6-7-94

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

[redacted]

JUN 7 1994 CASWELL FILE
JUN 1 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Thiodicarb: Mouse Carcinogenicity Study; 6(a)(2)

TO: Linda Deluise
Product Manager (52)
Reregistration Branch, SRRD (7508W)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 5/19/94
Toxicology Branch II, Section II
Health Effects Division (7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 5/23/94
Section II Head, Toxicology Branch II
Health Effects Division (7509C)

and

Marcia van Gemert, Ph.D. M. van Gemert 5/24/94
Chief, Toxicology Branch II/HFAS/HED (7509C)

Registrant: Rhône-Poulenc Secteur Agro
Chemical: Thiodicarb
Synonym: Larvin
Submission No.: S454310
Caswell No.: 900AA
Case.: 816454
Identifying No.: 114501-000264
Shaughnessey No.: 114501
MRID No.: 430005-01

Comment: The Registrant has submitted the final report of a mouse carcinogenicity study on Thiodicarb, which was flagged as Section 6(a)(2) data. This study has been reviewed by Dr. Alan Levy [TB II], and the DER [dated 5/11/94] is appended.

THIODICARB 97 Week Dietary Carcinogenicity Study in Mice with 52 Week Interim Kill (Results after 97 Weeks) - CJ Perry, C Atkinson, P Hudson, E Snodgrass, and V Iswariah; dated September 8, 1993 [MRID # 430005-01].

Under the conditions of the study, exposure of CD-1 mice [50/sex/group] to Thiodicarb via the diet for 97 weeks at dose levels of 0, 5, 70, and 1000 mg/kg/day [LIMIT DOSE] resulted in, at the 1000 mg/kg dose level, decreased body-weight gains in males

[33% of control], and in both sexes, increased mortality, decreased hemoglobin, hematocrit, and erythrocytes, increased alanine aminotransferase and total bilirubin values, increased spleen and liver weights, increased incidence of non-neoplastic changes in the kidney, liver, and spleen, and increased incidence of benign and malignant liver neoplasms. **The NOEL is 70 mg/kg/day, and the LOEL is 1000 mg/kg/day. Thiodicarb appears to be carcinogenic in mice at the limit dose.**

This study is classified Core Guideline, and it satisfies the guideline requirement [83-2] for a carcinogenicity study in mice.

Thiodicarb will be presented to the HED Carcinogenicity Peer Review Committee in the near future. Based on the fact that the dose level at which the liver tumors were observed was 1 gram of Thiodicarb/ kg/day, no further action is required at this time.

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

JUN 1 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: **THIODICARB** - Dietary Admix Carcinogenicity Study in Mice (§83-2)

DP Barcode: D197201
Submission: S454310
Identification No.: 114501-000264
Action: 625 6(A)(2)
Case: 816454
PC Code: 114501
MRID No.: 430005-01

FROM: Alan C. Levy, Ph.D., Toxicologist
Review Section IV, Toxicology Branch II
Health Effects Division (7509C)
Alan C. Levy
May 11, 1994

TO: Linda L. Taylor, Ph.D.
Review Section II, Toxicology Branch II
Health Effects Divsion (7509C)

THRU: Susan L. Makris, M.S., Acting Section Head
Review Section IV, Toxicology Branch II
Health Effects Division (7509C)
Susan L Makris
5/11/94

REQUEST: Review the carcinogenicity study in mice with THIODICARB.

Registrant: Rhone-Poulenc Secteur Agro, Lyon, France

COMMENT:

The attached DATA EVALUATION REPORT is a review of the carcinogenicity mouse study with THIODICARB.

3

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Reviewed by: Alan C. Levy, Ph.D. Alan C. Levy May 11, 1994
Section IV, Tox. Branch II

Secondary reviewer: Susan L. Makris, M.S. Susan L Makris 5/11/94
Section IV, Tox. Branch II

DATA EVALUATION REPORT

STUDY TYPE: Carcinogenicity Study - Mice (§83-2)

TEST MATERIAL: Thiodicarb

PC Code: 114501 **MRID No.:** 430005-01

STUDY NUMBERS: IRI Project No.: 439056; Report No.: 7749

SPONSOR: Rhone-Poulenc Secteur Agro, Lyon, France

TESTING FACILITY: Inveresk Research International (IRI), Scotland

TITLE OF REPORT: Thiodicarb, 97 Week Dietary Carcinogenicity Study in Mice with 52 Week Interim Kill (Results after 97 Weeks)

AUTHORS: C.J. Perry, C. Atkinson, P. Hudson, E. Snodgrass and V. Iswariah

REPORT ISSUED: September 8, 1993

EXECUTIVE SUMMARY:

In a carcinogenicity study, THIODICARB was administered by dietary admix to Charles River CD-1 mice (50/sex/group) at doses of 0, 5, 70 and 1,000 (LIMIT DOSE) mg/kg/day for 97 weeks with an additional 15/sex/group for a 52-week interim sacrifice. The following parameters were examined: mortality, clinical signs, body weights, food consumption, hematology, limited clinical chemistry, macroscopic pathology, organ weights and microscopic pathology.

The following effects were observed only at 1,000 mg/kg/day: increased mortality in both sexes (especially females); decrease in body weight gain (males only); decreases in hemoglobin, erythrocytes and hematocrit; increases in alanine aminotransferase and total bilirubin; increases in liver and spleen size; non-neoplastic kidney, liver and spleen changes; and an increase in the number of mice with benign and malignant liver neoplasms. **The NOEL is 70 mg/kg/day and the LOEL is 1,000 mg/kg/day.** [MRID No. 430005-01]

The test article appears to be a CARCINOGEN at 1,000 mg/kg/day.

Core classification is **Guideline.** This study satisfies the data requirement (§83-2) for a carcinogenicity study in mice.

A

I. MATERIALS, METHODS AND RESULTS

A. Statistical Analyses

Hematology, clinical chemistry, organ weight and body weights: F-max test for homogeneity of variance; if homogeneous, parametric ANOVA and pairwise comparisons by Student's t-test using Fisher's F-protected LSD; if heterogeneous, log or square root transformations; if variances remained heterogeneous, Kruskal-Wallis ANOVA non-parametric

Organ Weights: analysis of covariance, using body weight as the covariant factor

Incidences of histological findings: Fisher's Exact Probability test

Mortality: treated versus control, 2-sided Wilcoxon test modified for censoring

Fatal lesions (fatal or probably fatal): distribution of time-to-death; time-to-death due to lesion, logrank test (2-sided test); trend in the death rate due to lesion over actual dose levels (2-sided test)

Non-Fatal lesions: difference in prevalence rates over time, Hoel-Walburg test (2-sided test); trend in the prevalence rates of the lesion over actual dose levels (2-sided test)

B. Regulatory Compliance

A Good Laboratory Practice Compliance statement, Quality Assurance statement and a list of Quality Assurance inspections were included in the Report.

The Registrant applied the criteria of 40 CFR 158.34 for flagging studies for potential adverse effects to the results of the study and determined that criteria 1 and 2 were met or exceeded [an incidence of neoplasms in male or female animals which increases with dose; a statistically significant ($p \leq 0.05$) incidence of any type of neoplasm in any test group (male or female animals at any dose level) compared to concurrent control animals of the same sex].

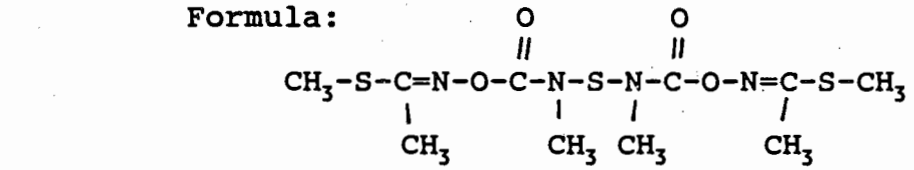
A signed statement of no confidentiality claim was provided.

C. Test Article

Name: Thiodicarb:

5

Formula:



Purity: 96% (Report page 153)
Lot No. (Batch): 09-02-84 (Report page 18);
DA616 (Report page 153)
Physical property: white powder
Storage: 4°C

D. Dose Selection

Doses of 30, 1,750, 3,500 and 7,000 ppm were administered by dietary admix to mice in a 4-week range-finding study (IRI Project No. 450148). Results were as follows:

7,000 = decreased body weight gain and food consumption, increased spleen and liver weights (both sexes) and decreased ovarian weights

3,500 = reduced body weight gain in males only; increased spleen and liver weights (both sexes)

1,750 = increased spleen and liver weights (both sexes)

30 = no effects

Erythrocyte, plasma and brain cholinesterase levels were measured. As there were no differences between the treated and control groups, these parameters were not measured in the carcinogenicity study.

The doses chosen for the carcinogenicity study were 0 (control), 5, 70 and 1,000 mg/kg/day as a dietary admix.

E. Test Article Analysis

Test article concentrations and homogeneity in dietary admixes were determined during weeks 1, 5, 7 (some doses, repeat of week 5 due to deviations outside acceptable limits), 9, 12, 14 (one dose, repeat of week 12 due to deviation outside acceptable limits), 22, 42, 46, 57 (1,000 mg/kg/day male only due to observed weight loss), 60, 70 (extra sample as no valid assay at week 60 for 5 and 70 mg/kg/day both sexes), 72, 86, 88 (1,000 mg/kg/day both sexes were outside acceptable limits at week 86) and 94 (Table 1). Since the study Authors reported that homogeneity testing was performed, it was

assumed by this Reviewer that multiple (generally triplicate) samples analyzed for each sex/dose and testing interval, provided information on the homogeneity of the mixes.

Dietary anlayses for concentrations and homogeneity were generally considered to be within acceptable limits.

Report page 22 indicated that the test article was stable in the diet for at least 3 weeks (IRI Project No. 340164).

Table 1

SELECTED INTERVAL TEST ARTICLE CONCENTRATIONS IN A 97-WEEK DIETARY ADMIX MOUSE STUDY WITH THIODICARB

mg/kg/day	Week						
	1	9	22	42	72	86	94
MALES							
5	-9	-23	-2	-5	+5	+5	-1
70	-1	-7	-2	-6	-6	+8	+4
1000	-1	-7	-2	-3	+5	-13	+5
FEMALES							
5	+3	-9	-3	-5	+5	+7	+3
70	-1	-2	-2	-1	-4	+6	+5
1000	0	+10	+2	+6	+6	-13	+6

Results are mean of 3 assays.
NOTE: Results expressed as % difference from theoretical concentration
Data extracted from Report Appendix 5, pages 159-163.

F. Diet Preparation

Dietary admixes were prepared by adding sieved test article to basal diet and mixing for 20 minutes (Winkworth Change Drum Tumble Mixer). The diets were made weekly during the first 13 weeks and every 2 weeks thereafter. Test article concentrations were adjusted each week for the first 13 weeks and every 4 weeks thereafter.

G. Animals

Male and female CD-1 mice were received from Charles River (UK) Limited, Margate, Kent, England. They were about 4 weeks old (18-21 g) upon arrival and were acclimated for 13 days prior to treatment. The animals were individually housed in suspended polypropylene cages in a barrier maintained animal room. Room temperature and humidity were 20 ± 2°C and 55 ± 10%, respectively. There was a 12-hour light/dark cycle. Food and water (bottle) were available ad libitum. Mice were assigned to treatment groups by a computer generated random number sequence.

H. Assignment of Mice

The study was originally designed for 104 weeks. Due to the rate of mortality in high-dose females, the Registrant and Testing Facility agreed to terminate the study after 97 weeks.

The carcinogenicity aspect of the study (mice intended to be dosed for 104 weeks) consisted of 50 animals/sex/dose group (0, 5, 70 and 1,000 mg/kg/day). An additional 15/sex/group (4 groups) were assigned to a 52-week interim sacrifice (10/sex/group were scheduled to be sacrificed, with the remainder of the 15/sex/group becoming part of the carcinogenicity group which continued until the week 97 terminal sacrifice). [Report page 21 indicated that, because of an error, extra animals from some interim sacrifice groups were killed; but, that this did not impinge upon the integrity of the study.]

I. Mortality and Clinical Signs

Mice were observed A.M. and late P.M. daily. A detailed clinical examination was performed at least weekly. The size, appearance, position and duration of masses were recorded. Table 2 presents mortality/survivor information.

At the end of 52 weeks, out of 50/sex/group that were scheduled to remain on study for 104 weeks (actually terminated at week 97), the number of survivors were (0, 5, 70 and 1,000 mg/kg/day): males = 44, 46, 49 and 48; females = 49, 48, 46 and 45. Of the 15/sex/group potentially scheduled for interim sacrifice after week 52, the number of survivors were (0, 5, 70 and 1,000 mg/kg/day): males = 15, 14, 14 and 12; females = 14, 13, 15 and 13.

Survivors from the 50/sex/group at week 96 (prior to terminal sacrifice) were (0, 5, 70 and 1,000 mg/kg/day): males = 28, 27, 29 and 22; females = 26, 35, 22 and 13. The only statistical significance ($p = 0.024$) was in females at 1,000 mg/kg/day.

There were no clinical signs which were attributed to test article administration.

8

Table 2

SURVIVORS IN A 97-WEEK DIETARY ADMIX MOUSE STUDY WITH THIODICARB

Week	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
0	50	50	50	50	50	50	50	50
2	-	49	-	-	-	-	-	-
11	-	-	-	49	-	-	-	-
28	49	-	-	-	-	-	-	-
32	48	-	-	-	-	-	-	49
34	-	-	-	-	-	-	-	48
36	-	48	-	-	-	-	-	47
38	-	-	-	-	-	-	-	46
42	47	-	-	-	-	49	-	-
44	45	-	-	-	-	48	48	-
46	-	47	49	-	-	-	47	45
48	44	-	-	-	-	-	46	-
52	-	46	-	48	49	-	-	-
54	43	45	-	47	48	47	-	-
56	-	-	-	45	47	-	-	43
58	-	-	-	-	-	-	45	-
60	-	-	48	-	-	46	-	41
62	-	44	-	44	44	-	-	-
65	42	-	47	42	42	45	-	-
66	-	43	-	-	-	-	-	39
68	40	-	45	-	-	-	40	35
70	38	-	42	41	40	43	-	34
72	37	40	41	39	39	42	39	33
74	36	38	-	-	38	-	38	32
76	-	-	40	-	37	41	37	-
78	34	36	38	37	35	39	-	29
80	-	35	37	32	-	-	36	27
82	31	33	-	31	-	-	35	26
84	-	32	36	29	33	-	-	25
86	-	-	-	26	31	-	33	-
88	30	-	34	23	29	38	29	22
90	29	29	33	-	28	36	26	-
92	-	-	-	22	-	-	24	19
94	28	-	31	-	-	35	22	16
96	-	27	29	-	26	-	-	13

Data extracted from Report Tables 1a and b, pages 56-58.

Table 3

SURVIVORS OF THE 52-WEEK DESIGNATED INTERIM SACRIFICE ANIMALS IN A 97-WEEK DIETARY ADMIX MOUSE STUDY WITH THIODICARB

Week	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
0	15	15	15	15	15	15	15	15
1	-	-	-	14	-	-	-	-
16	-	-	-	-	14	-	-	-
20	-	-	-	-	-	-	-	14
22	-	-	-	13	-	-	-	-
32	-	-	-	-	-	14	-	-
36	-	14	-	-	-	-	-	-
40	-	-	14	-	-	-	-	-
42	-	-	-	-	-	-	-	13
48	-	-	-	12	-	-	-	-
52	-	-	-	-	-	13	-	-
SAC	13	10	12	11	12	11	13	11
54	2	4	2	1	2	2	2	2
72	-	-	-	-	-	-	1	-
74	-	-	-	-	-	1	-	-
78	-	3	-	-	-	-	-	-
82	-	-	1	-	-	-	-	-
84	-	-	0	-	-	-	-	-
88	-	2	-	-	-	-	-	-
90	-	-	-	0	-	-	-	1
92	-	-	-	-	1	-	-	0
96	-	-	-	-	-	-	-	-

Data extracted from Report Table 16, pages 59 and 60, and Volume 3, pages 904-943.

J. Body Weights

Weekly individual weights were taken from one week prior to test article administration through week 13. Then, weights were recorded every 2 weeks until the end of the study. [Report page 23 indicated that, because of concern for the 1,000 mg/kg/day males at week 59, these mice had weights recorded at this time in addition to twice at week 60.] Mean body weights and body weight gains for selected study weeks are summarized in Table 4.

10

Table 4

GROUP MEAN BODY WEIGHTS (g) AND WEIGHT GAINS (g) IN A 97-WEEK DIETARY ADMIX MOUSE STUDY WITH THIODICARB

Week	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
-1	27	27	27	26	22	21	21	21
0	29	30	29	29	23	23	23	24
1	31	31	31	30*	24	24	24*	25**
2	32	33**	32	30***	24	25	26***	25*
3	33	34	33	30***	25	25	26	26*
4	33	34	34	31***	26	26	26	27***
6	35	35	35	33***	27	27	28	28*
8	36	36	36	34***	28	28	29*	29***
10	36	38**	37*	34***	29	29	29	31***
12	38	38	37	34***	30	29	30	31
16	38	39	39	35***	30	30	31*	32***
20	39	40	40	36***	31	31	32*	33***
24	40	42	41	37***	32	32	33	33
28	41	42	42	37***	32	33	34	34
32	43	44	43	37***	34	34	34	34
36	43	43	43	37***	35	34	35	34
40	43	44	43	37***	35	35	36	35
44	44	45	44	37***	35	36	35	35
48	45	45	45	38***	36	36	36	35
52	44	45	44	37***	36	36	37	35
60	46	46	45	36***	37	37	37	35
68	46	45	45	36***	37	36	38	35
76	46	46	46	37***	39	38	38	36
84	46	46	45	36***	38	38	38	34***
92	45	45	45	36***	37	37	38	35
96	45	44	44	35***	38	39	39	38
WT GAIN								
0-52	15.1	15.1	15.1	8.1	13.3	13.4	13.6	11.3
% Con	-	100	100	54	-	101	102	85
0-96	15.9	14.8	14.9	5.2	15.5	15.9	15.7	14.9
% Con	-	93	94	33	-	103	101	96

50 mice/sex/group at week -1
Statistical Significance: * = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$
Data extracted from Report Table 1a, pages 56-58.

For the 97-week carcinogenicity males, there was a statistically significant lower group mean body weight for the 1,000 mg/kg/day mice compared with controls starting with the week 1 measurement and continuing throughout the study ($p<0.05$ for week 1 and $p<0.001$ for the following intervals). This significant difference was 1-3 g during the first 6 weeks;

but by week 52, the group mean difference was 7 g and by week 96, 10 g. The weeks 0-52 weight gain was 54% of control and the weeks 0-96 weight gain was 33% of control. The 5 and 70 mg/kg/day males had about the same, or slightly greater, group mean weights and overall weight gains compared with controls.

All three female group mean body weights were generally similar to, or greater than, controls at all intervals during the 96 weeks.

Table 5 presents group mean body weights for the 15 mice/sex/group designated as 52-week "interim kill" animals.

Table 5

GROUP MEAN BODY WEIGHTS (g) AND WEIGHT GAINS (g) FOR THE 52-WEEK INTERIM SACRIFICE IN A 97-WEEK DIETARY ADMIX MOUSE STUDY WITH THIODICARB

Week	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
-1	27	27	27	27	21	21	21	21
0	30	29	29	30	23	23	23	24
1	31	31	31	30	23	24*	24*	25**
2	32	32	32	31	24	25	25	25
3	33	32	33	31**	24	25	26**	26**
4	34	34	34	32**	25	27*	28***	28***
6	36	35	35	33**	27	29**	29**	30***
8	37	36	36	33**	27	29**	30***	30***
10	38	37	38	33***	28	29*	31***	31***
12	38	37	37	34***	29	30	31***	31***
16	40	39	40	36**	29	31	33***	33***
20	41	41	41	37**	31	32	35***	34***
24	42	42	41	36***	32	33	35***	34
28	42	43	43	38**	33	34	37***	36*
32	44	44	44	38***	34	34	38*	35
36	44	44	44	38**	34	34	38*	36
40	45	46	46	38***	36	35	38	36
44	46	46	46	38***	36	35	39	36
48	46	47	46	38***	37	36	40	37
52	45	47	46	38***	37	36	39	37
WT GAIN 0-52	15.4	17.3	16.9	7.8	14.4	13.1	15.9	13.0
% Con	-	112	110	51	-	91	110	90

15 mice/sex/group at week -1
Statistical Significance: * = p<0.05; ** = p<0.01; *** = p<0.001
Data extracted from Report Table 1b, pages 59 and 60.

Males (12-15/group) receiving the test article at 1,000 mg/kg/day for 52 weeks had significantly less group mean body

weights ($p<0.01$ or 0.001) from weeks 3-52. By 52 weeks, this group gained about half the weight of the control or lower dose groups (5 or 70 mg/kg/day).

During 52 weeks, female weight gains in all 3 dose groups were 90-110% of the control mean. Primarily at 70 and 1,000 mg/kg/day, during weeks 4-24, there were statistically significant ($p<0.01$ or 0.001) greater group mean weights than in the control group.

K. Food Consumption

The amount of food consumed by each mouse was recorded weekly through week 13. During the remainder of the study, food intake over a 1-week period was recorded every 4 weeks. These data are summarized in Table 6.

Table 6

THE GROUP MEAN TOTAL AMOUNT OF FOOD CONSUMED (g) IN A 97-WEEK DIETARY ADMIX MOUSE STUDY WITH THIODICARB

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
Weeks 1-50 % of Con	2349 -	2386 102	2385 102	2412 103	2391 -	2453 103	2540 106	2515 105
Weeks 1-97 % of Con	4306 -	4367 101	4398 102	4466 104	4280 -	4333 101	4466 104	4530 106

Data extracted from Report Table 2a, pages 61 and 62.

For the 15/sex/group labelled 52-week interim kill animals, the percents of control were (5, 70 and 1,000 mg/kg/day): males = 99, 98 and 100; females = 98, 99 and 103.

Although there were "substantial" decreases in body weight gains in both 52- and 97-week males in the 1,000 mg/kg/day groups, the amount of food consumed (weeks 1-97) was slightly greater (104%) than that eaten by respective controls. Assuming that food spillage was not the cause of this difference (spillage was not indicated in the data), food efficiency may have been decreased for 1,000 mg/kg/day males compared to the control.

L. Water Consumption

The water bottles were visually inspected on a weekly basis.

There were no reported differences between the treated and control groups of either sex.

M. Test Article Consumption (Table 7)

Achieved dosages were calculated from theoretical dietary concentrations, actual body weights and actual food consumption data. For both the 97 week and 52-week interim sacrifice mice, data were presented weekly for the first 13 weeks and, with the exception of weeks 66-67 and 68-69, every 3 weeks thereafter. The group mean achieved dosages were within ± 4% of nominal.

Table 7

GROUP MEAN TEST ARTICLE CONSUMPTION IN A 97-WEEK DIETARY ADMIX MOUSE STUDY WITH THIODICARB

Nominal Dose mg/kg/day	Males		Females	
	Mean 97 Week	Mean 52 Week(a)	Mean 97 Week	Mean 52 Week(a)
5	5.05 (101)	5.20 (104)	5.01 (100)	4.97 (99)
70	71 (101)	72 (103)	70 (100)	68 (97)
1000	1008 (101)	1004 (100)	1006 (101)	1027 (103)

(a) = 52-week interim sacrifice group
#(#) = mg/kg/day (% of nominal)
Data extracted from Report Tables 3a and b, pages 64-66.

N. Clinical Pathology

Under light ether anesthesia, blood samples, for the determination of hematology parameters, were obtained at approximately week 52 from the orbital sinus of 10 male and 10 female randomly selected mice from the 52-week interim kill animals. Clinical chemistry blood samples (from the same mice, when possible) were obtained from the dorsal aorta at necropsy (carbon dioxide anesthesia).

Smears from tail blood were made at 52, 77 and 96 weeks from all survivors in the 97-week animals. A differential count was performed on all smears from 0 and 1,000 mg/kg/day mice.

14

HEMATOLOGY (Not a Guideline Requirement)

The following parameters were examined:

Hemoglobin	Leukocyte count
Erythrocytes	Leukocyte differential
Hematocrit	Mean corpuscular volume
Platelets	Mean corpuscular hemoglobin
	Mean corpuscular hemoglobin concentration

Results of hematological evaluations are summarized in Table 8.

Table 8

SELECTED GROUP MEAN HEMATOLOGY PARAMETERS AT 52 WEEKS IN A DIETARY ADMIX MOUSE STUDY WITH THIODICARB

Parameter	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
Hemoglobin	14.3	14.3	13.9	10.3***	14.3	14.1	13.9	12.7***
Erythrocytes	9.2	9.1	8.9	5.8***	8.9	8.9	8.9	7.0***
Hematocrit	43	43	42	32***	43	43	42	37***
MCH	15.5	15.8	15.5	17.8***	16.1	15.9	15.8	18.3***
MCV	46.9	47.5	47.3	55.2***	48.5	48.0	47.8	53.9***
MCHC	33.0	33.2	32.9	32.7	33.3	33.0	33.0	34.0
White Blood Cells	5.51	5.50	5.55	7.65**	4.01	4.18	3.79	4.95
Differential								
neutrophils ...	1.19	1.05	1.03	1.80*	0.82	0.78	0.95	1.00
lymphocytes ...	3.91	4.07	4.18	5.46**	2.94	3.17	2.63	3.36
large unclass. cells	0.15	0.13	0.13	0.29**	0.10	0.07	0.05	0.11

Hemoglobin = g/DL; Erythrocytes = $x10^{12}$/L; Hematocrit = %
MCH = Mean Corpuscular Hemoglobin (hemoglobin in g x 10 ÷ # RBC in millions)
MCV = Mean Corpuscular Volume (hematocrit x 10 ÷ # RBC in millions)
MCHC = Mean Corpuscular Hemoglobin Concentration (hemoglobin in g ÷ hematocrit)
WBCs, neutrophils, lymphocytes and large unclassified cells = 10^9/L
Statistical Significance: * = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$
Number of mice (0, 5, 70 1,000 mg/kg/day): males = 10, 10, 9 and 10; females = 9, 10, 10 and 10
Data extracted from Report Tables 4 and 5, pages 67 and 68.

In 1,000 mg/kg/day males and females, there were statistically significant ($p<0.01$ or 0.001) decreases, compared to control values, in hemoglobin, erythrocytes and hematocrit along with increases in Mean Corpuscular Hemoglobin and Mean Corpuscular Volume. In addition, in 1,000 mg/kg/day males only, there were significant ($p<0.05$ or 0.01) increases in mean leukocyte counts as well as the mean numbers of

neutrophils, lymphocytes and large unclassified cells, although these cell types were observed in approximately the same ratios of the total WBC count for the 1,000 mg/kg/day males as for control males. The Report also stated that, in males at 1,000 mg/kg/day, blood smears showed, "marked red blood cell polychromasia and in some cases Howell-Jolly bodies and basophilic stippling."

The peripheral (tail) blood differentials (at weeks 53, 79 and 97 for 0 and 1,000 mg/kg/day only) did not show any test article related effects (Report Tables 8, 9 and 10, pages 71, 72 and 73). However, the Report stated that polychromasia, with punctate basophilia also present, was more pronounced in the 1,000 mg/kg/day dose group.

CLINICAL CHEMISTRY (Not a Guideline Requirement)

The following parameters were examined:

Aspartate aminotransferase
Alanine aminotransferase
Total bilirubin

The results are presented in Table 9.

Table 9

GROUP MEAN CLINICAL CHEMISTRY PARAMETERS AT 52 WEEKS IN A DIETARY ADMIX MOUSE STUDY WITH THIODICARB

Parameter	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
Aspartate aminotransferase	73	67	75	93	92	74	94	92
Alanine aminotransferase	55	50	68	79	41	49	53	95***
Total bilirubin	1.8	1.7	2.0	5.3***	2.1	1.9	2.4	3.3***

NOTE: The mean values are from 8-12 mice.
Aspartate and Alanine aminotransferases are in IU
Total bilirubin is in µmol/L
Statistical Significance: *** = $p<0.001$
Data extracted from Report Tables 6 and 7, pages 69 and 70.

The following treatment-related findings were reported. In males, the only statistically significant difference ($p<0.001$) was an increase in group mean total bilirubin. For aspartate and alanine aminotransferases, the control and 1,000

mg/kg/day Standard Deviations were 22-37; therefore, increases in the mean values at 1,000 mg/kg/day did not achieve statistical significance.

There were significant ($p<0.001$) increases in alanine aminotransferase and total bilirubin in 1,000 mg/kg/day females compared with controls.

O. Sacrifice and Pathology

INTERIM (52 WEEK) SACRIFICE

There were 10/sex/group (from the 15/sex/group) scheduled for sacrifice and necropsy at 52 weeks (when possible, those on which hematology parameters were examined). Because of an error, extra mice from some groups were sacrificed (0, 5, 70 and 1,000 mg/kg/day): males = 13, 10, 12 and 11; females = 12, 11, 13 and 11. Therefore, the 0, 70 and 1,000 mg/kg/day groups of both sexes and the 5 mg/kg/day females have more than 10 mice for clinical chemistry and organ weights.

The following organs were weighed with weights being expressed as absolute and relative-to-body weights:

liver	kidneys	spleen	adrenals
testes	ovaries	prostate	uterus
brain	pituitary	thyroid/parathyroid	

The tissues listed below were fixed, and of these, the following were examined at the 52-week interim sacrifice: liver, gallbladder, kidneys, lungs and spleen.

DIGESTIVE	RESPIRATORY	UROGENITAL
Salivary glands*	Trachea*	Kidneys*
Esophagus*	Lungs*	Urinary bladder*
Stomach*		Testes*
Duodenum*	CARDIOVASC/HEMAT	Ovaries*
Jejunum*	Aorta*	Cervix*
Ileum*	Heart*	Prostate*
Cecum*	Lymph nodes*	Uterus*
Colon*	Spleen*	Seminal vesicles*
Rectum*	Thymus*	Vagina
Liver*		
Pancreas*		
Gallbladder*		
Tongue		

NEUROLOGIC	GLANDULAR	OTHER
Brain*	Adrenals*	Bone*
Peripheral nerve*	Mammary gland*	Skeletal muscle*
Spinal cord(3 levels)*	Parathyroids*	Skin*
Pituitary*	Thyroids*	Gross lesions and masses@
Eyes (with optic n.)*		Nasal cavity
		Ears

* = EPA Guideline Requirement [bone marrow not saved]
@ = Not on Report list; histopathology indicated lesions/masses were examined

Macroscopic

Those tissues with findings in a greater number of treated mice compared with controls are presented in Table 10.

Table 10

POSSIBLE TREATMENT-RELATED MACROSCOPIC FINDINGS AT THE 52-WEEK SACRIFICE IN A DIETARY ADMIX MOUSE STUDY WITH THIODICARB

Tissue/Observation	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
Liver - No. mice	13	10	12	11	12	11	13	11
mass(es)	1	0	1	3	0	0	0	1
Spleen - No. mice	13	10	12	11	12	11	13	11
enlarged	0	0	0	11	0	0	0	10

Data extracted from Report Table 23, pages 98-101.

There is the suggestion of an increase in the number of male mice with liver masses at 1,000 mg/kg/day. Enlarged spleens were reported for 11/11 males and 10/11 females in the 1,000 mg/kg/day groups.

Organ Weights (Table 11)

Table 11

ABSOLUTE AND COVARIATE ADJUSTED (TO BODY WEIGHT) ORGAN WEIGHTS (g) WHICH SHOWED STATISTICALLY SIGNIFICANT DIFFERENCES AT THE 52-WEEK INTERIM SACRIFICE IN A MOUSE DIETARY ADMIX STUDY WITH THIODICARB

	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
No. Mice	13	10	12	11	12	11	13	11
Body Wt. g	43	45	46	37**	35	36	38	36
Brain ab	.50	.49	.49	.48**	.51	.52	.52	.51
rel	.50	.49	.49	.48	.51	.52	.52	.51
Kidneys ab	.84	.79	.81	.71**	.50	.52	.49	.58**
rel	.84	.77	.80	.75	.51	.52	.48	.58**
Liver ab	2.29	2.20	2.38	2.92***	1.83	1.80	1.91	2.67***
rel	2.27	2.11	2.27	3.13***	1.90	1.80	1.81	2.71***
Spleen ab	.10	.09	.11	.40***	.13	.12	.14	.35***
rel	.10	.09	.10	.42***	.13	.12	.13	.35***

ab = absolute; rel = covariate adjusted relative
Statistical significance: ** = $p<0.01$; *** = $p<0.001$
Data extracted from Report Tables 14,15,18 & 19, pages 77,78,81 & 82.

Absolute and covariate adjusted relative (to body weight) liver and spleen group mean weights were above ($p<0.01$ or 0.001) respective controls for 1,000 mg/kg/day mice of both sexes. Kidney weights were below controls for males and above controls for females. There did not appear to be a test article effect on brain weight.

Microscopic (Table 12)

In livers, hepatocellular adenomas (single or multiple) were observed in 5/11 males and 1/11 females at 1,000 mg/kg/day compared with 1/11 control males (single) and no control females. Hepatocyte hypertrophy was noted for all 1,000 mg/kg/day males and females. Pigmented macrophages observed at a high incidence (10/11 males, 11/11 females) were found to contain hemosiderin. Single cell necrosis occurred in 10/11 males and 7/11 females at 1,000 mg/kg/day.

There did not appear to be a test article effect on lung bronchiolar adenomas (single or multiple).

At 1,000 mg/kg/day, in males and females, there was an increase in both the number of mice as well as the severity of the finding regarding the following splenic parameters: increased hemosidirin and increased extra-medullary hemopoiesis.

Table 12

STATISTICALLY SIGNIFICANT MICROSCOPIC FINDINGS AT THE 52-WEEK INTERIM SACRIFICE IN A DIETARY ADMIX MOUSE STUDY WITH THIODICARB

Tissues/Observations	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
LIVER No. tissues examined	13	10	12	11	12	11	13	11
hepatocellular adenoma,multiple B	0	0	1	3	0	0	0	0
hepatocellular adenoma B	1	0	0	2	0	0	0	1
hepatocellular hypertrophy	0	0	0	11***	0	0	0	11***
pigmented macrophages	0	0	0	10***	0	0	0	11***
single cell necrosis	0	0	1	10***	0	0	0	7**
centrilobular vacuolation	0	1	5*	0	0	0	0	0
LUNGS No. tissues examined	13	10	12	11	12	11	13	11
alveolar/bronchiolar adenoma,multiple B	0	0	1	0	0	0	0	0
alveolar/bronchiolar adenoma B ..	2	1	0	1	0	1	0	1
SPLEEN No. tissues examined	13	10	12	11	12	11	13	11
increased hemosidirin +/-	0	0	1	1	2	4	3	0
+	0	0	0	5*	0	0	1	1
++	0	0	0	5*	0	0	0	10***
total incidence	0	0	1	11***	2	4	4	11***
increased extramedullary hemopoiesis +/-	0	2	1	0	5	1	2	0*
+	0	0	0	0	1	0	0	0
++	0	0	0	11***	0	0	0	11*
total incidence	0	2	1	11***	6	1	2	11*

B = benign
Statistical Significance: * = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$
+/-, +, ++ = grades (severity)
Data extracted from Report Table 25, pages 142-145.

TERMINAL (97 WEEK) SACRIFICE

After about 97 weeks, all surviving mice scheduled to be dosed for 97 weeks plus those 52-week interim sacrifice animals which were not sacrificed and which survived to 97 weeks, were sacrificed and necropsied. The following organs were weighed (weights were expressed as absolute and relative-to-body weights) from 10/sex/group of those animals scheduled to be dosed for 97 weeks:

liver	kidneys	spleen	adrenals
testes	ovaries	prostate	uterus
brain	pituitary	thyroid/parathyroid	

All tissues listed at the 52-week interim sacrifice were saved and all except the following were examined: seminal vesicles, vagina, submandibular lymph node, tongue, nasal cavity and ears.

Macroscopic

Those tissues with findings in a greater number of treated than control animals are presented in Table 13.

Table 13

POSSIBLE TREATMENT-RELATED MACROSCOPIC FINDINGS AT THE 97-WEEK SACRIFICE IN A MOUSE DIETARY ADMIX STUDY WITH THIODICARB

Tissues/Observations	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
LIVER # Mice	50	50	50	50	50	50	50	50
Mass(es)	7	5	15	37	1	2	3	29
Pale focus(i)	5	3	6	8	0	0	2	11
SPLEEN # Mice	50	50	50	50	50	50	50	50
Enlarged	8	5	4	28	9	4	15	19

Data extracted from Report Table 22, pages 85-97.

Male and female mice with liver mass/masses and enlarged spleens were reported in larger numbers in the 1,000 mg/kg/day groups versus the control or lower dose groups.

Organ Weights (Table 14)

Absolute and covariate adjusted relative (to body weight) liver and spleen weights in 1,000 mg/kg/day males and females were greater than controls ($p<0.001$). Female 1,000 mg/kg/day mice had absolute and relative kidney weights greater ($p<0.001$) than controls (not males). Although adrenal and prostate weights in males at 1,000 mg/kg/day showed statistically significant ($p<0.05$) differences from controls, these are not considered to be of toxicological significance.

Table 14

ABSOLUTE COVARIATE ADJUSTED (TO BODY WEIGHT) ORGAN WEIGHTS (g) WHICH SHOWED STATISTICALLY SIGNIFICANT DIFFERENCES AT THE 97-WEEK TERMINAL SACRIFICE IN A DIETARY ADMIX MOUSE STUDY WITH THIODICARB

		Males (mg/kg/day)				Females (mg/kg/day)			
		0	5	70	1000	0	5	70	1000
Number of Mice		11	10	11	12	9	10	10	10
Body Weights g		44	44	43	34***	35	37	38	37
ADRENALS	absolute	.004	.005	.004	.006*	.008	.008	.008	.008
	relative	.004	.005	.003	.006*	.008	.008	.008	.008
KIDNEYS	absolute	.76	.79	.80	.74	.50	.50	.53	.67***
	relative	.76	.79	.81	.74	.50	.49	.52	.67***
LIVER	absolute	2.26	2.22	2.10	3.81***	1.68	1.76	2.10*	4.06***
	relative	2.06	2.01	1.96	4.30***	1.77	1.73	2.05	4.06***
PROSTATE	absolute	.04	.05	.05*	.03*	-	-	-	-
	relative	.04	.05	.05*	.03	-	-	-	-
SPLEEN	absolute	.08	.09	.11	.35***	.11	.10	.20*	.41***
	relative	.06	.07	.10	.41***	.11	.10	.20*	.40***

Statistical Significance: * = $p<0.05$; *** = $p<0.001$
Data extracted from Report Tables 16, 17, 20 and 21, pages 79, 80, 83 and 84.

Microscopic (Tables 15, 16 and 17)

ATTACHED TO THIS DATA EVALUATION REPORT IS A COPY OF REPORT TABLES 24-26, PAGES 102-146, WHICH INCLUDES NEOPLASTIC AND NON-NEOPLASTIC LESIONS

Table 15

STATISTICALLY SIGNIFICANT NON-NEOPLASTIC FINDINGS AT THE 97-WEEK TERMINAL SACRIFICE IN A DIETARY ADMIX MOUSE STUDY WITH THIODICARB

Tissues/Observations	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
HEART No. of mice	50	23	22	50	50	15	28	50
Cardiomyopathy +/-	13	5	5	16	6	2	9	6
+	7	4	4	12	3	2	3	7
++	0	0	1	5	0	0	1	2
+++	0	1	2	0	0	0	0	0
Total incidence	20	10	12	33*	9	4	13	15

TABLE 15 CONTINUED ON NEXT PAGE

Table 15 (CONTINUED)

Tissues/Observations	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
KIDNEYS No. of mice	50	50	50	50	50	50	50	50
Perivascular lymphocyte cuffing	6	9	5	13	5	10	14*	6
Tubular pigment deposit(s)	1	2	0	14***	10	1**	2*	15
Mineral deposit(s), cortical/papillary	4	5	8	21***	1	6	2	18***
Nephropathy +/-	15	26*	16	11	9	19*	15	7
+	10	8	5	14	6	3	5	12
++	3	3	3	8	3	2	5	7
+++	1	1	2	10**	9	4	4	6
++++	1	0	1	2	3	2	4	0
Total incidence	30	38	27	45***	30	30	33	32
Hydronephrosis +/-	1	2	3	1	3	0	0	2
+	2	1	1	3	1	1	1	2
++	2	1	1	6	1	0	1	2
+++	0	0	1	3	0	0	0	0
++++	0	0	0	1	0	0	0	0
Total incidence	5	4	6	14*	5	1	2	6
Papillary edema +/-	0	0	1	5	1	4	0	3
+	0	0	0	15***	0	0	0	7*
++	0	0	0	9**	0	0	0	2
Total incidence	0	0	1	29***	1	4	0	12**
Papillary necrosis ++	0	0	0	5	2	2	0	2
+++	1	0	0	4	0	0	0	0
Total incidence	1	0	0	9*	2	2	0	2
Urothelial hyperplasia +/-	0	1	3	12***	0	0	0	3
+	0	0	1	8**	0	0	0	7*
++	0	0	0	0	0	0	0	1
Total incidence	0	1	4	20***	0	0	0	11***
LIVER No. of mice	50	50	50	50	50	50	50	50
Increased hepatocyte pleiomorphism	5	10	13	29***	2	3	1	30***
Cellular change +/-	1	0	3	3	1	0	1	3
+	1	1	2	7	1	3	0	7
++	2	0	4	7	0	0	1	8**
+++	1	0	1	3	0	0	0	3
++++	0	0	0	1	0	0	0	0
Total incidence	5	1	10	21***	2	3	2	21***
Pigmented macrophages	0	0	1	48***	4	3	1	46***
Single cell necrosis	1	6	8*	7	5	4	3	13
Focus(i) of hemopoiesis ..	4	2	2	15**	3	3	4	7
Hepatocyte hypertrophy ...	2	6	6	20***	1	0	2	13***
Bile duct hyperplasia +/-	0	1	1	5	0	1	0	6*
+	1	0	0	5	0	0	0	5
++	1	0	0	2	0	0	0	2
Total incidence	2	1	1	12**	0	1	0	13***
Lobular hepatitis +/-	0	0	0	4	0	1	0	10**
+	0	0	0	2	0	0	0	0
Total incidence	0	0	0	6*	0	1	0	10**

TABLE 15 CONTINUED ON NEXT PAGE

Table 15 (CONTINUED)

Tissues/Observations	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
LUNGS No. of mice	50	50	50	50	50	50	50	50
Perivascular lymphocytic cuffing	5	1	5	5	0	6*	3	5
SPLEEN No. of mice	50	50	50	50	50	50	50	50
Increased hemosiderin +/-	0	3	5	21***	4	2	2	12
+	0	0	0	12***	0	0	2	12***
++	0	0	0	3	1	1	0	7
Total incidence	0	3	5	36***	5	3	4	31***
Increased extramedullary hemopoiesis +/-	4	6	10	3	4	5	6	9
+	2	4	1	12**	4	2	10	7
++	3	1	8	20***	5	5	4	12
+++	4	3	2	6	1	4	8*	8*
++++	1	0	0	0	1	0	3	2
Total incidence	14	14	21	41***	15	16	31**	38***
White pulp depletion	5	1	3	20***	4	0	4	12

Statistical Significance: * = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$
Data extracted from Report Table 24, pages 102-141.

All non-neoplastic treatment-related histopathologic differences from control were noted only in the 1,000 mg/kg/day mice. Statistically significant ($p<0.05$, 0.01 or 0.001) increases in the number of mice with specific findings are noted below. [M = Males; F = Females]

KIDNEY: tubular pigment deposits - M (possibly F)
mineral deposits, cortical/papillary - M and F
nephropathy - M only
hydronephrosis - M only
papillary edema - M and F
papillary necrosis - M only
urothelial hyperplasia - M and F

LIVER: increased hepatocyte pleiomorphism - M and F
cellular change - M and F
pigmented macrophages - M and F
focus(i) of hemopoiesis - M only
hepatocyte hypertrophy - M and F
bile duct hyperplasia - M and F
lobular hepatitis - M and F

SPLEEN: increased hemosiderin - M and F
increased extramedullary hemopoiesis - M and F
white pulp depletion - M (possibly F)

Table 16

SUMMARY OF NEOPLASTIC INCIDENCES AT THE 97-WEEK TERMINAL SACRIFICE IN A DIETARY ADMIX MOUSE STUDY WITH THIODICARB

	Males (mg/kg/day)		Females (mg/kg/day)	
	0	1000	0	1000
No. of mice	50	50	50	50
No. mice with tumors	25	43	32	42
No. mice with single tumors	19	27	23	26
No. mice with multiple tumors	6	16	9	16
No. mice with benign tumors	19	28	18	28
No. mice with malignant tumors ...	8	24	20	27
No. mice with metastisizing tumors	1	0	0	0
Total number of tumors	31	63	47	61
benign tumors	22	34	24	29
malignant tumors	9	29	23	32
metastisizing tumors	1	0	0	0
% mice with tumors	50	86	64	84
single tumors	38	54	46	52
multiple tumors	12	32	18	32
benign tumors	38	56	36	56
malignant tumors	16	48	40	54
metastisizing tumors	2	0	0	0

Animals with more than one tumor type are recorded as having multiple tumors.

Data reproduced from Report Table 26, page 146.

At the 97-week terminal sacrifice, the only histopathologically confirmed increase in tumor incidence which appeared to be the result of test article administration, concerned the liver. For both males and females at only 1,000 mg/kg/day, there were statistically significant ($p<0.01$ or 0.001) increases over the control values, in the number of mice which were reported to have hepatocellular carcinomas (malignant) and hepatocellular adenomas (benign). In addition, there was an increase ($p<0.05$) in the number of males with "associated hepatocellular adenomas" (9 versus 1 in controls) and the "suggestive" increase in females (4 versus 0 in controls).

Table 17

NEOPLASTIC INCIDENCES AT THE 97-WEEK TERMINAL SACRIFICE IN A DIETARY ADMIX MOUSE STUDY WITH THIODICARB

Tissues/Observations	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
ADRENALS No. tissues	49	22	22	50	49	14	28	50
Unilateral cortical carcinoma M	0	0	1	0	0	0	0	0
Unilateral subcapsular cortical adenoma B	0	0	0	0	1	0	0	0
Unilateral cortical adenoma B	0	2	1	2	0	0	0	0
(contains histiocytic sarcoma)	1	0	0	0	0	0	1	0
CECUM No. tissues	48	22	17	48	44	12	26	48
Leiomyoma B	0	0	0	0	0	0	1	0
(contains histiocytic sarcoma)	1	0	0	0	0	0	1	1
DUODENUM No. tissues	47	21	17	49	49	14	27	49
(contains histiocytic sarcoma)	1	0	0	0	0	0	0	0
ESOPHAGUS No. tissues	50	23	21	50	50	15	28	50
(contains histiocytic sarcoma)	1	0	0	0	0	0	0	0
GALLBLADDER No. tissues	46	45	41	45	48	47	45	48
(contains histiocytic sarcoma)	1	0	0	0	0	0	0	0
(contains sarcoma) ...	1	0	0	0	0	0	0	0
HARDERIAN GLAND No. tissues	1	0	1	0	0	0	0	1
Unilateral carcinoma M	0	-	1	-	-	-	-	1
Unilateral adenoma B	1	-	0	-	-	-	-	0
HEART No. tissues	50	23	22	50	50	15	28	50
(contains histiocytic sarcoma)	1	0	0	0	1	0	0	1
(contains sarcoma) ...	1	0	0	0	0	0	0	0
ILEUM No. tissues	50	22	19	48	47	14	27	49
(contains sarcoma) ...	1	0	0	0	0	0	0	0
JEJUNUM No. tissues	47	21	17	49	48	15	25	49
(contains sarcoma) ...	1	0	0	0	0	0	0	0
KIDNEYS No. tissues	50	50	50	50	50	50	50	50
Unilateral tubular carcinoma M	0	0	0	1	0	0	0	0
Unilateral tubular adenoma B	0	0	2	0	0	0	0	0

TABLE 17 CONTINUED ON NEXT PAGE

Table 17 (CONTINUED)

Tissues/Observations	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
LIVER No. tissues	50	50	50	50	50	50	50	50
Hepatocellular carcinoma **M**	2	0	3	14**	0	0	1	8**
(associated) hepatocellular adenoma(ta)	1	0	2	9*	0	0	0	4
Hepatocellular adenoma(ta) **B**	6	7	11	23***	1	1	2	20***
Cholangiocarcinoma **M** ...	0	0	0	1	0	0	0	0
(contains histiocytic sarcoma)	1	0	1	0	1	0	2	4
(Contains hemangiosarcoma)	0	0	2	2	0	1	1	1
LUNGS No. tissues	50	50	50	50	50	50	50	50
Alveolar/bronchiolar carcinoma **M**	2	6	2	3	2	0	2	0
(associated) alveolar/bronchiolar adenoma(ta)	1	0	1	0	0	0	0	0
Alveolar/bronchiolar adenoma(ta)**B**	13	16	13	5	5	6	8	4
(contains histiocytic sarcoma)	1	0	1	0	0	0	3	2
(contains sarcoma)	1	0	0	0	0	0	0	0
LYMPHORETICULAR/HEMATOPOIETIC TISSUE No. tissues	2	3	4	4	9	4	3	8
Histiocytic sarcoma **M** ..	1	0	1	0	2	0	3	4
Lymphoma **M**	1	3	3	3	7	4	0	4
Leukemia **M**	0	0	0	1	0	0	0	0
MAMMARY GLANDS No. tissues	50	22	22	48	50	15	28	50
Adenoacanthoma **M**	0	0	0	0	0	0	0	1
Carcinoma **M**	0	0	0	0	1	1	0	1
(contains histiocytic sarcoma)	0	0	0	0	0	0	0	1
MESENTERIC LYMPH NODE No. tissues	47	22	19	46	48	15	27	50
(contains histiocytic sarcoma)	1	0	1	0	1	0	2	1
(contains hemangiosarcoma)	0	0	0	0	4	1	1	1
(contains sarcoma)	1	0	0	0	0	0	0	0
MESENTERY No. tissues	1	0	0	0	0	0	0	0
Metastasizing sarcoma **M**	1	-	-	-	-	-	-	-

TABLE 17 CONTINUED ON NEXT PAGE

Table 17 (CONTINUED)

Tissues/Observations	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
OVARIES No. tissues	-	-	-	-	50	15	28	50
Granulosa/thecal cell tumor(s) B	-	-	-	-	1	1	1	1
Unilateral tubular adenoma B	-	-	-	-	1	0	0	0
Unilateral luteoma B	-	-	-	-	1	0	0	1
Cystadenoma(ta) B	-	-	-	-	6	2	1	1
(contains histiocytic sarcoma)	-	-	-	-	2	0	2	1
(contains hemangio-sarcoma)	-	-	-	-	0	0	0	2
PANCREAS No. tissues	50	23	22	48	50	15	28	50
Islet adenoma B	0	0	0	0	1	0	0	0
(contains histiocytic sarcoma)	1	0	1	1	1	0	0	3
(contains sarcoma)	1	0	0	0	0	0	0	0
PARATHYROIDS No. tissues	39	20	17	46	42	12	27	38
(contains histiocytic sarcoma)	0	0	0	0	0	0	0	1
PITUITARY No. tissues	49	22	22	48	50	15	28	48
Adenoma B	0	0	0	0	0	0	1	0
PROSTATE No. tissues	50	23	21	49	-	-	-	-
(contains histiocytic sarcoma)	1	0	0	0	-	-	-	-
SALIVARY GLAND No. tissues	50	23	22	50	50	15	28	50
(contains histiocytic sarcoma)	0	0	0	0	0	0	0	1
SEMINAL VESICLES No. tissues	20	5	12	2	-	-	-	-
(contains histiocytic sarcoma)	0	0	1	0	-	-	-	-
SKIN/SUBCUTIS No. tissues	50	23	22	50	50	15	28	50
Basal cell tumor M	0	0	0	0	0	0	0	1
Fibrosarcoma M	0	0	0	0	0	0	0	1
Lipoma B	1	0	0	0	0	0	0	0
Intracutaneous cornifying epithelioma B	0	0	0	1	0	0	0	0
Myxoma(ta) B	0	0	0	0	1	0	0	0
(contains histiocytic sarcoma)	0	0	0	0	1	0	0	0
(contains hemangio-sarcoma)	1	0	0	0	0	0	0	0
SPINAL CORD No. tissues	50	23	22	50	50	15	28	50
Sarcoma M	0	0	0	1	0	0	0	0

TABLE 17 CONTINUED ON NEXT PAGE

Table 17 (CONTINUED)

Tissues/Observations	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
SPLEEN No. tissues	50	50	50	50	50	50	50	50
(contains histiocytic sarcoma)	1	0	1	0	0	0	0	1
(contains hemangio-sarcoma)	1	0	1	2	0	1	1	4
STERNUM No. tissues	50	23	22	50	50	15	28	50
(contains histiocytic sarcoma)	1	0	0	0	0	0	1	0
STOMACH No. tissues	50	50	50	50	50	49	50	50
Basal cell tumor M	0	0	0	0	0	0	1	0
Sarcoma M	0	0	0	0	1	0	0	0
Tumor M	0	0	0	1	0	0	0	0
(contains histiocytic sarcoma)	1	0	0	1	0	0	0	0
(contains sarcoma)	1	0	0	0	0	0	0	0
SUBMANDIBULAR LYMPH NODE No. tissues	3	1	0	0	3	1	3	2
(contains histiocytic sarcoma)	0	0	-	-	0	0	0	1
TESTES No. tissues	50	23	22	50	-	-	-	-
Interstitial-cell adenoma(ta) B	1	0	0	3	-	-	-	-
Epididymides (contains histiocytic sarcoma)	0	0	1	0	-	-	-	-
(contains sarcoma)	1	0	0	0	-	-	-	-
THYMUS No. tissues	46	20	16	40	46	14	24	49
(contains histiocytic sarcoma)	1	0	1	0	0	0	2	2
(contains hemangio-sarcoma)	0	0	0	0	1	0	0	0
(contains sarcoma)	1	0	0	0	0	0	0	0
THYROIDS No. tissues	50	23	22	49	50	15	28	49
Unilateral follicular adenoma B	0	0	0	0	0	0	0	1
(contains histiocytic sarcoma)	0	0	0	0	0	0	0	1
URINARY BLADDER No. tissues	50	23	21	50	50	15	27	50
Sarcoma M	0	0	0	1	0	0	0	0
(contains histiocytic sarcoma)	1	0	0	0	0	0	0	1

TABLE 17 CONTINUED ON NEXT PAGE

Table 17 (CONTINUED)

Tissues/Observations	Males (mg/kg/day)				Females (mg/kg/day)			
	0	5	70	1000	0	5	70	1000
UTERUS No. tissues	-	-	-	-	50	15	28	50
Adenocarcinoma **M**	-	-	-	-	0	1	1	2
Stromal sarcoma **M**	-	-	-	-	1	0	2	0
Leiomyosarcoma **M**	-	-	-	-	2	1	0	0
Sarcoma **M**	-	-	-	-	1	0	0	0
Carcinoma **M**	-	-	-	-	1	0	1	0
Polyp **B**	-	-	-	-	5	2	1	1
(contains histiocytic sarcoma)	-	-	-	-	1	0	3	3
(contains hemangio-sarcoma)	-	-	-	-	0	0	2	1
(contains hemangioma) ...	-	-	-	-	1	0	1	0
VASCULAR SYSTEM No. tissues	3	0	3	3	5	4	4	8
Hemangiosarcoma **M**	2	-	3	3	4	4	3	8
Hemangioma **B**	0	-	0	0	1	0	1	0

B = benign
M = malignant
- = not examined
Statistical Significance: * = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$
Data extracted from Report Table 24, pages 102-141.

II. DISCUSSION

Analytical data for concentrations and homogeneity were within acceptable limits.

The study was originally designed for a 104-week duration. However, due to the rate of mortality in 1,000 mg/kg/day females (Highest Dose Tested), the decision was made by the Registrant and Testing Facility to terminate the study after 97 weeks.

There were no clinical signs which appeared to be the result of test article administration.

Of the 15/sex/group originally assigned to the 52-week interim sacrifice, the numbers of survivors at week 52 (prior to interim sacrifice) were as follows (0, 5, 70 and 1,000 mg/kg/day): males = 15, 14, 14 and 12; females = 14, 13, 15 and 13. There does not appear to be a clear-cut effect of the test article on mortality. In 1,000 mg/kg/day males, 3/15 died during weeks 1, 22 and 48 compared with 0/15 for controls.

For those 50/sex/group mice scheduled for 97 weeks, survivors were as follows (0, 5, 70 and 1,000 mg/kg/day): males = 28, 27, 29 and 22; females = 26, 35, 22 and 13. There appeared to be a slight increase in mortality in the 1,000 mg/kg/day males. As late in the

study as week 84, the numbers of male survivors in the 0, 5, 70 and 1,000 mg/kg/day groups were 31, 32, 36 and 29.

Mortality in the 1,000 mg/kg/day female group appeared to be approximately similar to the control until about study week 66 (42, 45, 45 and 39 at the above mentioned doses). During the last 30 weeks of the study (weeks 66-96), the number of female mice which died/group were 16, 10, 23 and 26.

Group mean body weights for the fifteen 1,000 mg/kg/day 52-week interim sacrifice males were significantly ($p<0.01$ or 0.001) lower than controls from week 3 through the 52nd week. These mice gained only about 1/2 of the control weight gain; whereas, the 5 and 70 mg/kg/day males gained 110-112% of controls. The 70 and 1,000 mg/kg/day 52-week interim sacrifice females weighed more than the controls (mostly $p<0.001$) for the first 26 weeks and the final body weights were similar for all four groups (0, 5, 70 and 1,000 mg/kg/day): 37, 36, 39 and 37 g. Weight gains of all three treated groups for the 52 weeks were 90-110% of the control value.

The 97-week males at 1,000 mg/kg/day weighed less than controls ($p<0.001$) during the entire study with total weight gain being 33% of controls (5.2 versus 15.9 g). All treated female groups had body weights equal to or greater than controls during most of the 97 weeks.

It should be noted that the 1,000 mg/kg/day males, which had lower group mean body weights compared with controls, had a greater number of survivors than did females at the same dose (similar mean body weights as controls).

A review of group mean as well as individual animal food consumption, indicated that there was no apparent effect of treatment as compared with control consumption. There was no mention of "spillage" in the Report. Although the 1,000 mg/kg/day males gained only about 1/2 the amount of weight as did the controls, the amount of food consumed was similar.

Test article consumption over the 52- or 97-week periods for both males and females was 97-104% of the nominal amount at all 3 dose levels.

Hemoglobin, erythrocyte counts and hematocrits in both sexes at 1,000 mg/kg/day were statistically ($p<0.001$) lower than comparative controls at the 52-week sampling. Mean Corpuscular Hemoglobin and Mean Corpuscular Volume were greater ($p<0.001$) than controls at this dose.

In males at 1,000 mg/kg/day (52 weeks), there were increases in aspartate aminotransferase (not-significant), alanine aminotransferase (not-significant) and total bilirubin ($p<0.001$). Both alanine aminotransferase and total bilirubin were significantly ($p<0.001$) increased, but aspartate aminotransferase was not, in the 1,000 mg/kg/day females.

At the 52-week sacrifice, 11/11 males and 10/11 females at 1,000 mg/kg/day had enlarged spleens compared with none in the other 3 groups. For the 97-week sacrifice, 28/50 males and 19/50 females had enlarged spleens. In males, the 5 and 70 mg/kg/day groups had fewer mice with this finding than did the control group (8/50). In females, there were 9, 4, 15 and 19 out of 50/group at 0, 5, 70 and 1,000 mg/kg/day.

The number of mice with liver masses noted at the 52-week sacrifice were (0, 5, 70 and 1,000 mg/kg/day): males = 1/13, 0/15, 1/12 and 3/11; females = 0/12, 0/11, 0/13 and 1/11. At 97 weeks, the respective numbers (out of 50/sex/group) were: males = 7, 5, 15 and 37; females = 1, 2, 3 and 29. In addition, pale livers were reported in 5, 3, 6 and 8 mice for males and 0, 0, 2 and 11 for females.

No treatment-related increase in the number of animals with enlarged lymph nodes was noted in the 52-week interim sacrifice. At 97 weeks, a total of 8 control males and 8 control females (out of 50/sex/group) had one or many enlarged nodes compared with 14/sex at 1,000 mg/kg/day.

Absolute and relative (covariate adjusted to body weight) liver and spleen weights were significantly ($p<0.001$) heavier in 1,000 mg/kg/day 52- and 97-week sacrifice males and females compared with respective control values. The significantly ($p<0.01$) lower absolute brain and kidney weights in 52-week sacrifice 1,000 mg/kg/day males appear to be a reflection of lower body weights as female brain weights were similar to controls and kidney weights were greater ($p<0.01$) than controls (body weight similar to control). At the 97-week sacrifice, 1,000 mg/kg/day male kidney weights were similar to controls (lower body weights in treated mice) and in females, both absolute and relative weights were greater ($p<0.001$) than controls.

Histopathologically, at the 52-week interim sacrifice, the numbers of mice with single or multiple hepatocellular adenomas were as follows (0, 5, 70 and 1,000 mg/kg/day): males = 1, 0, 1 and 5; females = 0, 0, 0 and 1. Alveolar/bronchiolar single or multiple adenomas were as follows: males = 2, 1, 1 and 1; females = 0, 1, 0 and 1. The number of male and female 1,000 mg/kg/day mice with hepatocellular hypertrophy, pigmented macrophages, single liver cell necrosis, increased splenic hemosiderin and increased splenic extramedullary hemopoiesis was increased ($p<0.001$) over the number of controls with these observations (5 and 70 mg/kg/day groups similar to controls).

Statistically significant neoplastic differences between treated and control animals at the 97-week terminal sacrifice occurred only in males and females of the 1,000 mg/kg/day group. Hepatocellular carcinomas were reported in the following numbers of mice (50/sex/group) at 0, 5, 70 and 1,000 mg/kg/day: males = 2, 0, 3 and 14 ($p<0.01$); females = 0, 0, 1 and 8 ($p<0.01$). Associated hepatocellular adenoma(ta): males = 1, 0, 2 and 9 ($p<0.05$); females = 0, 0, 0 and 4 (not-significant). Hepatocellular adenoma(ta): males = 6, 7, 11 and 23 ($p<0.001$); females = 1, 1, 2 and 20 ($p<0.001$).

Affected mice, which showed statistically significant non-neoplastic histopathological 97-week terminal sacrifice findings, were observed only at a dose of 1,000 mg/kg/day (kidney, liver and spleen). In the kidney, the following were significantly ($p<0.05$, 0.01 or 0.001) different and, for most parameters, primarily in males: tubular pigment deposits, cortical/papillary mineral deposits, nephropathy, hydronephrosis, papillary edema, papillary necrosis and urothelial hyperplasia. In the liver, statistical significance ($p<0.05$, 0.01 or 0.001), similar in both sexes, was reported for the following: increased hepatocyte pleiomorphism, cellular change, pigmented macrophages, focus(i) of hemopoiesis, hepatocyte hypertrophy, bile duct hyperplasia and lobular hepatitis. Significant ($p<0.001$) splenic findings for males and females were: increased hemosiderin and increased extramedullary hemopoiesis in addition to white pulp depletion ($p<0.001$ in males and not-significant in females).

Taking into consideration the clinical pathology, macroscopic pathology, organ weights and microscopic pathology, the target tissues in both males and females were the kidney, liver and spleen. These appeared to be affected only by a dose of 1,000 mg/kg/day.

III. CONCLUSIONS

In a carcinogenicity study, THIODICARB was administered by dietary admix to Charles River CD-1 mice (50/sex/group) at doses of 0, 5, 70 and 1,000 (LIMIT DOSE) mg/kg/day for 97 weeks with an additional 15/sex/group for a 52-week interim sacrifice. The following parameters were examined: mortality, clinical signs, body weights, food consumption, hematology, limited clinical chemistry, macroscopic pathology, organ weights and microscopic pathology.

The following effects were observed only at 1,000 mg/kg/day: increased mortality in both sexes (especially females); decrease in body weight gain (males only); decreases in hemoglobin, erythrocytes and hematocrit; increases in alanine aminotransferase and total bilirubin; increases in liver and spleen size; non-neoplastic kidney, liver and spleen changes; and an increase in the number of mice with benign and malignant liver neoplasms. **The NOEL is 70 mg/kg/day and the LOEL is 1,000 mg/kg/day. [MRID No. 430005-01]**

The test article appears to be a CARCINOGEN at 1,000 mg/kg/day.

Core classification is **Guideline**. This study satisfies the data requirement (§83-2) for a carcinogenicity study in mice.

Thiodicarb

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