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

#900AA DEC 19 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: **THIODICARB**: Rat Combined Chronic Toxicity/ Carcinogenicity Study; **6(a)(2)**

TO: Ron Kendall
PM Team Reviewer (52)
Reregistration Branch, SRRD (7508W)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 12/15/94
Toxicology Branch II, Section II,
Health Effects Division (7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 12/15/94
Section II Head, Toxicology Branch II
Health Effects Division (7509C)

and

Marcia van Gemert, Ph.D. Marcia van Gemert 12/16/94
Chief, Toxicology Branch II/HFAS/HED (7509C)

Registrant: Rhône-Poulenc Secteur Agro
Chemical: Thiodicarb
Synonym: Larvin
Submission No.: S470742
DP Barcode: D205971
Caswell No.: 900AA
Case: 819468
Identifying No.: 114501
Shaughnessey No.: 114501
MRID No.: 433082-01

Comment: The Registrant has submitted the final report of a rat carcinogenicity study on Thiodicarb, which was flagged as Section **6(a)(2)** data. This study has been reviewed, and the DER is appended.

THIODICARB 104 Week Dietary Carcinogenicity Study in Rats - C Atkinson, P Hudson, J Willerton, and V Iswariah; Title page not dated [MRID # 433082-01].

Under the conditions of the study, exposure of Sprague-Dawley rats [50/sex/group] to Thiodicarb via the diet at dose levels of 0 ppm, 60 ppm [♂♂ 3.3/♀♀ 4.5 mg/kg/day], 200 ppm [♂♂ 12/♀♀ 15 mg/kg/day], and 900 ppm [♂♂ 60/♀♀ 80 mg/kg/day] resulted in a marked decrease in body weight [♂♂ 85%/♀♀ 88% of control at week 13] and body-

weight gain [♂♂ 71%/♀♀ 80% of control overall] in both sexes at the high-dose level throughout the study compared to their respective control groups. With the exception of the first week on test, food consumption was not adversely affected. Survival was not adversely affected in either sex, and in fact, both sexes at the high- dose level displayed longer survival times than their respective controls. The high-dose groups of both sexes displayed changes in various hematology and clinical chemistry parameters [HGB, HCT, RBC, WBC, neutrophils, platelets] indicative of a mild red blood cell loss, as well as increased extramedullary hemopoiesis in the spleen. Mid-dose males also displayed an increase in extramedullary hemopoiesis, and absolute and relative spleen weights were increased in this group and in both sexes at the high-dose level. Increases in tubular atrophy [mid- and high-dose levels] and interstitial cell hyperplasia [all dose levels] were observed in the testes, although statistical significance was not attained, and the incidence of hyperplasia was not strictly dose-related. High-dose males displayed an increased incidence of interstitial cell tumors in the testes compared to the concurrent control males. The incidence of tumors of the pituitary and adrenal gland was decreased in the high-dose males compared to the control incidence. Tumor incidence in females was comparable among the groups. Compared to the control groups, both sexes at the high-dose level displayed fewer animals with tumors and fewer with multiple, benign, and malignant tumors. Only the number of rats with single tumors was greater at the high-dose level [both sexes] than the controls. **The systemic NOEL can be set at 60 ppm [♂♂ 3.3/♀♀ 4.5 mg/kg/day], the LEL at 200 ppm [♂♂ 12/♀♀ 15 mg/kg/day], based on the increased incidence of extramedullary hemopoiesis in males and decreased RBC cholinesterase in females.**

This study is classified Core Minimum, and it satisfies the guideline requirement (83-2) for a carcinogenicity study in a rodent. NOTE: The chronic toxicity phase [52-week interim report] of this study was submitted [Submission No. S475497; DP Barcode D208497; marked 6(a)(2)] as a separate final report [MRID # 434050-011] and is reviewed in a separate DER. The guideline requirement [§83-5] for a combined chronic toxicity/carcinogenicity study in the rat is satisfied also.

Thiodicarb will be presented to the HED Carcinogenicity Peer Review Committee in the near future. No further action is required at this time.

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Reviewed by: Linda L. Taylor, Ph.D. Linda Lee Taylor 12/6/94
Section II, Tox. Branch II (7509C)
Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 12/14/94
Section II Head, Tox. Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Chronic Toxicity/Carcinogenicity-rat PC Code: 114501

MRID NO.: 433082-01

TEST MATERIAL: Thiodicarb

SYNONYMS: Larvin

CHEMICAL NAME: dimethyl N,N'-[thiobis[[(methyliminocarbonyl] oxy]]bis[ethanimidothioate

STUDY NUMBER: IRI Project # 450441; Report # 11026

SPONSOR: Rhone-Poulenc

TESTING FACILITY: Inveresk Research International/Scotland

TITLE OF REPORT: 104-Week Dietary Carcinogenicity Study in Rats

AUTHOR(S): C Atkinson, P Hudson, J Willerton, and V Iswariah

REPORT ISSUED: Title page not dated; issue stamp on GLP Compliance page is dated July 5, 1994

EXECUTIVE SUMMARY: Under the conditions of the study, exposure of Sprague-Dawley rats [50/sex/group] to Thiodicarb via the diet at dose levels of 0 ppm, 60 ppm [♂♂ 3.3/♀♀ 4.5 mg/kg/day], 200 ppm [♂♂ 12/♀♀ 15 mg/kg/day], and 900 ppm [♂♂ 60/♀♀ 80 mg/kg/day] resulted in a marked decrease in body weight [♂♂ 85%/♀♀ 88% of control at week 13] and body-weight gain [♂♂ 71%/♀♀ 80% of control overall] in both sexes at the high-dose level throughout the study compared to their respective control groups. With the exception of the first week on test, food consumption was not adversely affected. Survival was not adversely affected in either sex, and in fact, both sexes at the high- dose level displayed longer survival times than their respective controls. The high-dose groups of both sexes displayed changes in various hematology and clinical chemistry parameters [HGB, HCT, RBC, WBC, neutrophils, platelets] indicative of a mild red blood cell loss, as well as increased extramedullary hemopoiesis in the spleen. Mid-dose males also displayed an increase in extramedullary hemopoiesis, and absolute and relative spleen weights were increased in this group and in both sexes at the high-dose level. Increases in tubular atrophy [mid- and high-dose levels] and interstitial cell hyperplasia [all dose levels] were observed in the testes, although statistical significance was not attained, and the incidence of hyperplasia was not strictly dose-related. High-dose males displayed an increased incidence of interstitial cell tumors in the testes compared to the concurrent control males. The incidence of tumors of

the pituitary and adrenal gland was decreased in the high-dose males compared to the control incidence. Tumor incidence in females was comparable among the groups. Compared to the control groups, both sexes at the high-dose level displayed fewer animals with tumors and fewer with multiple, benign, and malignant tumors. Only the number of rats with single tumors was greater at the high-dose level [both sexes] than the controls. **The systemic NOEL can be set at 60 ppm [♂♂ 3.3/♀♀ 4.5 mg/kg/day], the LEL at 200 ppm [♂♂ 12/♀♀ 15 mg/kg/day], based on the increased incidence of extramedullary hemopoiesis in males and decreased RBC cholinesterase in females.** This study is classified Core Minimum, and it satisfies the guideline requirement (83-2) for a carcinogenicity study in a rodent. Additionally, a separate report of the 52-week interim sacrifice animal data [MRID # 434050-01] was submitted and is reviewed in a separate DER. The guideline requirement [§83-5] for a combined chronic toxicity/ carcinogenicity study in the rat has also been satisfied.

A. MATERIALS

1. Test Compound: Thiodicarb; Description: white powder; Batch #: 09-02-84/CMP 90008/DA 616 and CMP 91079/DA 677; Purity: 96% and 94.86%. Additional analyses were performed on the latter batch [95.3-95.5%].

2. Test Animals: Species: Rat; Strain: Sprague-Dawley; Age: ≈4 weeks old on arrival; Weight: ≈85 g ♂, ≈60 g ♀ on arrival; Source: Charles River (UK) Limited, Margate, Kent, England.

3. Statistics: Body weight, hematology, clinical chemistry, urinalysis, and organ weights: analyzed for homogeneity of variance using the F-max test. When group variances appeared homogeneous, a parametric ANOVA was used and pairwise comparisons made via Student's t-test using Fisher's F-protected LSD. If the variances were heterogeneous, log or square root transformations were used in an attempt to stabilize the variances. If the variances remained heterogeneous, then a non-parametric test such as Kruskal-Wallis ANOVA was used. Organ weights were analyzed also conditional on body weight [analysis of covariance] according to Snedecor and Cochran, 1980. Histology data: analyze using Fisher's exact Probability test. Selected urinalysis parameters: analysis of variance using the F-max test.

B. STUDY DESIGN

1. Animal Assignment: Two hundred males and two hundred females were assigned to the study [60 rats/sex from the same shipment of rats were used in a 52-week Toxicity Study, 1993; IRI Project # 450441, Report # 7881; MRID # 434050-01]. The rats were assigned randomly as follows: cages were placed on racks and a transport box with male rats was opened and the first rat taken out was placed in the first cage followed by the second rat who was placed into the next cage [working left to right, top to bottom of the rack]. This procedure continued until the requisite number of cages contained one male and the procedure continued until each cage contained 5 males. The procedure was repeated with the female rats. The cages were assigned a treatment group by the use of computer-generated random number sequences. The test material was administered via the diet to groups of 50 rats/sex/dose [dose levels of 0, 60, 200, and 900 ppm] for a minimum of 104 weeks. The control groups received untreated diet. The selected rats were acclimated to the study room for 13 days prior to treatment. All rats had access to Rat and Mouse (modified) No. 1 Diet SQC Expanded (Fine Ground) [Special Diets Services Limited, Stepfield, Witham, Essex] and domestic mains water ad libitum. There was a 52-week interim sacrifice, and the data generated in that phase of the study were reported separately [MRID # 434050-01].

2. Diet Preparation: Sieved test material was mixed directly with untreated diet and blended in a mixer. Fresh diets were prepared at least once every 2 weeks. Previous stability analysis on Thiodicarb [IRI Project No. 340164] indicated that the test material was stable in the diet for at least 3 weeks. Mixed batches were stored at room

temperature. Samples of the diets prepared for weeks 1, 6, 10, 14, 25, 35, 47, 60, 72, 86, and 97 were taken for analysis of homogeneity and attained concentrations.

RESULTS

The concentrations attained throughout the study were satisfactory, with greater than 92% of target being attained, with one exception. The week 97 sample was ≈87% of the theoretical concentration. The results of the analyses indicated that the mixing procedure was adequate.

C. METHODS AND RESULTS

1. Observations

Daily observation of each animal was performed for signs of toxicity, and mortality/moribundity checks were made twice a day. Weekly physical examinations [palpation, checks of appearance, movement and behavior, skin and hair condition, eyes and mucous membranes, and respiration] were performed throughout the study.

Toxicity/Mortality (survival)

No clinical signs indicative of a toxic effect were noted at any dose level in either sex. Survival was not adversely affected in either sex. The percent mortality for all groups is listed in Table 1. Females at the high dose had significantly longer survival times compared to the control females, and the high-dose males displayed longer survival times also but statistical significance was not attained.

Dose (ppm)/ Sex	Table 1. Mortality (%)	
	MALES	FEMALES
0	58	62
60	58	52
200	66	72
900	46	36

2. Body Weight: Individual body weights were determined weekly from one week prior to study initiation through the 13th week of the study; thereafter, weights were measured once every 2 weeks throughout the dosing period.

RESULTS

MALES - Throughout the study, males at the high-dose level displayed statistically significant decreases in body weight compared to the control values, with the significant decreases beginning during the first week [85% of control; Tables 2 & 3]. Body-weight gains were

decreased also throughout the study, with the gain during the first 13 weeks at the high-dose level being 77% of the control value. The overall body-weight gain at the high dose was 71% of the control. No substantial differences in either body weight or body-weight gain were displayed at the mid- and low-dose levels at any time point, although statistical significance was attained initially for body weight at the mid-dose level [97% of control].

FEMALES - High-dose females displayed a similar decrease in body weight/body-weight gain throughout the study, although both the high- and low-dose groups showed a statistically significant decrease [98/97% of control initially] compared to the control group prior to the initial dosing [week 0]. By week 1, body weight for the high-dose females was 88% of the control value [Tables 2 & 3]. Body-weight gain during the first 13 weeks was 81% of the control value at the high-dose level. Overall body-weight gain was 78% of control. No substantial differences in either body weight or body-weight gain were displayed at the mid- and low-dose levels at any time point, although statistical significance was attained during the first three weeks for body weight at the mid-dose level [97% of control].

Table 2. Body Weight (% of control)

Week/Dose	60 ppm	200 ppm	900 ppm
MALES			
Pre-test	100	99	99
1	99	97**	85***
2	97	97*	87***
3	97*	97*	87***
4	99	97	87***
5	99	98	88***
6	100	99	89***
9	99	97	86***
13	100	97	85***
26	100	97	80***
52	101	97	75***
72	100	100	73***
90	108*	98	78***
104	110*	102	78***
FEMALES			
Pre-test	98*	99	97**
1	97**	97**	88***
2	98	97*	89***
3	98	97*	89***
4	99	98	89***
5	99	97*	89***
6	99	97	90***
9	99	98	89***
13	99	98	88***
26	100	100	86***
52	102	102	82***
72	102	102	80***
90	110*	101	81***
104	112	102	85***

* p<0.05; ** p<0.01; ***p<0.001

Table 3. Mean Cumulative Body-Weight Change♦ [g (% of control)]

Week/Group	0 ppm	60 ppm	200 ppm	900 ppm
MALES				
0-1	60	59	54	24(40)
1-2	50	49	49	49
2-3	41	31	39	36
0-13	359	359	345	278
0-26	474	471	453(96)	338(71)
0-52	618	629	598(97)	416(67)
0-104	594	675(114)	600	423(71)
FEMALES				
0-1	32	30	28(88)	15(47)
1-2	24	26	24	24
2-3	24	23	23	20(83)
0-13	181	180	178	146(81)
0-26	220	222	221	174(79)
0-52	300	313	313	223(74)
0-104♥	363	429	372	289(80)

♦ body-weight change data not provided in report (except overall); #'s calculated by reviewer; no statistics

♥NOTE: Overall body-weight gain for the female groups could not be confirmed by this reviewer. The numbers listed in Table 1 of the report for Total Weight Gain (weeks 0-104) are 291, 316, 316, and 228 grams for the control, low, mid, and high dose levels, respectively.

3. Water, Food Consumption, and Compound Intake

The quantity of food consumed by each cage of rats was determined weekly from one week prior to study start through the 13th week of the study; thereafter, food consumption was measured once every 4th week throughout the dosing period. Water consumption was monitored by visual inspection weekly.

RESULTS

The overall mean daily intake values of test material for both sexes are listed below (Table 4). Additionally, the range and mean of intakes at various intervals during the study are presented.

Table 4. Range/Mean Daily Thiodicarb Intake [mg/kg/day]

Interval/Sex/Dose	60 ppm	200 ppm	900 ppm
MALES			
weeks 1-13			
range	3.5-8.4	12-27	64-116
mean	4.8	26	81
weeks 14-52			
range	2.3-3.4	8-12	43-65
mean	2.7	9.4	50
weeks 53-100			
range	2.2-2.5	7-10	40-49
mean	2.3	8.3	45
weeks 1-100			
mean	3,3	12	60
FEMALES			
weeks 1-13			
range	4.5-8.8	16-29	78-135
mean	6.1	21	102
weeks 14-52			
range	3.1-4.7	11-17	61-95
mean	3.9	13	71
weeks 53-100			
range	3.0-3.6	10-12	55-72
mean	3.3	11	62
weeks 1-100			
mean	4.5	15	80

Overall, there was no difference in food consumption among the groups in either sex, although initially the high-dose groups displayed lower intake, which might have been due to a palatibility problem [Table 5]. Water consumption was not affected.

Table 5. Mean Food Consumption [g/rat/week; (% of control)]

Week/Group	0 ppm	60 ppm	200 ppm	900 ppm
MALES				
0	183	183	180	178
1	225	226	210	179(80)
2	239	230	230	223
3	225	211	224	208
6	215	222	228	233
9	219	216	216	212
total 1-101	22652	22499	22899	21918(97)
FEMALES				
0	139	134	135	134
1	163	158	154	133(82)
2	178	169	171	173
3	181	170	160	157
6	177	188	175	195
9	164	177	187	189
total 1-101	18466	18533	18523	18622

4. Ophthalmological examination

Ophthalmological evaluations were performed on the eyes of 20 rats

from each dose group [chosen at random] prior to study initiation using an indirect ophthalmoscope after application of a mydriatic agent [1% Mydriacyl]. Anterior, lenticular, and fundic areas were evaluated. Additional ophthalmoscopic examinations were performed during week 51 of treatment on 20 rats from the control and high-dose groups and during week 103 on all survivors in the control and high-dose groups.

RESULTS

There were no apparent treatment-related lesions observed at any dose level.

5. Clinical Laboratory Investigations

Blood samples [tail vein] were collected from all surviving rats at weeks 53, 78/79, and 103/104 for differential blood count [Technicon H-1 analyzer, which automatically analyzes for other hematology parameters] and from 10 rats/sex [randomly selected; computer-generated number sequences] from each group at weeks 79 and 104 [via the orbital sinus under light anaesthesia; except for measure of clotting time (tailsnip); non-fasted] for hematology and clinical chemistry evaluations [see below]. After separation of plasma from the red blood cells, all samples for cholinesterase assessment were snap frozen by immersion in liquid nitrogen and stored at -20°C until analyzed. No pre-test values were obtained.

a. Hematology: The CHECKED (X) parameters were examined.

X	Hematocrit (HCT)	X	Leukocyte differential count♦
X	Hemoglobin (HGB)	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)	X	Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)	X	Mean corpusc. volume (MCV)
X	Platelet count		Reticulocyte count
X	Blood clotting measurements♦		Red cell morphology
	(Thromboplastin time)	X	Large unclassified cells
	(Activated partial thromboplastin time)		
	(partial thromboplastin time)		♦ Hepato Quick
	Nucleated erythrocytes normoblasts		

RESULTS

At the high-dose level in both sexes, statistically significant differences from control values were observed in several parameters at various intervals [Table 6]. WBC's were increased in both sexes at the high-dose level throughout most of the study, although males displayed statistical significance only for the 10 selected males at week 104, while females lacked statistical significance only at this time point. Low-dose males displayed significantly decreased WBC's at week 79 in the 10 selected males and at study termination. In the high-dose females, neutrophils and lymphocytes were increased during most of the study, and the high-dose males displayed an increase in neutrophils for most of the study. Hemoglobin and hematocrit were decreased at the high-dose level in both sexes at all time points compared to their respective control values, and RBC's were decreased at the week 53 and 78(79) time points also. Platelets were increased at the high dose in both sexes at all sampling times except the values for the females at weeks 103/104 did not attain statistical significance.

Table 6. Hematology Parameters

Parameter/Dose/Sex	0 ppm	60 ppm	200 ppm	900 ppm
WBC x $10^9.l^{-1}$				
Males				
week 53	10.06	10.47	10.80	10.91
week 78(79)♦	10.55(13.19)	10.43(8.76**)	13.88(13.59)	12.73(12.23)
week 103(104)♦	13.36(11.15)	9.79*(10.08)	10.84(13.50)	14.53(16.80*)
Females				
week 53	5.70	5.86	6.42	8.16***
week 78(79)♦	6.24(6.62)	6.35(6.29)	6.83(8.38*)	7.95***(8.35*)
week 103(104)♦	6.87(6.92)	8.39(7.44)	8.41(8.32)	9.73(8.52)
Neut. x $10^9.l^{-1}$				
Males				
week 53	2.18	2.02	2.25	2.67
week 78(79)	2.71(2.84)	3.05(1.59**)	3.28(3.39)	4.73***(3.44)
week 103(104)	5.90(3.26)	3.41*(2.73)	4.16(5.91)	7.66(8.41**)
Females				
week 53	1.32	1.44	1.42	2.34***
week 78(79)	2.12(1.50)	2.01(1.55)	2.02(1.52)	2.83**(2.55**)
week 103(104)	2.86(1.84)	3.79*(2.82)	3.98(2.89)	4.70**(3.81**)
Lymp. x $10^9.l^{-1}$				
Males				
week 53	6.96	7.52	7.58	6.77
week 78(79)	6.85(8.95)	6.41(6.40**)	8.97(8.99)	6.74(7.79)
week 103(104)	6.13(6.57)	5.36(6.14)	5.50(6.04)	5.54(6.65)
Females				
week 53	4,05	3.93	4.45	5.18***
week 78(79)	3.58(4.64)	3.81(4.24)	4.25**(6.29*)	4.52***(5.27)
week 103(104)	3.33(4.30)	3.83(3.77)	3.63(4.58)	4.08(3.90)
Mono. x $10^9.l^{-1}$				
Males				
week 53	0.40	0.40	0.41	0.35
week 78(79)	0.38(0.55)	0.35(0.33**)	0.48(0.53)	0.48(0.38*)
week 103(104)	0.49(0.36)	0.38(0.29)	0.43(0.36)	0.48(0.45)
Females				
week 53	0.25	0.24	0.27	0.30
week 78(79)	0.26(0.22)	0.25(0.26)	0.24(0.25)	0.28(0.28)
week 103(104)	0.29(0.25)	0.36(0.28)	0.31(0.25)	0.42(0.23)
Baso. x $10^9.l^{-1}$				
Males				
week 53	0.03	0.03	0.03	0.03
week 78(79)	0.02(0.02)	0.01(0.01)	0.06(0.03)	0.02(0.02)
week 103(104)	0.03(0.02)	0.02**(0.02)	0.02*(0.03)	0.03(0.04)
Females				
week 53	0.01	0.01	0.02	0.02**
week 78(79)	0.01(0.01)	0.01(0.01)	0.01(0.02)	0.01*(0.01)
week 103(104)	0.01(0.01)	0.02(0.01)	0.02(0.01)	0.02(0.02)
LUC x $10^9.l^{-1}$				
Males				
week 53	0.27	0.28	0.29	0.27
week 78(79)	0.37(0.62)	0.37(0.29**)	0.82(0.51)	0.51(0.35**)
week 103(104)	0.62(0.79)	0.42(0.80)	0.49(1.03)	0.63(1.03)
Females				
week 53	0.10	0.10	0.12	0.14**
week 78(79)	0.15(0.13)	0.15(0.13)	0.16(0.19)	0.16(0.14)
week 103(104)	0.25(0.43)	0.30(0.44)	0.36(0.47)	0.40(0.48)

Table 6. Hematology Parameters

Parameter/Dose/Sex	0 ppm	60 ppm	200 ppm	900 ppm
Hb g.dl^{-1}				
Males				
week 53	15.3	15.3	14.9	14.2***
week 78(79)	15.0(14.9)	14.6(14.6)	14.2*(14.2)	13.4***(13.7)
week 103(104)	13.1(14.5)	13.7(13.8)	14.3(11.9)	11.5**(11.3)
Females				
week 53	14.5	14.6	14.4	13.1***
week 78(79)	13.9(13.8)	14.3(14.2)	14.4(14.2)	13.1***(13.1*)
week 103(104)	13.1(13.5)	12.5(12.2)	13.2(13.4)	11.8**(11.5)
RBC x 10^{12}.1^{-1}				
Males				
week 53	8.82	8.95	8.66	8.33***
week 78(79)	8.62(8.44)	8.63(8.28)	8.19(7.99)	7.91***(8.02)
week 103(104)	7.48(8.23)	7.83(7.71)	8.05(6.66)	7.07(6.92)
Females				
week 53	7.57	7.66	7.57	6.86***
week 78(79)	7.25(7.19)	7.59(7.41)	7.57(7.42)	6.83***(6.72*)
week 103(104)	6.84(6.94)	6.50(6.28)	6.91(6.99)	6.14(5.86)
Hct 1.1^{-1}				
Males				
week 53	0.432	0.434	0.426	0.413***
week 78(79)	0.445(0.444)	0.434(0.437)	0.422*(0.426)	0.403***(0.420)
week 103(104)	0.396(0.435)	0.413(0.415)	0.429(0.360)	0.359*(0.354)
Females				
week 53	0.407	0.406	0.404	0.373***
week 78(79)	0.402(0.403)	0.412(0.412)	0.415(0.408)	0.380***(0.380*)
week 103(104)	0.390(0.408)	0.373(0.369)	0.395(0.408)	0.357**(0.359)
Platelets x 10^{9}.1^{-1}				
Males				
week 53	942	923	1003	1085**
week 78(79)	864(941)	917(693)	891(1015)	984**(878)
week 103(104)	974(811)	1045(984)	976(1021)	1233***(1264**)
Females				
week 53	661	696	735	894***
week 78(79)	716(746)	726(674)	718(837)	875***(896*)
week 103(104)	796(815)	903(932)	940(912)	941(871)

♦(10 selected rats/sex/group sampled =weeks 79 and 104); LUC either large unclassified cells or large unstained cells; * $p<0.05$; ** $p<0.01$; *** $p<0.001$
NOTE: page 38 Text Table 2, for high-dose ♂♂, week 104, lists +158% for the high-dose neutrophil findings; should be +258

b. Clinical Chemistry: The CHECKED (X) parameters were examined.

	Electrolytes:		Other:
X	Calcium	X	Albumin
X	Chloride	X	Blood creatinine
	Magnesium	X	Blood urea nitrogen
X	Phosphorous	X	Cholesterol
X	Potassium	X	AG ratio
X	Sodium	X	Glucose
	Iron		Phospholipids
	Enzymes	X	Total bilirubin
X	Alkaline phosphatase (ALK)	X	Total Protein
X	Cholinesterase (ChE)♦		Triglycerides
X	Creatine phosphokinase (CPK)		Lipids, total
X	Lactate dehydrogenase (LDH)		Triiodothyronine, total T_3
X	Serum alanine aminotransferase		
X	Serum aspartate aminotransferase		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase (GLDH)		
	Ornithine carbamyltransferase (OCT)		
	protein electrophoresis		
	Thyroxine, total T_4		
	Thyroid stimulating hormone (TSH)		

♦ plasma, RBC, brain

RESULTS

Plasma cholinesterase was decreased at all dose levels in males at both time points, with statistical significance being attained at all dose levels at week 79 [no dose response] and at the highest dose at week 104 [Table 7]. Females at the high-dose level displayed decreased values at both time points, but statistical significance was attained only at week 104. At week 104, the mid-dose females and both sexes at the high dose displayed decreased RBC cholinesterase [dose related]. Males at the high-dose level displayed decreased [88% of control] brain cholinesterase at week 104, but statistical significance was not attained.

Table 7. Clinical Chemistry Parameters

Parameter/Dose/Sex	0 ppm	60 ppm	200 ppm	900 ppm
plasma cholinesterase				
males				
week 79	1388	905**(65)	1011*(73)	553***(40)
week 104	1221	950(78)	839(69)	318***(26)
females				
week 79	2830	3321	2681	2595(92)
week 104	2050	2361	1839(90)	1052**(51)
RBC cholinesterase				
males				
week 79	921	998	908	833(90)
week 104	1594	1819*(114)	1530	1314*(82)
females				
week 79	683	845	683	826
week 104	1658	1546	1365***(82)	1072***(65)

Table 7. Clinical Chemistry Parameters

Parameter/Dose/Sex	0 ppm	60 ppm	200 ppm	900 ppm
brain cholinesterase				
males				
week 79	-	-	-	-
week 104	13970	15879	16154	12262(88)
females				
week 79	-	-	-	-
week 104	12412	16530	15182	15829
total protein				
males				
week 79	71	69	70	65**(92)
week 104	68	68	67	65(96)
females				
week 79	79	78	77	77
week 104	68	74**(109)	72	73*(107)
BUN				
males				
week 79	5.0	4.8	5.2	6.2*(124)
week 104	5.6	6.6	5.6	4.9
females				
week 79	5.6	5.7	6.1	6.4(114)
week 104	5.5	5.0	5.0	5.5

c. Urinalysis: Samples were obtained from a randomly selected [by computer-generated random number sequence] 10 rats/sex/group at ≈weeks 79 and 104, who were housed in metabolism cages over a 4-hour period of food and water deprivation. The CHECKED (X) parameters were examined.

X		X	
	Appearance (transparency)	X	Glucose
X	Volume	X	Ketones
X	Specific gravity	X	Bilirubin
X	pH	X	Blood pigments
X	Sediment (microscopic)		Nitrite
X	Protein	X	Urobilinogen
	Leukocytes		Color

RESULTS

None of the findings were considered indicative of systemic toxicity.

6. Sacrifice and Pathology

At termination, all survivors were sacrificed [CO_2 asphyxiation followed by exsanguination] and necropsied. All rats dying on test were necropsied also. The brain, kidneys, liver, spleen, adrenals, lung, heart, thymus, pituitary, thyroid, parathyroid, prostate/uterus, and testes/ovaries from each of the rats were weighed from 10 rats/sex/group. The CHECKED (X) tissues were collected from all rats and preserved. Blood smears were obtained only from those sacrificed in extremis. All of the tissues listed below were

processed and examined from all control and high-dose rats and those dying on test, except for the nasal cavity, parotid salivary glands, ears, rectum, and rib. Additionally, the liver, kidney, and lung were examined in all low- and mid-dose rats, and the testes of the low-and mid-dose males and the spleen of the low- and mid-dose rats of both sexes were examined following findings at the high-dose level in the current study and in the 52-week study.

X	Digestive system	X	Cardiovasc./Hemat.	X	Neurologic
X	Tongue	X	Aorta	X	Brain♦
X	Salivary glands	X	Heart	X	Periph. nerve
X	Esophagus		Bone marrow	X	Spinal cord
X	Stomach	X	Lymph nodes♦	X	Pituitary
X	Duodenum	X	Spleen	X	Eyes & optic n.
X	Jejunum	X	Thymus		Glandular
X	Ileum		Urogenital	X	Adrenal gland
X	Cecum	X	Kidneys		Lacrimal gland
X	Colon	X	Urinary bladder	X	Mammary gland
X	Rectum	X	Testes	X	Parathyroids
X	Liver		Epididymides	X	Thyroids
	Gall bladder	X	Prostate		Other
X	Pancreas	X	Seminal vesicle	X	Bone (rib/sternum)
	Respiratory	X	Ovaries	X	Muscle (thigh)
X	Trachea	X	Uterus	X	Skin
X	Lung	X	Vagina	X	All gross lesions
X	Nasal cavity		Cervix		and masses
	Pharynx		Coagulating gl.	X	Ears
	Larynx				

♦ submandibular/mesenteric

RESULTS

a. Organ Weight: There were no statistically significant differences in organ weights observed in either sex [Table 8], but it is to be noted that the number of organs weighed per group was ≈ 10. Males at the high-dose level displayed a statistically significant decrease [79% of control] in terminal body weight compared to the control males, and the high-dose females displayed a decrease that was 86% of the control value but statistical significance was not attained. In females, increases in absolute and relative to body weight [covariance analysis] were observed at all dose levels in liver [dose-related], pituitary, spleen, and thymus weights. Ovarian weight showed a wide variation among the groups, and there was a dose-related decrease in testes weight [both absolute and relative to body weight [covariance analysis]. In general, the increases noted in relative organ weight may be attributed to decreased body weight at the high-dose level.

Table 8. Organ Weights

Sex/Group/ Organ Weight (g)	MALES		FEMALES	
	absolute	relative	absolute	relative
liver				
0	23.5	23.1	17.2	16.89
60	25.8	24.5	19.0	17.90
200	22.9	22.4	18.5	18.44
900	21.1(90)♦	23.3	20.3(118)	21.76(129)
pituitary				
0	0.0226	0.0229	0.0279	0.0285
60	0.0261	0.0275	0.0316(113)	0.0344(121)
200	0.0246	0.0255	0.0632(227)	0.0633(222)
900	0.0224	0.0198(86)	0.0470(168)	0.0435(153)
thyroids				
0	0.0475	0.0473	0.0357	0.0353
60	0.0509(107)	0.0504	0.0302(85)	0.0286(81)
200	0.0410(86)	0.0408	0.0362	0.0362
900	0.0430(91)	0.0439(93)	0.0297(83)	0.0319(90)
spleen				
0	1.43	1.41	0.93	0.92
60	1.48	1.41	0.98	0.96
200	1.61(113)	1.58(112)	1.01	1.01(110)
900	1.58(110)	1.71(121)	1.25(134)	1.28(139)
thymus				
0	0.116	0.114	0.112	0.110
60	0.128	0.123	0.133(119)	0.128(116)
200	0.148	0.145	0.125(112)	0.125(114)
900	0.107	0.116	0.131(117)	0.138(125)
kidneys				
0	5.74	5.70	3.45	3.42
60	5.58	5.43	3.80	3.68
200	5.71	5.64	3.58	3.57
900	5.08(89)	5.32(93)	3.61(105)	3.77(110)
ovaries				
0	-	-	0.2433	0.2380
60	-	-	0.0985(40)	0.0653(27)
200	-	-	0.1181(49)	0.1142(48)
900	-	-	0.3500(144)	0.3918(165)
uterus				
0	-	-	0.72	0.72
60	-	-	0.94(131)	0.92(128)
200	-	-	0.73	0.72
900	-	-	0.62(86)	0.65(90)
testes				
0	5.02	5.01	-	-
60	5.17	5.15	-	-
200	5.00	5.00	-	-
900	4.56(90)	4.58(91)	-	-

♦ (% of control)

b. Gross Pathology: The only notable finding at necropsy was an increased incidence of tail lesions and footsores of the hindfeet in the high-dose males compared to the control males [Table 9]. There was no discussion as to whether increased fighting had been observed in this dose group that might explain the finding [rats housed 5/cage].

Table 9. Incidence of Hindlimb and Tail Lesions in Males

Lesion/Dose	0 ppm	60 ppm	200 ppm	900 ppm
hindfeet: sore(s)	9	15	14	26
hindfeet: swollen	3	5	0	6
tail: abnormal	0	2	1	8
tail: scab(s)/sore(s)	4	7	8	15
tail: mass	0	0	1	1

c. Microscopic Pathology: **Non-neoplastic Findings** - MALES: In the spleen, there was a dose-related increase in the incidence of extramedullary hemopoiesis, with the mid- and high-dose groups displaying a slight increase in the severity also compared to the control males. [Table 10]. Additionally, a slight increase in hemosiderin in the spleen was observed in the high-dose males. Tubular atrophy in the testes was increased at the high-dose level compared to the control incidence, but statistical significance was not attained. Additionally, significantly fewer high-dose males displayed testes with no abnormality. There were several lesions that were decreased at the high-dose level compared to the controls; e.g., lower incidences of degeneration of the sciatic nerve, skeletal muscle atrophy, and dilated/cystic mammary glands. At the high-dose level, there was an increase in the number of males with hindfoot inflammation and/or tail inflammation/abscesses, which correlate with the gross findings. FEMALES: At the high-dose level, the incidences of hemosiderin and extramedullary hemopoiesis were increased slightly compared to the control values, but statistical significance was not attained. Lymphangiectasis or sinusoidal edema of the lumbar lymph nodes were observed only in the high-dose females, but since inflammatory lesions such as footsores or ulcerated tumors were not observed, the findings was not considered treatment related. Galactocoeles in the mammary glands were observed only in Thiodicarb-treated females, but these common age-related changes were not considered treatment-related in the absence of other findings in the mammary glands.

Table 10. Non-neoplastice Findings

Lesion/Sex/Group	0 ppm	60 ppm	200 ppm	900 ppm
MALES				
Spleen N=	49	50	50	49
† extramedullary hemopoiesis				
total	21	23	33*	37**
grade ±	11	11	13	11
grade +	1	7	8*	8*
grade++	3	1	0	5
grade +++	4	1	5	9
grade ++++	2	3	7	4
† hemosiderin				
total	7	7	8	11
grade ±	5	5	5	6
grade +	2	2	2	3
grade ++	0	0	1	2
grade +++	0	0	0	0
no abnormality	21	14	5***	5***
Testes N=	50	50	50	49
no abnormality	28	30	23	17*
focal interstitial cell hyperplasia				
total	2	4[1]♥	7[2]	6[2]
grade ±	1	2	2	2
grade +	1	2	5	3
grade ++	0	0	0	1
tubular atrophy				
total	19[3]	16[7]	22[11]	27[10]
grade ±	7	5	12	10
grade +	4	6	0	6
grade ++	6	3	6	8
grade +++	2	2	4	3
Hindfeet N=	11	14	12	34
inflammation	9	9	11	27
Tail N=	11	14	12	34
inflammation/abscesses	3	3	4	12
FEMALES				
Spleen N=	50	50	50	49
† extramedullary hemopoiesis				
total	32	35	30	37
grade ±	4	4	9	11
grade +	11	6	6	10
grade++	4	10	4	2
grade +++	8	8	6	7
grade ++++	5	7	5	7
† hemosiderin				
total	26	22	23	31
grade ±	15	15	11	9
grade +	9	5	9	8
grade ++	2	2	3	12**
grade +++	0	0	0	2
no abnormality	4	2	7	1
Lymph Node - lumbar N=	30	15	19	26
lymphangiectasis/sinusoidal edema	0	0	0	7**
Mammary Gland N=	50	26	36	50
galactocoele(s)	0	2	2	6*

♥[# bilateral]

Neoplastic Findings - MALES: There was an increased incidence of benign interstitial cell tumors [adenoma] in the testes at the high-dose level compared to the control and other dose groups, but

statistical significance was not attained. The first interstitial cell adenoma occurred at weeks 89, 95, 105, and 75 in the control, low-, mid-, and high-dose groups, respectively. Of the adenomas observed in each group, the percentage observed at termination was 60%, 67%, 100%, and 42% for the control, low-, mid-, and high-dose groups, respectively. With the exception of one control, one low-, and two high-dose rats with unilateral interstitial cell adenomas only, all other males with interstitial cell adenomas also displayed tubular atrophy and/or interstitial cell hyperplasia. With the exception of the high dose group, which displayed only unilateral interstitial cell adenomas, both unilateral and bilateral tumors were observed. A decreased incidence of benign pituitary tumors and an absence of malignant adrenal medulla tumors were observed in the high-dose males compared to the controls. FEMALES: The incidence of tumors in the females was comparable among the groups. [Table 27 of the report is appended, which lists the incidence of tumors; Table 28 provides other tumor information and is appended also]

Table 11. Neoplastic Findings in Males

Tumor/Dose	0 ppm	60 ppm	200 ppm	900 ppm
MALES				
Testes N=	50	50	50	49
interstitial cell adenoma total	5	3	3	12
unilateral	4	1	1	12
bilateral	1	2	2	0
mesothelioma	0	0	1	0
U-seminoma dysgerinoma	0	0	0	1
Seminal Vesicles	50	29	32	50
unilateral Adenoma	0	0	0	1
Thyroids N=	49	29	31	50
C-cell carcinoma(ta)	0	0	0	2
unilateral C-cell adenoma	7	2	2	3
pituitary N=	50	29	34	50
adenoma	28	16	17	5***

D. DISCUSSION

Exposure of Sprague-Dawley rats to Thiodicarb via the diet at dose levels of 0 ppm, 60 ppm [♂♂ 3.3/♀♀ 4.5 mg/kg/day], 200 ppm [♂♂ 12/♀♀ 15 mg/kg/day], and 900 ppm [♂♂ 60/♀♀ 80 mg/kg/day] resulted in a marked decrease in body weight [♂♂ 85%/♀♀ 88% of control at week 13] and body-weight gain [♂♂ 71%/♀♀ 80% of control overall] in both sexes at the high-dose level throughout the study compared to their respective control groups. With the exception of the first week on test, food consumption was not adversely affected. Survival was not adversely affected in either sex and in fact, the high-dose rats had longer survival times, which may be related to their decreased body weight. There were indications throughout the study of a mild red blood cell loss in both sexes at the high-dose level. Additionally, these two groups displayed changes in white blood cell parameters, increased platelets, and increased hemopoiesis. The incidence of tubular atrophy in the testes was increased in the high-dose males, which the author states may be a reflection of the reduced body weights observed in these males, and increases in the incidence of interstitial cell hyperplasia were displayed at all dose levels

compared to the control males. Additionally, there was a higher incidence of interstitial cell tumors in the testes in the high dose compared to the control males, which the author suggested may be a contributory factor since the tumors were often accompanied by atrophic tubules. Because there was no increase in the severity of the tubular atrophy with increasing dose and no significant dose related trend, the author did not consider the finding [tubular atrophy] directly related to Thiodicarb treatment. Similarly, the lack of statistical significance and a dose response in tumor incidence, along with only a slight, non-dose-related increase in interstitial cell hyperplasia led to the conclusion by the author that the higher tumor incidence may not be related to Thiodicarb treatment. TB II notes that the lack of an apparent dose response might be due to the spacing of the dose levels. With regard to the lower incidences of pituitary and adrenal medulla tumors in the high-dose males compared to the control incidence, it is suggested that the finding may be due to the reduced body weights at the high dose. The author also points out that lower body weights with reduced incidences of other tumors accompanied by an increase in interstitial cell tumors have been reported in rats fed restricted diets [Tucker, 1979; Roe, 1991] and suggests that the reduced body weights in the current study may have resulted in a similar tumor incidence. TB II points out that food consumption was **not** decreased in the current study so the decreased body weight was not due to restricted/reduced food intake; therefore, it appears that the observed tumors may not be related exclusively to this mechanism and may be due in part to Thiodicarb.

E. CONCLUSION

Exposure of Sprague-Dawley rats [50/sex/group] to Thiodicarb via the diet at dose levels of 0 ppm, 60 ppm [♂♂ 3.3/♀♀ 4.5 mg/kg/day], 200 ppm [♂♂ 12/♀♀ 15 mg/kg/day], and 900 ppm [♂♂ 60/♀♀ 80 mg/kg/day] resulted in a marked decrease in body weight [♂♂ 85%/♀♀ 88% of control at week 13] and body-weight gain [♂♂ 71%/♀♀ 80% of control overall] in both sexes at the high-dose level throughout the study compared to their respective control groups. With the exception of the first week on test, food consumption was not adversely affected. Survival was not adversely affected in either sex, and in fact, both sexes at the high-dose level displayed longer survival times than their respective controls. The high-dose groups of both sexes displayed changes in various hematology and clinical chemistry parameters [HGB, HCT, RBC, WBC, neutrophils, platelets] indicative of a mild red blood cell loss, as well as increased extramedullary hemopoieses in the spleen. Mid-dose males also displayed an increase in extramedullary hemopoiesis, and absolute and relative spleen weights were increased in this group and in both sexes at the high-dose level. Increases in tubular atrophy [mid- and high-dose levels] and interstitial cell hyperplasia [all dose levels] were observed in the testes, although statistical significance was not attained, and the incidence of hyperplasia was not strictly dose-related. High-dose males displayed an increased incidence of interstitial cell tumors in the testes compared to the concurrent control males. The incidence of tumors of the pituitary and adrenal gland was decreased in the high-dose males compared to the control incidence. Tumor incidence in females was comparable among the

groups. Compared to the control groups, both sexes at the high-dose level displayed fewer animals with tumors and fewer with multiple, benign, and malignant tumors. Only the number of rats with single tumors was greater at the high-dose level than the controls. **The systemic NOEL can be set at 60 ppm [♂♂ 3.3/♀♀ 4.5 mg/kg/day], the LEL at 200 ppm [♂♂ 12/♀♀ 15 mg/kg/day], based on the increased incidence of extramedullary hemopoiesis in males and decreased RBC cholinesterase in females.** This study is classified Core Minimum, and it satisfies the guideline requirement (83-2) for a carcinogenicity study in a rodent.

NOTE: The title of this study report indicates that the study described is a carcinogenicity study, but the data requirement for which it was submitted is listed as §83-5 [combined chronic toxicity/carcinogenicity study]. A separate study report [MRID # 434050-01; a study addendum to the current study] describes the results of the toxicity phase of the study up to 52 weeks. This addendum is reviewed in a separate DER. The guideline requirement [§83-5] for a combined chronic toxicity/carcinogenicity study in the rat has also been satisfied.

Table 12. Summary of Effects

Effects	MALES			FEMALES		
	60 ppm	200 ppm	900 ppm	60 ppm	200 ppm	900 ppm
body-weight/gain	-	-	↓***	↓**♦	↓**♦	↓***
survival time	-	-	↑	-	-	↑*
hemosiderin/extramedullary hemopoiesis in spleen	-	↑*	↓**	-	-	↑
HGB/HCT/RBC	-	-	↓***	-	-	↓***
platelets	-	-	↑***	-	-	↑***
WBC/NEUT	↓*	-	↑*	-	↑*	↑***
incidence of footsores & tail lesions	-	-	↑	-	-	-
plasma cholinesterase	?	↓	↓***	-	-	↓*
RBC cholinesterase	-	-	↓*	-	↓***	↓***
incidence of tubular atrophy	-	↑	↑	N/A	N/A	N/A
incidence of interstitial cell hyperplasia	↑	↑	↑	N/A	N/A	N/a
incidence of benign interstitial cell tumors	-	-	↑	N/A	N/A	N/a

Thiodicarb

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