6-28-95

MRID
436193-01

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

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JUN 28 1995

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **THIODICARB**: Historical Control Data of Tumor Incidence in the Mouse; 4-Week Oral Toxicity Study in Mice; Additional Supplemental Data to Support Registrant's Contention that Dose Levels in Mouse Carcinogenicity Study are Adequate

TO: Bonnie Adler
PM Team Reviewer (52)
Reregistration Branch, SRRD, (7508W)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 6/21/95
Toxicology Branch II, Section II,
Health Effects Division (7509C)

THRU: K. Clark Swentzel K Clark Swentzel 6/21/95
Section II Head, Toxicology Branch II
Health Effects Division (7509C)

and

Marcia van Gemert, Ph.D. J. M. Loannou for
Chief, Toxicology Branch II/HFAS/HED (7509C)

Registrant: Rhône-Poulenc Secteur Agro
Chemical: Thiodicarb
Synonym: Larvin
Submission No.: S485444
DP Barcode: D214346
Caswell No.: 900AA
Case: 816454
Identifying No.: 114501-000264
Shaughnessey No.: 114501 [PC Code]
MRID No.: 436193-01 and 436117-01
Action Requested: Please review the historical mouse data submitted.

Comment: The Registrant has submitted supplemental data relevant to the issue of dose selection for the mouse carcinogenicity study on Thiodicarb [MRID #430005-01; DER dated 5/11/94; Document # 011030].

The submission consists of: (1) MRID # 436193-01: (a) a preliminary report of a mouse LD_{50} study, (b) a rat LD_{50} study, (c) a 7-day mouse dietary study, (d) historical control data on mouse tumor incidence

at Inveresk Laboratories [where mouse carcinogenicity study was performed]; and (2) MRID # 436117-01: the final report of a 4-week dietary dose range-finding study on Thiodicarb in mice.

MRID # 436193-01: At issue is the spacing of the dose levels in the mouse carcinogenicity study [MRID # 430004-01]. The Registrant contends that the high dose [1000 mg/kg/day] exceeded the MTD and that the mid dose [70 mg/kg/day] is adequately high in that it approximates a daily LD_{50} dose and, therefore, should be considered near the MTD and adequate for assessing the carcinogenic potential of Thiodicarb. The supporting data include: (a) Based on data from an on-going study, the LD_{50} for male mice [vehicle not identified] is stated to be 73 mg/kg. The female phase of the study has not been completed. (b) The rat LD_{50} studies submitted were previously reviewed [Accession # 071181; Document # 003062]. TB II notes that there are numerous LD_{50} studies on Thiodicarb, and no explanation as to why these two were chosen was provided. In the study using methyl cellulose aqueous solution as the vehicle, the LD_{50} = ♂♂ ≈69/ ♀♀ ≈39 mg/kg; Toxicity Category I. When corn oil was the vehicle, the LD_{50} ♂♂ = ≈129/♀♀ 59 mg/kg; Toxicity Category II. (c) The 7-day study was reviewed previously [Document # 003697; no Accession # or MRID # associated with it] and was classified Core Supplementary. The one-liner lists the NOEL as 15 mg/kg/day, the LEL as 45 mg/kg/ day, based on a slight increase in kidney weight in males. (d) A booklet entitled: Background Tumour Incidences-From carcinogenicity studies in Crl:CD-1 Swiss mice (February 1995); Inveresk Research International. This contains a list of focal hyperplasia, benign, and malignant neoplasia for each tissue/organ. This will be made available to the HED Cancer Peer Review Committee for their consideration.

MRID # 436117-01: This study has been reviewed, and the DER is appended. Under the conditions of the study, oral administration of Thiodicarb [96%] to CD-1 mice [10/sex/group] for 4 weeks <u>via</u> the diet at dose levels of 0, 30 ppm [♂♂ 6.2/♀♀ 8.3 mg/kg], 1750 ppm [♂♂ 346/♀♀ 491 mg/kg], 3500 ppm [♂♂ 734/♀♀ 954 mg/kg], and 7000 ppm [♂♂ 1538/♀♀ 2030 mg/kg] resulted in decreased body weight at the 7000 ppm dose level [♂♂ 80%/♀♀ 88% of control], a negative body-weight gain [-1.6 grams] overall in high-dose males, a decreased body-weight gain overall in the high-dose females [47% of control], and a decreased overall body-weight gain in males at the 3500 ppm dose level [76% of control]. Overall food consumption was slightly decreased in both sexes at 7000 ppm, which might be due to a palatability problem. There were no treatment-related effects observed on cholinesterase activity in plasma, RBC, or brain in either sex. There was a dose-related increase in (1) liver weight in females and (2) spleen weight in males. The high-dose females also displayed an increase in spleen weight, although the increase was not strictly dose-related. Additionally, there was a decrease in ovarian weight at the high-dose level compared to the control value. **The NOEL can be set at 30 ppm (♂♂ 6.2/♀♀ 8.3 mg/kg), the**

LOEL at 1750 ppm (♂♂ 346/♀♀ 491 mg/kg), based on increased liver weight in females and increased spleen weight in both sexes.

This study is classified Acceptable. This study does not satisfy any guideline requirement nor was it intended to.

DISCUSSION

TB II notes that in the 4-week study, the interval between the NOEL and LEL [low and next highest dose] is large: 30 ppm vs 1750 ppm [♂♂ 6.2 vs 346 mg/kg/day and ♀♀ 8.3 vs 491 mg/kg/day]. One cannot conclude that a NOEL of 1000 or 1500 ppm [≈ 200-300 mg/kg/day] would not be found following a 4-week exposure. A similar situation was found in the mouse carcinogenicity study, where the gap between the high- and mid-dose was large: 70 mg/kg/day vs 1000 mg/kg/day. With regard to the Registrant's argument that the mid-dose level in the carcinogenicity study [70 mg/kg/day] is comparable to giving an LD_{50} dose each day, TB II points out that in an LD_{50} study, the animals are given the dose as a bolus dose [acute], whereas in the carcinogenicity study, the test material is in the diet, which is ingested over a longer period of time.

CONCLUSION

The data and information submitted regarding the historical control incidence of tumors, as well as the information/arguments presented as evidence that the mid-dose level [70 mg/kg/day] is adequately high for the assessment of carcinogenic risk will be presented as part of the data package submitted to the HED RfD and Cancer Peer Review Committees for their consideration.

Reviewed by: Linda L. Taylor, Ph.D. Linda Lee Taylor 6/21/95
Tox. Branch II, Section II (7509C)
Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 6/21/95
Tox. Branch II, Head Section II (7509C)

DATA EVALUATION REPORT

STUDY TYPE: 4-Week Oral - mouse TOX. CHEM. NO.: 900AA

MRID NO.: 436117-01 Shaughnessey No.: 114501

TEST MATERIAL: Thiodicarb [CAS No. 59669-26-0]

SYNONYMS: Larvin

CHEMICAL NAME: dimethyl N,N'-[thiobis[(methyliminocarbonyl) oxy]bis]ethanimidothioate; 3,7,9,13-tetramethyl-5,11-dioxa-2,8,14-trithia-4,7,9,12-tetraaza pentadeca-3,12-diene-6,10-dione

STUDY NUMBER: IRI Project # 450148; Report # 7430

SPONSOR: Rhône-Poulenc Agrochimie/France

TESTING FACILITY: Inveresk Research International/Scotland

TITLE OF REPORT: Thiodicarb 4 Week Dietary Dose Range Finding Study in Mice

AUTHOR: C Atkinson, CJ Perry, and P Hudson

REPORT ISSUED: March 8, 1991

QUALITY ASSURANCE: A Quality Assurance statement and a Good Laboratory Practices Compliance statement were provided.

EXECUTIVE SUMMARY: Under the conditions of the study, oral administration of Thiodicarb [96%] to CD-1 mice [10/sex/group] for 4 weeks via the diet at dose levels of 0, 30 ppm [♂♂ 6.2/♀♀ 8.3 mg/kg], 1750 ppm [♂♂ 346/♀♀ 491 mg/kg], 3500 ppm [♂♂ 734/♀♀ 954 mg/kg], and 7000 ppm [♂♂ 1538/♀♀ 2030 mg/kg] resulted in decreased body weight at the 7000 ppm dose level [♂♂ 80%/♀♀ 88% of control], a negative body-weight gain [-1.6 grams] overall in high-dose males, a decreased body-weight gain overall in the high-dose females [47% of control], and a decreased overall body-weight gain in males at the 3500 ppm dose level [76% of control]. Overall food consumption was slightly decreased in both sexes at 7000 ppm, which might be due to a palatability problem. There were no treatment-related effects observed on cholinesterase activity in plasma, RBC, or brain in either sex. There was a dose-related increase in (1) liver weight in females and (2) spleen weight in males. The high-dose females also displayed a decrease in ovarian weight. **The NOEL can be set at 30 ppm (♂♂ 6.2/♀♀ 8.3 mg/kg), the LOEL at 1750 ppm (♂♂ 346/♀♀ 491 mg/kg), based on increased liver weight in females and increased spleen weight in both sexes.**

This study is classified Acceptable. This study does not satisfy any guideline requirement nor was it intended to.

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A. MATERIALS:

1. Test compound: Thiodicarb; Description: fine white powder; Batch #: DA 616; Purity: 96 % listed in Analytical Certificate.

2. Test animals: Species: mouse; Strain: CD-1; Age: ≈4 weeks; Weight: 18-21 g when ordered; Source: Charles River [UK] Limited, Margate, Kent, England.

3. Statistics: Clinical chemistry, organ weight, and body weight: analyzed for homogeneity of variance using the F-max test. If group variances appeared homogeneous, a parametric ANOVA was used and pairwise comparisons were assessed by the Student's "t" test using Fisher's F-protected LSD. If variances were heterogeneous, log or square root transformations were used in an attempt to stabilize the variances; if they were still heterogeneous, a nonparametric test [Kruskal-Wallis ANOVA] was used. Organ weights: Also analyzed with respect to body weight [Snedecor & Cochran].

B. STUDY DESIGN

1. Methodology: Fifty mice/sex [acclimated for 10 days] were assigned as follows: Cages were placed on racks and an shipping box was opened and one mouse was placed in the first rack, then the next in the next cage working left to right, top to bottom of each rack. The procedure was repeated for each sex. The mice were housed individually. Each cage was assigned a treatment group by the use of computer-generated random number sequences. There were five groups, each composed of 10 mice/sex, and each [except controls] was administered the test material [30, 1750, 3500, or 7000 ppm] via the diet for 4 consecutive weeks. The controls received untreated diet. Dose levels were based on the results of an 8-day study [IRI Project # 438995]. The dietary concentration was maintained at a constant level for each treatment group. The mice were provided with feed [SQC Expanded Rat and Mouse Maintenance Diet No. 1 (Fine Ground); Special Diet Services Limited, Stepfield, Witham, Essex CM8 3AB] and water ad libitum.

   Dose preparation: The test material was incorporated into the diet by direct admixture and blended with a mixer. No other details were provided. The diets were prepared once a week and stored at room temperature. No analyses of the diets were performed during this study. Previous analytical work [IRI Project 340164] had been performed with respect to stability and homogeneity at 10 ppm and 3000 ppm.

2. Clinical Observations/Body Weight/Food/Compound Consumption: The animals were observed at least twice daily for mortality/ moribundity and evidence of systemic toxicity or ill health. A detailed [not defined] clinical examination was performed once a week. Individual body weights were determined weekly beginning one week prior to dosing and on Day 4 of dosing due to an apparent deterioration in condition. Food consumption was determined once a week for each mouse from one week prior to dosing through the dosing period. Water consumption was assessed each week by visual

inspection only. Achieved dosages were calculated weekly [calculated from the theoretical dietary concentrations but the actual body weight and food consumption data].

RESULTS

Survival and Clinical Observations

There was one death during the study [control female], but it was attributed to the bleeding procedure during week 4. Only the high-dose group [both sexes] displayed clinical signs during the study, which included a thin appearance [6 of 10 males and 8 of 10 females], hunched posture in 5 mice of each sex, and pale extremities [8/10 males and 7/10 females].

Body Weight and Food Consumption

MALES - At the lowest dose [30 ppm] level, males displayed a significant decrease in body weight at study initiation [95% of control], which persisted throughout the study [91-93% of control]. At the highest dose [7000 ppm], males displayed a significant decrease [78-83% of control] in body weight from day 4 to termination. At the next highest dose level [3500 ppm], males displayed a significant decrease [93% of control] in body weight during week 2 only. Males at the highest dose level displayed an overall negative body-weight gain [-1.6 grams], although during the latter part of the first week and during weeks 2 and 3 a positive weight gain was observed. **FEMALES** At the highest dose, females displayed a decreased body weight compared to the controls throughout the dosing period, but overall there was a positive body-weight gain [2.2 grams]. Females at the lowest dose level showed body weights that were comparable to those of the control, but overall body-weight gain in this group was 89% of the control value. At the highest dose level, females displayed a body-weight gain that was 47% of the control value.

Table 1. Mean Body Weight (% of control)

WEEK/DOSE	30 ppm	1750 ppm	3500 ppm	7000 ppm
MALES				
Pre-dose	98	99	99	100
0	95*	100	99	102
1♦	93*	98	95	78***
1	93*	98	95	80***
2	91**	97	93*	80***
3	92*	99	95	83***
4	93*	99	95	80***
FEMALES				
Pre-dose	99	102	99	97
0	100	103	99	97
1♦	99	103	94	82***
1	101	103	101	87***
2	98	102	100	86***
3	100	106	104	92*
4	98	103	100	88**

* $p<0.05$; ** $p<0.01$; *** $p<0.001$; ♦ Day 4 of dosing during Week 1

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Table 2. Mean Body-Weight Change [grams (% of control value)]♥

Interval/Group	0 ppm	30 ppm	1750 ppm	3500 ppm	7000 ppm
MALES					
PD♦-0	3.4	2.4(71)	3.8	3.3	4.0(118)
PD-Day 4	5.2	3.5(67)	5.0	4.0(77)	-1.4
0-Day 4	1.8	1.1(61)	1.2(67)	0.7(39)	-4.6
0-Week 1	2.2	1.6(73)	1.6(73)	0.9(41)	-4.4
Day 4-Week 1	0.4	0.5	0.4	0.2(50)	1.0(250)
Week 1-Week 2	1.9	1.1(58)	1.3(68)	1.2(63)	1.6(84)
Week 2-Week 3	1.1	1.4	1.9	1.7	1.9(173)
Week 3-Week 4	0.6	0.8	0.6	0.6	-0.7
Week 0-Week 4	5.8	4.9(84)	5.4	4.4(76)	-1.6
FEMALES					
PD♦-0	1.8	2.0	2.0	1.8	1.6(89)
PD-Day 4	2.7	2.6	3.0	1.6(59)	-0.8
0-Day 4	0.9	0.6(67)	1.0	-0.2	-2.4
0-Week 1	0.7	0.9	0.7	1.1(157)	-1.5
Day 4-Week 1	-0.2	0.3	-0.3	1.3	0.9
Week 1-Week 2	1.6	0.9	1.5	1.5(94)	1.3(81)
Week 2-Week 3	1.1	1.6	2.0	2.0(182)	2.2(200)
Week 3-Week 4	1.3	0.8(62)	0.8(62)	0.3(23)	0.2(15)
Week 0-Week 4	4.7	4.2	5.0	4.9	2.2(47)

♥ no statistics run; ♦PD=predose

Overall food consumption at the highest dose level was decreased compared to the control for both sexes. Additionally, males at the lowest dose level displayed decreased consumption during the first week [Table 3]. There was no discussion of whether palatability may have contributed to these differences. Water consumption was comparable among the groups for both sexes.

Table 3. Mean Food Consumption per Week [grams (% of control)]

Week/Dose	0 ppm	30 ppm	1750 ppm	3500 ppm	7000 ppm
MALES					
Predose	48	46(96)	44(92)	44(92)	45(94)
1	44	39(89)	41	44	37(84)
2	44	43	42	43	38(86)
3	42	43	44	42	44
4	51	44(88)	45(88)	47(92)	43(84)
Total	181	169(93)	172(95)	176	162(90)
FEMALES					
Predose	41	42	42	41	40
1	46	47	46	45	38(82)
2	47	44	47	43	38(81)
3	42	39(93)	47	45	46
4	49	51	51	50	50
Total	184	181	191	183	172(93)

Test Material Intake: The mean daily intake of test material for each group is listed below.

Dose level (ppm)	Table 4. Mean Daily Test Material Intake (mg/kg/day)	
	MALES	FEMALES
30	6.2	8.3
1750	346	491
3500	734	954
7000	1538	2030

3. Blood Analyses

Cholinesterase - Plasma and RBC: Blood samples were obtained from each mouse during week 4 of dosing. Samples were collected from the orbital sinus under light anesthesia. Plasma was separated from the red blood cells and all samples were frozen by immersion into liquid nitrogen. Plasma and RBC cholinesterase values were determined. Additionally, at necropsy and prior to fixation, a sample of brain [not defined further] was removed, weighed, and frozen in liquid nitrogen until analyzed for brain cholinesterase.

RESULTS

There were no apparent treatment-related effects. Although all treatment groups for the males displayed increased values for RBC cholinesterase compared to the control, there was no dose response. Females displayed decreases in RBC cholinesterase at all dose levels except the low dose, which was slightly elevated compared to the control.

Table 5. Mean Cholinesterase Values

Sex/Dose (ppm)/Parameter	Plasma ChE [iu/L]	RBC ChE [iu/L]	Brain ChE [iu/g]
MALES			
0	5764	1903	17953
30	4910(85)♦	2210(116)	17871
1750	8302*(144)	2795(147)	21464(120)
3500	6413(111)	2569(135)	17753
7000	7425(129)	2152(113)	18169
FEMALES			
0	8652	2434	22434
30	8755(91)	2758(113)	14812**(66)
1750	9727	2159(89)	17726(79)
3500	7362(76)	1718(71)	21271
7000	8066(84)	2054(84)	20337(91)

♦ (% of control); * p<0.05; ** p<0.01

4. Urinalysis: No samples were collected.

6. Ophthalmoscopy: The eyes were not examined for pathological changes.

7. Gross Pathology: All mice were subjected to gross dissection and necropsy (not clear if mice were fasted). The following organs were weighed: brain, kidneys, liver, testes and epididymides (♂), heart, spleen, lungs, ovaries (♀), and adrenal glands. The following tissues were examined in situ and preserved [all mice]: brain, kidneys, liver, testes and epididymides (♂), heart, spleen, lungs, ovaries, adrenal glands, and any abnormal tissue.

RESULTS

There were no apparent treatment-related findings at necropsy. The only findings reported were pale patches in the liver of two high-dose males and one high-dose female. **Organ Weights: LIVER** In females, there was a statistically significant increase in

absolute liver weight at the three highest dose levels, but the increase was inversely related to dose. When assessed with respect to body weight, a dose-related increase in liver weight was found. In males, increased absolute liver weight was observed at the three highest dose levels also, but only the increase at the 1750 ppm dose level wa2s statistically significant, and there was no dose response. Relative-to-body-weight liver weight was statistically significantly increased at the three highest dose levels, but again there was no dose response. **SPLEEN** Absolute spleen weight was significantly increased in females at the three highest dose levels, but the increases were not dose-related. In males, there was a dose-related increase in absolute spleen weight, which was statistically significant at the two highest dose levels. **HEART and KIDNEY** Both absolute heart and kidney weights were significantly decreased in the high-dose mice of both sexes compared to the control values, which may be attributed to the decreased body weight. **OVARIES** Both the absolute [$p<0.05$ not attained] and relative [statistically significant] ovarian weights at the high dose were decreased relative to the control value.

Dose (ppm)/ Organ	Table 6. ABSOLUTE ORGAN WEIGHT [grams (% of control)]				
	0	30	1750	3500	7000
MALES					
liver	1.99	1.83	2.34**(118)♦	2.05	1.83
spleen	0.12	0.11	0.15125)	0.16*(133)	0.18***(180)
kidney	0.61	0.58	0.60	0.57	0.49***(80)
heart	0.18	0.19	0.19	0.17	0.15**(83)
Terminal BW	33	31*(94)	33	31	27***(82)
FEMALES					
liver	1.39	1.28	1.66***(119)	1.64***(118)	1.58**(114)
spleen	0.16	0.18	0.21*(131)	0.25***(156)	0.22**(138)
kidney	0.37	0.35	0.37	0.37	0.33**(89)
heart	0.144	0.147	0.170(118)	0.145	0.124**(86)
ovaries	0.020	0.017	0.018	0.018	0.013(65)
Terminal BW	25	24	26	25	22***(88)

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

Dose (ppm)/ Organ	Table 7. RELATIVE ORGAN WEIGHT♦ [g or mg (% of control)]				
	0	30	1750	3500	7000
MALES					
liver	1.83	1.85	2.19***(120)	2.01(110)	2.17***(119)
spleen	0.114	0.114	0.142*(125)	0.157**(138)	0.197***(173)
kidney	0.58	0.58	0.57	0.56	0.55
heart	0.173	0.187	0.179	0.172	0.169
FEMALES					
liver	1.35	1.28	1.58***(116)	1.59***(118)	1.73***(128)
spleen	0.16	0.18	0.21(131)	0.24***(150)	0.23**(144)
kidney	0.368	0.351	0.358	0.360	0.361
heart	0.14	0.15	0.16	0.14	0.14
ovaries	0.021	0.017	0.020	0.018	0.010**(48)

♦ adjusted for BW at necropsy; * $p<0.05$; ** $p<0.01$

Dose (ppm)/ Organ	Table 8. RELATIVE ORGAN WEIGHT♦ [g or mg (% of control)]				
	0	30	1750	3500	7000
MALES					
liver	4.326	3.813	4.979	4.457	3.978(92)
spleen	0.261	0.229	0.319	0.348	0.391(150)
kidney	1.326	1.208	1.277	1.239	1.065(80)
heart	0.391	0.396	0.404	0.370	0.326(83)
FEMALES					
liver	3.022	2.783	3.458	3.565	3.591
spleen	0.348	0.391	0.438	0.543	0.500(144)
kidney	0.804	0.761	0.771	0.804	0.750
heart	0.313	0.320	0.354	0.315	0.282
ovaries	0.043	0.037	0.038	0.039	0.030(70)

♦ relative to brain weight [calculated by LLT; no statistics; * $p<0.05$; ** $p<0.01$

7. Histopathology: Microscopic examinations were not performed.

DISCUSSION

At the highest dose level in both sexes, there were significant decreases in both body weight and body-weight gain during the 4-week exposure period. It is not evident whether the initial decrease was due to a palatability problem. There was no effect of treatment on cholinesterase [plasma, RBC, or brain]. At necropsy, increased spleen and liver weights were observed in both sexes, but a true dose response was seen only in the males in the spleen and only in females in the liver. Additionally, ovarian weight was decreased in the high-dose females. There were no apparent gross lesions observed at necropsy in these organs.

CONCLUSION

Under the conditions of the study, oral administration of Thiodicarb to CD-1 mice [10/sex/group] for 4 weeks via the diet at dose levels of 0, 30 ppm [♂♂ 6.2/♀♀ 8.3 mg/kg], 1750 ppm [♂♂ 346/♀♀ 491 mg/kg], 3500 ppm [♂♂ 734/♀♀ 954 mg/kg], and 7000 ppm [♂♂ 1538/♀♀ 2030 mg/kg] resulted in decreased body weight in mice at the 7000 ppm dose level [♂♂ 80%/♀♀ 88% of control] at termination, negative body-weight gain overall in males at the 7000 ppm dose level [weeks 0-4], decreased body-weight gain overall in the high-dose females compared to the control females [47% of control] and a decreased overall body-weight gain in males at the 3500 ppm dose level compared to the control males [76% of control]. Overall food consumption was slightly decreased in both sexes at the highest dose level, which might be due to a palatability problem. There were no apparent treatment-related effects observed on cholinesterase activity in plasma, RBC, or brain at any dose level in either sex. There was a dose-related increase in liver weight in females and a dose-related increase in spleen weight in males. The high-dose females also displayed an increase in spleen weight, although there was no apparent dose

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response. Additionally, the high-dose females displayed a decrease in ovarian weight. **The NOEL can be set at 30 ppm (♂♂ 6.2/♀♀ 8.3 mg/kg), the LOEL at 1750 ppm (♂♂ 346/♀♀ 491 mg/kg), based on increased liver weight in females and increased spleen weight in both sexes.**

This study is classified Acceptable. This study does not satisfy any guideline requirement nor was it intended to.

TABLE 9 - Summary of Observations

7000 ppm	- ↓ body weight/body/weight gain [both sexes]
	- ↓ food consumption
	- ↑ # thin with pale extremities [both sexes]
	- ↑ absolute and relative liver weight [females]
	- ↑ absolute and relative spleen weight [both sexes]
	- ↓ absolute kidney weight [both sexes]
	- ↓ absolute heart weight [both sexes]
	- ↓ absolute ovarian weight [females]
3500 ppm	- ↓ body-weight gains initially [both sexes]
	- ↑ absolute and relative liver weight [females]
	- ↑ absolute and relative spleen weight [both sexes]
1750 ppm	- ↑ absolute and relative liver weight [females]
	- ↑ relative spleen weight [males]
	- ↑ absolute spleen weight [females]