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

TOPP

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: April 13, 1999

SUBJECT: **TPTH: Acute Dietary Exposure Analysis.**
Chemical #:083601. DP Barcode: D254712. Case #: 0099.

FROM: Sarah Law, Chemist *Sarah Law*
Reregistration Branch 3
Health Effects Division

THROUGH: Steve Knizner, Branch Senior Scientist *St Kn*
Reregistration Branch 3
Health Effects Division

TO: Angel Chiri, Chemical Review Manager
Special Review Branch
Special Review and Reregistration Division 7508C

Action Requested

Provide a refined Tier 3 acute dietary exposure and risk analysis for triphenyltin hydroxide (TPTH) uses (40 CFR §180.236) that are supported through reregistration using revised acute anticipated residues. Dietary refinements, such as anticipated residues (ARs), are a way to gain a better understanding of potential dietary exposures, as opposed to high-end (tolerance level) estimates. HED has provided revised acute ARs of TPTH for the acute risk from the following commodities: pecans, potatoes, sugar beets, meat and milk; see Table 2 for details (C. Eiden, D255118, 04/12/99).

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Executive Summary

Acute dietary risk estimates associated with the consumption of TPTH regulable residues representing the high-end (Tier I) of exposure in food (tolerance level residues without the use of percent crop-treated [%CT] information) exceeded HED's level of concern for females 13+ years old. Acute dietary risk concerns using the Dietary Exposure Evaluation Model (DEEM™) prompted HED to conduct a Tier 3 (Monte Carlo) dietary risk analysis for TPTH. ARs, %CT and processing factors, where applicable, were utilized in this analysis. The assessment used the consumption data from the 1989-1992 Continuing Survey of Food Intakes by Individuals (CSFII). The acute dietary risk assessment was conducted as a probabilistic risk assessment, assuming single day exposure.

Refined (Tier III) acute dietary risk estimates associated with the consumption of TPTH regulable residues in food **exceed HED's level of concern** for females 13+ years old, the population subgroup of concern for acute oral exposure (approximately 300% of the acute PAD). No acute dietary risk assessment is required for the general population (no acute toxicity endpoint identified).

The latest percent crop treated (%CT) information was available from BEAD (electronic correspondence, 4/2/99, J. Faulkner) and is summarized in Table 2 along with existing and reassessed tolerance levels.

Toxicological Information

For the acute dietary exposure risk assessment, the dose selected was the no observed adverse effect level (NOAEL) of 0.3 mg/kg/day based on increased incidents of hyoid body and/or arches unossified in rabbit fetuses from an oral developmental toxicity study in rabbits. The uncertainty factor used to calculate the acute reference dose (RfD) was 100x. This included 10x for inter-species extrapolation and 10x for intra-species variation, resulting in an acute RfD of 0.003 mg/kg (See HIARC Document 11/13/98). Females 13+ years old are the population subgroup of concern for this risk assessment.

The HED FQPA Safety Factor Assessment Review Committee has determined that the 10x FQPA Safety Factor should be reduced to 3x for acute dietary risk assessment for all populations that include infants and children. The 3x factor reflects increased susceptibility of offspring seen in the two generation reproduction study in rats and the concern for the potential immunotoxic effects that resulted in the requirement for a developmental immunotoxicity study (data gap). Application of the 3x FQPA Safety Factor resulted in the **acute Population Adjusted Dose (acute PAD) of 0.001 mg/kg** for acute risk assessment (See FQPA Document, 12/17/98).

Table 1: Summary of Toxicological Endpoints for TPTH.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL= 0.3 mg/kg/day (100 UF) (3x FQPA)	Increased incidents of hyoid body and/or arches unossified in rabbit fetuses.	Oral Developmental toxicity - Rabbit (MRID No.: 40104801)
	Acute PAD = 0.001mg/kg for Females 13+		
	No acute oral endpoint identified for general population; risk assessment not required.		
Chronic Dietary ¹	NOAEL= 0.1 mg/kg/day (300 UF) (10x FQPA)	Decreased white blood cells.	Chronic feeding study -Rat (Accession No.: 099050)
	Chronic PAD = 0.00003 mg/kg/day		
Carcinogenicity ¹ (oral/dermal/inhalational)	Oral Q1* 1.83 Mg/kg/day ⁻¹	TPTH is classified as a B2 Carcinogen -probable human carcinogen based on pituitary and testicular tumors in rats and liver tumors in mice. A dermal absorption of 10% should be used for this risk assessment.	
Short-Term (Dermal)	Dermal NOAEL= 3 mg/kg/day	No effects a the highest dose tested.	Dermal Developmental toxicity - Rabbit (MRID No.: 42909101)
Intermediate-Term (Dermal)	Dermal NOAEL = 3 mg/kg/day	No effects a the highest dose tested.	Dermal Developmental toxicity - Rabbit (MRID No.: 42909101)
Long-Term Non-cancer (Dermal)	None	Use pattern does not indicate exposure will be for this interval.	
Inhalation (Any Time Period)	0.00034 mg/L (100 UF)	Deaths following lung lesions.	Subchronic inhalation toxicity -Rat (MRID No.: 41017701)

¹ Note that the chronic and cancer assessment is handled in a separate document (memo, S. Law, 04/13/99, D254712).

The available toxicity data base for TPTH is considered to partially define the potential toxicity of TPTH. There are questions remaining concerning the potential for immunotoxicity and there are no series 81-1, 82-7 and 83-6 acute, subchronic and developmental neurotoxicity studies. In general, there is a high degree of confidence in the existing toxicity data base especially for the studies used in assessing developmental toxicity and carcinogenicity. Additional data to define the potential for TPTH to cause true developmental immunotoxicity are required (data gap).

Residue Information

Tolerances for residues of TPTH are currently expressed in terms of TPTH *per se* (40 CFR §180.236). For purposes of tolerance enforcement, TPTH residues of concern in plant and animal commodities have been determined to include TPTH and its regulable metabolites MPTH and DPTH. The qualitative nature of the residue in plants and animals is adequately understood based on potato, soybean and rice metabolism studies, and acceptable ruminant and poultry metabolism studies. The terminal residues of concern are TPTH and its metabolites DPTH and MPTH (J. Doherty, PP#3F2823/FAB#3H5384, 10/28/83). Reregistration requirements for magnitude of the residue in meat, milk, poultry and eggs are fulfilled. The animal feed items used to estimate secondary residues in livestock commodities include sugar beet tops and processed potato waste. Table 2 summarizes the tolerances, %CT and AR values.

Sugar beet and potato ARs were based on the addition of ½ the sum of the limit of quantitation (LOQ) (0.01 ppm) for each regulable metabolite (TPTH-parent, MPTH and DPTH) for samples with non-detectable residues. For pecans, the distribution of field trial results, corrected for %CT was used (value for pecans is based on total tin method - i.e., TPTH and its regulable metabolites plus any other form(s) of tin). Processing factors were used in the DEEM™ adjustment factor #1 column where data were available (refined sugar = 0.02x, molasses = 3x, baked potatoes = 0.03x, boiled potatoes = 0.04x and potato wet peel = 3x). To further refine the residues, the boiled potato processing factor (0.04x) was used for potato uncooked, cooked, canned and frozen food forms because data were not available for these food forms (personal communication with C. Swartz, 3/25/99). The DEEM™ default processing factor of 1.92 was used for dried meat. The estimated maximum of %CT for pecans, sugar beets and potatoes was used.

Meat and milk anticipated residues were calculated; the values were inserted probabilistically into this assessment as follows: assumed that the resulting concentration in milk (or meat) applies only to that percentage of milk (or meat) corresponding to the highest %CT for any one feed item for that chemical. For example, the %CT for potatoes and sugar beets (feed items) are 23% and 44%; assume that 44% of the milk contains residues corresponding to the maximum theoretical dietary burden (MTDB) and the remaining 56% of milk are residue free. This is inserted into the Monte Carlo assessment by including the appropriate number of zeroes in an RDF file such that there is only a 44% probability of encountering a residue corresponding to the MTDB and an 56% probability of encountering a zero value (Guidance for Submission of Probabilistic Human Health Exposure Assessments to OPP, 11/5/99).

Table 2. Tolerances, Percent Crop Treated and Anticipated Residues for TPTH.

Commodity	Current Tolerance (ppm) ¹	Tolerance Reassessment (ppm) ^{2,3}	% Crop Treated ⁴	Acute Anticipated Residue Value (ppm) ⁵
Pecan	0.05	0.05	56%	Distribution of Field Trial Results
Sugar Beet	0.05	0.05	44%	0.015
Sugar beet, refined sugar	N/A ⁷	N/A ⁷	N/A ⁷	0.015
Molasses	N/A ⁷	N/A ⁷	N/A ⁷	0.015
Potato	0.05	0.05	23%	0.015
Potato, chips	N/A ⁷	N/A ⁷	N/A ⁷	0.015
Potato, baked	N/A ⁷	N/A ⁷	N/A ⁷	0.015
Potato, boiled	N/A ⁷	N/A ⁷	N/A ⁷	0.015
Potato, granules	N/A ⁷	N/A ⁷	N/A ⁷	0.015
Meat ⁶ , muscle	None	0.5	N/A	0.30
Meat ⁶ , kidney	0.05	2.0	N/A	1.0
Meat ⁶ , liver	0.05	4.0	N/A	3.16
Meat ⁶ , fat	None	0.2	N/A	0.12
Milk	None	0.06	N/A	0.006
Milk, cream	N/A	N/A	N/A	0.026
Milk, skim	N/A	N/A	N/A	0.004

1: Expressed in terms of TPTH *per se*.

2: Expressed in terms of the combined residues of TPTH, and its metabolites MPTH and DPTH.

3: According to TPTH Chemistry Chapter (C. Eiden, 3/29/99, D254190).

4: % Crop Treated Information from BEAD (Electronic Correspondence, 4/2/99, J. Faulkner).

5: Acute ARs presented here in Table 2 do not include Processing Factors or % CT (where applicable). Processing factors were incorporated into the DEEM™ Adjustment Factor #1 (Processing Factors); %CT was incorporated into the residue distribution files (RDF). AR calculated based on the addition of ½ the sum of LOQs (0.01 ppm) for each metabolite (TPTH, DPTH and MPTH) or based on distribution of field trial results (C. Eiden, 3/29/99, D254190).

6: Meat includes cattle, goats, horses and sheep.

7: Covered by the respective raw agricultural commodity (RAC).

Results/Discussion

The Dietary Exposure Evaluation Model (DEEM™) analysis evaluated the dietary exposure based on individual consumption data from USDA 1989-1992 Nationwide Continuing Surveys of Food Intake by Individuals (CSFII), and ARs for selected commodities. HED's level of concern for acute dietary risk is greater than 100% acute PAD. A complete list of dietary exposures for all

female subpopulations are presented in Attachment 2.

Table 3. Acute Dietary Exposure Results for TPTH.

Subgroups	95 th Percentile Exposure (% acute PAD)	99 th Percentile Exposure (% acute PAD)	99.9 th Percentile Exposure (% acute PAD)
Females (20+ years old/np/nn)	0.000647 (64.75%)	0.001150 (115.02%)	0.003613 (361.28%)
Females (13-19 yrs/np/nn)	0.000762 (76.23%)	0.001402 (140.16%)	0.002729 (272.89%)
Females (13+/preg/not nsg)	0.000676 (67.63)	0.001215 (121.53)	0.003091 (309.12)
Females (13+ nursing)	0.000692 (69.19%)	0.001275 (127.47%)	0.003452 (345.23%)
Females (13-50 years)	0.000688 (68.82%)	0.001226 (122.58%)	0.003062 (306.24%)

The results of the acute analysis indicate that the acute dietary risk estimates associated with the proposed uses of TPTH are **above the Agency's level of concern (> 100% acute PAD)** for females 13+ years old.

List of Attachments

- Attachment 1: Acute Residue Information
- Attachment 2: Acute DEEM™ Analysis (S. Law, 4/05/99)
- Attachment 3: Acute Residue Distribution Files

cc: S. Law 4/12/99 (RRB3), S. Knizner 4/12/99 (RRB3), L. Richardson (CEB1)
 RDI: Dietary SAC (4/6/99)
 S. Law: 821E,CM#2: (703)305-0783:7509C:RRB3

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Attachment 1: Acute Residue Information

U.S. Environmental Protection Agency

Ver. 6.73

DEEM Acute analysis for TPTH

1989-92 data

Residue file name: D:\83601Ra.R96

Adjust. #2 used

Analysis Date 04-07-1999

Residue file dated: 04-06-1999/14:53:01/8

Reference dose: aRfD = 0.001 mg/kg bw/day NOEL = 0.3 mg/kg bw/day

Comment: The above RfD number (0.001) is the Acute PAD

RDF indices and file names for Monte Carlo Analysis

- 1 C:\deem\resdata\TPTH\pecan.rdf
- 2 C:\deem\resdata\TPTH\potato.rdf
- 3 C:\deem\resdata\TPTH\sugarbeet.rdf
- 4 C:\deem\resdata\TPTH\milkskim.RDF
- 5 C:\deem\resdata\TPTH\milkcream.RDF
- 6 C:\deem\resdata\TPTH\liver.RDF
- 7 C:\deem\resdata\TPTH\muscle.RDF
- 8 C:\deem\resdata\TPTH\meatfat.RDF
- 9 C:\deem\resdata\TPTH\kidney.RDF

Food Crop	Grp	Food Name	RESIDUE (ppm)	RDF #	Adj. Factors #1	Code #2
47	14	Pecans	2.000000	1	1.000	1.000
207	1C	Potatoes/white-whole				
		11-Uncooked	2.000000	2	0.040	1.000
		12-Cooked: NFS	2.000000	2	0.040	1.000
		13-Baked	2.000000	2	0.030	1.000
		14-Boiled	2.000000	2	0.040	1.000
		15-Fried	2.000000	2	1.000	1.000
		31-Canned: NFS	2.000000	2	0.040	1.000
208	1C	Potatoes/white-unspecified	2.000000	2	1.000	1.000
209	1C	Potatoes/white-peeled				
		12-Cooked: NFS	2.000000	2	0.040	1.000
		13-Baked	2.000000	2	0.030	1.000
		14-Boiled	2.000000	2	0.040	1.000
		15-Fried	2.000000	2	1.000	1.000
		32-Canned: Cooked	2.000000	2	0.040	1.000
		34-Canned: Boiled	2.000000	2	0.040	1.000
		42-Frozen: Cooked	2.000000	2	0.040	1.000
		43-Frozen: Baked	2.000000	2	0.030	1.000
		45-Frozen: Fried	2.000000	2	1.000	1.000
210	1C	Potatoes/white-dry				
		12-Cooked: NFS	0.015000	0	1.000	0.230
		14-Boiled	0.015000	0	1.000	0.230
		15-Fried	0.015000	0	1.000	0.230
		31-Canned: NFS	0.015000	0	1.000	0.230
		34-Canned: Boiled	0.015000	0	1.000	0.230
		42-Frozen: Cooked	0.015000	0	1.000	0.230
211	1C	Potatoes/white-peel only				
		13-Baked	2.000000	2	3.000	1.000
		15-Fried	2.000000	2	3.000	1.000
282	1A	Sugar-beet				
		98-Refined	0.015000	0	0.020	0.440
318	D	Milk-nonfat solids	2.000000	4	1.000	1.000
319	D	Milk-fat solids	2.000000	5	1.000	1.000
320	D	Milk sugar (lactose)	2.000000	4	1.000	1.000
321	M	Beef-meat byproducts	2.000000	6	1.000	1.000
322	M	Beef-other organ meats	2.000000	6	1.000	1.000
323	M	Beef-dried	2.000000	7	1.920	1.000
324	M	Beef-fat w/o bones	2.000000	8	1.000	1.000
325	M	Beef-kidney	2.000000	9	1.000	1.000
326	M	Beef-liver	2.000000	6	1.000	1.000
327	M	Beef-lean (fat/free) w/o bones	2.000000	7	1.000	1.000
328	M	Goat-meat byproducts	2.000000	6	1.000	1.000
329	M	Goat-other organ meats	2.000000	6	1.000	1.000
330	M	Goat-fat w/o bone	2.000000	8	1.000	1.000

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331 M	Goat-kidney	2.000000	9	1.000	1.000
332 M	Goat-liver	2.000000	6	1.000	1.000
333 M	Goat-lean (fat/free) w/o bone	2.000000	7	1.000	1.000
334 M	Horsemeat	2.000000	7	1.000	1.000
336 M	Sheep-meat byproducts	2.000000	6	1.000	1.000
337 M	Sheep-other organ meats	2.000000	6	1.000	1.000
338 M	Sheep-fat w/o bone	2.000000	8	1.000	1.000
339 M	Sheep-kidney	2.000000	9	1.000	1.000
340 M	Sheep-liver	2.000000	6	1.000	1.000
341 M	Sheep-lean (fat free) w/o bone	2.000000	7	1.000	1.000
342 M	Pork-meat byproducts	2.000000	6	1.000	1.000
343 M	Pork-other organ meats	2.000000	6	1.000	1.000
344 M	Pork-fat w/o bone	2.000000	8	1.000	1.000
345 M	Pork-kidney	2.000000	9	1.000	1.000
346 M	Pork-liver	2.000000	6	1.000	1.000
347 M	Pork-lean (fat free) w/o bone	2.000000	7	1.000	1.000
379 1A	Sugar-beet-molasses	0.015000	0	3.000	0.440
398 D	Milk-based water	2.000000	4	1.000	1.000
424 M	Veal-fat w/o bones	2.000000	8	1.000	1.000
425 M	Veal-lean (fat free) w/o bones	2.000000	7	1.000	1.000
426 M	Veal-kidney	2.000000	9	1.000	1.000
427 M	Veal-liver	2.000000	6	1.000	1.000
428 M	Veal-other organ meats	2.000000	6	1.000	1.000
429 M	Veal-dried	2.000000	7	1.920	1.000
430 M	Veal-meat byproducts	2.000000	6	1.000	1.000

Attachment 2: Acute DEEM™ Analysis

U.S. Environmental Protection Agency Ver. 6.73
 DEEM ACUTE analysis for TPTH (1989-92 data)
 Residue file: 83601Ra.R96 Adjustment factor #2 used.
 Analysis Date: 04-07-1999/11:15:25 Residue file dated: 04-06-1999/14:53:01/8
 Acute Reference Dose (aRfD) = 0.001000 mg/kg body-wt/day
 NOEL (Acute) = 0.300000 mg/kg body-wt/day
 MC iterations = 1000 MC list in residue file MC seed = 10
 Run Comment: The above RfD number (0.001) is the Acute PAD

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Summary calculations:

	95th Percentile			99th Percentile			99.9th Percentile		
	Exposure	% aRfD	MOE	Exposure	% aRfD	MOE	Exposure	% aRfD	MOE
U.S. pop - all seasons:									
0.000865	86.52	346	0.001732	173.21	173	0.005299	529.90	56	
All infants (<1 year):									
0.000536	53.57	560	0.001715	171.54	174	0.003210	321.01	93	
Nursing infants (<1 year):									
0.000203	20.30	1477	0.001702	170.18	176	0.002112	211.21	142	
Non-nursing infants (<1 yr):									
0.000578	57.75	519	0.001626	162.55	184	0.003326	332.62	90	
Children (1-6 years):									
0.001675	167.54	179	0.003115	311.48	96	0.008519	851.86	35	
Children (7-12 years):									
0.001187	118.67	252	0.002153	215.29	139	0.005884	588.41	50	
Females (13+/preg/not nsg):									
0.000676	67.63	443	0.001215	121.53	246	0.003091	309.12	97	
Females (13+/nursing):									
0.000692	69.19	433	0.001275	127.47	235	0.003452	345.23	86	
Females (13-19 yrs/np/nn):									
0.000762	76.23	393	0.001402	140.16	214	0.002729	272.89	109	
Females (20+ years/np/nn):									
0.000647	64.75	463	0.001150	115.02	260	0.003613	361.28	83	
Females (13-50 years):									
0.000688	68.82	435	0.001226	122.58	244	0.003062	306.24	97	
Males (13-19 years):									
0.000845	84.51	355	0.001341	134.09	223	0.002267	226.71	132	
Males (20+ years):									
0.000787	78.70	381	0.001414	141.43	212	0.006107	610.74	49	
Seniors (55+):									
0.000635	63.52	472	0.001182	118.16	253	0.006917	691.67	43	

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Attachment 3: Acute Residue Distribution Files

#1
TPTH PECANS
TOTALNZ = 8
TOTALZ = 6

0.0025
0.005
0.005
0.005
0.005
0.005
0.005
0.008

#2
TPTH POTATO
TOTALZ = 77
TOTALFREQ = 1

23, 0.015

#3
TPTH SUGARBEET
TOTALZ = 56
TOTALFREQ = 1

44, 0.015

#4
TPTH SUGARBEET: MILKSKIM
TOTALZ = 56
TOTALFREQ = 1

44, 0.004

#5
TPTH SUGARBEET: MILKCREAM
TOTALZ = 56
TOTALFREQ = 1

44, 0.026

#6
TPTH SUGARBEET: LIVER
TOTALZ = 56
TOTALFREQ = 1

44, 3.16

#7
TPTH SUGARBEET: MUSCLE
TOTALZ = 56
TOTALFREQ = 1

44, 0.30

#8
TPTH SUGARBEET: MEAT FAT
TOTALZ = 56
TOTALFREQ = 1

44, 0.12

#9
TPTH SUGARBEET: KIDNEY
TOTALZ = 56
TOTALFREQ = 1

44, 1.0