

201-14200

Ciba Specialty Chemicals Corporation
Business Support Group
540 White Plains Road
Tarrytown, New York USA 10591

RECEIVED
OPPT NCIC

2003 JAN -2 PM 2:45



US Environmental Protection Agency
HPV Challenge
Attn: Oscar Hernandez, Director
Risk Assessment Division
P.O. Box 1473
Marrifield, VA 22116

December 20, 2002

Subject: Response to EPA Comments on the HPV Challenge Test Plan for the Phenolic Benzotriazole Category

Dear Dr. Hernandez:

Ciba Specialty Chemicals Corporation and Cytec Industries Inc. submitted a test plan and robust summaries to the EPA for the phenolic benzotriazole category in October 2001. EPA posted comments on the test plan on June 19, 2002.

EPA generally agreed with the submitted test plan. There were two areas, however, where additional information was recommended:

Reproduction Testing

- The original study plan proposed conducting reproductive toxicity studies. The agency responded that reproductive/developmental toxicity endpoints might be satisfied if existing repeated-dose studies had adequate evaluation of reproductive organs and if developmental toxicity studies were available.
- In the enclosed document, a review of available testing related to reproduction is provided. It is concluded from this review that existing data satisfy reproductive/developmental toxicity endpoints and no further testing is necessary.

Ecotoxicity and Chemistry Testing

- The agency proposed that the submitted solubility data on the four compounds was inadequate and that studies should be conducted to measure the solubility unless the value is less than or equal to 1µg/L. Based on the results of this testing, "the least hydrophobic chemical should be re-tested at or below its water solubility limit for acute toxicity in fish. If effects are observed, the submitter should proceed to acute toxicity testing on invertebrates and algae. If no effects are observed in the fish acute test, no further acute testing would be warranted."

- While Ciba Specialty Chemicals and Cytec believe that the available acute aquatic toxicity studies provide adequate information for safety assessment purposes, we agree to conduct the additional solubility and acute fish toxicity testing. The testing will be conducted in 2003 and provided to the agency as soon as it is completed.

Sincerely yours,

Richard Balcomb
Head, Toxicology and Environmental Assessments

For joint sponsors:

Ciba Specialty Chemicals Corporation
540 White Plains Road
Tarrytown, New York 10591

Cytec Industries Inc.
Five Garret Mountain Plaza
West Paterson, NJ 07424

Enclosure

Review of the Existing Reproductive Toxicity Testing
For four Phenolic Benzotriazoles

In the initial submission on the phenolic benzotriazole category, reproductive toxicity testing was listed as a data gap. EPA's comments indicated that this requirement may be satisfied if reproductive organs were adequately evaluated in repeat-dose testing and if developmental toxicity studies are available. We have reevaluated the available data and concluded that sufficient information does exist to satisfy the requirement for reproductive toxicity testing.

The available testing related to reproduction for the four phenolic benzotriazole compounds included in this category is summarized in the following table and discussion (summaries of the repeat-dose studies with additional details related to reproductive organs are provided in the appendix):

Test	CAS 2440-22-4	CAS 3147-75-9	CAS 25973-55-1	CAS 70321-86-7
Teratology / Development	Rat and Mouse NOEL = 1000 mg/kg *	Not tested	Not tested	Rat NOEL = 3000 mg/kg*
Repeat-dose: Rodent	No effect on reproductive organs (24-month studies Rat and Mouse)	Not tested	No effect on reproductive organs 90-day rat study [organ weights only]	No effect on reproductive organs 90-day rat study
Repeat-dose: Non-rodent	No effect on reproductive organs 90-day dog study	Not tested	Treatment effects noted on male and female reproductive organs 90-day dog study	Not tested

*highest dose tested

Teratology / Developmental Toxicity. Studies are available in rats and mice for CAS 2440-22-4 and in rats for CAS 70321-86-7.

- Testing for CAS 2440-22-4 showed no maternal toxicity, no effects on rates of implantation, no embryotoxicity and no teratogenic effects at doses of 0, 150, 500 and 1000 mg/kg/day in rats or mice.

- Testing in rats (0, 300, 1000 and 3000 mg/kg/day) for CAS 70321-86-7 showed no maternal toxicity or treatment effects on pregnancy rates, embryo mortality or fetal development.

Repeat-Dose Toxicity Testing (Rodents). Repeat-dose testing that includes histological and reproductive organ weight analysis is available for CAS 2440-22-4 and CAS 70321-86-7. A 90-day rat study was available for CAS 25973-55-1, however, only gonad weights were examined.

- The studies for CAS 2440-22-4 and CAS 70321-86-7 showed no treatment-related effects on reproductive organs.
- The 90-day rat study for CAS 25973-55-1 evaluated testis and ovary weights and found no treatment-related effects. No histopathology was done on reproductive organs.

Repeat-Dose Toxicity Testing (Non-rodents). Repeat-dose testing in dogs with histological and reproductive organ weight analysis is available for CAS 2440-22-4 and CAS 25973-55-1.

- The 90-day dog study for CAS 2440-22-4 showed no histological effects or effects on organ weights related to treatment.
- In the 90-day study for CAS 25973-55-1, dogs were treated with doses of 0, 15, 30, 60, 120 and 240 mg/kg/day. Treatment levels of 60, 120 and 240 mg/kg/day reduced food consumption and body weights and caused histopathological effects in liver, kidney, and testes. Atrophy of the uterus was also noted at higher doses. Effects were more pronounced in male dogs and one male died in the high dose group in week 8 (the attached study summary in the appendix provides details of effects on reproductive organs).

Based on this body of evidence, it is concluded that:

- Available developmental / teratogenicity toxicity testing is adequate and does not indicate the benzotriazole compounds in this category cause developmental or teratogenic effects
- Available rodent repeat-dose testing is adequate and does not indicate that male or female reproductive organs are affected by the benzotriazole compounds in this category
- Of the two available repeat-dose tests with dogs, one provides reliable evidence that indicates neither male or female reproductive organs were affected by CAS 2440-22-4. Testing in dogs with a second compound, CAS 25973-55-1, indicates effects on testes and uterus, however, the principal effects occur at doses that cause broad systemic toxicity and body weight loss.
- Results of the dog study with CAS 25973-55-1 should be given some consideration but are of limited value in assessing the potential reproductive hazards of the chemicals in this category given the number and consistency of the studies available for rodents. Furthermore, the noted testicular lesions are common in control dogs, may be greatly enhanced in cases of toxicity or stress¹, and therefore may be a secondary effect that should not be generalized.

¹ Rehm, S. 2000. Spontaneous testicular lesions in purpose-bred beagle dogs. *Toxicologic Pathology*, 28 (6): 782-787.

- Additional reproduction testing is considered unnecessary as rodents have shown in all studies that reproductive organs and fetal development are not affected and regulatory protocols for reproduction studies are not available for dogs.

APPENDIX: Summaries for Repeat-dose Studies²

² The summaries presented here are intended to provide additional details on the evaluation of reproductive organs; see robust summaries submitted previously for other study information.

CAS No. 2440-22-4

A. 24-Month Toxicity Study in Rats:

Test substance: 2-(2'-Hydroxy-5'-methylphenyl) benzotriazole
CAS No. 2440-22-4

Method: Five hundred, 25 ± 1 days old, CFY rats, a hysterectomy-derived strain of Sprague-Dawley origin, were obtained for allocation to the following five treatment groups:

	<u>Group and treatment</u>	<u>No. of rats</u>	
		males	females
1	Control (untreated diet)	50	50
2	100 ppm	50	50
3	300 ppm	50	50
4	1000 ppm	50	50
5	3000 ppm	50	50

Species/strain: Rats (CFY strain)

Age: 25 ± 1 days old

No. of animals/group: 50 males and 50 females/group

Route of administration: Dietary

Total duration of dietary intake: 104 weeks

Frequency of treatment: Daily

Dose: 100 ppm (4-6 mg/kg bodyweight/day)
300 ppm (14-17 mg/kg bodyweight/day)
1000 ppm (47-58 mg/kg bodyweight/day)
3000 ppm (142-169 mg/kg bodyweight/day)

GLP: No

Year: 1975

Results: Reactions to treatment at the various dietary levels are summarized as follows:

3000 ppm

Slightly decreased bodyweight gain among males during the second year of treatment ($P < 0.05$) and slightly reduced food intake among females during the period 53 to 80 weeks of treatment ($P < 0.05$).

1000, 300 or 100 ppm

The performance of rats treated at these levels was comparable with that of the controls.

Gonad Organ Weight Analysis

Organ weight analysis performed on the gonads of male and female rats killed after 104 weeks of treatment revealed no differences between control and treatment groups (Table 1).

General histopathology of the gonads of rats killed after 104 weeks of treatment showed no abnormalities.

Conclusion:

Based on the above findings it was concluded that 1000 ppm (47-58 mg/kg bodyweight/day) was the no-effect level.

Reference:

Long - Term Feeding of TK 10047 to Rats (Final Report 0 -104 weeks), Ciba - Geigy Limited, Basel, Switzerland, March 20, 1975.

Table 1. Gonad Organ Weight Analysis: male and female rats at 104 weeks

Males

Group Ppm Diet	Absolute Gonad Wt (g)	% Body wt. x 100
0	4.9	53
100	4.6	54
300	4.8	53
1000	4.5	51
3000	4.5	56

Females

Group Ppm Diet	Absolute Gonad Wt. (g) x 1000	% Body wt. x 100
0	113	1.7
100	103	1.4
300	90	1.3*
1000	90	1.7
3000	101	1.6

*P<0.05

B. 24-Month Toxicity Study in Mice:

Test substance:	2-(2'- Hydroxy-5'-methylphenyl) benzotriazole CAS No. 2440-22-4 Batch No.: EN 71000
Method:	Although this study was not conducted under OECD guidelines, the study was monitored for compliance with Ciba's internal QA guidelines.
Species/strain:	Mice Tif: MAGf (SPF)* * F3 -hybrid of (inbred NMRI = MAG Tif) x NIH/NMRI Tif
No. of animals:	50 Males and 50 Female/ group (total 400)
Initial mean group body weight: (week - 1)	21.7 - 22.3 g (males) 20.4 - 21.0 g (females)
Initial Age:	Approx. 4 weeks
Route of administration:	Diet
Duration of the test:	24 months
Dose:	0, 5, 50, 500 ppm
Year:	1981
Summary And Assessment:	<p>A total of 400 mice (50 males and 50 females per dose group) were used. The test article was administered in the diet for 24 months at dosages of 0, 5, 50 and 500 ppm. The results of the study may be summarized as follows:</p> <p>The mean body weight gain of all treated male and female groups was similar to the controls. The mean food consumption of all treated male and female groups was similar to that of the respective controls.</p>

No clinical symptoms and no signs of local and/or systemic toxicity were observed.

The effects observed were a marked decrease of the liver weight in the male 50 ppm group and a slight increase in adrenal weights in treated female groups.

Neither gross nor microscopical changes in the reproductive organs were related to the treatment with the test compound.

Analysis of organ weights and ratios revealed no consistent effects (Table 1).

Exposure to the test substance in the diet over a period of 24 months at dietary levels of 5, 50 and 500 ppm [corresponding to a mean daily intake of 0.8, 6.5 and 64 mg/kg bw. in male and 0.8, 6.7 and 62 mg/kg bw. in female animals, respectively] did not produce inflammatory, degenerative, proliferative or neoplastic lesions.

Reference:

Final Report TK 10047 - Lifetime Carcinogenicity Study in Mice, Project No. 784334. Ciba Geigy Limited, Basel, Switzerland. Prof. Dr. Med. R. Hess, 08/17/81.

Table 1. Gonad Organ Weight Analysis: male and female mice at 105 weeks

Males

Group Ppm Diet	Absolute Gonad Wt (g)	Gonads / Body wt. ratio
0	0.215	0.562
5	0.213	0.522
50	0.220	0.543
500	0.209	0.548

Females

Group Ppm Diet	Absolute Gonad Wt. (g)	Gonads / Body wt. ratio
0	0.098	0.298
5	0.085	0.237
50	0.170	0.481
500	0.088	0.260

C. 90- Day Toxicity study in dogs:

Test substance: 2-(2'- Hydroxy-5'-methylphenyl) benzotriazole
CAS No. 2440-22-4

Method: Although this study was not formally conducted under OECD guidelines, the method paralleled OECD Guideline 409 "Subchronic Oral Toxicity – Non-Rodent: 90-Day Study." The study was monitored for compliance with Ciba's internal QA guidelines. In this study, each group was administered the test chemical in the diet at the specified concentration for 13 weeks. The test chemical was dissolved in PEG 400, and mixed with dog food. After the 13 week period, 1 animal/sex/dose group was fed the control diet for a period of 1 month to test for recovery.

The gonads were evaluated macroscopically and weighed. For microscopic evaluation, the ovaries or testes and uterus or prostate were examined.

Species/strain: Beagle dog

Age: 31 - 34 weeks

Initial weight: Male: 8.1 kg -12.4 kg, Female: 6.4 kg - 10.7 kg

No. of animals/group: 6/sex/group

Route of administration: Dietary

Exposure period: 91 days (13 weeks)

Frequency of treatment: Daily

Dose: 0, 1000, 3000, and 10,000 ppm in food

GLP: No

Year: 1981

Results: NOEL = 1000 ppm (Males: 31.75 mg/kg; Females: 34.6 mg/kg)

No mortality or symptoms of local and/or systemic toxicity was observed. Decreased food consumption and body weight gain for the 10,000 ppm group were noted.

Ovary weights decreased in a dose-dependent manner but changes were not reported to be statistically significant. Gonad weight analysis is presented in Table 1. There were no gross or histopathological changes in gonads or other organs related to treatment.

Reference:

Final report, TK 10047 - three-month toxicity study on dogs, Project No. 790858, Ciba-Geigy Limited, Basel, Switzerland, November 25, 1981.

Table 1. Summary of findings related to reproductive organs at test week 14.

Test Week 14

Species/ Sex	Organs	Dose in PPM							
		0.0		1,000		3,000		10,000	
Dog / Male		No.	Mean	No.	Mean	No.	Mean	No.	Mean
	Gonads Wt. (g)	5	16.62	5	17.180	5	15.330	5	16.266
	Gonads / Body Wt. ratio	5	0.144	5	0.158	5	0.135	5	0.160
	Gonads / Brain Wt. ratio	5	19.337	5	21.996	5	19.517	5	20.330

Species/ Sex	Organs	Dose in PPM							
		0.0		1,000		3,000		10,000	
Dog / Female		No.	Mean	No.	Mean	No.	Mean	No.	Mean
	Gonads Wt. (g)	5	2.356	5	1.498	5	1.050	5	1.090
	Gonads / Body Wt. ratio	5	0.023	5	0.016	5	0.010	5	0.014
	Gonads / Brain Wt. ratio	5	2.985	5	2.018	5	1.339	5	1.488

No. = Number of values/group

* = significant difference (P= 0.050)

CAS No. 25973-55-1

A. 90-Day Toxicity Study in the Rats

Test substance: 2-(2'-Hydroxy-3,5-di-tert-amylphenyl) benzotriazole
CAS No. 25973-55-1

Method: Although this study was not formally conducted under OECD guidelines, the method parallels OECD Guideline 408 "Sub-chronic Oral Toxicity – Rodent: 90-Day study". Female and male albino rats were fed with a diet containing 0, 100, 200, 400, 800 and 1600 ppm for 90 days.

Species/strain: Albino rats, (derived from the Wistar strain)

Age at initiation: Newly weaned rats

Average body weight: 43 - 56 g

Sex: Male/Female

No. animals/group: 10 / sex / treatment level

Route of administration: Incorporated into the diet

Exposure period: 7 days per week, 3 months.

Frequency of treatment: Daily

Dose: 0, 100, 200, 400, 800 and 1600 ppm.

Control group: Concurrent (diet without admixing the test article)

GLP: No

Year: 1968

Results: NOEL: < 100 ppm
NOAEL: 100 ppm
~ 22 mg/ kg bw / day

No mortality occurred. Body weight gain and food consumption were reduced in the highest dose group. The NOAEL showing no adverse toxic

blood, liver or kidney effects is estimated to be at 100 ppm.

There was no treatment-related effect on female body weight or ovary weight (reported at ovary weight per 100 g body weight). Body weights of males were reduced at the two highest treatment levels (-4% and -16%, respectively). Testes weights (reported as testes weight per 100 g body weight) were statistically significantly increased at levels of 400, 800 and 1600 ppm. This, however, was apparently largely a result of the decrease in body weight and not judged of toxicological significance. Gonads were not evaluated microscopically.

Reference:

Short-Term (49-Day) and Subchronic (90-Day) Toxicity Studies with RY 1137 in Rats. Central Institute for Nutrition and Food Research, Zeist, The Netherlands; Report No. R2640. March 1968.

Table 1. Body weights and relative gonad weights

Males (10 / group)

Treatment Group (ppm)	Ave. Body Wt. (g)	Testes Wt. (g / 100 g body Wt.)
0	299	0.92
100	314	0.95
200	296	0.98
400	303	1.02*
800	287	1.01**
1600	252	1.19**

* 0.01 < P < 0.05

** 0.001 < P < 0.01

Females (10 / group)

Treatment Group (ppm)	Ave. Body Wt. (g)	Ovary Wt. (g / 100 g body Wt.)
0	195	0.043
100	199	0.044
200	197	0.042
400	207	0.044
800	201	0.044
1600	195	0.042

B. 90-Day Toxicity Study in Dogs:

Test substance: 2-(2'-Hydroxy-3,5-di-tert-amylphenyl) benzotriazole
CAS No. 25973-55-1

Method: Although this study was not formally conducted under OECD guidelines, the method parallels OECD Guideline 409 "Subchronic Oral Toxicity – Non-Rodent: 90-Day study". A total of 20 female and 20 male Beagle dogs were fed with a diet containing 0, 15, 30, 60, 120 and 240 mg/kg body weight for 3 months.

Species/strain: Beagle Dogs, registered by the American Kennel Club, New York (USA)

Age at initiation: Mean Age:
male dogs 35 weeks
female dogs 32 weeks

Mean weight:
male dogs 11.5 kg
female dogs 8.1 kg

Sex: Male/Female

No. animals/group: 3 / sex / each chemical treatment level
5 / sex in control group.

Route of administration: Incorporated into the diet

Exposure period: 7 days per week, 3 months.

Frequency of treatment: Daily

Dose: 15, 30, 60, 120, 240 mg/ kg body weight.

Control group: Concurrent (diet without admixing the test article)

GLP: No

Year: 1970

Results: NOEL: > 15 mg/ kg bw

One male from the high dose group died on the 8th week of treatment. Toxicity was more pronounced in the males than in the females. Body weight loss and depression of food consumption occurred in the high dose group.

Gross and histopathological investigation showed increased liver weights associated with severe liver damage including icterus (jaundice) in a few dogs in the 120 and 240 mg / kg groups. Microscopic changes in some animals of the higher dose groups included: atrophy of the uterus, abnormal spermatogenesis and atrophy of the prostate (Table 1). Reproductive organ weight data are presented in Tables 2-3.

From the observations made, the NOEL was found to be < 15 mg/kg body weight with liver as the most sensitive organ.

Reference:

Report (A 0176/049): Three-Months Toxicity Study, TINUVIN 328, Dietary Administration - Beagle Dogs, Institute for Industrielle und Biologische Forschung, Koln, Den; Project-no. A 0176/049. May 20, 1970.

Table 1. Treatment-related effects in male and female gonads

Males

Dose mg/kg	Body weights	Food Consumption	Testes**	Epididymis	Mortality
Control / 0			Dog #3: 9	-	
15			No effect	No effects	
30			Dog #3: 1, 3	No effects	
60	Reduced		Dog #3: 1, 8 Dog #5: 1, 3, 4, 5	No effects	
120	Reduced	Reduced*	Dog #1: 4 Dog #3: 3, 4 Dog #5: 3, 6	No effects	
240	Reduced	Reduced* (especially dog 5e)	Dog #3: 2, 3, 4 Dog #5e: 2, 3, 4	No effects	Dog 5e: died in week 8

- 1/ Giant spermatogonia *some dogs offered supplemental pet diet to increase intake
 2/ Multinucleated giant cells in tubules
 3/ Disturbances of spermatogenesis
 4/ Atrophy of the tubules
 5/ Hyperchromia and hyperplasia of spermatogonia
 6/ Round cell infiltration of interstitial tissue
 7/ Hyperplasia of the leydig cells
 8/ Slight chronic inflammation of the capsule
 9/ Several tubules composed on just sertoli cells

** Dogs 120-#3, 120-#5 and 240-#5e had reduced testes and epididymis weights

Females

Dose mg/kg	Body weights	Food Consumption	Uterus*	Ovaries	Mortality
15			No effect	No effect	No effect
30			No effect	No effect	No effect
60			1 of 3 dogs: Slight atrophy of all layers of the uterus wall	No effect	No effect
120	Dog #4: reduced wt. (0.5 kg)		1 of 3 dogs: Slight atrophy of all layers of the uterus wall	No effect	No effect
240	Dog #4: reduced wt (0.8 kg)	Slight reduction	2 of 3 dogs: Slight to moderate atrophy of all layers of the uterus wall	No effect	No effect

*uterus : body weight ratio reduced in dose-related manner in groups 60, 120 and 240 mg/kg/day

Table 2. Male Body and Reproductive Organ Weights

Group Ppm Diet	Ave. Body Wt. (kg)	Ave. Testes Wt (g) [right / left]	Ave. Epididymis Wt (g) [right / left]	Ave. Prostate Wt. (g)
0	11.2	8.21 / 8.40	1.69 / 1.65	7.56
15	13.5	8.73 / 8.41	1.84 / 1.82	6.42
30	11.2	8.36 / 8.64	1.46 / 1.63	3.36
60	12.7	8.73 / 8.32	1.58 / 1.51	2.23
120	8.9	4.41 / 4.16	0.989 / 0.968	2.64
240	8.9	5.75 / 5.32	1.09 / 1.10	1.89

Table 3. Female Body and Reproductive Organ Weights

Group Ppm Diet	Ave. Body Wt. (kg)	Ave. Ovary Wt (mg) [right / left]	Ave. Uterus Wt (g)
0	8.5	345 / 440	2.10
15	7.9	381 / 415	2.24
30	9.4	399 / 434	2.40
60	8.6	365 / 376	1.76
120	9.9	395 / 447	1.80
240	7.2	322 / 355	1.28

CAS 70321-86-7

90-Day Toxicity Study in the Rats

Test substance: 2-(2H-Benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl) phenol
CAS No. 70321-86-7
Project No.: 840860
Batch No. EN 02885.32

Method: This study was conducted under OECD guideline for testing of chemicals, subchronic oral Toxicity-Rodent: 90 day study, No. 408, adopted May 12, 1981.

This toxicity study was conducted in order to determine the potential oral toxicity of the test article upon continuous administration in feed for 3 months and to estimate a no-observable effect level of exposure. The experiment was carried out under specified pathogen free standard laboratory conditions. The temperature was maintained at 22 ± 2 °C, relative humidity of 55 ± 10 % and 12 hour light per day was used.

Species/strain: Albino Rats, Tif: RAIF (SPF), hybrid of RII 1/if x RII 2/Tif

Age at initiation: approximately 4 weeks at delivery

Mean weight:
males: 64-96 g
females: 63 - 86 g

Sex: Male/Female

No. animals/group: 20 males and females per dose group

Route of administration: Dietary, Incorporated into the diet

Exposure period: 92-94 days

Frequency of treatment: Daily

Dose: 0, 50, 300, 2000, and 10,000 ppm

GLP: Yes.

Year: 1987

Results: No treatment related clinical symptoms and no signs of systemic toxicity were observed during the study. No death occurred during the course of study. No evidence of a reaction to the treatment was observed in: eyes, hearing, body- weight, hematological investigations, blood chemistry, urine analysis and macroscopical findings. A NOEL of 50 ppm was set based on effects on liver.

Gonad weights were not affected by treatment (Tables 1 and 2). There were histological effects on reproductive organs.

Reference: Final Report, TK 12443 - Three-Month Oral Toxicity Study In Rats (Administration In Feed); GU Project No. 840860, 01/22/87, Dr. Phil II W. Basler, Dr. Med. Vet. W. Gfeller, Ciba-Geigy Limited, Basel, Switzerland.

Table 2. Mean Organ Weights (g) and organ to body weight / brain ratios after a 4 week recovery period.

Test Week 18

Species/ Sex	Organs	Dose in PPM									
		0.0		50.0		300.0		2000.0		10000	
Rat/ Male		No.	Mean	No.	Mean	No.	Mean	No.	Mean	No.	Mean
	Gonads Wt. (g)	10	3.619	10	3.783	10	4.025*	10	3.862	10	3.898*
	Gonads / Body Wt. ratio	10	0.731	10	0.805	10	0.796	10	0.759	10	0.785
	Gonads / Brain Wt. ratio	10	150.677	10	157.165	10	164.162*	10	159.500	10	161.574*

Species/ Sex	Organs	Dose in PPM									
		0.0		50.0		300.0		2000.0		10000	
Rat/ Female		No.	Mean	No.	Mean	No.	Mean	No.	Mean	No.	Mean
	Gonads Wt. (g)	10	3.627	10	3.603	10	3.861*	10	3.695	10	3.703
	Gonads / Body Wt. ratio	10	0.860	10	0.850	10	0.884	10	0.821	10	0.799
	Gonads / Brain Wt. ratio	10	158.430	10	158.8920	10	167.634	10	161.147	10	158.546

NO. = Number of values/group

* = significant difference (P= 0.05)

Table 1. Mean Organ Weights (g) and organ to body weight / brain ratios

Test Week 14

Species/ Sex	Organs	Dose in PPM									
		0.0		50.0		300.0		2000.0		10000	
Rat/ Male		No.	Mean	No.	Mean	No.	Mean	No.	Mean	No.	Mean
	Gonads Wt. (g)	10	3.627	10	3.603	10	3.861*	10	3.695	10	3.703
	Gonads / Body Wt. ratio	10	0.860	10	0.850	10	0.884	10	0.821	10	0.799
	Gonads / Brain Wt. ratio	10	158.430	10	158.8920	10	167.634	10	161.147	10	158.546

Species/ Sex	Organs	Dose in PPM									
		0.0		50.0		300.0		2000.0		10000	
Rat/ Female		No.	Mean	No.	Mean	No.	Mean	No.	Mean	No.	Mean
	Gonads Wt. (g)	10	0.181	10	0.167	10	0.145	10	0.163	10	0.167
	Gonads / Body Wt. ratio	10	0.065	10	0.060	10	0.054	10	0.057	10	0.057
	Gonads / Brain Wt. ratio	10	8.060	10	7.563	10	6.587	10	7.550	10	7.364

No. = Number of values/group

* = significant difference (P = 0.050)