US EPA ARCHIVE DOCUMENT

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

005299

JUN 9 1986

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Testing for Decreasing Dose-Related Trends for Immunoglobulins G, A, M, in the 13-Week Clinical Biochemistry of Mouse Subchronic Feeding Studies with Triphenyltin Hydroxide (TPTH). EPA Reg. No. 8340-17

FROM: Richard Levy, Statistician
Mission Support Staff
Toxicology Branch/HED (TS-769)

TO: John Doherty, Toxicologist
Section II, Toxicology Branch/HED (TS-769)

THRU: Bertram Litt, Leader, Statistical Team
Mission Support Staff
Toxicology Branch/HED (TS-769)

THRU: Reto Engler, Chief
Mission Support Staff
Toxicology Branch/HED (TS-769)

OK

Summary:

Statistically significant ($p < .01$), decreasing, dose related trends are found in male and female mice for immunoglobulins (IgG, IgA, and IgM) after 13 weeks of TPTH treatment[1]. Thus, the immunoglobulin data cannot be considered incidental and of normal biological variation. Therefore, the significant decrease in the immunoglobulins G, A and M, in both sexes, strongly suggest an immunosuppressive response or decreased synthesis of the immunoglobulins.

Data Analysis:

Arranging the mouse immunoglobulin (IgG, IgA, and IgM) data in tabular form by group and frequency of observation (see attachement 1), attention is drawn to the recurrent measurements within each immunoglobulin type. This repeated occurrence and classification of values below the applicable detection limit, require that the data be, at best, considered discrete and ordered with an assumed continuous background population.

Using a distribution-free K sample trends test against order alternatives, p-values are calculated showing highly significant ($p < 0.01$) decreasing trends by dose, for immnoglobulins G, A and M (see attachment 2). These results are further verified by viewing the data in tables of attachment 1. For example, the male and female values of IgA classified as high, decreases, as the dose, increases. This also demonstrates the inherent order that is greatly influenced by the many low values in the high dose group.

REFERENCES

1. RCC (Research & Consulting Company AG), Project 046991, 13 Week Oral Toxicity (feeding) Study With TPTH-Technical, January 20, 1986, EPA Accession No. 261753.

2. IMSL Library Reference Manual, Ed. 9, Houston, Texas, June 1982, Volume 3, Subroutine NMHTS.

3. Walsh, J. E., Handbook of Non-Parametric Statistics, Vol. II, D. Van Nostrand Company, New Jersey, 326.

Attachment

#10 6/4/86 sb

005299

ATTACHMENT NO 1

FEMALE

IgG

	I	II	III	IV
30				2
32			1	1
34				2
38			1	
40				1
54				2
57	3	2		1
60	1	1	1	1
64	2	3		
70	1	1		
110		1	3	
115	1		3	
125	1	1		
130	1		1	
235		1		

IgA

	I	II	III	IV
*(44.4		2	2	7
44.4		1	4	
75.9	3	3	2	
111.0	1	3	2	
50.0	3	1		1
193.0	1			

IgM

	I	II	III	IV
(5.56				3
5.56		1	2	3
9.48				2
9.49	1		1	
13.90		4	1	2
14.80			1	
18.80	2	1	1	
18.90		1		
24.10	5	1	3	
29.90	1	2	1	
42.80	1			

MALE

IgG

	I	II	III	IV
30		1		
32	1			
40			1	2
54		1	1	4
57		2	3	3
60	1	3		
64		1		1
65	1			
70			1	
80	1		1	
110	3		1	
115	2			
125	1	1	1	
130		1		
220			1	

IgA

	I	II	III	IV
*(44.4	2		1	7
44.4	1	4	1	3
75.9	3	1	3	
111.0		2	2	
150.0			2	
193.0	2	3	1	
289.0	2			

IgM

	I	II	III	IV
(5.56	2		1	2
5.56	3		3	7
9.94	5	5	4	1
13.90		4	1	
18.80		1	1	

LEGEND: GROUP I 0 ppm
GROUP II 4 ppm
GROUP III 20 ppm
GROUP IV 100 ppm

* Value preceded by open an parenthesis are below the applicable detection limit.

ATTACHMENT NO. 2

K - Sample Trends Tests Against Ordered Alternatives*

	P - Value
IgG - Female	0.236787461E-02
IgA - Female	0.402884179E-04
IgM - Female	0.118121898E-04
IgG - Male	0.157631864E-02
IgA - Male	0.724312617E-03
IgM - Male	0.377132744E-02

* NMKTS[2] was used to perform a distribution-free K sample trends test against ordered alternatives. This test is essentially equivalent to Terpstra's test[3]. A basic assumption of continuous background populations is required. NMKTS follows two choices when ties occur between samples. The one chosen unties ties by randomization.