11-18-92

CASWELL FILE

MRID 423813-01

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

NOV 18 1992

009832

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Thiodicarb: 2-Generation Reproduction Study (range-finding and definitive studies); **6(a)(2)**

TO: Napoleon Kotey
Product Manager (52)
Reregistration Branch, SRRD (H7508W)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor C 11/9/92
Toxicology Branch II, Section II,
Health Effects Division (H7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 11/12/92
Section II Head, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D. J M Saunders for M.v.G. 11/13/92
Chief, Toxicology Branch II/HFAS/HED (H7509C)

Registrant: Rhône-Poulenc Ag Company
Chemical: Thiodicarb
Synonym: Larvin
Submission No.: S423028
Caswell No.: 900AA
Case.: 816454
Identifying No.: 114501-000264
Schaughnessy No.: 114501
MRID No.: 423813-01 and 423813-02
Action Requested: Not specified.

Comment: The Registrant has submitted the final report of a definitive 2-generation reproduction study in rats and a range-finding reproduction study in rats. Both studies have been reviewed, and the DER's are appended. Preliminary results of the range-finding study had been submitted to the Agency earlier (January, 1991) under Section 6(a)(2). The current submission was also submitted under 6(a)(2).

1. Range-Finding Reproduction Study with Thiodicarb Technical in Rats. SM Henwood, 7/17/91 (MRID # 423813-02).

Under the conditions of the study, exposure to Thiodicarb via the diet during pre-mating and through gestation and lactation, at dose

levels of 0, 200, 600, 1800, and 3000 ppm, resulted in maternal toxicity at the three highest dose levels. Reproductive effects/ offspring toxicity in the form of decreased pup growth occurred at 600, 1800 and 3000 ppm and a decreased viability index was observed at 1800 and 3000 ppm. The NOEL for maternal toxicity can be set at 200 ppm, the LEL at 600 ppm, based on decreased body weight/gain and food consumption. The NOEL for effects on the offspring can be set at 200 ppm, the LEL at 600 ppm, based on altered growth. The NOEL for reproductive effects can be set at 200 ppm, the LEL at 600 ppm, based on reduced offspring growth. This study is a range-finding study and as such, does not satisfy the guideline requirements (83-4) for a 2-generation reproduction study. It is classified Acceptable.

2. Two-Generation Reproduction Study with Thiodicarb Technical in Rats. SM Henwood, 6/9/92 (MRID # 423813-01).

Under the conditions of the study, exposure to Thiodicarb via the diet during pre-mating and through gestation and lactation of F0 rats (one litter) and F1 rats (two litters) at dose levels of 0, 100, 300, and 900 ppm resulted in maternal toxicity (decreased body weight/gain and food consumption) at the two highest dose levels. Reproductive effects occurred at all dose levels (decreased F2b pup body weight) and at 300 and 900 ppm (decreased viability index for F1, F2a, and F2b litters). Offspring viability and growth were adversely affected at dose levels of 300 and 900 ppm and 100, 300, and 900 ppm, respectively. The NOEL for maternal toxicity can be set at 100 ppm, the LEL at 300 ppm, based on decreased body weight/gain and food consumption. The NOEL for effects on the offspring cannot be set, based on altered growth at all dose levels. The NOEL for reproductive effects cannot be set, based on reduced offspring growth at all dose levels. The study is classified Core Supplementary. This study does not satisfy the guideline requirement (83-4) for a 2-generation reproduction study in rats, due to the lack of a NOEL for effects on reproduction and offspring (altered growth of pups).

Although the preliminary results of the range-finding study were submitted under **6(a)(2)**, they do not meet the criteria, and the results of the final reports of both the range-finding and definitive reproduction studies also are not 6(a)(2) data. No further action with respect to 6(a)(2) is required for these studies.

NOTE: Volume 10 [Analytical Method Report] should be routed to the appropriate section for review.

Reviewed by: Linda L. Taylor, Ph.D. Linda Lee Taylor 11/9/92
Section II, Tox. Branch II (H7509C)
Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 11/9/92
Section II Head, Tox. Branch II (H7509C)

009832

DATA EVALUATION REPORT

STUDY TYPE: 1-generation reproduction - rat (range-finding) TOX. CHEM. NO.: 900AA

MRID NO.: 423813-02

TEST MATERIAL: Thiodicarb technical

SYNONYMS:

STUDY NUMBER: HLA 6224-164

SPONSOR: Rhône-Poulenc Ag Company, Research Triangle Park, NC

TESTING FACILITY: Hazleton Laboratories America, Inc.

TITLE OF REPORT: Range-Finding Reproduction Study with Thiodicarb Technical in Rats

AUTHORS: SM Henwood

REPORT ISSUED: July 17, 1991

QUALITY ASSURANCE: A quality assurance statement was provided.

CONCLUSIONS: Under the conditions of the study, exposure to Thiodicarb via the diet during pre-mating and through gestation and lactation, at dose levels of 0, 200, 600, 1800, and 3000 ppm, resulted in maternal toxicity at the three highest dose levels. There was no effect demonstrated on the number of days to mate, fertility, pregnancy rate, gestation times, or the ability to rear young to weaning. There was a statistically-significant decrease in the number of pups/litter at birth at 3000 ppm and at day 4 precull at 1800 and 3000 ppm. Offspring viability was adversely affected at dose levels of 1800 and 3000 ppm; growth was affected at dose levels of 600, 1800 and 3000 ppm. The NOEL for maternal toxicity can be set at 200 ppm, the LEL at 600 ppm, based on decreased body weight/gain and food consumption. The NOEL for effects on the offspring can be set at 200 ppm, the LEL at 600 ppm, based on altered growth. The NOEL for reproductive effects can be set at 200 ppm, the LEL at 600 ppm, based on reduced offspring growth.

Classification: Acceptable. This study is a range-finding study and as such, does not satisfy the guideline requirements (83-4) for a 2-generation reproduction study.

4

A. MATERIALS

1. Test Compound: Thiodicarb technical; Description: white powder; Batch #: Lot #: 211159-169-061; Purity: 94.5%.

2. Test Animals: Species: rat; Strain: Crl:CD®BR; Age: ≈ 9 weeks old at start of treatment; Weight: ♂♂ 283-342 grams; ♀♀ 173-224 grams; Source: Charles River Laboratories, Wilmington, MA.

3. Statistics: Methods used are outlined in Figures 1, 2, & 3, copies appended. Body weights, body-weight changes, food consumption, litter data, days to mate, and length of gestation - one-way ANOVA as described in Figure 1; Clinical pathology data - one-way ANOVA, as described in Figure 2; Reproduction indices - Cochran-Armitage test for trend and departure and Fisher-Irwin exact test; Pup body weights (♀&♀), with the number of live pups in litter as covariate - one-way analysis of covariance.

B. STUDY DESIGN

1. Methodology: Animals were assigned to the F0 generation using a computer-generated randomization procedure. The weight variation of the animals per sex was stated to be within ± 2 standard deviations of the mean body weight for each sex and the group mean body weights for each sex were not statistically significantly different at the 5% probability level. Ten F0 animals per sex were assigned to dose levels of 0, 200, 600, 1800, 3000 ppm Thiodicarb technical. At weaning of the F1 litters, 20 animals per sex from the 0 to 1800 ppm groups and 12 ♂♂, 11 ♀♀ from the 3000 ppm group were selected to remain on test for 3 weeks following weaning. The test material was incorporated into the diet and fed continuously for 6 weeks before mating, throughout mating, gestation, and lactation of the F1 litters, and until necropsy. The F1 males and females were offered the test diets postweaning, at the same dose levels as their parents, for at least 3 weeks.

   The animals were acclimated for ≈ 3 weeks before treatment began and examined for health status. Except during breeding, the animals were housed individually. Feed (Certified Rodent Chow® # 5002, Purina Mills, Inc.) and water were available ad libitum.

2. Dose preparation: The test material was weighed out and mixed with basal diet in a Waring® blender; this premix was then transferred to a mixing bowl and additional basal diet was added to the blender to recover residual test material. This latter amount of basal diet was added to the mixing bowl and the contents were mixed thoroughly. Each dose level was prepared separately in order of increasing concentration. The diets were prepared weekly and were stored at room temperature until used. Homogeneity, stability, and concentration analyses were performed.

RESULTS

The homogeneity analyses indicated that the mixing procedures were adequate (± 4% of theoretical levels at each sample location). Stability analyses indicated that the test material was stable when mixed with basal diet under various storage procedures at all dose levels (92.5-105% of theoretical level). The overall mean concentrations of Thiodicarb in the dose formulations analyzed from weeks 1 through 17 of the study were 100, 100, 99.9, and 101% of the theoretical levels of 200, 600, 1800, and 3000 ppm, respectively.

3. Parental and Offspring Investigations

(a) Clinical Observations: All animals were observed twice daily for mortality, moribundity, and signs of toxicity. Females were observed for signs of abortion, excessive bleeding, premature delivery, or difficult and prolonged parturition. At the scheduled body weight interval, the animals were subjected to a detailed examination (not further defined), and females were examined weekly after the lactation phase until necropsy.

(b) All litters: Birth: As soon after parturition as possible, the sex of each pup was determined, and the litter size (total # of pups born live or found dead) was recorded. Each live pup was examined for external abnormalities and weighed. Dead pups were examined macroscopically for cervical, thoracic, and abdominal visceral abnormalities, then discarded. Day 4: The sex of each pup was determined and the litter size (# live) was recorded. Pups were examined for external abnormalities and weighed individually. Litters with more than 8 pups were culled at random to produce, as nearly as possible, litters that contained 4 pups/sex. Culled pups were sacrificed and examined for cervical, thoracic, or abdominal visceral abnormalities, and discarded. Day 7, 14, and 21: Litter size (live) was recorded; live pups were examined for external abnormalities and were weighed individually.

Selection and Procedures for F1 Weanlings: On day 21 of lactation, weanlings were selected at random from the F1 litters to provide 20 weanlings per sex per group, where possible. At least 2 weanlings per sex (where possible) were selected at random from each litter. The remaining weanlings were sacrificed and discarded. The selected F1 animals remained on test for 3 weeks after weaning and were provided test diets at the same concentration fed their parents. These offspring were subjected to detailed clinical examinations, and individual body weight and food consumption data were recorded weekly.

RESULTS

Survival and Clinical Observations: **F0 Generation** - One high-dose male died, but this was not thought to be related to

treatment (malocclusion noted). Emaciation was the only clinical sign observed that was treatment-related. During week 1, 50% of the high-dose and 20% of the mid-dose females displayed emaciation. There were no treatment-related clinical signs noted during gestation or lactation. **F1 Generation** - All of the pups in the control, 200, and 600 ppm dose levels survived. During week 0, one male was found dead and one was sacrificed moribund in the 1800 ppm dose group (one was languid and small, the other was prostrate and small). At the 3000 ppm dose level, one male was sacrificed moribund at week 0 (emaciated, languid, and small). The clinical sign most frequently noted in males and females at the 1800 and 3000 ppm dose levels was small in size. Both the deaths and small size are considered to be related to treatment.

(b) Food Consumption: Food consumption (individual) data were recorded weekly during the premating phase of the F0 generation and weekly for the F1 animals after weaning. For the mated females, food consumption was measured for days 0-7, 7-14, 14-20 of gestation and for females that delivered litters for days 0-4, 4-7, 7-10, and 10-14 of lactation. Food consumption was measured weekly for the F1 pups selected on day 21 of lactation for continuation on test for 3 weeks.

RESULTS

Pre-mating period: **F0 Generation** - Food consumption was comparable to the control values for both sexes at the 200 ppm dose level. There was a dose-related decrease in food consumption at the 3 other dose levels in both sexes between weeks 0 and 6 of the study (see Table A below). Gestation: At the 1800 and 3000 ppm dose levels, food consumption was significantly lower than the control during days 7 through 20, and during days 14 through 20 at the 600 ppm dose level. Lactation: A dose-related decrease in food consumption was observed at the 600, 1800, and 3000 ppm dose levels during days 0-4 and at the 1800 and 3000 ppm dose levels during days 4-14 (Table B). **F1 Generation** - Males at the 600, 1800, and 3000 ppm dose levels displayed a dose-related decrease in food consumption throughout the observation period (weeks 0-3). Females displayed a similar decrease, but the 600 ppm dose group was comparable to control value during weeks 2-3 (Table C).

7

Table A. F0 Generation Food Consumption (g/day)

Week/ dose (ppm)	Males (% of Control)				Females (% of Control)			
	200	600	1800	3000	200	600	1800	3000
0-1	91	62**	34**	18**	90	67**	34**	26**
1-2	96	95	83**	61**	90	103	91	79*
2-3	99	96	91	82**	92	96	88	87
3-4	99	94	89*	73**	90	97	93	89
4-5	98	93	86**	75**	92	96	84**	84**
5-6	102	95	85	65**	95	102	88	88

* p< 0.05; ** p<0.01

Table B. Food Consumption During Gestation and Lactation

Interval (days, G/L)	Gestation (% of Control)				Lactation (% of Control)			
	200	600	1800	3000	200	600	1800	3000
0-7/0-4	98	88	88	91	95	78*	65**	55**
7-14/4-7	95	93	85*	78**	95	93	85**	81**
14-20/7-10	86	75**	60**	63**	98	91	83**	78**
10-14	-	-	-	-	98	91	80**	79**

* p<0.05; ** p<0.01

Table C. F1 Generation Food Consumption (g/day)

Week/ dose (ppm)	Males (% of Control)				Females (% of Control)			
	200	600	1800	3000	200	600	1800	3000
0-1	95	77**	58**	39**	96	88**	59**	45**
1-2	97	89**	73**	50**	96	91**	77**	58**
2-3	99	87**	73**	54**	98	96	84**	72**

* p< 0.05; ** p<0.01;

(c) Body Weight: Body weights were recorded for each male on the first day of treatment and weekly thereafter. Females were weighed on the first day of treatment, weekly during the premating phase, on presumed days 0, 7, 14, and 20 of gestation, and on days 0, 4, 7, 14, and 21 of lactation. F1 pups were weighed weekly.

NOTE: In general, TB II was not able to verify the numbers presented for most of the parameters (body weight, food consumption, etc.), apparently due to the restrictions in the computer system employed by the study author.

RESULTS

F0 Generation: Mean body weight for both sexes (weeks 1 through 9 ♂♂/ weeks 1 through 6 ♀♀) at the 1800 and 3000 ppm dose levels was significantly lower than control values. At the 600 ppm dose level, body weight was significantly lower than control during week 1 only. Low-dose animals were comparable to the controls. Gestation: Mean maternal body weight was significantly lower at the 1800 and 3000 ppm dose levels on days 0, 7, 14, and 20 and on days 7, 14, and 20 at the 600 ppm dose level compared to the control value. Gestational body weights at the lowest dose (200 ppm) were comparable to the control values. Lactation: During lactation, dams at the 600, 1800, and 3000 ppm dose levels displayed body weights that were significantly lower than the control value on days 0, 4, 7, and 14. No difference was noted at the low-dose level.

Table D. F0 Generation Group Mean Body Weight

Week/ dose (ppm)	Males (% of Control)				Females (% of Control)			
	200	600	1800	3000	200	600	1800	3000
0	99.5	103.4	103.6	100.9	97.4	98.6	99.1	98.2
1	97.4	91.9**	81.4**	70.6**	94.5	90.0*	78.9**	75.0**
2	97.0	94.6	84.4**	71.3**	93.4	93.5	87.1**	84.7**
3	96.8	94.0	85.7**	73.3**	94.2	93.7	89.2**	86.9**
4	97.0	94.0	86.3**	73.2**	93.3	92.7	87.7**	87.7**
5	97.7	93.9	85.9**	73.1**	92.7	92.7	85.7**	85.7**
6	97.6	94.0	85.9**	70.4**	92.1	92.6	85.6**	85.9**
7	98.3	95.4	88.1**	72.2**	see body weight data for gestation period (Table E)			
8	99.0	94.8	88.1**	73.2**				
9	99.4	94.5	87.6**	73.3**				

Table E. Body Weight During Gestation and Lactation

Day	Body Weight - gestation (% of Control)				Body Weight - lactation (% of Control)			
	200	600	1800	3000	200	600	1800	3000
0	92.6	93.6	85.7**	87.6**	91.4	87.3**	72.0**	72.7**
4	-	-	-	-	94.5	88.9**	79.0**	75.7**
7	91.8	91.2*	85.5**	85.8**	95.0	91.2*	82.5**	82.4**
14	93.0	91.6*	85.7**	83.2**	94.1	91.9*	85.0**	85.1**
20/21	92.6	87.7**	76.1**	75.2**	96.4	97.0	92.7	92.9

* p< 0.05; ** p<0.01;

F1 Generation: The body weights of the pups (both sexes) at the low-dose level (200 ppm) were comparable to those of the controls throughout the 3-week observation period. Mean body weight was significantly lower than control values in both sexes at the 600, 1800, and 3000 ppm dose levels throughout the treatment period (see Table F).

Table F. F1 Generation (Pup) Group Mean Body Weight

Week/ dose (ppm)	Males (% of Control)				Females (% of Control)			
	200	600	1800	3000	200	600	1800	3000
0	97.3	81.9**	64.4**	57.4**	100.2	84.9**	67.6**	63.2**
1	95.7	81.4**	58.3**	42.1**	98.9	84.6**	60.4**	48.1**
2	97.7	83.3**	62.9**	43.9**	99.7	87.4**	66.4**	53.4**
3	97.6	84.2**	66.5**	48.1**	97.7	89.2**	73.1**	61.6**

* p< 0.05; ** p<0.01;

Body-Weight Changes: **F0 Generation:** With regard to body-weight changes, a dose-related decrease in body-weight gain was observed in the parental (F0) animals of both sexes at dose levels of 600 ppm and above during the premating period and during gestation (Tables D1 and E1) and in the F0 dams during lactation at these same dose levels (Table E1). **F1 Generation:** Similar decreases in body-weight gain were observed in the F1 pups (both sexes) at dose levels of 600 ppm and above during the observation period (Table F1).

Table D1. F0 Generation Group Mean Body-Weight Change (grams)

Week/ dose (ppm)	Males					Females				
	0	200	600	1800	3000	0	200	600	1800	3000
0-1	40	32	1**	-36**	-66**	19	12**	2**	-25**	-32**
0-2	69	59	38**	-2**	-42**	29	19	17*	2**	-2**
0-3	101	90	66**	31**	-10**	37	29	25*	13**	10**
0-6	162	152	123**	84**	20**	64	49*	48**	28**	31**
0-9	197	195	158*	122**	60**	see gestation weight changes				

Table E1. Body-Weight Gain (F0 Dams) During Gestation and Lactation (grams)

Day	Body Weight - gestation					Body Weight - lactation				
	0	200	600	1800	3000	0	200	600	1800	3000
0-7/0-4	33	29	24	28	24	5	14	9	16	5
7-14/4-7	22	24	21	20	11*	5	6	11	15**	24**
14-20/7-14	64	57	43	18**	23**	19	15	19	23	24
0-20/14-21	119	110	89*	66**	57**	-18	-10	-1**	8**	8**
0-21	-	-	-	-	-	10	24	39**	62**	61**

Table F1. F1 Generation (pup) Group Mean Body-Weight Gain (grams)

Week/ dose (ppm)	Males					Females				
	0	200	600	1800	3000	0	200	600	1800	3000
0-1	43	40	34**	21**	9**	36	35	30**	18**	9**
0-2	99	97	83**	61**	36**	77	76	68**	50**	36**
0-3	161	157	136**	107**	72**	109	105	100*	83**	66**

* p< 0.05; ** p<0.01;

(d) Pregnancy Rate, Mating Performance, Gestational Period and Litter Data

During the mating period (≥ 21 days), one male and one female were housed together in plastic breeding cages. Daily vaginal examinations were performed during the mating period, and the presence of sperm in the vaginal smear or a copulatory plug was considered evidence of mating. When mating was confirmed, the sexes were separated. Mated females (at ≈ day 15 of gestation) and females with pups were housed in individual breeding cages, and suitable nesting material was provided. Females showing no evidence of mating were placed in nesting boxes after completion of the mating period.

RESULTS

F0 Generation: There were no differences noted among the groups in fertility for either sex. The mating (100% for all groups), gestation (89-100%), and weaning indices and the length of gestation were comparable among the groups. The mean number of days to mate was longest for the high-dose group (Table G) but not significantly different from the control value. NOTE: TB II was not able to locate individual data regarding the number of days to mate for each female.

Table G. Number of Days to Mate

Group (ppm)	0	200	600	1800	3000
days to mate	2.7±0.8	2.4±1.4	3.2±4.0	2.4±1.2	4.6±3.8

One dam from the control and 3000 ppm dose group delivered nonviable litters. The viability indices for the 1800 and 3000 ppm dose groups were significantly lower than the control group, indicating a treatment-related effect on the offspring survival early in the lactation period. At the 1800 and 3000 ppm dose levels, there were 2 and 5 liveborn litters, respectively, that did not survive to day 4 of lactation. Mean body weights (covariate-adjusted) were significantly lower than the control values at the 600, 1800 and 3000 ppm dose levels at birth (except the 600 ppm dose level) through lactation (Table H).

Table H. Summary of Delivery and Litter Data

Parameter/Dose (ppm)	0	200	600	1800	3000
# dams delivering	10	8	9	10	9
♀♀ with live pups	9	8	9	10	8
♀♀ with stillborn pups	3	3	3	5	3
♀♀ with no live pups	1	0	0	0	1
# pups delivered	132	113	114	132	100
mean	13.2	14.1	12.7	13.2	11.1
liveborn	128	109	111	125	82
stillborn	3	4	3	7	10
uncertain	1	0	0	0	8
viability index	126/128	107/109	111/111	84/125**	27/82**
%	98	98	100	67	33
weaning index	72/72	63/63	71/72	63/63	24/24
%	100	98	99	98	100
pup disposition					
culled day 4	54	43	39	20	3
culled day 21	32	23	31	23	1
died	1	1	0	22	31
cannibalized	0	0	0	2	1
missing	1	2	1	18	23
pups surviving at day 21	72	63	71	63	24
entire litter died	0	0	0	2	5
# live pups/litters with live pups (mean)					
day 0	14.2	13.6	12.3	12.5	10.3*
day 4 precull	14.0	13.4	12.3	10.5**	9.0**
♂♂ pup weight/litter (g)					
day 0	6.5	6.1	5.8	4.9**	4.9**
day 4 pre/post cull	10.1/10.2	9.9/9.8	8.7*/8.6**	6.3**/6.5**	4.9**/5.1**
day 7	16.1	15.6	13.3**	9.6**	8.2**
day 14	33.5	32.8	27.9**	21.4**	18.3**
day 21	54.9	53.9	45.3**	35.5**	31.4**
♀♀ pup weight/litter (g)					
day 0	6.1	5.8	5.6	4.6**	4.7**
day 4 pre/post cull	9.8/9.9	9.5/9.6	8.4*/8.4*	6.1**/6.2**	4.5**/4.7**
day 7	15.6	15.2	13.1**	9.3**	8.1**
day 14	32.5	31.6	27.2**	20.9**	18.9**
day 21	52.7	52.5	44.3**	35.2**	32.9**

* $p<0.05$; ** $p<0.01$

(e) Sacrifice and Pathology

Parent Animals: At scheduled necropsy (F0 ♂♂ after the mating period, F1 offspring 3 weeks after weaning, parental F0 ♀♀ after F1 pups were weaned), the animals were anesthetized and blood was collected from the retro-orbital plexus and brain tissue was harvested. Cholinesterase activity levels in the plasma, red blood cells, and brain of the F0 adult animals and of 10 F1 animals/sex/group selected to remain on test were evaluated. Necropsy included a macroscopic examination of the external surface of the body; all orifice; the cranial cavity; the external surface of the brain and spinal cord; the nasal cavity and paranasal sinuses; and the thoracic, abdominal, and pelvic cavities and viscera. The following organs/tissues were preserved : kidneys*, liver*, ovaries, uterus, vagina, cervix,

testes, epididymides, prostate, seminal vesicles, coagulating gland, and gross lesions (*F1 animals only). Uteri from F0 females that did not deliver a litter were stained with an ammonium sulfide solution to confirm pregnancy status.

RESULTS

Gross Pathology: **F0 Adults** - There were no apparent differences in the incidences of macroscopic changes at any dose level for either sex compared to their respective controls. **F1** - The only treatment-related changes in the incidence of macroscopic findings among the groups were an increase in the number of pups/tissues too autolyzed for examination at the 1800 and 3000 ppm dose levels and an increase in the number of pups with no milk in the stomach.

Table I. Macroscopic Findings in Pups at Necropsy

Parameter/Dose (ppm)	0	200	600	1800	3000
No milk in stomach					
# pups (%)	2 (3)	4 (4)	2 (5)	16 (33)	25 (57)
# litters (%)	2 (22)	3 (38)	2 (22)	4 (40)	5 (71)

Organ Weights: Organ weight data were not recorded.

Histopathology: None of the organs/tissues preserved were examined microscopically.

Cholinesterase Activity: **F0 Generation** - There were no statistically significant differences observed at any dose level, although the 3000 ppm males displayed a 25% decrease in plasma activity compared to the control value (week 9 of study). **F1 Generation** - There was a dose-related, statistically significant, decrease in plasma activity levels at the 600, 1800, and 3000 ppm dose levels in females at week 3; the 3000 ppm males also displayed a statistically significant increase at week 3 compared to control levels.

Table J. Cholinesterase Activity

Parameter/ dose (ppm)	Males (% of control)				Females (% of control)			
	200	600	1800	3000	200	600	1800	3000
F0 Generation								
plasma	98	89	86	75	94	96	95	98
RBC	103	106	106	113	107	111	117	116
brain♦	-	-	-	-	92	98	106	117
F1 Generation								
plasma	98	90	89	76**	89	76*	62**	57**
RBC	104	104	94	94	104	106	105	106
brain	131	129	115	100	99	116	100	89

* $p<0.05$; ** $p<0.01$; ♦ due to technical problems, brain levels in F0 males were not obtained

C. DISCUSSION

There was evidence of maternal toxicity at the 600, 1800, and 3000 ppm dose level, as evidenced by decreases in body weight/gain and food consumption. Females at all dose levels displayed treatment-related decreases in body-weight gains compared to the controls during the premating period. Fertility and mating indices, as well as gestation time and the mean number of days to mate were not affected by treatment. Offspring viability was adversely affected at dose levels of 1800 and 3000 ppm, and growth was adversely affected at dose levels of 600, 1800, and 3000 ppm, as evidenced by the lower viability indices, number of live pups per litter, and mean pup weight. There were treatment-related decreases in plasma cholinesterase activity levels in F0 and F1 males at 3000 ppm and a dose-related decrease in F1 females at 600, 1800, and 3000 ppm. At necropsy, the macroscopic findings were comparable among the groups.

D. CONCLUSION

Under the conditions of the study, exposure to Thiodicarb technical via the diet during pre-mating (6 weeks) and through gestation and lactation, at dose levels of 0, 200, 600, 1800, and 3000 ppm, produced maternal toxicity at the three highest dose levels, as evidenced by decreased food consumption and body weight/gain. There was no effect demonstrated on the number of days to mate, fertility, pregnancy rate, gestation times, or the ability to rear young to weaning. There was a statistically-significant decrease in the number of pups/litter at birth at 3000 ppm and at day 4 precull at 1800 and 3000 ppm. Following culling at day 4, litter sizes were comparable among the groups, although the number of litters was not; i.e., the 3000 ppm dose group consisted of 3 litters; the other groups and control consisted of 8-9 litters. Offspring viability was adversely affected at dose levels of 1800 and 3000 ppm. Pup growth was adversely affected at the 600, 1800, and 3000 ppm dose levels. The NOEL for maternal toxicity can be set at 200 ppm, the LEL at 600 ppm, based on decreased body weight/gain and food consumption. The NOEL for effects of the offspring can be set at 200 ppm, the LEL at 600 ppm, based on lower body weights. A NOEL for reproductive effects can be set at 200 ppm, the LEL at 600, based on reduced offspring growth. This study is a range-finding study and it does not satisfy the guideline requirements (83-4) for a 2-generation reproduction study, nor was it intended to.

14

Thiodicarb

Page_____ is not included in this copy.

Pages 15 through 17 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

X FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Reviewed by: Linda L. Taylor, Ph.D. Linda Lee Taylor 11/9/92
Section II, Tox. Branch II (H7509C)
Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 11/12/92
Section II Head, Tox. Branch II (H7509C)

009832

DATA EVALUATION REPORT

STUDY TYPE: 2-generation reproduction - rat TOX. CHEM. NO.: 900AA

MRID NO.: 423813-01

TEST MATERIAL: Thiodicarb technical

SYNONYMS: Larvin

STUDY NUMBER: HWI 6224-166

SPONSOR: Rhône-Poulenc Ag Company, Research Triangle Park, NC

TESTING FACILITY: Hazleton Wisconsin, Inc.

TITLE OF REPORT: Two-Generation Reproduction Study with Thiodicarb Technical in Rats

AUTHORS: SM Henwood

REPORT ISSUED: June 9, 1992

QUALITY ASSURANCE: A quality assurance statement was provided.

CONCLUSIONS: Under the conditions of the study, exposure to Thiodicarb via the diet during pre-mating and through gestation and lactation of F0 rats (one litter) and F1 rats (two litters) at dose levels of 0, 100, 300, and 900 ppm resulted in maternal toxicity (decreased body weight/gain and food consumption) at the two highest dose levels. Reproductive effects occurred at all dose levels (decreased F2b pup body weight) and at 300 and 900 ppm (decreased viability index for F1, F2a, and F2b litters). Offspring viability and growth were adversely affected at dose levels of 300 and 900 ppm and 100, 300, and 900 ppm, respectively. The NOEL for maternal toxicity can be set at 100 ppm, the LEL at 300 ppm, based on decreased body weight/gain and food consumption. The NOEL for effects on the offspring cannot be set, based on altered growth at all dose levels. The NOEL for reproductive effects cannot be set, based on reduced offspring growth at all dose levels.

Classification: Core: Supplementary. This study does not satisfy the guideline requirement (83-4) for a 2-generation reproduction study in rats, due to the lack of a NOEL for effects on reproduction and offspring (altered growth of pups).

18

A. MATERIALS

1. Test Compound: Thiodicarb technical; Description: white powder; Batch #: Lot #: 211159-169-061; Purity: 94.5%.

2. Test Animals: Species: rat; Strain: Crl:CD®BR/VAF/Plus®; Age: ≈ 46 days old at start of treatment; Weight: ♂♂ 213-256 grams; ♀♀ 140-171 grams; Source: Portage, Michigan, a facility of Charles River Laboratories, Wilmington, MA.

3. Statistics: Significant differences were based on comparisons of the treated groups with the control group. Levene's test was performed to test for variance homogeneity; in the case of heterogeneity of variance at $p \leq 0.05$, transformations were used to stabilize the variance. ANOVA was performed on the homogeneous or transformed data; if ANOVA was significant, Dunnett's t test was used for pairwise comparisons between treated and control groups. When no transformation established variance homogeneity at $p \leq 0.05$, the data were examined by nonparametric techniques (Kruskal-Wallis H-test ANOVA and, if this was significant, the Nemenyi-Kruskal-Wallis test for multiple comparisons/Wilcoxon-Mann-Whitney two-sample rank-sum test). Body weights, body-weight changes, food consumption, litter data, days to mate, length of gestation, and cholinesterase levels - one-way ANOVA; Reproduction indices - Cochran-Armitage test for trend and departure and Fisher-Irwin exact test; Pup body weights (♀&♀), with the number of live pups in litter as covariate - one-way analysis of covariance.

B. STUDY DESIGN

1. Methodology: Animals were assigned to the F0 generation using a computer-generated randomization procedure. The weight variations of the animals per sex were stated to be within ± 2 standard deviations of the mean body weight for each sex and the group mean body weights for each sex were not statistically significantly different at the 5% probability level. Twenty-eight F0 animals per sex were assigned to dose levels of 0, 100, 300, and 900 ppm Thiodicarb technical. The test material was incorporated into the diet and fed continuously for 10 weeks before mating, throughout mating, gestation, and lactation of the F1 litters, and until necropsy. During the mating period (≥ 21 days), one male and one female were housed together. Daily vaginal examinations were performed during the mating period, and the presence of sperm in the vaginal smear or a copulatory plug was considered evidence of mating. When mating was confirmed, the sexes were separated. Mated females (at ≈ day 15 of gestation) and females with pups were housed in individual cages, and bedding material (heat-treated hardwood chips) was provided. Females showing no evidence of mating were placed in nesting boxes after completion of the mating period. At weaning of the F1 litters, animals of each sex were selected at random from as many litters as possible in each treatment group and assigned

to continue as the F1 generation adult animals according to the same study design. The F1 males and females were offered the test diets postweaning, at the same dose levels as their parents, for at least 10 weeks before mating, throughout mating, gestation, and lactation of F2a and F2b litters, during the rest period between litters, and until necropsy.

Initially, the animals were acclimated for 10 days before treatment began and examined for health status. Except during breeding, the animals were housed individually. Mated females (starting at ≈ day 15 of gestation) and females with pups were provided nesting material. Feed (Certified Rodent Chow® # 5002, Purina Mills, Inc.) and water were available ad libitum.

2. Dose preparation: The diets were prepared weekly and were stored at room temperature until used. The test material was weighed out and mixed with basal diet in a Waring® blender; this premix was then transferred to a mixing bowl and additional basal diet was added to the blender to recover residual test material. This latter amount of basal diet was added to the mixing bowl and the contents were mixed thoroughly. Each dose level was prepared separately in order of increasing concentration. Homogeneity (Weeks 1, 11, and 17), stability (day of mixing, 9, 14, 16) and concentration (first 4 weeks, then at four week intervals) analyses were performed on samples taken directly from the mixing bowl.

RESULTS

The homogeneity analyses indicated that the mixing procedures were adequate (± 8% of theoretical levels at each sample location) for both the 100 and 900 ppm dose levels. Stability analyses indicated that the test material was stable when mixed with basal diet under study conditions (14 days at room temperature) at the 100 and 900 ppm dose levels (94 and 100 % of theoretical levels, respectively). The overall mean concentrations of Thiodicarb in the dose formulations were 99.1, 99.2, and 100% of the theoretical levels of 100, 300, and 900 ppm, respectively.

3. Parental Investigations

(a) Clinical Observations: All animals were observed twice daily for mortality and moribundity. Following mating, females were observed for signs of abortion, excessive bleeding, premature delivery, or difficult and prolonged parturition. At the scheduled body weight interval, the animals were subjected to a detailed examination (not further defined). F1 adult females were examined weekly during the rest period and after the lactation phase of the F2a and F2b litters until necropsy.

RESULTS

Survival and Clinical Observations: **F0 Generation** - One high-

20

dose male died, but this was not thought to be related to treatment (swollen hind limb, malocclusion noted). None of the clinical signs observed in either sex during the premating and mating periods appeared treatment-related. There were no treatment-related clinical signs noted during gestation or lactation. **F1 Generation** - One F1 male at the 100 ppm dose level was sacrificed at week 4 of the F2b premating phase due to an apparent mechanical injury. No treatment-related clinical signs were observed in the F1 adults in either sex during premating or in females throughout gestation and lactation for the F2a or F2b litters.

(b) Food Consumption: Food consumption (individual) data were recorded weekly for each sex during the premating phase of the F0 and F1 generations, during postmating for males only, during the rest period following weaning of the F2a litters, and before mating for the F2b litters. For the mated females, food consumption was measured for days 0-4, 4-7, 7-14, and 14-20 of gestation and for females that delivered litters for days 0-4, 4-7, 7-10, and 10-14 of lactation.

RESULTS

Pre-mating period: **F0 Generation** - Food consumption was comparable to the control values for both sexes at the 100 ppm dose level and in males at the 300 ppm dose level. Males at the 900 ppm dose level displayed a statistically significant decrease in food consumption throughout the mating period and to sacrifice, although after the initial decrease during the first week (74% of control value), the amount of food consumed by this group remained essentially stable (but lower than control), suggesting a palatability problem. There was a dose-related decrease in food consumption at the 300 and 900 ppm dose levels in females during the first week only (see Table A, appended). Thereafter, food consumption was comparable among the females. Gestation: At the 300 and 900 ppm dose levels, food consumption was significantly lower (dose-related) than the control during days 14 through 20 (Table B). Lactation: The dams at the 900 ppm dose level displayed decreased food consumption during days 7-10 and 10-14 (Table B). **F1 Generation** - FIRST MATE: Males at the 300 and 900 ppm dose levels displayed a dose-related decrease in food consumption throughout the observation period (weeks 0-18). The low-dose males also displayed statistically-significant decreases during the first, second, fifth, and sixth week, but these decreases were of small magnitude (92-94 % of control). Females displayed comparable food intakes among the groups throughout the mating period (Table C). Gestation: There was a dose-related decrease in food consumption, which occurred throughout gestation at the mid- and high-dose levels and during days 14 to 20 at the low dose (Table D). Lactation: Food intake was comparable to control values at the low-dose level throughout lactation and from days 0 to 7 at the mid- and high-dose levels. During days 7-10 and 10-14, a dose-

21

related decrease was observed in the mid- and high-dose dams (Table D). SECOND MATE: Males at the high dose displayed decreased consumption throughout the mating period, with the magnitude of the decrease from control value becoming larger with time (Table E). Dams displayed comparable values among the groups during the rest period (Table F). Gestation: With the exception of the statistically significant decrease in intake observed during days 14-20 at the mid dose, food intake was comparable among the groups (Table G). Lactation: There were no statistically-significant differences observed among the groups (Table G).

(c) Body Weight: Body weights were recorded for each male on the first day of treatment, weekly thereafter, and at necropsy. Females were weighed on the first day of treatment, weekly during the premating phase, on presumed days 0, 7, 14, and 20 of gestation, and on days 0, 4, 7, 14, and 21 of lactation; weekly during the 2-week rest period (F1 females only), and at necropsy. Females not showing positive evidence of mating or delivering a litter were weighed weekly.

RESULTS

F0 Generation: The mean body weights (Table H) were comparable to the control values for both sexes at the low dose throughout the F0 generation (adults). Statistically-significant decreases in mean body weight were observed in males at the mid- (from week 1 to week 12) and high-dose (throughout the observation period) levels, although the magnitude of the decrease at the mid dose was small (93-96% of control value). Females at the mid dose displayed statistically significant but modest decreases at weeks 1,2,5,6 (96-97% of control), and the high dose displayed statistically significant decreases throughout the mating period, although the magnitude of the decrease was small (93-95% of control). Gestation: Mean maternal body weight was significantly lower at the 900 ppm dose level from day 7 (95% of control) to day 20 (89% of control) and at the 300 ppm dose level on day 20 (94% of control). Gestational body weights at the low dose (100 ppm) were comparable to the control values (Table I). Lactation: During lactation, dams at the 300 and 900 ppm dose levels displayed body weights that were significantly lower than the control value, although the decrease at the 300 ppm dose level was small and statistical significance was not attained on day 21. The magnitude of the decrease diminished with time at both dose levels. No difference was noted at the low-dose level (Table I).

Body-weight gains are shown in Table 1, below (% body-weight change data not provided in report; statistical analysis not performed). Additionally, the percent body-weight change is listed. The mid- and high-dose animals of both sexes displayed lower gains throughout the pre-mating period. The % change was lower in the high-dose males and the mid- and high-dose

females compared to their respective controls.

Table 1. F0 Adult Body-Weight Gains (g)

Interval/ Dose (ppm)	MALES				FEMALES			
	0	100	300	900	0	100	300	900
0-1	47.5	46.3	38.6**	18.4**	18.4	18.2	13.1**	7.5**
0-2	91.1	88.4	76.8**	56.4**	35.9	37.0	29.4**	24.0**
0-3	125.3	122.5	109.2**	87.0**	48.3	48.8	40.2**	36.1**
0-4	153.7	149.7	136.9**	111.2**	58.7	58.7	51.4**	46.8**
0-5	178.8	172.9	156.1**	131.2**	68.7	70.0	58.2**	55.3**
0-6	201.9	194.1	174.4**	148.1**	76.6	77.4	66.2**	61.5**
0-7	219.7	214.7	192.9**	162.7**	81.0	86.2	72.9*	67.5**
0-8	233.6	223.7	205.1**	170.2**	84.5	90.3	76.3	71.3**
0-9	248.1	239.0	219.1**	180.3**	92.2	95.7	82.2	76.1**
0-10	263.0	254.4	232.2**	191.6**	99.0	102.2	86.7*	79.0**
% Δ	113.1	108.4	100.7	82.8	65.1	65.9	56.9	51.0

F1 Generation: Adults - The mean body weights of the males (Tables J and L) and females (Tables J, K, M, and N) at the low-dose level (100 ppm) were comparable to those of the controls throughout the study, with the exception of the dams during lactation of the F2b pups. MALES: Mean body weight was significantly lower than the control value in males at the 300 and 900 ppm dose levels (dose-related) throughout the study (Tables J and L). FEMALES: The mid-dose dams displayed comparable or slightly decreased (sometimes statistically significant) body weights compared to the control group. The significant decreases were observed mainly during lactation (both litters). There was a statistically significant decrease in body weight at the high dose throughout the study (Tables J, K, M, and N).

Body-weight gain data are presented in Table 2, below. The high-dose males displayed lower gains compared to the control group, although the % gain was comparable among the groups. Females displayed comparable gains among the groups.

Table 2. F1 Adult Body-Weight Gains (grams)

Interval/ Dose (ppm)	MALES				FEMALES			
	0	100	300	900	0	100	300	900
0-1	62.0	54.4**	52.4**	46.0**	24.5	26.3	23.2	24.7
0-2	118.3	107.3**	101.2**	91.1**	42.8	45.9	41.4	44.3
0-3	165.6	152.9**	143.0**	129.7**	61.5	65.4	58.8	61.9
0-4	201.7	188.2*	176.1**	160.7**	71.9	77.9	70.0	74.9
0-5	232.5	219.2	204.5**	187.2**	84.8	89.5	80.8	85.6
0-6	260.8	246.0	230.5**	209.6**	94.1	100.4	89.1	94.6
0-7	281.1	269.0	246.1**	225.8**	102.7	107.2	98.2	101.2
0-8	299.8	288.7	262.4**	242.2**	105.9	115.0	105.0	107.0
0-9	314.4	304.8	278.9**	254.6**	112.9	121.9	111.1	112.2
0-10	329.7	319.6	291.7**	266.8**	118.7	128.2	115.4	118.0
% Δ	191.4	192.6	188.6	197.3	90.5	95.8	91.5	106.1

(d) Pregnancy, Mating, Gestation, Delivery, and Litter Data

During the mating period (≥ 21 days), one male and one female (from same dose group) were housed together in plastic breeding cages. Daily vaginal examinations were performed during the mating period, and the presence of sperm in the vaginal smear or a copulatory plug was considered evidence of mating. The day evidence of mating was found was considered day 0 of gestation, and the female was housed individually. Pregnancy status was confirmed by the presence of a vascular membrane in the vagina or palpation of uterine contents. F0 adults were paired for F1 litters following at least 10 weeks on the test diets. After all F1 litters were weaned, at least one weanling/sex/litter (when possible) was selected at random to provide 28 male and 28 female weanlings per group to continue as F1 adults in their respective treatment groups. F1 adults were paired for F2a litters following at least 10 weeks on test diets and again after a 2-week rest period to produce the F2b litters (sibling matings of F1 adults were avoided). Pairing for the F2b litters was done avoiding previous pairings for the F2a litters.

RESULTS

F0 Generation: There were no differences noted among the groups in fertility (92.9-100%) for either sex. The mating (100% for all groups) and gestation (96.2-100%) indices and the length of gestation were comparable among the groups. The mean number of days to mate was longest (and most variable) for the high-dose group (see Table 3, below) but not significantly different from the control value.

Table 3. Number of Days to Mate

Group (ppm)	0	100	300	900
days to mate	3.1±1.6	3.0±2.6	3.0±3.3	3.9±5.1

None of the dams delivered nonviable litters. Viability was decreased at the low- and high-dose levels (ratio statistically significant, $p<0.01$), with the mean % being 99, 94, 98, and 86 at the control, low-, mid-, and high-dose levels, respectively. The high-dose level displayed an increase in the number of stillborns (and the number of dams with stillborns) compared to the control values. The mean number of pups delivered per dam was comparable among the groups, as was the weaning index (98.4-100%). The entire litter of one high-dose dam died. Although there were no significant differences in the number of pups surviving at day 21, the high-dose group displayed an increased incidence of pups dying or being cannibalized compared to the control (Table 4, below).

Table 4. Summary of Delivery and Litter Data (F0 Generation-F1 Litters)

Parameter/Dose (ppm)	0	100	300	900
# dams delivering ♀♀ with live pups ♀♀ with stillborn pups ♀♀ with no live pups	27 (96%) 27 7 (26%) 0	25(89%) 25 1 (4%) 0	28 (100%) 28 6 (21%) 0	26 (93%) 26 12 (46%) 0
# pups delivered mean	334 12.88	305 12.20	386 13.79	325 12.50
liveborn stillborn - # stillborn - mean litter % uncertain	326 8 2.22 0	304 1 0.28 0	374 11 2.94 1	308 17 11.85 0
viability index mean % ratio	99 322/326	94 287/304**	98 365/374	86 261/308**
weaning index mean % ratio	100 212/212	100 187/188	100 223/224	99 186/189
pup disposition culled day 4 culled day 21 culled after day 21 next generation died cannibalized missing	 110 32 124 56 2 2 0	 99 32 99 56 10 8 0	 141 20 147 56 2 8 0	 72 25 105 56 23 27 0
pups surviving at day 21♦	212 (65%)	187 (62%)	223 (60%)	186 (60%)
entire litter died	0	0	0	1

* $p<0.05$; ** $p<0.01$; ♦ (# pups alive at day 21 + # delivered alive, as presented in report)

Mean pup body weights (covariate-adjusted) were significantly lower than the control values at the 300 and 900 ppm dose levels at birth through lactation (Table O, appended). Body-weight gains were decreased at the high-dose level compared to the control for both sexes [63-79% of control; calculated by this reviewer (Table P); no statistical analysis was performed].

F1 Generation - F2a Litters: The mating index was 100% for all groups. There was a slight decrease (not statistically significant) in the male/female fertility indices at the high-dose level (85.7%) compared to the control (96.4%) and previous generation values (92.9-100%). The gestation index was comparable among the groups, although incorrectly listed for the mid- and high-dose groups in Table 43 (page 150) of the report. There was no dose-related difference in the number of days to mate.

None of the dams delivered nonviable litters. Viability was decreased at the mid- and high-dose levels, and the weaning index (ratio, # pups surviving to day 21/# pups alive at day 4 postcull) was significantly decreased at the high-dose level. There was an increase in the number of stillborns and the number of dams with stillborns, although statistical significance was not attained. The mean number of pups delivered per dam was comparable among the groups. The weaning index (mean %) was not significantly different among the groups, although the high-dose group displayed the lowest value (100 vs 93%). The percent of pups surviving to day 21 was decreased (dose-related; not statistically significant) at the mid- and high-dose levels compared to the control and low-dose groups and to the F1 pups. The entire litter of 2 mid-dose and 4 high-dose dams died. There was a dose-related increase in the numbers of pups dying and cannibalized at the mid- and high-dose levels.

Table 5. Summary of Delivery and Litter Data (F1 Generation-F2a Litters)

Parameter/Dose (ppm)	0	100	300	900
# dams delivering	27 (96%)	26 (93%)	27 (96%)	24 (86%)
♀♀ with live pups	27	26	27	24
♀♀ with stillborn pups	7 (26%)	5 (19%)	9 (33)	11 (46%)
♀♀ with no live pups	0	0	0	0
# pups delivered	339	346	368	310
mean	12.56	13.31	13.63	12.92
liveborn	329	338	352	287
stillborn - #	8	7	13	23
stillborn - mean litter %	2.43	1.93	3.28	7.70
uncertain	2	1	3	0
viability index mean %	98	98	81	61
ratio	323/329	330/338	285/352**	171/287**
weaning index				
mean %	100	100	100	93
ratio	215/215	207/208	192/192	133/139**
pup disposition				
culled day 4	108	122	93	32
culled day 21	183	167	168	105
culled after day 21	32	40	24	28
died	0	2	15	50
cannibalized	6	7	52	72
missing	0	0	0	0
pups surviving at day 21♦	215 (63%)	207 (60%)	192 (52%)	133 (43%)
entire litter died	0	0	2	4

* $p<0.05$; ** $p<0.01$; ♦ (# pups alive at day 21 ÷ # delivered alive, as presented in report)

F2b Litters: The mating index was 96.4% at the high dose and 100% in all other groups. The mid dose displayed the lowest fertility

rate. There were no significant differences in the days to mate, and the gestation index was 100% for all groups. The number of stillborns was comparable among the groups, although each treatment group had greater numbers compared to the control. The number of pups delivered per dam was comparable among the groups. The entire litter of one low-dose and four high-dose dams died. The viability index (ratio) was decreased at the mid- and high-dose levels (dose-related), and the weaning index (ratio) was decreased at the high-dose level. The number of pups surviving to day 21 was decreased at the high-dose level compared to the control value (57% vs 46%). There was a dose-related increase in the numbers of pups dying and cannibalized.

Table 6. Summary of Delivery and Litter Data (F1 Generation-F2b Litters)

Parameter/Dose (ppm)	0	100	300	900
# dams delivering	26 (93%)	26 (93%)	20 (71%)	26 (93%)
♀♀ with live pups	26	26	20	26
♀♀ with stillborn pups	5 (19%)	8 (31%)	8 (40%)	7 (27%)
♀♀ with no live pups	0	0	0	0
# pups delivered	357	369	280	347
mean	13.73	14.19	14.00	13.35
liveborn	347	345	272	339
stillborn - #	8	23	8	7
stillborn - mean litter %	2.7	5.8	2.9	1.9
uncertain	2	1	0	1
viability index mean %	98	94	92	73
ratio	341/347	334/345	248/272**	248/339**
weaning index				
mean %	100	98	99	91
ratio	205/206	196/200	152/153	157/168**
pup disposition				
culled day 4	135	134	95	80
culled day 21	181	172	112	144
culled after day 21	24	24	40	13
died	1	10	2	40
cannibalized	6	5	23	62
missing	0	0	0	0
pups surviving at day 21♦	205 (57%)	196 (53%)	152 (54%)	157 (45%)
entire litter died	0	1	0	4

* $p<0.05$; ** $p<0.01$; ♦ (# pups alive at day 21 ÷ # delivered alive, as presented in report)

NOTE: For all litterings, it is not clear why some pups were culled at day 21 and beyond, or why survival was presented as the number of pups alive on day 21 divided by the number born alive, or what either signifies.

(e) Sacrifice and Pathology

Parent Animals: At scheduled necropsy, ten animals/sex/group (selected at random) were anesthetized and blood was collected from the retro-orbital plexus and brain tissue was harvested. Cholinesterase activity levels in the plasma, red blood cells, and brain were evaluated. A necropsy was performed on F0 and F1 adult animals that died or were sacrificed in a moribund condition; findings were recorded. Females that failed to mate or mated but failed to deliver a litter (F1 or F2b generations) were

anesthetized, weighed, exsanguinated, and necropsied, with particular attention being given to the reproductive tract. Similarly, after the F1 and F2b pups were weaned, the respective F0 and F1 adult males and females examined. The necropsy included a macroscopic examination of the external surface of the body; all orifices; the cranial cavity; the external surface of the brain and spinal cord; and the thoracic, abdominal, and pelvic cavities and viscera. The following organs/tissues were preserved: ovaries, uterus, vagina, testes, epididymides, prostate, seminal vesicles, and gross lesions. These were examined microscopically from all F0 and F1 adults in the control and high-dose groups. Lesions were examined microscopically for F0 and F1 adults. The reproductive organs of females in the low- and mid-dose groups that failed to mate or mated but failed to deliver were examined microscopically also. NOTE: It is not clear from the text on page 26 of the report (third paragraph) whether all reproductive organs of all groups were examined. Additionally, the ovaries and uteri of females that did not produce a litter were examined for corpora lutea and implantations, respectively. Uteri of females that appeared to be nongravid were stained with an ammonium sulfide solution to confirm pregnancy status.

RESULTS

Gross Pathology: **F0 Adults** - No treatment-related differences were observed. **F1 Adults** - No treatment-related differences were observed.

Clinical Pathology: **F0 Adults** - There were no differences in cholinesterase activities noted among the groups of either sex. **F1 Adults** - At the high-dose level, plasma cholinesterase values (Table Q) were lower (≈68% in ♂♂, ≈70% in ♀♀) than the respective control values, but only the male value attained statistical significance. The high-dose males also displayed higher red blood cell cholinesterase values compared to the control value.

Organ Weights: Organ weight data were not recorded.

Histopathology: There were no treatment-related changes observed in any of the organs/tissues examined microscopically.

4. Offspring Investigations

(a) All litters: Birth: As soon after parturition as possible, the sex of each pup was determined, and the litter size (total # of pups born live or found dead) was recorded. Each live pup was examined for external abnormalities and weighed. Dead pups were examined macroscopically for cervical, thoracic, and abdominal visceral abnormalities and congenital abnormalities, then discarded. Day 4: The sex of each pup was determined and the litter size (# live) was recorded. Pups were examined for external abnormalities and weighed individually. Litters with more than 8 pups were culled at random to produce, as nearly as possible, litters that contained 4 pups/sex. Culled pups were sacrificed and examined for cervical, thoracic, or abdominal visceral and congenital abnormalities, and discarded. Days 7, 14, and 21: Litter size (# live) was recorded;

28

live pups were sexed, examined for external abnormalities and were weighed individually.

RESULTS

F1 Litters - There were no apparent adverse effects of treatment on litter size at birth. Mean body weight of males and females was significantly decreased (dose-related) at birth and throughout lactation at the mid- and high-dose levels (Table O, appended). Body-weight gains (calculated by this reviewer, Table P) were decreased (63-79% of control) at the high-dose level for both sexes, but no statistical analysis was performed on the data. The sex ratio was not affected by treatment. Survival was comparable among the groups, although the mid- and high-dose levels were slightly lower than the control (65 vs 60%; Table 7, below). It is to be noted that these % are those provided in the study report, which were calculated using the number of pups surviving at termination divided by the number of pups delivered. In order to decide whether treatment affected survival, a more useful calculation would involve the use of the number of pups post cull on day 4 as the denominator (**bolded #'s in Table 7**).

Table 7. Pup Survival

F1 Pup Survival at Day 21 (%)			
0 ppm	100 ppm	300 ppm	900 ppm
65	62	60	60
98	**94**	**100**	**89**

F2a Litters - There were no apparent adverse effects of treatment on litter size at birth. Mean body weight of males and females was significantly decreased (dose-related) at birth and throughout lactation at the mid- and high-dose levels, and on day 7 at the low dose for both sexes (Table O, appended). Body-weight gains (Table P) also showed a dose-related decrease. The sex ratio was not affected by treatment. Survival was slightly lower at the mid- and high-dose levels compared to the control (Table 8, below).

Table 8. Pup Survival

F2a Pup Survival at Day 21 (%)			
0 ppm	100 ppm	300 ppm	900 ppm
65	61	55	46
98	**100**	**89**	**69**

F2b Litters - There were no apparent adverse effects of treatment on litter size at birth. There was a dose-related (statistically significant) decrease in mean body weight (both sexes; all dose levels) at birth and from days 7-21 (males) and days 14-21 (females) compared to the control values (Table O, appended). Body-weight gains (Table P) also showed a dose-related decrease. The sex ratio was not affected by treatment. Survival was slightly

lower at the high-dose level compared to the control (Table 9, below).

Table 9. Pup Survival

F2b Pup Survival at Day 21 (%)			
0 ppm	100 ppm	300 ppm	900 ppm
57	57	56	46
99	94	95	75

(c) Terminal studies: On day 21 of lactation of the F1, F2a, and F2b litters, one weanling/sex/ litter was selected at random from 10 litters/group for cholinesterase evaluation of the plasma, red blood cells, and brain. Selected pups were anesthetized and bled from the retro-orbital plexus, and subsequently examined macroscopically. Selected weanlings (1/sex/litter, from 10 litters that were delivered in each group) from each phase (F1, F2a, and F2b) were subjected to a necropsy and processed as described above for the parents. Abnormal tissues were retained for possible microscopic examination. The remaining pups were discarded. Whenever possible, any offspring found dead were examined externally and internally.

RESULTS

F1 Litters: Significantly lower plasma cholinesterase (CHEP) levels (≈ 81% of control value) were displayed in females at the 900 ppm dose level. Males at this dose level displayed significantly higher brain cholinesterase values compared to the control values. There were no significant differences noted among the groups at necropsy (Table Q).

F2a Litters: Lower plasma cholinesterase (CHEP) levels (≈ 84% of control value) were displayed in males at the 900 ppm dose level, although statistical significance was not attained. Females at this dose level displayed significantly lower (83% of control) red blood cell cholinesterase values compared to the control values. There were no significant differences noted among the groups at necropsy (Table Q).

F2b Litters: Both sexes displayed significantly lower (≈78% ♂♂/≈80% ♀♀ of control) red blood cell cholinesterase values compared to the control values. There were no significant differences noted among the groups at necropsy (Table Q).

C. DISCUSSION

Exposure of F0 rats to Thiodicarb via the diet for 10 weeks prior to mating and through gestation and lactation (one litter) and of F1 rats for at least 10 weeks prior to mating and through gestation and lactation for 2 litters (F2a and F2b) resulted in decreased body weight, body-weight gains, and food consumption at the high-dose (900 ppm) level in both sexes and at the mid-dose (300 ppm) level (both sexes) at various times during the study. In

general, males were more severely affected than females and F1 animals were more affected than F0 animals. When body-weight gain is viewed as a %, the high-dose F1 animals displayed larger gains than the controls, but the F0 animals show a lower gain at the mid- and high-dose levels. There was no effect of treatment on survival, mating, fertility, pregnancy rate, gestation, parturition, or litter size. The viability index was decreased at the high-dose level in both generations/all three (F1, F2a, and F2b) litters, and the mid-dose level also displayed a decrease in the F2a and F2b litters (dose-related). Although the low-dose displayed a statistically significant decrease in viability of the F1 litters (94%), the mid dose was not decreased (98%). Also observed in both generations (all litterings) was an increased incidence of pups dying and/or being cannibalized at the mid- and high-dose levels. Although a comparable percent of pups survived to day 21 among the groups (93.5-100%), the weaning index (as a ratio) for the F2a and F2b litters was significantly lower at the high-dose level than the respective controls. The number of dams with stillborns and the number of stillborns were increased at the high-dose level in the F0/F1 litters and F1/F2a litters. Additionally, the number of dams whose entire litter died was increased at the high-dose level at each littering. Offspring growth was adversely affected at the mid- and high-dose levels (both sexes; F1, F2a, & F2b litters), as evidenced by decreased body weights. Pup body weights (both sexes, F1 litters) at the low dose were comparable to the control values at birth and throughout lactation. In the F2a litters, both male and female pups displayed a statistically-significant decrease in body weight compared to the controls on day 7 of lactation only, while the low-dose F2b litters displayed a statistically-significant decrease in body weight at birth (both sexes) and days 7 (males only), 14 (both sexes), and 21 (both sexes) of lactation compared to the control values. Although the magnitude of the decreases in the low-dose F2a and F2b litters is small (89-93% of control value), the effect appears to increase with subsequent litterings. Cholinesterase activity was slightly affected in the plasma of adults and weanlings at the high-dose level, and red blood cell cholinesterase activity was lower in some of the high-dose F2a and F2b weanlings. No historical control data were provided for comparison with the findings in this study. See Summary table (Table 10) below.

D. CONCLUSION

Under the conditions of the study, exposure to Thiodicarb via the diet during pre-mating and through gestation and lactation of F0 rats (one litter) and F1 rats (two litters) at dose levels of 0, 100, 300, and 900 ppm resulted in maternal toxicity at the two highest dose levels. Reproductive effects, as evidenced by decreased pup body weight in F2b litters and a decreased viability index for F1, F2a, and F2b litters, occurred at all three dose levels and at 300 and 900 ppm, respectively. Offspring viability and growth were adversely affected at dose levels of 300 and 900 ppm, and growth was also affected at the 100 ppm dose level. The NOEL for maternal toxicity can be set at 100 ppm, the LEL at 300 ppm, based on decreased body weight/gain and food consumption. The

NOEL for effects on the offspring cannot be set, based on altered growth at all dose levels. The NOEL for reproductive effects cannot be set, based on reduced offspring growth observed at all dose levels. This study is classified Core Supplementary; it does not satisfy the guideline requirement (83-4) for a 2-generation reproduction study in rats.

Table 10. Summary Data

Parameter/Group	0 ppm	100 ppm	300 ppm	900 ppm
Pregnancy Rate				
F0/F1 litters	96	89	100	93
F1/F2a litters	96	93	96	86
F1/F2b litters	93	93	71	93
Viability Index				
F0/F1 litters	99	94	98	86
F1/F2a litters	98	98	81	61
F1/F2b litters	98	94	92	73
Weaning Index				
F0/F1 litters	100	100	100	99
F1/F2a litters	100	100	100	93
F1/F2b litters	100	98	99	91
# Dams w/ Stillborns				
F0/F1 litters	26%	4%	21%	46%
F1/F2a litters	26%	19%	33%	46%
F1/F2b litters	19%	31%	40%	27%
# of Stillborns♦				
F0/F1 litters	8 (2.22)	1 (0.28)	11 (2.94)	17 (11.85)
F1/F2a litters	8 (2.43)	7 (1.93)	13 (3.28)	23 (7.70)
F1/F2b litters	8 (2.7)	23 (5.8)	8 (2.9)	7 (1.9)
Entire Litter Died				
F0/F1 litters	0	0	0	1
F1/F2a litters	0	0	2	4
F1/F2b litters	0	1	0	4
# Pups Died/Cannibalized				
F0/F1 litters	2/2	10/8	2/8	23/27
F1/F2a litters	0/6	2/7	15/52	50/72
F1/F2b litters	1/6	10/5	2/23	40/62
Pup Weight-Day 0♣				
F0/F1 litters	100/100	97/96	92**/91**	85**/83**
F1/F2a litters	100/100	98/98	82**/89**	66**/81**
F1/F2b litters	100/100	92*/92*	81**/83**	81**/80**
Pup Weight-Day 21♣				
F0/F1 litters	100/100	98/99	93**/92**	78**/78**
F1/F2a litters	100/100	96/95	87**/87**	71**/74**
F1/F2b litters	100/100	93**/94*	85**/87**	71**/73**

♦ (mean litter %); ♣ % of control (♂♂/♀♀)

Discrepancies: (1) On page 1002, data on F2b litters (100 ppm) indicates that 11 pups died (8 during days 0-4 and 3 during days 5-21) and 4 were listed as cannibalized; Table 47 on page 161 shows 10 died and 5 were cannibalized for this group. (2) On page 1003, # C70233 dam (300 ppm) is listed with 9 live and one died (day 0). Page 995 lists this dam with 9 live and one stillborn. For this group (300 ppm), Table 47 (page 160) lists 8 stillborns, but page 1003 (individual data) shown only 7 stillborns. Apparently, the one pup was considered "died" for dam # C70233 at one point and stillborn at another. On page 1436 [Certificate of Analysis of Thiodicarb, technical (reference # 211159-169-061)], the date of analysis was January 19, 1990 and the Expiration date is listed as January 19, 1993. The next page (1437) is a Certificate of Composition (Lot No. 211159-169-061), which has an analysis date of November 14, 1990 and an Expiration date of November 14, 1992. It is not clear why there are two different expiration dates. The purity of 211159-169-061 was listed as 94.5% on 1/19/90 and 94.9% on November 14, 1990. On March 17, 1992, the sample was 93.31%. The study dates were 10/5/90 to 6/9/92. Additionally, many of the means could not be confirmed, apparently due to rounding and the computer handling of numbers.

TABLES OF 2-GENERATION REPRODUCTION STUDY ON THIODICARB

Table A. F0 Adult Generation Food Consumption (g/day)

Week/ dose (ppm)	Males (% of Control)			Females (% of Control)		
	100	300	900	100	300	900
0-1	100	97	74**	104	94**	81**
1-2	100	97	92**	102	95	95
2-3	100	100	95*	104	98	99
3-4	99	98	92**	99	98	97
4-5	100	97	93*	105	96	98
5-6	99	94	92**	102	96	97
6-7	100	97	94**	108	100	98
7-8	98	99	93	106	101	103
8-9	101	97	91**	105	100	101
9-10	101	98	93	106	97	93
13-14	104	104	95	see under gestation/lactation		
14-15	102	102	95			
15-16	100	100	93**			
16-17	100	101	93*			
17-18	101	100	93**			

* p< 0.05; ** p<0.01

Table B. Food Consumption of F0 Dams During Gestation and Lactation (g/day)

Interval (days, G/L)	Gestation (% of Control)			Lactation (% of Control)		
	100 ppm	300 ppm	900 ppm	100 ppm	300 ppm	900 ppm
0-7/0-4	95	97	95	102	106	94
7-14/4-7	96	99	101	96	105	93
14-20/7-10	102	99	99	95	103	88**
10-14	96	87**	78**	96	101	89**

* p<0.05; ** p<0.01

Table C. F1 Adult Generation Food Consumption (g/day)

Week/ dose (ppm)	Males (% of Control)			Females (% of Control)		
	100	300	900	100	300	900
0-1	92*	87**	80**	108*	99	99
1-2	92**	89**	83**	106	102	104
2-3	95	91**	85**	110**	98	102
3-4	95	90**	84**	102	102	99
4-5	94*	90**	85**	101	97	101
5-6	94*	88**	84**	102	98	99
6-7	97	91**	86**	99	98	99
7-8	96	91**	87**	104	101	102
8-9	98	95	89**	105	99	101
9-10	98	93*	90**	104	101	108
13-14	99	96	87**	see under gestation/lactation		
14-15	100	93**	84**			
15-16	99	97	88**			
16-17	97	92*	86**			
17-18	99	95	88**			

* p< 0.05; ** p< 0.01;

Table D. Food Consumption (g/day) of F1 Dams During Gestation and Lactation-F2a Litters

Interval (days gest./lact.)	Gestation (% of Control)			Lactation (% of Control)		
	100 ppm	300 ppm	900 ppm	100 ppm	300 ppm	900 ppm
0-4	94	89**	85**	98	95	96
4-7	94	92**	89**	97	100	94
7-14/7-10	97	93*	90**	96	92*	83**
14-20/10-14	92**	81**	66**	97	89**	80**

* p<0.05; ** p<0.01

36

TABLE E. F1 Male Food Consumption (g/day) Prior to Mating for F2b Litters

Dose (ppm) Time Interval (week)	Food Consumption (% of Control)		
	100	300	900
0-1	101	97	91**
1-2	100	96	91**
5-6	101	97	91**
6-7	101	97	90**
7-8	101	97	90**
8-9	100	94	87**
9-10	99	93*	85**

* $p<0.05$; ** $p<0.01$

TABLE F. Food Consumption (g/day) of F1 Dams During Rest Period

Dose/Time Interval (weeks)	% of Control		
	100 ppm	300 ppm	900 ppm
0-1	100	97	103
1-2	101	108	103

Table G. Food Consumption (g/day) of F1 Dams During Gestation and Lactation-F2b Litters

Interval (days gest./lact.)	Gestation (% of Control)			Lactation (% of Control)		
	100 ppm	300 ppm	900 ppm	100 ppm	300 ppm	900 ppm
0-4	95	94	89	93	75	86
4-7	98	96	93	92	100	97
7-14/7-10	98	96	90	96	92	93
14-20/10-14	94	85*	94	104	98	86

* $p<0.05$; ** $p<0.01$

37

Table H. F0 Generation Adult Group Mean Body Weight

Week/ dose (ppm)	Males (% of Control)			Females (% of Control)		
	100	300	900	100	300	900
0	101	99	99	102	100	102
1	100	96**	89**	102	97*	95**
2	100	95**	89**	102	97	95**
3	100	95**	89**	102	96*	95**
4	99	95**	89**	101	97	96**
5	99	94**	88**	102	95*	95**
6	99	93**	87**	102	96*	95**
7	99	94**	87**	103	97	95*
8	98	93**	86**	104	97	96
9	99	94**	86**	103	96	95*
10	99	93**	85**	102	95	93**
12	99	94*	86**	see under gestation/lactation		
14	100	96	86**			
18	100	95	85**			

* p< 0.05; ** p<0.01;

Table I. F0 Dams-Group Mean Body Weight During Gestation and Lactation

Day/ dose (ppm)	Body Weight - gestation (% of Control)			Body Weight - lactation (% of Control)		
	100	300	900	100	300	900
0	102	96	95	99	91**	85**
4	-	-	-	99	92**	88**
7	100	96	95*	98	93**	89**
14	101	96	95*	99	95**	91**
20/21	98	94*	89**	100	97	95*

Table J. F1 Generation Adult Group Mean Body Weight-F2a Litters

Week/ dose (ppm)	Males (% of Control)			Females (% of Control)		
	100	300	900	100	300	900
0	96	90*	78**	102	96	85**
1	94	88**	77**	103	96	87**
2	94	88**	78**	103	96	89**
3	94	88**	78**	103	96	90**
4	95	88**	79**	104	97	92**
5	95	89**	80**	103	96	91**
6	95	88**	80**	104	96	91**
7	96	88**	80**	103	96	91**
8	96	88**	80**	105	97	92**
9	97	89**	80**	105	97	92**
10	97	89**	80**	105	97	92**
14	97	88**	79**	see under gestation/lactation		
18	97	88**	79**			

* $p < 0.05$; ** $p < 0.01$;

Table K. F1 Dams-Group Mean Body Weight During Gestation and Lactation-F2a Litters

Day/ dose (ppm)	Body Weight - gestation (% of Control)			Body Weight - lactation (% of Control)		
	100	300	900	100	300	900
0	104	98	90**	98	92**	78**
4	-	-	-	98	91**	81**
7	102	95	88**	98	93**	83**
14	102	96	89**	98	93**	84**
20/21	100	93**	83**	100	97	90**

Table L. F1 Generation Adult Group Mean Body Weight-F2b Litters

Week/ dose (ppm)	Males (% of Control)		
	100	300	900
0	97	88**	78**
1	97	89**	78**
2	97	89**	78**
3	97	89**	78**
4	98	90**	78**
5	98	90**	78**
6	99	90**	78**
7	99	90**	78**
8	99	90**	78**
9	99	90**	77**
10	99	90**	77**

* p< 0.05; ** p<0.01;

TABLE M. Group Mean Body Weight of F1 Dams During Rest Period

Dose/Week	% of Control		
	100 ppm	300 ppm	900 ppm
0	101	95	89**
1	100	95*	88**
2	100	96	89**

Table N. F1 Dams-Group Mean Body Weight During Gestation and Lactation-F2b Litters

Day/ dose (ppm)	Body Weight - gestation (% of Control)			Body Weight - lactation (% of Control)		
	100	300	900	100	300	900
0	101	96	89**	98	88**	79**
4	-	-	-	95*	85**	80**
7	100	94	87**	95*	89**	84**
14	100	94	87**	97	92**	85**
20/21	99	91**	82**	99	96*	92**

40

Table O. Mean Pup Body Weight (% of Control)

Sex Dose Litter Day	MALES			FEMALES		
	100 ppm	300 ppm	900 ppm	100 ppm	300 ppm	900 ppm
	F1 Litter					
0	97	92**	85**	96	91**	83**
4 precull	100	93*	77**	98	92*	76**
4 postcull	100	93*	77**	99	92*	76**
7	101	93*	78**	99	92*	76**
14	101	93**	79**	98	93**	79**
21	98	93**	78**	98	92**	78**
F2 Litter						
0	98	89**	81**	98	89**	81**
4 precull	94	82**	66**	94	82**	66**
4 postcull	93	82**	66**	93	82**	67**
7	92*	82**	65**	92*	83**	67**
14	96	88**	71**	95	88**	73**
21	96	87**	71**	95	87**	74**
F2b Litter						
0	92*	81**	81**	92*	83**	80**
4 precull	91	80**	70**	92	82**	69**
4 postcull	91	80**	71**	92	83**	70**
7	89*	82**	69**	91	82**	70**
14	92*	85**	70**	93*	86**	72**
21	93*	85**	71**	94*	87**	73**

* $p<0.05$; ** $p<0.01$

41

Table P. Mean Pup Body-Weight Gain (grams-% of control)

Sex/Dose /Litter/ Interval	MALES				FEMALES			
	0 ppm	100 ppm	300 ppm	900 ppm	0 ppm	100 ppm	300 ppm	900 ppm
F1 Litters								
0-4 pre	3.43	3.65-106%	3.22-94%	2.16-63%	3.33	3.4-102%	3.13-94%	2.11-63%
0-7	9.14	9.43-101%	8.53-93%	6.72-74%	8.87	8.94-101%	8.23-93%	6.33-71%
0-14	25.2	24.81-99%	23.52-93%	19.48-79%	24.33	24.03-99%	22.75-94%	18.86-78%
0-21	46.4	45.66-98%	43.1-93%	35.9-76%	44.44	43.36-98%	41.17-93%	34.53-78%
% ▵♦	7.44	7.52	7.79	6.77	7.47	7.63	7.68	7.05
F2 Litters								
0-4 pre	3.97	3.49-88%	2.83-71%	1.71-43%	3.91	3.37-86%	2.82-72%	1.72-44%
0-7	10.11	9.01-89%	7.89-78%	5.64-56%	9.69	8.55-88%	7.69-79%	5.7-59%
0-14	26.9	25.63-95%	23.47-87%	18.57-69%	25.83	24.36-94%	22.56-87%	18.48-72%
0-21	47.77	45.87-96%	41.44-87%	33.4-70%	45.16	42.95-95%	38.99-86%	33.14-73%
% ▵	7.62	7.48	7.39	6.60	7.59	7.34	7.37	6.90
F2b Litters								
0-4 pre	3.71	3.26-88%	2.85-77%	1.93-52%	3.66	3.34-91%	2.94-80%	1.83-50%
0-7	10.0	86.6-87%	8.19-82%	6.1-61%	9.73	8.75-90%	7.9-81%	6.2-64%
0-14	27.48	25.26-92%	23.58-86%	18.51-67%	26.72	24.75-93%	23.16-87%	18.79-70%
0-21	49.03	45.59-93%	42.17-86%	33.97-69%	46.83	43.95-94%	40.93-87%	33.8-72%
% ▵	7.69	7.75	8.13	6.62	7.75	7.89	8.17	7.00

♦ total body-weight gain (days 0-21) ÷ day 0 body weight; no statistics performed on body-weight gain data

42

Table Q. Cholinesterase Values (% of control)

Group/ Parameter/ Dose (ppm)	MALES			FEMALES		
	CHEP (MU/ML)	CHER (MU/ML)	CHEB (MU/ML)	CHEP (MU/ML)	CHER (MU/ML)	CHEB(MU/ML)
F0 adult						
100	101	100	97	125	97	110
300	92	104	98	97	100	87
900	90	108	105	92	100	149
F1 weanlings						
100	95	94	116	93	113	122
300	91	91	125	93	107	91
900	91	94	143**	81**	96	101
F1 adults						
100	83	105	79	88	93	93
300	88	113	84	75	98	111
900	68**	128**	88	70	102	105
F2a weanlings						
100	90	102	103	98	91	102
300	87	109	92	98	93	95
900	84	91	93	97	83*	85
F2b weanlings						
100	98	97	99	88*	97	91
300	103	95	93	102	102	91
900	95	78**	75	87	79**	86