11-28-89

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Subject: TPTH - Qualitative Risk Assessment,
Dietary Studies in Mice and Rats
Caswell no. 896E

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Summary

The qualitative risk assessment of TPTH, based upon two chronic/oncogenicity dietary studies in NMRI mice and Wistar rats resulted in the following statistical outcomes.

Survival - Male mice had no differential mortality with incremental doses of TPTH. Female mice had significant dose related increasing mortality but no statistically significant differences in the pair-wise comparisons between controls and any dose group.

Male rats had no significant mortality changes with incremental doses of TPTH. Female rats had a significant increasing dose related trend in mortality. In addition, the females had statistically significant differences in mortality in the pair-wise comparison with control and each of the three dose levels.

Tumors - Both male and female mice had significantly increasing dose related trends in combined hepatocellular (adenoma and/or carcinoma) tumors. The both sexes also had significantly increasing dose related trends in hepatocellular adenomas. While only the female mice had an increasing dose related trend in the hepatocellular carcinomas. In the pair-wise comparisons of controls and the highest (80ppm) dose group, both sexes had significant differences in the combined hepatocellular (adenoma and/or carcinoma) and the hepatocellular adenomas only tumor rates. The male mice also had a significant difference in the pair-wise comparison of controls and the mid (20ppm) dose group in hepatocellular adenomas.

Male rats had a significant increasing dose related trend in Lydig cell tumors as well as a pair-wise significant difference with controls and the highest (80ppm) dosed group in these tumors.

Female rats had significant differences in the pair-wise comparison of controls and both the mid (20ppm) and the high (80ppm) dose groups in pituitary gland adenomas.

Background

Two chronic feeding/oncogenicity studies, one of mice and the other of rats, were used for the qualitative risk assessment of triphenyltin hydroxide (TPTH).

Both the rat and mouse studies were conducted by RCC Laboratory for Hoechst-Celanese Corporation and submitted in April and in May, 1989 respectively. The NMRI mouse study (study no. 047002) included 50 males and 50 females, each assigned to one of four dose levels of 0, 5, 20, and 80 ppm. The Wistar rat study (study no. 046980) included 70 males and 70 females, each assigned to one of four dose levels of 0, 5, 20, and 80 ppm. In the rat study there was an interim sacrifice of 10 animals in each sex/dose group at week 53. Dietary exposures lasted 80 weeks for the mice and 104 weeks for the rats.

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Survival Anaylsis

In male mice there was no statistical evidence of dose related mortality either in the trend analysis or in the pair-wise comparisons of control and each dose group (Table 1).

In female mice there was a statistically significant ($p<.05$) increasing trend in mortality, but there was no significant differences between the control and any dose level (Table 2).

In male rats there were no significant differences in survival with incremental doses of TPTH (Table 3).

In female rats there was a significant ($p<.01$) dose related increasing trend in mortality. In addition, the pair-wise comparison with control and the mid and the high dose groups resulted in significant ($p<.01$) differences in mortality. Also significant ($p<.05$) was the difference between control and the low dose group (Table 4).

For both the mouse and the rat study, statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Tumor Analysis

In mice, elevated tumor activity was observed in the liver, in both sexes with dose increments of TPTH.

In male mice, since there was no significant dose related survival findings, the Cochran-Armitage Trend test and Fisher's Exact test for pair-wise comparisons with control was used to statistically evaluate incremental tumor rates in the liver by dose levels.

In male mice combined hepatocellular (adenomas and/or carcinomas) tumor rates had a significantly ($p<.01$) increasing trend with dose increments of TPTH, mainly due to the significantly ($p<.05$) increasing trend in the adenomas. In the pair-wise comparison with controls and the high (80ppm) dose level, there was a significant ($p<.01$) difference in the combined hepatocellular (adenoma and/or carcinoma) tumors and also in the hepatocellular adenoma only group. Also in the pair-wise comparison of control and mid (20ppm) dose level there was a statistically significant ($p<.05$) difference in the hepatocellular adenoma tumors (Table 5).

For the female mouse data, the Peto Prevalence method was most appropriate to use for the analysis of tumor rate changes with incremental doses of TPTH. However since all of the liver tumors occurred in only the high dose group after 58 weeks in the study, the Peto method failed to produce any results. Thus the Cochran-Armitage Trend test and the Fisher Exact test for pair-wise comparisons with controls was substituted for use in the statistical evaluations of tumor rates among the given dose levels of TPTH.

In female mice a significant ($p<.01$) dose related increasing trend occurred in the combined hepatocellular (adenoma and/or carcinoma) tumors, and separately in carinomas and in adenomas. Both the adenoma tumor rates and the combined (adenoma and/or carcinoma) tumors were significantly ($p<.01$) different in the pair-wise comparison of control and the highest (80ppm) dose group (Table 6).

For male rats, since there were no significant dose related mortality changes, the Cochran-Armitage Trend test and Fisher's Exact test for pairwise comparisons with control was used to statistically evaluate the Lydig cell tumors of the testes with dose increments of TPTH.

Male rats had a significant ($p<.01$) dose related increase in Lydig cell tumors with incremental doses of TPTH. These tumors were also signifiacantly ($p<.01$) different in the pair-wise comparison of the control and the highest (80ppm) dose group (Table 7).

Since Dr. Doherty designated the pituitary adenomas as possibly fatal, a statistical procedure for fatal tumors (which excluded all animals that were sacrificed from the analysis) was used to statistically evaluate the tumors in both sexes.

No statistically significant changes occurred in pituitary gland adenomas in male rats with increasing doses of TPTH (Table 7). However in female rats, the fatal tumor analysis indicated that there was a significant ($p<.01$) difference in the pituitary gland adenomas in the pair-wise comparison of controls with mid (20ppm) dose and the high (80ppm) dose groups of TPTH. Also pituitary gland adenomas in the females had a dose related trend only with borderline statistical significance ($p<.054$) with incremental doses of TPTH (Table 8).

Since the fatal tumor analysis of the pituitary gland adenomas in both sexes excluded data from the interim and final sacrificed groups, Tables 9 and 10 were prepared to show the total distribution of these tumors by different time periods as well as the totals that were observed throughout the rat study.

Table 1. TPTH - Male Mouse Study, Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks			
Dose(ppm)	1-26	27-52	53-80[a]	Total
0	0/50	1/50	10/49	11/50(22)
5	1/50	1/49	7/48	9/50(18)
20	0/50	3/50	13/47	16/50(32)
80	1/50	1/49	14/48	16/50(32)

[+] Number of animals that died during interval/ Number of animals alive at the beginning of the interval.

( ) percent

a Final sacrifice at weeks 81-83

Note: Time intervals were selected for display purposes only. Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level.

if * then $p<.05$ and if ** then $p<.01$.

Table 2. TPTH - Female Mouse Study, Mortality Rates+ and Cox or Generalized K/W Test Results

	Weeks			
Dose(ppm)	1-26	27-52	53-80[a]	Total
0	0/50	2/50	16/48	18/50(36)*
5	0/50	2/50	22/48	24/50(48)
20	0/50	1/50	19/49	20/50(40)
80	1/50	5/49	20/44	26/50(52)

+ Number of animals that died during interval/ Number of animals alive at the beginning of the interval.

( ) percent

a Final sacrifice at weeks 81-82

Note: Time intervals selected for display purposes only. Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level.

if * then $p<.05$ and if ** then $p<.01$.

Table 3. TPTH - Male Rat Study, Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose(ppm	1-26	27-52	53[a]	53-78	79-104[b]	Total
0	1/70	1/69	9/9	4/59	15/55	21/61(34)
5	0/70	0/70	10/10	2/60	12/58	14/60(23)
20	0/70	0/70	10/10	2/60	17/58	19/60(32)
80	0/70	0/70	10/10	1/60	12/59	13/60(22)

[+] Number of animals that died during interval/ Number of animals alive at the biginning of the interval.

( ) percent

a Interim sacrifice
b Final sacrifice at weeks 105-106.

Note: Time intervals selected for display purposes only.
Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

if * then $p<.05$ and if ** then $p<.01$.

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Table 4. TPTH - Female Rat Study, Morality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose(ppm)	1-26	27-52	53[a]	53-77	78-104[b]	Total
0	0/70	1/70	10/10	1/59	17/58	19/60(32)**
5	2/70	1/68	10/10	7/57	20/50	30/60(50)*
20	3/70	3/67	10/10	5/54	29/49	40/60(67)**
80	2/70	1/68	9/9	10/58	35/48	48/61(79)**

[+] Number of animals that died during interval/ Number of animals alive at the beginning of the interval.

( ) percent

a Interim sacrifice
b Final sacrifice at weeks 105-107

Note: Time intervals selected for display purposes only.
Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

if * then p<.05 and if ** then p<.01.

Table 5. TPTH - Male Mice, Hepatocellular Tumor Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose(ppm)			
Tumors	0	5.00	20.00	80.00
Adenoma	5/49	10[a]/48	13/47	15/48
(%)	(10)	(21)	(28)	(31)
p=	0.017*	0.122	0.026*	0.010**
Carcinoma	2[b]/49	1/48	0/47	3/48
(%)	(4)	(2)	(0)	(6)
p=	0.126	0.508(n)	0.258(n)	0.490
Both	7/49	11/48	13/47	18/48
(%)	(14)	(23)	(28)	(38)
p=	0.007**	0.203	0.086	0.008**

+ Number of tumor bearing animals/ Number of animals at risk (excluding those that died before 52 weeks).

(n) negative change from control.

a First adenoma observed at week 55, dose 5ppm
b First carcinoma observed at week 82, dose 0ppm

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

if * then $p<.05$ and if ** then $p<.01$.

Table 6. TPTH - Female Mice, Hepatocellular Tumor Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values)

	Dose(ppm)			
Tumor	0	5.00	20.00	80.00
Adenoma (%)	0/48 (0)	0/48 (0)	0/49 (0)	8[a]/44 (18)
p=	0.000**	1.000	1.000	0.002**
Carcinoma (%)	0/48 (0)	0/48 (0)	0/49 (0)	3[b]/44 (7)
p=	0.001**	1.000	1.000	0.106
Both (%)	0/48 (0)	0/48 (0)	0/49 (0)	11/44 (25)
p=	0.000**	1.000	1.000	0.000**

+ Number of tumor bearing animals/ Number of animals at risk, excluding those that died before 52 weeks.

a First adenoma observed at week 59, dose 80ppm.
b First carcinoma observed at week 72, dose 80ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

if * then p<.05 and if ** then p<.01.

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Table 7. TPTH - Male Rat, Tumor Rates[+] and Statistical Test Results (p values)

	Dose(ppm)			
Tumors	0	5.00	20.00	80.00
Testes Leydig(%) Cell	1/68 (1)	5/69 (7)	3/70 (4)	11[a]/70 (16)
$p^{++}=$	0.001**	0.108	0.321	0.003**
Pituitary Gland Adenoma(%)	10/19 (53)	7/13 (54)	12[b]/19 (63)	10/13 (77)
$p^{+++}=$	0.151	0.620	0.428	0.320

[+] Number of tumor bearing animal/ Number of animals at risk, excluding those that died before observation of the first tumor.

[++] Cochran-Armitage Trend test and Fisher Exact test results

[+++] Fatal tumor analytic results (Cox's test)
Excludes all final sacrificed animals from the analysis

a First Leydig cell tumor at week 53, dose 80ppm.
b First pituitary gland adenoma at week 53, dose 20ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

if * then $p<.05$ and if ** then $p<.01$.

Table 8. TPTH - Female Rat, Pituitary Gland Adenoma Tumor Rates[+] and Fatal Tumor Analytic Results (p values)

	Dose(ppm)			
Tumor	0	5.00	20.00	80.00
Pituitary Gland (%) Adenoma	14/19 (74)	20/29 (69)	33[a]/38 (87)	43/46 (93)
p=	0.054	0.028(n)	0.006**	0.010**

[+] Number of tumor bearing animals/ Number of animals at risk, excluding those that were killed at final sacrifice.

(n) negative change from control.

a First adenoma observed at week 48, dose 20ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

if * then $p<.05$ and if ** then $p<.01$.

Table 9. TPTH - Wistar Rats, Male Pituitary Adenoma Rates+ by Selected Time Periods

Dose (ppm)	Weeks 1-52	53-IS	53-77	78-104	FS	Total
0	-	3/9(33)	2/4(50)	8/15(53)	11/40(28)	24/70(34)
5	-	0/10(0)	1/2(50)	6/12(50)	13/36(36)	20/70(29)
20	-	2/10(20)	1/1(100)	11/18(61)	23/41(56)	37/70(53)
80	-	0/10(0)	1/1(100)	9/12(75)	16/47(34)	26/70(37)

+ Number of tumor bearing animals/Number of animals that died & were examined during this time period.

( ) percent

IS Interim Sacrifice
FS Final Sacrifice

Table 10. TPTH - Wistar Rats, Female Pituitary Adenomas by Selected Time Periods

Dose (ppm)	Weeks 1-52	53-IS	53-77	78-104	FS	Total
0	0/1(0)	1/10(10)	1/1(100)	13/17(76)	24/32(75)	39/70(56)
5	0/3(0)	1/10(10)	5/7(71)	15/20(75)	16/30(53)	37/70(53)
20	1/6(17)	0/10(0)	5/5(100)	27/29(93)	10/20(50)	43/70(61)
80	0/3(0)	2/9(22)	10/10(100)	33/35(94)	11/13(85)	56/70(80)

+ Number of tumor bearing animals/Number of animals that died & were examined during this time period.

( ) percent

IS Interim Sacrifice
FS Final Sacrifice