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

#900AA JAN 10 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **THIODICARB**: 52-Week Interim Report for 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 1/5/95
Toxicology Branch II, Section II,
Health Effects Division (7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 1/5/95
Section II Head, Toxicology Branch II
Health Effects Division (7509C)

and

Marcia van Gemert, Ph.D. Marcia van Gemert 1/9/95
Chief, Toxicology Branch II/HFAS/HED (7509C)

Registrant: Rhône-Poulenc Secteur Agro
Chemical: Thiodicarb
Synonym: Larvin
Submission No.: S475497
DP Barcode: D208497
Caswell No.: 900AA
Case: 816454
Identifying No.: 114501-000264
Shaughnessey No.: 114501
MRID No.: 434050-01

Comment: The Registrant has submitted this interim sacrifice report of the two year [104 week] rat dietary carcinogenicity study on Thiodicarb, which was reviewed recently in a separate DER [dated 12/6/94; Document # 011359]. It is stated that certain European countries require an interim sacrifice report at the end of the first year, and the Registrant was unaware of the existence of the report at the time they submitted the final report to EPA. The interim report has been reviewed, and the DER is appended. It is to be noted that this report was flagged as Section **6(a)(2)** data.

THIODICARB 104 Week Dietary Carcinogenicity Study in Rats - With 52 Week Interim Kill (Results After 52 Weeks). Study Addendum to MRID

433082-01. C Atkinson, P Hudson, and V Iswariah [Title page not dated].

Under the conditions of the study, exposure of Sprague-Dawley rats [15/sex/group] to Thiodicarb via the diet at dose levels of 0 ppm, 60 ppm [♂♂ 3.9/♀♀ 5.4 mg/kg/day], 200 ppm [♂♂ 13.6/♀♀ 18.5 mg/kg/day], and 900 ppm [♂♂ 69.5/♀♀ 96.8 mg/kg/day] for 52 weeks resulted in a decrease in body weight [♂♂ 86%/♀♀ 90% of control at week 13] and body-weight gain [♂♂ 79%/♀♀ 82% of control during weeks 0-13] in both sexes at the high-dose level compared to their respective control groups. Neither food consumption nor survival was adversely affected. The high-dose group of both sexes displayed changes in red blood cell parameters [↓ HGB, HCT, RBC] indicative of a mild red blood cell loss, as well as an increased incidence of increased hemosiderin in females and increased extramedullary hemopoieses in both sexes at the high dose in the spleen. Absolute and adjusted spleen weights were increased in mid- and high-dose females, and decreased plasma and red blood cell cholinesterase were observed in both sexes at the high-dose level, but statistical significance was attained in males only. Because this report presents the results from the chronic toxicity phase [52 week interim sacrifice] of the study reported in MRID # 433082-01 [DER dated 12/6/94; Document # 011359], no NOEL is determined. **The NOEL for the study as a whole is set at 60 ppm [♂♂ 3.9/♀♀ 5.4 mg/kg/day], the LEL at 200 ppm [♂♂ 13.6/♀♀ 18.5 mg/kg/day], based on the increased incidence of extramedullary hemopoiesis in males and decreased RBC cholinesterase in females.** Both studies together satisfy the guideline requirement (83-5) for a combined chronic toxicity/carcinogenicity study in the rat.

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

Reviewed by: Linda L. Taylor, Ph.D. Linda Lee Taylor 1/5/95
Section II, Tox. Branch II (7509C)
Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 1/5/95
Section II Head, Tox. Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Interim Sacrifice-Chronic Toxicity/Carcinogenicity-rat

PC Code: 114501

MRID NO.: 434050-01

TEST MATERIAL: Thiodicarb

SYNONYMS: Larvin

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

STUDY NUMBER: IRI Project # 450441; Report # 7881

SPONSOR: Rhone-Poulenc

TESTING FACILITY: Inveresk Research International/Scotland

TITLE OF REPORT: 104-Week Dietary Carcinogenicity Study in Rats With 52 Week Interim Kill (Results After 52 Weeks)

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

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

EXECUTIVE SUMMARY: Exposure of Sprague-Dawley rats [15/sex/group] to Thiodicarb via the diet at dose levels of 0 ppm, 60 ppm [♂♂ 3.9/♀♀ 5.4 mg/kg/day], 200 ppm [♂♂ 13.6/♀♀ 18.5 mg/kg/day], and 900 ppm [♂♂ 69.5/♀♀ 96.8 mg/kg/day] for 52 weeks resulted in a decrease in body weight [♂♂ 86%/♀♀ 90% of control at week 13] and body-weight gain [♂♂ 79%/♀♀ 82% of control during weeks 0-13] in both sexes at the high-dose level compared to their respective control groups. Neither food consumption nor survival was adversely affected. The high-dose group of both sexes displayed changes in red blood cell parameters [↓ HGB, HCT, RBC] indicative of a mild red blood cell loss, as well as an increased incidence of increased hemosiderin in females and increased extramedullary hemopoieses in both sexes at the high dose in the spleen. Absolute and adjusted spleen weights were increased in mid- and high-dose females, and decreased plasma and red blood cell cholinesterase were observed in both sexes at the high-dose level, but statistical significance was attained in males only. Because this report presents the results from the chronic toxicity phase [52 week interim sacrifice] of the study reported in MRID # 433082-01 [DER dated 12/6/94; Document #

011359], no NOEL is determined. **The NOEL for the study as a whole is set at 60 ppm [♂♂ 3.9/♀♀ 5.4 mg/kg/day], the LEL at 200 ppm [♂♂ 13.6/♀♀ 18.5 mg/kg/day], based on the increased incidence of extramedullary hemopoiesis in males and decreased RBC cholinesterase in females.** Both studies together satisfy the guideline requirement (83-5) for a combined chronic toxicity/ carcinogenicity study in the rat.

A. MATERIALS

1. Test Compound: Thiodicarb; Description: fine white powder; Batch #: 09-02-84 and CMP 91079; Purity: 96% is listed in APPENDIX 1 for Batch # DA616, which was stated in MRID # 433082-01 to be Batch # 09-02-84; CMP 91079 was stated to be 94.86% in MRID # 433082-01. No purity information is provided in the current study report.

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: analyzed 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 carcinogenicity phase of the study [see DER for MRID # 433082-01]. Sixty rats/sex from the same shipment of rats were used in the 52-week Toxicity Phase of the study, which is reviewed here. 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 15 rats/sex/dose [dose levels of 0, 60, 200, and 900 ppm] for 52 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.

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, and 47 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. 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. There were 13 deaths, but none is attributed to treatment [Table 1].

Dose (ppm)/ Sex	Table 1. Mortality (%)	
	MALES	FEMALES
0	1/65	1/65
60	2/65	3/65
200	1/65	0/65
900	3/65	2/65

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 [86% 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 79% of the control value. The overall body-weight gain at the high dose was 70% 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.

FEMALES - High-dose females displayed a similar decrease in body weight/body-weight gain throughout the study. By week 1, body weight for the high-dose females was 89% of the control value [Tables 2 & 3]. Body-weight gain during the first 13 weeks was 82% of the control value at the high-dose level. Overall body-weight gain was 72% 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.

Table 2. Body Weight (% of control)

Week/Dose	60 ppm	200 ppm	900 ppm
MALES			
Pre-test	102	100	101
0	102	99	99
1	102	100	86***
2	102	98	88***
3	97	97	86***
4	100	97	87***
5	100	97	88***
6	101	97	87***
13	102	94	86***
38	102	95	80***
FEMALES			
Pre-test	97	99	99
0	99	101	100
1	99	99	89***
2	100	100	91***
3	100	100	90***
4	100	99	90***
5	98	99	89***
6	98	99	89***
13	97	99	90***
38	97	100	86***

* 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	61	61	61	27(44)
1-2	47	49	42	47
2-3	46	30	42	34(74)
0-13	359	365	329	284(79)
0-26	463	476	429	353(76)
0-52	613	640	585	430(70)♦

Week/Group	0 ppm	60 ppm	200 ppm	900 ppm
FEMALES				
0-1	32	31	29	13(41)
1-2	22	24	23	24
2-3	22	21	21	18(82)
0-13	179	170	173	146(82)
0-26	210	203	208	175(83)
0-52	309	304	285	223(72)

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

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

With the exception of weeks 1 [82% of control] and 9 [76% of control] in males and week 1 [85% of control] in females, food consumption was comparable among the groups. The initial decrease in both sexes may have been due to a palatability problem. The overall mean daily intake values and range of intakes of test material for both sexes are listed below (Table 4).

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

Interval/Sex/Dose	60 ppm	200 ppm	900 ppm
MALES			
weeks 1-13			
range	3.6-8.1	13-27	51-126
mean	4.8	16.8	84.5
weeks 14-52			
range	2.3-3.5	8-12	43-63
mean	2.8	9.4	49.9
weeks 1-51			
mean	3.9	13.6	69.5
FEMALES			
weeks 1-13			
range	5.1-8.3	17-30	85-156
mean	6.5	22	111.8
weeks 14-52			
range	3.3-5.8	11-18	63-97
mean	4.1	14	77.3
weeks 1-52			
mean	5.4	18.5	96.8

4. Ophthalmological examination

Ophthalmological evaluations were performed on the eyes of 20

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rats from each carcinogenicity phase 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 reported in this report].

RESULTS

One high-dose female displayed a point opacity in the lens of the right eye, but this was not considered treatment-related.

5. Clinical Laboratory Investigations

Blood samples from the orbital sinus under light ether anaesthesia [not fasted] were collected [randomly selected via computer-generated random numbers] from 10 rats/sex in each toxicity study group during weeks 25 and 52 of dosing, and whole blood [EDTA] and plasma [heparin] were obtained 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. Samples for the measure of clotting time were obtained without anaesthesia (tailsnip). 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

Statistically significant decreases in hemoglobin, hematocrit, and RBC's were observed at the high-dose level in both sexes at both time points compared to their respective control values, with the magnitude of the decrease increasing with time. Other differences from control values were observed in several other parameters at various intervals [Table 6], but for the most part no dose response was observed nor was statistical significance attained. Table 6 lists the various differences for comparison with the data contained in MRID # 433082-01 [DER dated 12/6/94].

Table 6. Hematology Parameters

Parameter/Dose/Sex	0 ppm	60 ppm	200 ppm	900 ppm
WBC x $10^9.l^{-1}$				
Males				
week 25	12.07	13.23(110)	13.05(108)	12.09
week 52	12.20	13.02(107)	11.29(93)	10.95(90)
Females				
week 25	9.83	8.06(82)	10.39(95)	10.53(107)
week 52	6.58	6.68	9.69**(147)	8.73*(133)
Neut. x $10^9.l^{-1}$				
Males				
week 25	1.48	1.60(108)	1.54(104)	1.29(87)
week 52	2.60	2.27(87)	1.46(56)	1.88(72)
Females				
week 25	0.96	0.87(91)	1.24(129)	1.04(106)
week 52	1.09	1.22(112)	2.74**(251)	1.93*(177)
Lymp. x $10^9.l^{-1}$				
Males				
week 25	9.80	10.84(111)	10.76(110)	10.08(103)
week 52	8.63	9.74(113)	8.99	8.27(96)
Females				
week 25	8.39	6.71*(80)	8.51	8.91(106)
week 52	5.03	4.94	6.24*(124)	6.18*(123)
Mono. x $10^9.l^{-1}$				
Males				
week 25	0.36	0.33	0.34	0.33
week 52	0.44	0.44	0.35(80)	0.38(86)
Females				
week 25	0.22	0.23	0.29(132)	0.27(123)
week 52	0.21	0.26	0.32(152)	0.32(152)
Platelets x $10^9.l^{-1}$				
Males				
week 25	715	778(109)	834(117)	790(110)
week 52	836	679(81)	924(111)	909(109)
Females				
week 25	694	669	804(116)	791(114)
week 52	696	794(114)	938(135)	906(130)
LUC x $10^9.l^{-1}$				
Males				
week 25	0.23	0.26	0.22	0.20
week 52	0.33	0.36(109)	0.32	0.25(76)
Females				
week 25	0.11	0.12	0.18**(164)	0.16(145)
week 52	0.12	0.13	0.20(167)	0.16(133)
Hb $g.dl^{-1}$				
Males				
week 25	15.5	15.1	15.4	14.5(94)
week 52	15.4	15.1	15.2	13.8***(90)
Females				
week 25	15.0	14.6	14.7	13.8***(92)
week 52	14.6	14.3	13.9	13.2***(90)
RBC x $10^{12}.l^{-1}$				
Males				
week 25	8.89	9.06	8.95	8.50(96)
week 52	8.59	8.79	8.57	8.02*(93)
Females				
week 25	8.20	8.04	8.11	7.48***(91)
week 52	7.58	6.75*(89)	7.39	6.81***(90)

Table 6. Hematology Parameters

Parameter/Dose/Sex	0 ppm	60 ppm	200 ppm	900 ppm
Hct $l.l^{-1}$				
Males				
week 25	0.459	0.444	0.454	0.427*(93)
week 52	0.440	0.427	0.436	0.397***(90)
Females				
week 25	0.428	0.422	0.424	0.403**(94)
week 52	0.404	0.369	0.389	0.371*(92)

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

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

X	Electrolytes:
X	Calcium
X	Chloride
	Magnesium
X	Phosphorous
X	Potassium
X	Sodium
	Iron
	Enzymes
X	Alkaline phosphatase (ALK)
X	Cholinesterase (ChE)♦
X	Creatine phosphokinase (CPK)
X	Lactate dehydrogenase (LDH)
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)

X	Other:
X	Albumin
X	Blood creatinine
X	Blood urea nitrogen
X	Cholesterol
X	AG ratio
X	Glucose
	Phospholipids
X	Total bilirubin
X	Total Protein
	Triglycerides
	Lipids, total
	Triiodothyronine, total T_3

♦ plasma, RBC, brain

RESULTS

There was a statistically significant decrease in plasma cholinesterase in the high-dose males at both time points. Females at the high-dose level displayed decreased values [≈20%] at both time points also, but statistical significance was not attained. At week 25, the mid-dose females displayed decreased plasma cholinesterase values also [dose-related], but statistical significance was not attained. At the high-dose level in both sexes at both time points, decreased RBC cholinesterase values were observed, but statistical significance was attained only at week 52 in males. There were no significant differences in brain cholinesterase observed in either sex. Total bilirubin values were increased relative to the control in both sexes at the high-dose level at both time points and at the mid-dose level [♀♀ at week 25; both sexes at week 52], but statistical significance was attained only in the females [Table 7].

Table 7. Clinical Chemistry Parameters

Parameter/Dose/Sex	0 ppm	60 ppm	200 ppm	900 ppm
plasma cholinesterase iu.L^{-1}				
males				
week 25	551	533	550	384**(70)
week 52	724	715	788	503**(63)
females				
week 25	2688	2607	2310(86)	2175(81)
week 52	2715	2301(85)	2530(93)	2146(79)
RBC cholinesterase iu.L^{-1}				
males				
week 25	1065	980(92)	1229	873(82)
week 52	930	983	961	586**(63)
females				
week 25	1392	1389	1519	1327(95)
week 52	1436	1391	1432	1205(84)
Brain cholinesterase iu.L^{-1}				
males				
week 25	-	-	-	-
week 52	14635	13874	14286	13990(96)
females				
week 25	-	-	-	-
week 52	13962	16109	13279	13656(98)
total bilirubin µmol.$^{-1}$				
males				
week 25	1.2	1.1	1.1	1.4(117)
week 52	1.8	1.9	2.1(117)	2.4(133)
females				
week 25	1.2	1.2	1.4(117)	2.1**(175)
week 52	1.1	0.9(82)	1.7*(155)	1.6*(145)

* p <0.05; ** p <0.01

c. Urinalysis: Samples were obtained from 10 rats/sex/group [housed in metabolism cages over a 4-hour period of food and water deprivation] at weeks 25 and 52 [method of selection not provided]. The CHECKED (X) parameters were examined.

	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

pH was reduced at the mid-dose level in females and in both sexes at the high-dose level at both time points [Table 8]. Although the decreases were dose-related, without pre-dose values, no definitive statement can be made attributing the effect to treatment. Similarly, the statistically significant increase observed in specific gravity at all dose levels in females at week 25, and the comparable increases observed at week 52 cannot be attributed to treatment without pre-dose

data. Additionally, at both time points, females displayed a dose-related decrease in urine volume [statistical significance not attained], which is consistent with increased specific gravity, but there was no correlating histopathology. None of the findings are considered indicative of systemic toxicity.

Table 8. Urinalysis Findings

Parameter/Sex/Dose	0 ppm	60 ppm	200 ppm	900 ppm
pH				
MALES				
week 25	7.9	8.2	7.8	6.8**
week 52	8.0	8.2	7.2	7.0*
FEMALES				
week 25	7.7	7.2	6.9*	6.4***
week 52	8.2	7.7	6.8**	6.6***
Specific gravity				
MALES				
week 25	1.037	1.034	1.042	1.040
week 52	1.041	1.029	1.049	1.031
FEMALES				
week 25	1.022	1.033**	1.031**	1.041***
week 52	1.027	1.034	1.029	1.043**
Volume				
MALES				
week 25	2.4	2.2	2.5	1.7
week 52	2.8	5.0**	1.8	2.4
FEMALES				
week 25	2.3	1.6	1.5	1.2
week 52	2.7	2.6	1.8	1.4

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

6. Sacrifice and Pathology

At week 52, all survivors of the toxicity phase of the study 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 all rats/sex/group. The CHECKED (X) tissues were collected from all rats and preserved. Blood smears were not obtained from the toxicity phase rats. 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 parotid salivary glands, rectum, and rib. Additionally, the liver, kidney, and lung were examined in all low- and mid-dose rats, and the spleen of the low- and mid-dose rats of both sexes were examined following findings at the high-dose level.

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/submaxillary; ♦ 3 cross sections: frontal cortex & basal ganglia, parietal cortex & thalamus, cerebellum & medulla oblongata; ♦ cervical/midthoracic/lumbar

RESULTS

a. Organ Weight: MALES - The absolute weights [Table 8] of the adrenals, heart, kidneys, liver, and thyroids were statistically significantly decreased in the high-dose males, but these, with the exception of the adrenals and thyroids, may be attributed to the decreased body weight observed in these rats at termination [77% of control]. No significant differences were observed when the organ weights were adjusted for final body weight, but the adrenal and thyroid weights remained decreased relative to the control values. Both the absolute and adjusted pituitary weights in the high-dose males were decreased relative to control also, but statistical significance was not attained. FEMALES - In the high-dose females, final body weight was 80% of the control value. There was a decrease in liver weight [84% of control] in the high-dose females, but statistical significance was not attained. Spleen weight when adjusted for final body weight was significantly increased in females at the high-dose level. Several other adjusted organ weights were increased relative to the control values and for the thymus, spleen, and ovaries the increases were dose-related. With the exception of the spleen, the differences appear to be attributable to the decreased body weight.

Table 8. Organ Weights

Sex/Group/ Organ Weight (g)	MALES		FEMALES	
	absolute	relative	absolute	relative
Body weight (g)				
0	800	758	445	415
60	833	758	437	415
200	774	758	420	415
900	615***(77)	758	357***(80)	415
liver				
0	25.03	23.81	14.85	13.76
60	26.07	23.90	14.69	13.91
200	23.96	23.50	14.12	13.94
900	21.25*(85)	25.38(107)	12.50(84)	14.65(106)
pituitary				
0	0.013	0.012	0.014	0.013
60	0.012	0.011(92)	0.014	0.014
200	0.011(85)	0.011(92)	0.015(107)	0.015
900	0.010(77)	0.010(83)	0.013(93)	0.014
thyroids				
0	0.040	0.039	0.030	0.029
60	0.042	0.040	0.032	0.031(107)
200	0.040	0.040	0.030	0.030(103)
900	0.034*(85)	0.038(92)	0.029	0.031(107)
spleen				
0	1.08	1.06	0.67	0.64
60	1.20	1.15(108)	0.65	0.63
200	1.13	1.12(106)	0.75(112)	0.75(117)
900	1.08	1.16(109)	0.74(110)	0.81**(127)
thymus				
0	0.14	0.14	0.14	0.13
60	0.18	0.17(121)	0.12	0.11(85)
200	0.16	0.16(114)	0.15	0.14(108)
900	0.14	0.16(114)	0.14	0.16(123)
kidneys				
0	4.70	4.55	3.00	2.91
60	4.63	4.36	2.76	2.69
200	4.53	4.47	2.83	2.81
900	4.05**(86)	4.55	2.79	2.98
ovaries				
0	-	-	0.065	0.061
60	-	-	0.064	0.061
200	-	-	0.069	0.068(111)
900	-	-	0.062(95)	0.069(113)
lungs				
0	2.18	2.14	1.65	1.62
60	2.24	2.17(101)	1.58	1.56
200	2.26	2.25(105)	1.73	1.73*(107)
900	2.13	2.26(106)	1.63	1.68(104)
testes				
0	5.61	5.59	-	-
60	5.46	5.43	-	-
200	5.53	5.53	-	-
900	5.40	5.46	-	-
adrenals				
0	0.065	0.063	0.074	0.073
60	0.060	0.058	0.078	0.077
200	0.060	0.059	0.077	0.077
900	0.053**(82)	0.058	0.072	0.074
heart				
0	1.97	1.92	1.29	1.24
60	1.96	1.88	1.28	1.24
200	1.91	1.90	1.32	1.31
900	1.73**(88)	1.89	1.20(93)	1.30(105)

♦ (% of control); * p <0.05; ** p <0.01; *** p <0.001

b. Gross Pathology: There were no notable findings at necropsy

that could be attributed to treatment.

c. Microscopic Pathology: **Non-neoplastic Findings** - MALES: In the spleen, the incidence of extramedullary hemopoiesis was significantly increased at the high-dose level [Table 10]. There was no increase in hemosiderin in the spleen at any dose level. Tubular atrophy [unilateral] in the testes was increased at the high-dose level compared to the control incidence, but statistical significance was not attained. Additionally, there were slight increases in follicular cell hyperplasia in the thyroid and unilateral papillary degeneration in the kidney at the high dose compared to the control. FEMALES: At the high-dose level, the incidence of hemosiderin was significantly increased and the severity increased with dose. Extramedullary hemopoiesis was increased at all dose levels [dose-related] compared to the control, but statistical significance was not attained. In the thymus, cystic ducts were increased at the high-dose level relative to the control. Craniopharyngeal hyperplasia [pituitary] was observed only in the high-dose females, while cysts and focal hyperplasia were observed only in the control. In the adrenals, there was a higher incidence of diffuse hemopoiesis, cortical hypertrophic focus(i), unilateral cortical hyperplastic focus(i), and hemorrhagic degeneration in the high-dose females than in the controls.

Table 10. Non-neoplastic Findings

Lesion/Sex/Group	0 ppm	60 ppm	200 ppm	900 ppm
MALES				
Spleen N=15				
† extramedullary hemopoiesis				
total	7	7	6	14*
grade ±	5	6	5	9
grade +	2	1	1	5
grade +++	0	0	0	0
† hemosiderin				
total	4	1	2	2
grade ±	4	1	2	2
grade +	0	0	0	0
no abnormality	4	7	7	0
Testes N=15		(0)	(0)	
no abnormality	14			12
bilateral interstitial cell hyperplasia	1			0
tubular atrophy				
total	0			2
grade ±	0			1
grade +	0			1
focal mineralization	0			1
Thyroids N=15		(0)	(0)	
follicular cell hyperplasia				
total	1			4
grade ±	1			3
grade +	0			1
Kidneys N=15				
unilateral papillary degeneration	0	0	0	2
focal tubular epithelial hypertrophy	0	0	0	1
FEMALES				
Spleen N=15				
† extramedullary hemopoiesis				
total	3	7	8	9
grade ±	3	6	6	6
grade +	0	0	2	2
grade+++	0	1	0	1
† hemosiderin				
total	4	10	9	11*
grade ±	3	5	4	3
grade +	1	5	5	8*
no abnormality	8	3	2	3
Adrenals N=15		(1)	(0)	
diffuse hemopoiesis	0	0		1
cortical hypertrophic focus	0	0		3
hemorrhagic degeneration	5	0		9
Thymus N=15		(1)	(0)	
cystic ducts	2	0		8

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

Neoplastic Findings - MALES: Only one tumor, a unilateral pheochromocytoma [benign] in the adrenals at the high-dose, was observed in the male rats. FEMALES: In the high-dose females, a carcinoma in the mammary gland and a squamous-cell papilloma [benign] of the stomach were observed. Two control females displayed pituitary adenomas. No other tumors were reported.

D. DISCUSSION

Exposure of Sprague-Dawley rats to Thiodicarb via the diet at dose levels of 0 ppm, 60 ppm [♂♂ 3.9/♀♀ 5.4 mg/kg/day], 200 ppm [♂♂ 13.6/♀♀ 18.5 mg/kg/day], and 900 ppm [♂♂ 69.5/♀♀ 96.8 mg/kg/day] resulted in a decrease in body weight [♂♂ 86%/♀♀ 90% of control at week 13] and body-weight gain [♂♂ 79%/♀♀ 82% of control during weeks 0-13] 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. There were changes in red blood cell parameters at the high-dose level in both sexes that were indicative of a mild red blood cell loss. Combined with the observations of increased spleen weight and a higher incidence of increased hemosiderin in the high-dose females and increased extramedullary hemopoiesis in both sexes at the high-dose level, a higher turnover of red blood cells results from exposure to Thiodicarb as early as 25 weeks at a dose level of 900 ppm. Total bilirubin was increased in the high-dose females, but no liver pathology was observed. Reduced pH and increased specific gravity in urine was observed in both sexes at the high-dose and to a lesser extent in the mid-dose females, but no other changes were observed to explain these findings. There was a low incidence of papillary degeneration in the kidneys of both sexes at the high-dose level, but the author stated that five similar studies in the rat have not duplicated this finding, and its meaning is not apparent.

E. CONCLUSION

Exposure of Sprague-Dawley rats [15/sex/group] to Thiodicarb via the diet at dose levels of 0 ppm, 60 ppm [♂♂ 3.9/♀♀ 5.4 mg/kg/day], 200 ppm [♂♂ 13.6/♀♀ 18.5 mg/kg/day], and 900 ppm [♂♂ 69.5/♀♀ 96.8 mg/kg/day] for 52 weeks resulted in a decrease in body weight [♂♂ 86%/♀♀ 90% of control at week 13] and body-weight gain [♂♂ 79%/♀♀ 82% of control during weeks 0-13] in both sexes at the high-dose level compared to their respective control groups. Neither food consumption nor survival was adversely affected. The high-dose group of both sexes displayed changes in red blood cell parameters [↓ HGB, HCT, RBC] indicative of a mild red blood cell loss, as well as an increased incidence of increased hemosiderin in females and increased extramedullary hemopoieses in both sexes at the high dose in the spleen. Absolute and adjusted spleen weights were increased in females at the mid- and high-dose levels. Decreased plasma and red blood cell cholinesterase were observed in the high-dose groups at both the 25- and 52-week intervals, but statistical significance was attained in males only. Because this report is an addendum to the 104-week rat study [MRID # 433082-01], which presents the results from the 52-week interim sacrifice, no NOEL is set here. **The NOEL for the rat dietary combined chronic toxicity/carcinogenicity [104 week] study is set at 60 ppm [♂♂ 3.9/♀♀ 5.4 mg/kg/day], the**

LEL at 200 ppm [♂♂ 13.6/♀♀ 18.5 mg/kg/day], based on the increased incidence of extramedullary hemopoiesis in males and decreased RBC cholinesterase in females. The combined reports [MRID #'s 433082-01 and 434050-01] constitute the final report for this study, and the study is classified Core Minimum. Both study reports together satisfy the guideline requirement (83-5) for a combined chronic toxicity/carcinogenicity study in the rat.

Table 11. Summary of Effects

Effects	MALES			FEMALES		
	60 ppm	200 ppm	900 ppm	60 ppm	200 ppm	900 ppm
body-weight/gain	-	-	↓***	-	-	↓***
survival time	-	-	-	-	-	-
hemosiderin in spleen	-	-	-	↑	↑	*↑
extramedullary hemopoiesis in spleen	-	-	↑*	↑	↑	↑
HGB	-	-	↓***	↓*	-	↓***
HCT	-	-	↓***	↓**	-	↓*
RBC	-	-	↓*	↓*	-	↓***
WBC	-	-	↓	-	↑**	↑*
NEUT	↓	↓	↓	-	↑**	↑*
LYMP	-	-	-	-	↑*	↑*
plasma cholinesterase	-	-	↓**	↓	-	↓
RBC cholinesterase	-	-	↓**	-	-	↓
incidence of testicular tubular atrophy	-	-	↑	N/A	N/A	N/A