



8EHQ-0302-15097

GE Specialty Chemicals

General Electric Company  
1000 Morgantown Industrial Park  
Morgantown, WV 26501

MR 56673



8EHQ-02-15097

**CERTIFIED MAIL R.R.R.**

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February 22, 2002

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Office of Pollution Prevention and Toxics  
US Environmental Protection Agency  
401 M Street, SW  
Washington, DC 20460

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2002 APR 11 11:11:49  
CERTIFIED MAIL

Attn: TSCA 8(e) Coordinator

Re: Phosphorous Acid, Cyclic Neopentetetrayl Diphenyl Ester (DPPEDP)  
CAS Number 144-35-4

This submission is made by:

General Electric Specialty Materials  
GE Specialty Chemicals (GESC)  
1000 Morgantown Industrial Park  
Morgantown, WV 26501 USA



88020000083

GESC is currently sponsoring a study entitled *Range-finding Study for the Combined Repeated Dose Toxicity Study With Reproductive/ Developmental Toxicity Screening Test of Diphenyl Pentaerythritol Diphosphite (DPPEDP) Administered by Gavage to CD® (Sprague-Dawley) Rats (OECD 422)* at RTI International (formerly Research Triangle Institute). The laboratory has reported interim results from the range-finding study that GESC is submitting pursuant to current guidance issued by the Environmental Protection Agency (EPA) giving EPA's interpretation of Section 8(e) of the Toxic Substances Control Act. DPPEDP is a site-limited intermediate that does not leave the closed system from production to interim storage to subsequent use in manufacturing the final material for which it is an intermediate. The possibility of worker exposure is extremely small and when the closed system is interrupted for maintenance or repair, the workers are protected by appropriate personal protective equipment. DPPEDP is highly irritating and protective equipment used to prevent that exposure is sufficient to protect from other potential exposures. DPPEDP may contain up to 15% of triphenyl phosphite (CAS # 101-02-0), which is a starting material in its production.

The preliminary range-finding results reported by the laboratory indicate excessive toxicity to both the males and females at all three DPPEDP doses (100, 300, and 1000 mg/kg/day). All treated groups were terminated early, with all animals in all groups exhibiting morbidity prior to demise. There was a dose response on the study day of termination, earliest at 1000 mg/kg/day, and latest at 100 mg/kg/day; weight loss was similarly dose related. The clinical observations were dominated by hindlimb weakness in all

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groups, and the gross findings were dominated by lesions in the stomach (the nonglandular portion) and little or no ingesta in the entire gastrointestinal tract. Weight loss increased over time in all three doses, i.e., the animals were not adjusting successfully to the doses employed.

Based on the recommendations of the testing laboratory, a second range-finding study with the same study design and endpoints will be conducted at three lower doses (1, 10, and 50 mg/kg/day). The selection of doses for the second range-finding study were based on the desire to provide a top dose with some signs of toxicity, a middle dose with little or no signs of toxicity, and a lowest dose with no signs of toxicity.

The results of the second range-finding study are expected in March 2002 and the definitive study will be started shortly thereafter with doses derived from the second range-finding study. Results of these studies will be sent to EPA when completed.

Please do not hesitate to contact me if you have general questions at (304) 284-2214 or Dr. Ronald L. Joiner at (413) 448-6323 if you have technical questions.

Sincerely,  
GE Specialty Chemicals



Sheri L. Blystone, Ph. D.  
Product Steward  
(304) 284-2231 (fax)  
Sheri.Blystone@gesm.ge.com

cc: Stephen F. Austin  
Ronald L. Joiner, Ph. D.

Attachment



Chemistry and Life Sciences

3040 Cornwallis Road ■ PO Box 12194 ■ Research Triangle Park, NC 27709-2194 ■ USA  
Telephone 919-541-5972 ■ Fax 919-541-5956 ■ rwt@rti.org ■ www.rti.org

Rochelle W. Tyl, Ph.D., DABT  
Research Director  
Life Sciences and Toxicology

January 30, 2002

Dr. Ronald L. Joiner  
Manager, Global Toxicology  
General Electric Company  
One Plastics Avenue  
Pittsfield, MA 01201

Re: RTI Project No. 07895.100

Dear Dr. Joiner:

Please consider this correspondence the letter report detailing the results of the study entitled "Range-finding Study for the Combined Repeated Dose Toxicity Study With Reproductive/Developmental Toxicity Screening Test of Diphenyl Pentaerythritol Diphosphite (DPPEDP) Administered by Gavage to CD® (Sprague-Dawley) Rats (OECD 422)" (RTI Study Code Rt02-GE5A). This preliminary study was not performed under formal GLP compliance.

As you recall, the study design involved five male and five female rats per group (and four groups) administered DPPEDP by oral gavage once daily for ten consecutive days at 0, 100, 300, and 1000 mg/kg/day (vehicle was Mazola® corn oil and dosing volume was 5 ml/kg). Study animals were to be weighed on sd 0 (first day of dosing), 2, 4, 6, 8, 9 (last day of dosing), and 10 (day of necropsy). Clinical observations of all animals were recorded at least once daily. At scheduled necropsy of surviving animals, the following organs were to be weighed: for both sexes the kidneys (paired), brain, and liver; for females also the paired ovaries; for males also the paired testes.

## RESULTS

The results are presented in six summary tables (attached), with data presented as mean ± SEM and statistical analyses performed to identify any effects of treatment.

### Males

No males in any of the DPPEDP-dosed groups survived to the last day of dosing (sd 9) or to scheduled necropsy on sd 10. When greater than 50% of the males in each group had died or were sacrificed moribund, the remaining males in that group were euthanized for humane reasons. Male body weights were equivalent across all groups on sd 0. By sd 2, body weights were significantly reduced at 300 and 1000 mg/kg/day. By sd 6, body weights at 100 mg/kg/day were also significantly reduced. Body weight change was significantly reduced at 300 and 1000

mg/kg/day for sd 0-2. For sd 2-4, all three treatment groups exhibited significantly reduced weight gain. By sd 6-8, with only the control and 100 mg/kg/day group males remaining, the controls gained an average of 3.3 g for the interval; the males at 100 mg/kg/day lost an average of 28 g. All four remaining males at 1000 mg/kg/day were euthanized moribund on sd 6, all five males at 300 mg/kg/day were euthanized moribund on sd 7, and all five males at 100 mg/kg/day were euthanized moribund on sd 7. The definition of "moribund" for this study was greater than a 10% loss of body weight, profound clinical signs, and reduced or no feed consumption (evaluated visually). All five males in the vehicle control group were euthanized on sd 9 since there were no DPPEDP-dosed males left on study in any of the groups (Table 1).

Clinical observations are presented in Table 2. Prior to euthanization, the treated males exhibited ataxia, audible breathing, lethargy, piloerection, rough coat, chromodacryorrhea, rust-colored fur (from grooming the pigment from the eyes), feces soft or matted to perianal area, hindlimb splay, lack of support of hindlimbs, and rooting in bedding postdose. This last observation is not indicative of toxicity but most likely of the "bad taste" of the dosing solution, exhibiting a dose-related pattern of 0, 1, 1, and 5 males at 0, 100, 300, and 1000 mg/kg/day, respectively.

Gross findings of the males during unscheduled necropsy (Table 3) indicated little or no ingesta (feed) and dark green ingesta in stomach, small and large intestine, stomach smooth (nonglandular) portion reddened with local pinpoint ulcerations, sloughing of the smooth lining, and smooth lining thickened and white. Chromodacryorrhea on nose and paws (the latter from grooming) was also observed in one male at 1000 mg/kg/day. The control males were not necropsied.

### Females

As with the males, no females in any of the DPPEDP-dosed groups survived to scheduled necropsy on gd 10. By gd 4, females at 1000 mg/kg/day exhibited significantly reduced body weights. By sd 6, all three dosed groups exhibited significantly reduced body weights. Body weight change was significantly reduced at 1000 mg/kg/day for sd 0-2 and in all groups for sd 2-4. For sd 4-6 (sd 6 being the last day all females in all groups were still on study), the control females gained an average of 1.2 g, the females at 100 mg/kg/day lost 12.4 g, the females at 300 mg/kg/day lost 18.1 g, and the females at 1000 mg/kg/day lost 21.8 g.

All females were euthanized moribund at 1000 mg/kg/day on sd 6, all females were euthanized moribund at 300 mg/kg/day on sd 7, and all females at 100 mg/kg/day were euthanized moribund on sd 7. The control females were euthanized on sd 9 since all treated females in all groups had already been euthanized (Table 4).

Clinical observations are presented in Table 5. The observations of females prior to euthanasia were identical to those of the males prior to euthanasia in the DPPEDP-treated groups, with loss of hindlimb function (ataxia, unnatural gait of hindlimbs, hindlimb splaying, cannot use hindlimbs), chromodacryorrhea and rust-colored fur, lethargy, piloerection, rough coat, prone position, and rooting in bedding postdosing; the last with an incidence identical to the males (0, 1, 1, and 5 females at 0, 100, 300, and 1000 mg/kg/day, respectively (Table 5).

Gross findings from the unscheduled necropsy of the DPPEDP-treated females are presented in Table 6. The five control females were not necropsied. The gross findings in the gastrointestinal tract, including little or no ingesta and effects on the smooth (nonglandular) portion of the stomach, were exactly the same as in the treated males. In addition, one female at 100 mg/kg/day exhibited bilateral pale kidneys, with 1-2 mm darkened areas on the surface, and one female at 300 mg/kg/day exhibited multiple dark red areas on all lobes of the lungs (Table 6).

### SUMMARY

In summary, all three DPPEDP doses (100, 300, and 1000 mg/kg/day) were excessively toxic to both the males and females. All treated groups were terminated early, with all animals in all groups exhibiting morbidity prior to demise. There was a dose response on the study day of termination, earliest at 1000 mg/kg/day, and latest at 100 mg/kg/day; weight loss was similarly dose related. The clinical observations were dominated by hindlimb weakness in all groups, and the gross findings were dominated by lesions in the stomach (the nonglandular portion) and little or no ingesta in the entire gastrointestinal tract. Figure 1 presents the treated male body weights as percentage of the control body weight on sd 2, 4, and 6 for 0, 100, and 300 mg/kg/day. For each of the two graphed doses (and for the 1000 mg/kg/day group not graphed), the weight loss increased over time, i.e., the animals were not adjusting successfully to the dose levels employed.

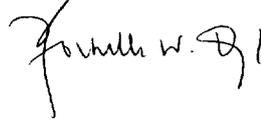
### RECOMMENDATIONS

Based on the excessive toxicity in both sexes at all DPPEDP doses, I strongly recommend a second range-finding study with the same study design and endpoints. The selection of target doses for the second range-finding study can be crudely derived from the grid on Figure 1 for males. If we assume linearity of body weights from 0 to 100 mg/kg/day (and that is not necessarily a reasonable assumption), then 10 mg/kg/day would result in a 1% weight loss by day 6, 20 mg/kg/day would result in a 2% weight loss, and 50 mg/kg/day would result in greater than a 5% weight loss by sd 6. Please note that these values in Figure 1 were reductions relative to the control group value, but they also represent actual weight losses (not reduced weight gain) from the sd 0 weight for both males (Table 1) and females (Table 4) at all doses. The definitive study will involve dosing F0 males for four weeks (28 days) and F0 females for six to eight weeks (42-56 days), and direct dosing of the F1 offspring for seven weeks (49 days). The range-finding animals did not adjust to the very high doses over a ten-day period. Therefore, I recommend 0, 0.1, 1.0, and 10.0 mg/kg/day (or 0, 1.0, 2.0, and 20.0 mg/kg/day; or 0, 1.0, 3.0, and 30.0 mg/kg/day) for the second range-finding study. My preference is 0, 0.1, and 10.0 mg/kg/day. We have stability at 2 and 200 mg/ml. If we change the dosing volume from 5.0 ml/kg to 1.0 ml/kg, we will still have to perform homogeneity and stability on 0.1 mg/ml formulation (to get 0.1 mg/kg/day). If we keep the same dosing volume, we will have to do homogeneity and stability at 0.02 mg/ml (to get 0.1 mg/kg/day).

Dr. Ronald L. Joiner  
January 30, 2002  
Page 4

Let me know at your earliest convenience of your decision to perform a second range-finding study and target doses for the study if performed.

Sincerely,

A handwritten signature in black ink, appearing to read "Rochelle W. Tyl". The signature is fluid and cursive, with a large initial "R" and "T".

Rochelle W. Tyl, Ph.D., DABT  
Study Director/Research Director  
Center for Life Sciences & Toxicology

RWT/cw  
Attachments

cc: M.C. Marr  
C.B. Myers  
N.P. Castillo (lo)  
M.M. Veselica (lo)  
C.S. Parker (lo)

Table 1. Summary and Statistical Analysis of the Male Body Weights and Weight Changes  
 (page 1 of 2)

	Diphenyl Pentaerythritol Diphosphite (mg/kg/day, po)			
	0	100	300	1000
No. Males on Study	5	5	5	5
Body Weight (sd 0) (g) <sup>a</sup>	336.3 ± 7.5 N=5	333.6 ± 3.8 N=5	330.6 ± 4.3 N=5	336.5 ± 5.7 N=5
Body Weight (sd 2) (g) <sup>a</sup> #	347.1 ††† ± 8.2 ††† N=5	343.4 ± 3.2 N=5	328.4 † ± 4.0 N=5	321.5 † ± 7.5 N=5
Body Weight (sd 4) (g) <sup>a</sup> #	351.4 ††† ± 10.6 ††† N=5	334.2 ± 4.5 N=5	319.4 †† ± 4.3 N=5	301.4 ††† ± 8.2 N=5
Body Weight (sd 6) (g) <sup>a</sup>	357.3 ††† ± 11.4 ††† N=5	318.5 * ± 7.8 N=5	295.3 *** ± 8.0 N=5	270.3 *** ± 9.1 N=4 <sup>b</sup>
Body Weight (sd 8) (g) <sup>a</sup>	360.6 ††† ± 11.8 ††† N=5 <sup>c</sup>	290.8 *** ± 6.1 N=5 <sup>d</sup>	± . N=0 <sup>e</sup>	± . N=0 <sup>f</sup>
Body Weight Change (sd 0 to 2) (g) <sup>a</sup>	10.8 ††† ± 1.7 ††† N=5	9.9 ± 1.8 N=5	-2.2 ** ± 2.0 N=5	-14.9 *** ± 3.3 N=5
Body Weight Change (sd 2 to 4) (g) <sup>a</sup>	4.3 †† ± 2.9 ††† N=5	-9.2 * ± 3.2 N=5	-9.0 * ± 3.6 N=5	-20.1 *** ± 4.1 N=5
Body Weight Change (sd 4 to 6) (g) <sup>a</sup>	5.9 ††† ± 1.1 †† N=5	-15.8 ** ± 4.8 N=5	-24.1 *** ± 4.0 N=5	-30.1 *** ± 2.0 N=4 <sup>b</sup>

(continued)

Table 1. Summary and Statistical Analysis of the Male Body Weights and Weight Changes  
 (page 2 of 2)

	Diphenyl Pentaerythritol Diphosphite (mg/kg/day, po)			
	0	100	300	1000
Body Weight Change (sd 6 to 8) (g) <sup>a</sup>	3.3 ††† ± 0.8 ††† N=5 <sup>c</sup>	-27.7 *** ± 3.0 N=5 <sup>d</sup>	± . N=0 <sup>e</sup>	± . N=0 <sup>f</sup>

<sup>a</sup>Reported as the mean ± S.E.M.; sd = study day with the first day of exposure being study day 0.

<sup>b</sup>Decrease in N is due to one male being euthanized moribund on study day 4.

<sup>c</sup>All males in this group were euthanized on study day 9 since all of the dosed animals had already been euthanized.

<sup>d</sup>All males in this group were euthanized moribund on study day 8.

<sup>e</sup>All males in this group were euthanized moribund on study day 7.

<sup>f</sup>All remaining males in this group were euthanized moribund on study day 6.

#Levene's test for homogeneity of variances was significant (p<0.05). Therefore, robust regression methods were used to test all treatment effects.

†††p<0.001; Wald Chi-square Test for overall treatment effect in robust linear regression model.

†p<0.05; Individual t-test for pairwise comparisons to control in robust linear regression model.

††p<0.01; Individual t-test for pairwise comparisons to control in robust linear regression model.

†††p<0.001; Individual t-test for pairwise comparisons to control in robust linear regression model.

††p<0.01; Linear trend test in robust regression model.

†††p<0.001; Linear trend test in robust regression model.

††p<0.01; ANOVA Test.

†††p<0.001; ANOVA Test.

\*p<0.05; Dunnett's Test for pairwise comparisons to control.

\*\*p<0.01; Dunnett's Test for pairwise comparisons to control.

\*\*\*p<0.001; Dunnett's Test for pairwise comparisons to control.

††p<0.01; Test for Linear Trend.

†††p<0.001; Test for Linear Trend.

Table 2. Summary of the Male Clinical Observations (page 1 of 2)

**A. Clinical Observations Summarized by Group**

Observation	Diphenyl Pentaerythritol Diphosphite (mg/kg/day, po)			
	0	100	300	1000
Animal received 0.05 ml more of the dosing solution than it should have	1			
Ataxia		1	1	4
Audible breathing, postdosing		1		
Chromodacryorrhea		1	1	2
Efflux of the dosing solution	2	1	3	3
Euthanized moribund		5	5	5
Euthanized since all of the dosed animals had already been euthanized	5			
Feces: soft and/or matted to tail or perianal area				3
Hindlimb splay		3	5	1
Lethargic			2	
No support of hindlimbs				1
Piloerection			1	2
Rooting, postdosing		1	1	5
Rough coat			5	3
Rust-colored fur: back			1	

**B. Clinical Observations Summarized by Group and Day**

Day <sup>a</sup>	Observation <sup>b</sup>	Diphenyl Pentaerythritol Diphosphite (mg/kg/day, po)			
		0	100	300	1000
0	Audible breathing, postdosing		1		
	Efflux of the dosing solution		1	1	
1	Chromodacryorrhea: nose				1
	Efflux of the dosing solution			1	
	Rooting, postdosing				2
2	Animal received 0.05 ml more of the dosing solution than it should have	1			
	Chromodacryorrhea: nose				1
	Efflux of the dosing solution	1			
	Rooting, postdosing			1	3
3	Animal received 0.05 ml more of the dosing solution than it should have	1			
	Efflux of the dosing solution	1	1		1
	Rooting, postdosing		1		4
4	Efflux of the dosing solution			2	2
	Euthanized moribund				1
	Feces: soft				1
	Piloerection				1
	Rooting, postdosing			1	3
5	Rooting, postdosing				1

(continued)

Table 2. Summary of the Male Clinical Observations (page 2 of 2)

**B. Clinical Observations Summarized by Group and Day**

Day <sup>a</sup>	Observation <sup>b</sup>	Diphenyl Pentaerythritol Diphosphite (mg/kg/day, po)			
		0	100	300	1000
6	Ataxia			1	3
	Ataxia: severe				1
	Euthanized moribund				4
	Feces: matted to perianal area				1
	matted to tail				1
	present in perianal area and soft				1
	soft				1
	Hindlimb splay				1
	No support of hindlimbs				1
	Piloerection			1	1
	Rooting, post dosing				3
	Rough coat				3
	7	Ataxia: severe			1
Chromodacryorrhea				1	
Euthanized moribund				5	
Hindlimb splay				4	
Hindlimb splay, unable to use hindlimbs				1	
Lethargic				2	
Rough coat				5	
Rust colored fur: back				1	
8	Ataxia		1		
	Chromodacryorrhea: nose		1		
	Euthanized moribund		5		
	Hindlimb splay		3		
9	Euthanized since all of the dosed animal had already been euthanized	5			

<sup>a</sup>Study day.

<sup>b</sup>Clinical observations are tabulated once per day per animal.

Table 3. Summary of the Male Gross Necropsy Findings (page 1 of 1)

**Gross Findings for Unscheduled Necropsy<sup>a</sup>**

Finding	Diphenyl Pentaerythritol Diphosphite (mg/kg/day, po)			
	0	100	300	1000
Chromodacryorrhea: nose and paws				1
Large Intestines: no feces		1		3
no ingesta or feces				1
soft feces				1
Lung: red foci all lobes				1
Small Intestines: abnormally dark green ingesta		1		
abnormally dark ingesta		1		
distended with gas				1
little ingesta				1
no ingesta		2		
no ingesta or feces				1
very little ingesta				2
Stomach: abnormally dark green food			1	
abnormally distended with large amount of food			1	
lining of smooth portion thickened and white				2
lining of smooth portion white and easily sloughed off with reddened area underneath				1
little food		1		
multiple pinpoint ulcerations in lining of smooth portion		1	2	
no food		1		1
smooth portion reddened				1

<sup>a</sup>All animals were unscheduled necropsies and the control animals were not necropsied.

Table 4. Summary and Statistical Analysis of the Female Body Weights and Weight Changes  
 (page 1 of 2)

	Diphenyl Pentaerythritol Diphosphite (mg/kg/day, po)			
	0	100	300	1000
No. Females on Study	5	5	5	5
Body Weight (sd 0) (g) <sup>a</sup>	235.8 ± 6.9 N=5	226.4 ± 4.4 N=5	229.1 ± 2.6 N=5	231.1 ± 2.3 N=5
Body Weight (sd 2) (g) <sup>a</sup>	236.1 ± 5.1 § N=5	226.6 ± 4.3 N=5	228.0 ± 4.0 N=5	217.2 ± 5.9 N=5
Body Weight (sd 4) (g) <sup>a</sup>	243.8 †† ± 5.9 §§ N=5	224.3 ± 4.4 N=5	224.9 ± 2.7 N=5	210.7 ** ± 7.7 N=5
Body Weight (sd 6) (g) <sup>a</sup>	245.0 ††† ± 3.6 §§§ N=5	211.9 ** ± 5.6 N=5	206.7 ** ± 2.2 N=5	188.8 *** ± 10.1 N=5
Body Weight (sd 8) (g) <sup>a</sup>	247.7 ± 7.6 N=5 <sup>b</sup>	. ± . N=0 <sup>c</sup>	. ± . N=0 <sup>d</sup>	. ± . N=0 <sup>e</sup>
Body Weight Change (sd 0 to 2) (g) <sup>a</sup>	0.3 †† ± 2.0 §§§ N=5	0.1 ± 1.2 N=5	-1.1 ± 2.4 N=5	-13.9 ** ± 4.2 N=5
Body Weight Change (sd 2 to 4) (g) <sup>a</sup> #	7.7 ††† ± 1.0 ¥ N=5	-2.2 ††† ± 2.4 N=5	-3.1 ††† ± 1.7 N=5	-6.6 †† ± 4.6 N=5
Body Weight Change (sd 4 to 6) (g) <sup>a</sup>	1.2 ††† ± 3.3 §§ N=5	-12.4 ** ± 2.2 N=5	-18.1 *** ± 2.4 N=5	-21.8 *** ± 2.8 N=5

(continued)

Table 4. Summary and Statistical Analysis of the Female Body Weights and Weight Changes  
 (page 2 of 2)

	Diphenyl Pentaerythritol Diphosphite (mg/kg/day, po)			
	0	100	300	1000
Body Weight Change (sd 6 to 8) (g) <sup>a</sup>				
	2.7	.	.	.
	$\pm$ 4.9	$\pm$ .	$\pm$ .	$\pm$ .
	N=5 <sup>b</sup>	N=0 <sup>c</sup>	N=0 <sup>d</sup>	N=0 <sup>e</sup>

<sup>a</sup>Reported as the mean  $\pm$  S.E.M.; sd = study day, with the first day of exposure being study day 0.

<sup>b</sup>All females in this group were euthanized on study day 9 since all of the dosed animals had already been euthanized.

<sup>c</sup>Four females in this group were euthanized moribund on study day 7, and one female was euthanized on study day 7 since 80% of this dose group had already been euthanized.

<sup>d</sup>All females in this group were euthanized moribund on study day 7.

<sup>e</sup>All females in this group were euthanized moribund on study day 6.

#Levene's test for homogeneity of variances was significant ( $p < 0.05$ ). Therefore, robust regression methods were used to test all treatment effects.

†† $p < 0.01$ ; ANOVA Test.

††† $p < 0.001$ ; ANOVA Test.

\*\* $p < 0.01$ ; Dunnett's Test for pairwise comparisons to control.

\*\*\* $p < 0.001$ ; Dunnett's Test for pairwise comparisons to control.

\$ $p < 0.05$ ; Test for Linear Trend.

\$\$ $p < 0.01$ ; Test for Linear Trend.

\$\$\$ $p < 0.001$ ; Test for Linear Trend.

†††† $p < 0.001$ ; Wald Chi-square Test for overall treatment effect in robust linear regression model.

††††† $p < 0.01$ ; Individual t-test for pairwise comparisons to control in robust linear regression model.

†††††† $p < 0.001$ ; Individual t-test for pairwise comparisons to control in robust linear regression model.

††††††† $p < 0.05$ ; Linear trend test in robust regression model.

Table 5. Summary of the Female Clinical Observations (page 1 of 2)

**A. Clinical Observations Summarized by Group**

Observation	Diphenyl Pentaerythritol Diphosphite (mg/kg/day, po)			
	0	100	300	1000
Ataxia		1	1	4
Cannot use hindlimbs		1	1	2
Chromodacryorrhea		1	3	2
Dragging hindlimbs				1
Efflux of the dosing solution	2	2	3	2
Euthanized moribund		4	5	5
Euthanized since 80% of this group had already been euthanized moribund		1		
Euthanized since all of the dosed animals had already been euthanized	5			
Hindlimb splay		2	4	
Lethargic			1	1
No support of hindlimbs			3	
Piloerection		2		
Prone			1	1
Rooting, postdosing		1	1	5
Rough coat			4	5
Rust-colored fur		2	1	
Unnatural gait of hindlimbs		3		

**B. Clinical Observations Summarized by Group and Day**

Day <sup>a</sup>	Observation <sup>b</sup>	Diphenyl Pentaerythritol Diphosphite (mg/kg/day, po)			
		0	100	300	1000
0	Efflux of the dosing solution		2	1	
1	Efflux of the dosing solution	2			2
	Rooting, pos dosing				1
3	Rooting, postdosing				1
4	Efflux of the dosing solution			2	
	Rooting, postdosing			1	1
5	Dragging hindlimbs				1
	Lethargic				1
	Rooting, postdosing				5
6	Ataxia				2
	Ataxia: severe				2
	Cannot use hindlimbs				2
	Chromodacryorrhea				2
	Chromodacryorrhea: mouth and paws			1	
	Euthanized moribund				5
	No support of hindlimbs			3	
	Prone				1
	Rooting, postdosing		1		2
	Rough coat				5

(continued)



Table 6. Summary of the Female Gross Necropsy Findings (page 1 of 1)

**Gross Findings for Unscheduled Necropsy<sup>a</sup>**

Finding	Diphenyl Pentaerythritol Diphosphite (mg/kg/day, po)			
	0	100	300	1000
Kidney: pale with 1-2 mm darkened areas on surface, bilateral		1		
Large Intestines: little ingesta or feces		1	1	
no feces			1	
Lung: multiple dark red areas all lobes			1	
Small Intestines: abnormally dark green ingesta		2	2	
little ingesta		1	2	
little ingesta or feces		1	1	
Stomach: abnormally dark green food		1	1	
lining of smooth portion thickened and white				4
lining of smooth portion thickened and white and sloughing				1
little food		1		
multiple pinpoint to 1 mm ulcerations in lining of smooth portion			1	
multiple pinpoint ulcerations in lining of smooth portion			3	
small amount of abnormally dark green food		1		
very little food		1		

<sup>a</sup>All animals were unscheduled necropsies and the control animals were not necropsied.

Figure 1

