphenyltin for processed commodities.

Data Submitted:

The following reports were submitted by Hoechst: 1) Determination of triphenyltin compounds in formulations and in the technical grade active principle (Hoechst #A07164, Acc.# 258228); 2) Recovery of Diphenyl and Triphenyl Tin from Fortified Soybeans; 3) Method Verification of the Analytical Method for Residue Analysis of Tri-, Di- and Monophenyltin Compounds in Meat, Eggs and Milk - Preliminary Report; and, 4) The Analysis of Organotin Compounds - Report No. A27247 (Acc.#258332).

§62-3 Analytical Methods and Data for Enforcement of Limits

The current submission (Acc.#258228) describes analysis of triphenyltin compounds in formulations and in TGAI (Hoechst Method AO7164, 9/6/76) by potentiometric titration with a glass electrode. TPTH is extracted with chloroform. Mono- and Diphenyl tin compounds are converted to water-soluble complexes by extraction of the chloroform solution with aqueous sodium tartrate. The chloroform solution containing the TPTH is then titrated with standard HCl. Neutral tetraphenyltin does not react with the titrant. Although this method appears satisfactory for the determination of TPTH as the sole active ingredient in pesticide formulations, no validation or precision data were submitted with this report.

Methodology for estimation of the active ingredient was presented by Hoechst in a recent product chemistry submission (Memo of A. Reiter, 8/27/85). The above-cited method for the determination of the a.i. was a published, CIPAC accepted method (JAOAC, 61, 1507-1512 (1978). It involves conversion of TPTH to the volatile butyltriphenyltin by a Grignard reaction and measurement of the latter compound by GC using either TC or FI detector. Impurities described by Hoechst are known not to interfere with this method. The precision of this method (avg. 1.5% in an interlaboratory comparison) is better than the 2% maximum allowed in the product chemistry guideline.

Detailed, validated procedures have still not been submitted for the assay of the potential impurities. Thus, the data gap is considered not satisfied by the current submission. ✓

§171-4 Residue Analytical Method for Plant and Animal Residues

Tolerances are pending (PP#3F2823) for residues of TPTH in/on soybeans at 0.05 ppm. Other tolerances, either pending or established (40CFR180.236), range from 0.05 to 3 ppm.

In order to comply with the reregistration notice for TPTH, Hoechst has submitted three reports on the analysis of plant and animal residues.

1) The first report entitled "Recovery of Diphenyl- and Triphenyltin from Fortified Soybeans" was conducted by Borriston Laboratories. Its objective was to determine the precision and accuracy for measuring diphenyltin dichloride (DPTD) and triphenyltin hydroxide (TPTH) in fortified soybeans using a procedure based on GC/FPD. Fortified samples (0.01-0.10 ppm) were prepared by addition of DPTD or TPTH to soybean meal in a Waring blendor. After sequential extraction in various solvents, reduction by perevaporation, the methyl derivatives were prepared by reaction with methylmagnesium chloride. Excess reagent is consumed by addition of saturated ammonium chloride. After cleanup and concentration the samples were analyzed by GC/FPD in the sulfur mode.

The results of these recovery studies are summarized in the following table.

Table 1. Recovery of Phenyltin Residues from Soybean Matrix

	Fortification Levels in ppm [average (range)]			
	0.010	0.025	0.050	0.100
Soybean matrix:				
DPTD	52(30-80)*	56(32-76)	69(38-79)	82(79-86)
TPTH	78(50-110)	63(48-84)	73(38-118)	78(66-88)
	(n=20)†	(n=14)	(n=20)	(n=3)
Solvent solutions:				
DPTD	55(40-70)	70(66-76)	58(33-78)	83(74-91)
TPTH	100(80-120)	85(76-93)	84(74-92)	99(98-100)
	(n=2)	(n=3)	(n=7)	(n=2)

*One outlier of 0% was not included in this range or average.
†Number of samples analyzed

Summary data sheets and typical chromatograms were also submitted. In general, recoveries and precision improved at higher fortification levels for DPTD, whereas recoveries of TPTH from soybean matrix remained fairly constant over the same range. Recoveries from solvent fortified samples were overall better for TPTH than for DPTD. In general the recoveries from both solvent and soybean matrix samples do not meet the minimum criterion prescribed in the Residue Chemistry Guidelines for method validation §171-4b(2). Recoveries should be at least 70% and demonstrate suitable method precision. Finally, in Dr. Arne's review of this method (PP#3F2823, 7/14/83) a question was raised about the feasibility of the derivatization of TPTH directly with methylmagnesium chloride. This discrepancy remains unanswered.

This method is unsatisfactory for measuring levels of the parent and the two prescribed metabolites and tetraphenyltin.

2) The second submitted analytical report entitled Method Verification of the Analytical Method for Residue Analysis of Tri-, Di- and Monophenyltin Compounds in Meat, Eggs and Milk (Preliminary Report) was prepared by Hoechst's Analytical Laboratory in Germany. They tried to modify an earlier published method based upon "drastic hydrogenative reduction" of all phenyltin bonds to benzene which is then trapped and quantitatively determined by GC/MS.

The sample material (meat, milk or eggs without shells) is fortified at 0.1 or 0.05 ppm with TPTH, diphenyltin dichloride (DPTD) or phenyltin trichloride (MPTT) and stirred in an aqueous

suspension of zinc powder and antifoaming agent for 30 min at 90°C in a reaction flask. HCl is dropped into the mixture and the generated nascent hydrogen causes the cleavage of the phenyl-tin bond with formation of benzene. The vaporised benzene is absorbed onto a charcoal plug. The charcoal is then shaken with methylene chloride in a head space vial at room temperature and the desorbed benzene is determined by GC/MS using benzene-D_6 as the internal standard or benzene as an external standard; SIM is conducted at 78.0 and 84.1 amu.

Recoveries of the parent fungicide and its two biological metabolites are summarized in the following table.

Table 2. Recovery of Phenyltin Residues from Animal Tissues

% Recovery Rates

(at the 0.1ppm, 0.05 ppm fortification levels)

	Meat	Eggs	Milk
TPTH	25,--	163,171	30,17
DPTD	171,62	138,62	33,24
MPTT	132,76	116,59	79,--

We are in agreement with this report's conclusion, that "the recoveries of this preliminary study ... scatter rather widely ... and is not yet fully satisfactory". However, their analysis of the individual steps pointed out a problem with the efficiency of desorption from charcoal which is amenable to improvement. RCB will welcome a review of any improved method.

Thus, the data gap for guideline §171-4 remains unsatisfied.

3) The third study submitted in Acc.#258232 is a translation from German of Hoechst document A27247 entitled "The Analysis of Organotin Compounds" by K. Bürger dated Oct. 1960.

The principle of this method is based upon the complexometric determination of di-, tri- and tetravalent metal ions using pyro-catechosulfophthalein (pyrocatechol violet, PV). Mono- and dialkyl(aryl)tin complexes have an intense blue color. Advantage of this property is taken in the qualitative detection of these compounds; quantitative estimation may also be accomplished by subsequent backtitration of the PV complex with standard EDTA solution to a yellow endpoint. All four species of organotin may be quantitatively analyzed by liberating the aromatic portion as benzene via treatment with concentrated HCl in the presence of zinc at 60°C.

An alternative quantitative method specific for organotin compounds is also described. After reductive cleavage of the

carbon bonded alkyl(aryl) moieties from tin with Zn-HCl, the benzene is nitrated with 50/50 HNO_3/H_2SO_4 to yield m-dinitrobenzene. After neutralization of the excess acid and extraction into methyl ethyl ketone, conversion is effected to a nitronic acid which absorbs in the visible spectrum at 565 nm. A detection limit of 2 ug was reported; reproducibility with "an accuracy of 10-20% was obtained". The method will detect/determine phenyltin compounds in toto. It is subject to interferences by any other substances which might liberate benzene under the same reaction conditions.

Finally, several modifications of this reductive cleavage/nitration procedure are described for plant materials and milk. A detection limit for tetraphenyltin acetate in milk was reported to be 1 ug/L with a SD of approx. 5 ug was reported. A validation study was performed only on milk; it involved fortification in the 5-40 ug/L (ppb) range. No statistical analysis of the recovery data was provided for review.

Since a validated method for the analysis of the TGAI and all metabolites in plant and animal tissues is not satisfied with this report, the data gap remains.

Conclusions

1. §62-3 Analytical Method and Data for Enforcement of Limits

A satisfactory method has been previously reviewed for the analysis of of the active ingredient in TPTH. However, methods for impurities analysis are still lacking. The data gap remains unsatisfied.

2. On the issue raised by the registrant of not amending the tolerance expression to include the mono- and diphenyltin metabolites, RCB bases its decision to recommend for their inclucsion for several reasons:

a) Metabolism studies in plants and animals suggest that the translocation of residues of TPTH which does occur involves the breaking of the carbon tin bond.

b) Known chemistry of organotin compounds.

c) Radiolabeled metabolism studies in rice showed the presence of diphenyltin species.

In addition, because of the likely formation of di- and tetraphenyltin in the sugar beet drying process, the TPTH PD-1 also required residue data on tetraphenyltin (TPT) in processed commodities. A validated method for TPT is thus required.

3. §171-4 Residue Analytical Method for Plant and Animal Residues

Several methods were submitted for review. The first (Borriston Report) is not suitable for determination of the parent TPTH and mono- and diphenyltin metabolites in soybean. Also, it was not validated for tetraphenyltin in processed crops. The second report (Hoechst Doc. No. A27247, Report No. B127/85) displayed widely variable recoveries for TPTH and its mono- and diphenyl metabolites in meat, milk and eggs at the 0.05 and 0.1 ppm fortification levels. Finally, a complexometric titration method for TPTH and its three metabolites was described and validated on milk. It appeared to provide satisfactory recoveries in the 5-40 ppb range. Since a validated method for the analysis of the active ingredient and all metabolites in plant and animal tissues is not satisfied with this report, the data gap remains.

Recommendation

The registrant should be apprised of the above data gaps.

cc: Circu., TPTH SF., RF, Reiter, PMSD/ISB, G. Beusch, RD/SRB, SIS, Special Review File-Reiter

RDI:E.Zager:9/23/85
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