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

OCT 28 1987

006398

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Dimethoate: 0,0 dimethyl S[N-(methylcarbamoyl) methyl]phosphorodithioate. EPA ID # 241-75
Acc. No. 265610

To: William H. Miller, PM # 16,
Insecticide/Rodenticide Branch
Cas. No. 358
Proj. No. 7-0172

From: Joycelyn E. Stewart, Ph.D. JES 10/7/87
Toxicology Branch/HED (TS-769C)

Thru: Albin B. Kocialski, Ph.D. ABK 10/28/87
Supervisory Pharmacologist
Toxicology Branch/HED (TS-769C)

10/28/87

Registrant: American Cyanamid Company
Agricultural Research Division
Princeton, N.J. 08540

Action Requested:

Review chronic/oncogenicity study in rats submitted in response to the Data Call-In for dimethoate.

Recommendation

The chronic/oncogenicity study of dimethoate in the rat was reviewed by Dynamac, who concluded that dimethoate caused significant increases in angiogenic tumors in male rats at all doses studied. The NOEL for AChE inhibition was 5 ppm and the LEL was 25 ppm. The reviewer's detailed comments are contained in the Conclusion section of the attached review. The study is classified core-Guideline.

Based on the increased incidence($p < 0.05$) of combined hemangiomas/hemangiosarcomas (all sites) observed at all dose levels in male rats, dimethoate will be presented to the Toxicology Branch Peer Review Committee in order to determine the oncogenic potential of the compound.

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006398

EPA: 68-02-4225
DYNAMAC No. 262-A
September 9, 1987

DATA EVALUATION RECORD

DIMETHOATE

Chronic Toxicity/Oncogenicity Feeding Study in Rats

APPROVED BY:

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 9-9-87

EPA: 68-02-4225
DYNAMAC No. 262-A
September 9, 1987

DATA EVALUATION RECORD

DIMETHOATE

Chronic Toxicity/Oncogenicity Feeding Study in Rats

REVIEWED BY:

William L. McLellan, Ph.D. and
Brenda Worthy, M.T.
Principal Reviewers
Dynamac Corporation

Signature: William L McLellan
Date: Sept. 9, 1987

Margaret Brower, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: Margaret Brower
Date: Sept. 9, 1987

APPROVED BY:

I. Cecil Felkner, Ph.D.
Technical Quality Control
Dynamac Corporation

Signature: I Cecil Felkner
Date: 9-9-87

Joycelyn Stewart, Ph.D.
EPA Reviewer

Signature: Joycelyn E Stewart
Date: 9/24/1987.

Albin Kocialski, Ph.D.
EPA Section Head

Signature: A. Kocialski
Date: 9/24/87

DATA EVALUATION REPORT

TOX. CHEM. NO.:
MRID NO.:

STUDY TYPE: Chronic toxicity/oncogenicity feeding study in rats.

ACCESSION NUMBER: 265610.

TEST MATERIAL: Dimethoate.

SYNONYM(S): Phosphorodithioic acid O,O-dimethyl S-[2-(methylamino)-2-oxoethyl]ester.

STUDY NUMBER(S): 70C0326/8241.

SPONSOR: Dimethoate Task Force Committee, Farmoplant S.p.A., Milano, Italy. American Cyanamid Company, Princeton, NJ.

TESTING FACILITY: BASF Aktiengesellschaft, Ludwigshafen/Rhein, FRG; Inveresk Research International, Itingen, Switzerland (Histopathology).

TITLE OF REPORT: Report on the study of the toxicity of dimethoate in rats after 24-month administration in the diet.

AUTHOR(S): Hellwig, J., Deckardt, K., Mirea, Dr., and Hildebrand, B.

REPORT ISSUED: October 9, 1986.

CONCLUSIONS:

Under the conditions of the study, dimethoate was oncogenic in male rats, causing a significant ($p < 0.015$) increase in hemangiomas and hemangiosarcomas (combined) at all 5, 25, and 100 ppm. There was a significant increase in the incidence of pheochromocytoma in males receiving 5 and 25 ppm, but no dose-related trend. Mortality was slightly increased in females receiving 100 ppm, and growth was retarded in 100-ppm males during the first half of the study. In rats receiving 100 ppm there was a slight anemia which was predominant in males and an increase in leukocytes in both sexes during the second half of the study. There was a dose-dependent lowering of cholinesterase activity in plasma, erythrocytes, and brain in both males and females receiving 25 and 100 ppm, but no effects of biological importance on cholinesterase activity at 1 or 5 ppm.

Core Classification: Core Guideline.

A. MATERIALS:

1. Test Compound: Dimethoate; description: a solid, crystalline whitish gray substance, batch No. 611A; purity: 96.71%; contaminants: list in CBI appendix, supplement Part A, Section 3.

2. Test Animals: Species: rats; strain: Wistar SPF; age: 35 days at initiation of study; weight: 112-180 g--males, 111-159 g--females; source: Karl Thomae, Biberach and Riss, FRG.

B. STUDY DESIGN:

1. Animal Assignment: After a 7-day acclimation period, the animals were assigned randomly to the following test groups:

Test group	Dose in diet (ppm)	Main study (24 months)		Satellite study[a] (24 months)	
		Male	Female	Male	Female
0 Control	0	50	50	15	15
1 Low (LDT)	1	--	--	20	20
2 Low (LDT)	5	50	50	15	15
3 Mid (MDT)	25	50	50	15	15
4 High (HDT)	100	50	50	15	15

[a]Satellite animals used for clinical chemistry, hematology, and urinalysis.

Dose Selection: Dose selection was based on a range finding study in the study laboratory, and a previously conducted chronic feeding study published by the National Cancer Institute.

2. Diet Preparation: Diet was prepared once weekly and stored at room temperature. Samples of treated food were analyzed for concentration at start of study, at weeks 4 and 12, and every 3 months thereafter.

   Results: Diet samples were analyzed for stability in a range finding study.[1] Samples of the test material were found to be stable for 7 days at room temperature. Diet samples were homogeneous with overall mean concentrations of 1.0±0.06, 4.8±0.14, 24.7±1.1, and 97.4±2.1 at diet levels of 1, 5, 25, and 100 ppm, respectively.

3. Animals received food (Kliba 343 feed) and water ad libitum. They were individually housed in wire mesh cages in an environmentally controlled room.

4. Statistics: The following procedures were utilized in analyzing the numerical data: Body weight, body weight changes, food consumption and test material intake were analyzed by an analysis of variance (ANOVA) followed by Dunnett's test. Clinical chemistry and hematology were analyzed by the Nalimov criterion and a t-test; the Chi square test was used to assess the urinalysis data. Organ weight differences were evaluated using a t-test that was generalized by Williams' test. Histopathology tumor data were subjected to the Fisher exact test.

5. A quality assurance statement was signed and dated October 8, 1986.

C. METHODS AND RESULTS:

1. Observations: Animals were inspected once daily for signs of toxicity and twice a day for mortality; they were palpated once a week for tissue masses.

   Results--Toxicity: No adverse changes were observed in the general behavior of the test animal. Although decubitus, alopecia, skin and tail lesions (see Table 1) were observed more often in the high-dose groups, the authors regarded these findings as spontaneous rather than compound-related changes.

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[1] 28-Day feeding study of dimethoate in the rat (range finding study) carried out by the Department of Toxicology, BASF Aktiengesellschaft (Project No. 30S0326/8231) from Nov. 23, 1982 to Dec. 22, 1982.

TABLE 1. Selected Clinical Findings in Rats Fed Dimethoate for 2 Years

	Males/Dose Group (ppm)					Females/Dose Group (ppm)				
	0	1	5	25	100	0	1	5	25	100
Finding	(65)[a]	(20)	(65)	(65)	(65)	(65)	(20)	(65)	(65)	(65)
Decubitus, tarsal area	6	3	12	10	14	0	0	0	0	3
Alopecia/sparse hair	1	0	0	1	3	3	1	8	7	13
Skin lesions (excluding tail)	4	0	3	7	11	0	0	2	1	2
Tail lesions	0	0	1	0	13	0	0	0	2	1

[a]Number in parenthesis equals the number of animals examined.

Results--Mortality: Table 2 summarizes mortality data and percent survival at selected intervals. At study termination, survival was between 52 and 84% in all groups. No compound-related effects were noted in the male dose groups; however, at ≈104 weeks, survival in the female high-dose (100 ppm) group was reduced (52%) when compared to the control group (68%). Evaluation of survival revealed no statistical differences.

2. Body Weight: Animals were weighed weekly for the first three months, and every 14 days thereafter.

   Results: Table 3 summarizes the body weight data of rats in the main study groups (dose levels: 0, 5, 25, and 100 ppm) and rats in the low (1 ppm) dose satellite study.

   The male rats in the high-dose (100 ppm) group had significantly ($p < 0.01$–0.05) decreased mean body weights with comparable significant decreases in mean body weight gain, during the first year of the study. No significant decreases were observed in the lower (1, 5, and 25 ppm) dose groups.

   No significant decrease in body weights were noted in the female dose groups; however, females receiving 100 ppm of the test material had slightly lower body weights with significant ($p < 0.01$ or 0.05) decreases in body weight gain during the first 8 months of the study.

   The male and female rats in the satellite dose (0, 1, 5, 25, and 100 ppm) groups showed no significant decreases in body weight or body weight gain when compared to the control groups.

3. Food Consumption and Compound Intake: Consumption was determined weekly for the first 3 months and every 2 weeks thereafter; mean daily diet consumption was calculated. Compound intake was calculated from the consumption and body weight gain data.

   Results--Food Consumption: No significant differences in food consumption were reported for dosed animals when compared to their respective control groups.

   Results--Compound Intake: The amount of test material ingested by the animals (mg/kg bw) in each dose group was calculated and found to agree with the target values.

4. Ophthalmology: Ophthalmological examinations were performed at the start of study and at 6-month intervals on all animals in the main study groups. Examinations of the fundus were performed on 10 males (day 623) and 10 females (day 616) of the control and high-dose (100 ppm) groups.

TABLE 2. Mortality and Percent Survival of Rats Fed Dimethoate for 2 Years

Dose Group[a] (ppm)	Week 13	26	52	78	≈104
			Males		
0	0(100)[b]	1 (98)	1 (98)	3 (94)	10 (84)
1	0(100)	0(100)	0(100)	2 (90)	8 (60)
5	0(100)	0(100)	2 (96)	3 (94)	12 (76)
25	1 (98)	1 (98)	1 (98)	1 (98)	11 (78)
100	0(100)	0(100)	2 (96)	3 (94)	13 (74)
			Females		
0	0(100)	0(100)	0(100)	1 (98)	16 (68)
1	0(100)	0(100)	0(100)	1 (95)	6 (70)
5	0(100)	0(100)	1 (98)	2 (96)	16 (68)
25	0(100)	0(100)	0(100)	2 (96)	21 (58)
100	0(100)	0(100)	1 (98)	4 (92)	24 (52)

[a]Group = 50 rats/group; except for the 1 ppm dose group which had 20 rats/group.

[b]The numbers in parentheses are percent survival.

TABLE 3. Representative Mean Body Weight Results[a] from Rats Fed Dimethoate for 2 Years

Dose Group (ppm)	Week	Mean ± SD Body Weights (g) at Selected Weeks						
		1	13	27	39	51	77	104
					Males			
0		209.8±15.3	467.6±42.0	553.3±49.9	598.0±57.9	628.9±63.5	691.6± 78.2	700.7± 90.3
1		212.9± 9.4	482.7±34.8	577.4±44.2	626.1±47.2	663.0±55.5	736.9± 72.2	760.8±109.3
5		209.2±13.9	469.2±41.8	555.3±55.4	607.1±66.7	641.3±80.1	712.7±100.5	716.6± 98.7
25		206.3±12.9	456.4±39.3	537.8±51.3	592.7±63.0	623.8±70.6	697.9± 87.2	711.4±108.1
100		197.0±11.9**	436.0±35.8**	513.9±50.0**	561.3±58.1**	592.7±69.0*	669.5± 83.7	709.8± 80.8
					Females			
0		156.6± 9.4	278.3±21.3	309.3±27.1	327.9±33.6	342.8±36.0	384.9± 51.0	400.5± 56.5
1		159.4±11.7	284.5±29.2	318.1±37.2	336.8±43.1	355.9±50.8	405.0± 73.8	419.6± 68.0
5		155.7± 9.7	276.8±23.2	307.2±32.2	329.6±38.2	346.1±44.1	392.2± 59.4	427.0± 69.3
25		153.2±10.5	275.9±23.3	307.4±34.9	332.7±48.6	350.8±58.1	390.2± 69.6	417.3± 64.8
100		151.5± 8.0*	269.9±19.2	297.6±22.6	316.7±30.3	337.8±39.9	383.8± 61.4	441.1± 91.2

*Significantly different from control at $p < 0.05$.

**Significantly different from control at $p < 0.01$.

[a]Results from main study dose groups (0, 5, 25, and 100 ppm) with 50 animals/sex initially; the 1-ppm dose group (satellite study) had 20 animals/sex initially.

Results: No test material-related effects were observed in any of the test animals. Mature cataracts were detected, primarily in the male animals, with equal frequency in dosed and control groups, at the 24-month examination. Examination of the fundus did not show any test material-related changes.

5. Blood was collected from 10 rats/sex/group before treatment and at weeks 4, 13, 26, 52, 78, and 104 for hematology and cholinesterase (plasma and RBC) analysis. Brain cholinesterase was performed at week 104 only. Blood samples for clinical chemistry and clotting analysis were collected at weeks 26, 52, 78, and 104. The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)†	X	Leukocyte differential count
X	Hemoglobin (HGB)†	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)†	X	Mean corpuscular HGB concentration (MCHC)
X	Erythrocyte count (RBC)†	X	Mean corpuscular volume (MCV)
X	Platelet count†	X	Reticulocyte count
X	Thromboplastin time		

Results: The authors reported signs of slight anemia in the males of the high-dose (100 ppm) group. Significant ($p < 0.01$-0.05) decreases in erythrocyte count, hemoglobin, and hematocrit (see Table 4) were observed in these parameters starting at week 26 and continuing throughout the study. Slight increases were noted in mean corpuscular hemoglobin content (MCHC) and reticulocyte counts. The erythrocyte morphology showed a higher incidence of polychromasia, anisocytosis, and microcytes in the male high-dose group which further indicated an anemic condition. No signs of anemia were reported for the lower dose (1, 5, and 25 ppm) groups.

Signs of anemia were not as prevalent in the female high-dose group (see Table 5). The erythrocyte counts did not show a consistent decrease from control. Significant ($p < 0.01$ or 0.05) decreases in hemoglobin and hematocrit were observed at weeks 52-104. Significant increases in the MCHC and a higher incidence of anisocytosis and microcytes were noted at the 24-month test interval. Animals dosed with 1, 5, or 25 ppm of the test material showed no signs of anemia.

The authors stated that the increased incidence in the abnormal erythrocyte morphology was found in both the dosed and control animals; therefore, the morphological variations were considered to be incidental and not compound related.

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†Recommended by Subdivision F (October 1982) guidelines for chronic studies.

TABLE 4. Selected Hematology Results of Male Rats Fed Dimethoate for 2 Years

Parameter/Interval	Dose Group[a] (ppm)/Mean ± SE				
	0	1	5	25	100
Erythrocyte (tera/L)[b]					
Pretest	5.5±0.12	5.7±0.11	5.9±0.10	5.8±0.09	5.3±0.15
4 Week	7.4±0.14	7.3±0.11	7.5±0.16	7.3±0.12	7.0±0.15
13 Week	7.6±0.25	7.4±0.16	7.8±0.12	7.7±0.18	7.1±0.11
26 Week	8.4±0.24	8.3±0.14	8.4±0.16	8.3±0.12	7.7±0.16*
52 Week	8.2±0.13	8.1±0.11	8.1±0.20	7.8±0.20	7.5±0.12**
78 Week	8.1±0.17	7.8±0.14	8.0±0.08	7.5±0.26	7.3±0.19**
104 Week	8.2±0.12	7.9±0.13	8.2±0.14	7.7±0.56	7.5±0.29*
Hemoglobin (mmol/L)					
Pretest	7.2±0.14	7.3±0.05	7.6±0.09	7.5±0.11	7.2±0.07
4 Week	9.3±0.11	9.2±0.11	9.5±0.15	9.2±0.13	8.9±0.13*
13 Week	9.4±0.16	9.3±0.09	9.6±0.13	9.2±0.15	8.8±0.09**
26 Week	9.4±0.22	9.3±0.09	9.4±0.11	9.2±0.14	8.8±0.11*
52 Week	9.0±0.10	8.9±0.05	9.2±0.15	8.8±0.16	8.6±0.12**
78 Week	9.1±0.13	9.2±0.10	9.1±0.08	9.0±0.17	8.5±0.17*
104 Week	8.7±0.10	8.8±0.11	8.9±0.12	8.5±0.51	8.2±0.32
Hematocrit (L/L)					
Pretest	0.32±0.01	0.33±0.00	0.34±0.00	0.34±0.01	0.32±0.01
4 Week	0.39±0.00	0.38±0.01	0.39±0.01	0.38±0.01	0.37±0.01*
13 Week	0.37±0.01	0.36±0.01	0.38±0.01	0.37±0.01	0.34±0.00*
26 Week	0.40±0.01	0.40±0.01	0.41±0.01	0.40±0.01	0.37±0.01*
52 Week	0.39±0.00	0.39±0.00	0.40±0.01	0.38±0.01	0.37±0.01**
78 Week	0.41±0.01	0.40±0.00	0.41±0.01	0.39±0.01	0.37±0.01**
104 Week	0.39±0.01	0.39±0.01	0.40±0.00	0.38±0.02	0.36±0.02*
Leukocytes (giga/L)[c]					
78 Week	5.6±0.24	5.7±0.28	5.7±0.31	6.0±0.30	6.8±0.48*

[a]Group = Nine to ten rats/group.

[b]10^{12} cells/L.

[c]10^{9} cells/L.

*Significantly different from control at $p < 0.05$.

**Significantly different from control at $p < 0.01$.

TABLE 5. Hematology Results from Selected Intervals in Female Rats Fed Dimethoate for 2 Years

Parameter/ Interval	Dose Group[a] (ppm)/Mean ± SE				
	0	1	5	25	100
Erythrocyte (tera/L)[b]					
52 Weeks	7.8±0.09	7.9±0.12	7.7±0.21	8.0±0.16	7.5±0.10*
78 Weeks	7.2±0.18	7.0±0.10	7.0±0.30	7.1±0.12	6.8±0.13
104 Weeks	7.0±0.23	6.8±0.21	7.5±0.22	7.3±0.11	6.8±0.10
Hemoglobin (mmol/L)					
52 Weeks	8.9±0.08	8.8±0.08	8.7±0.18	8.8±0.12	8.5±0.10**
78 Weeks	8.6±0.13	8.4±0.08	8.6±0.36	8.3±0.17	8.3±0.08*
104 Weeks	7.9±0.28	7.5±0.24	8.2±0.21	7.9±0.15	7.5±0.09
Hematocrit (L/L)					
52 Weeks	0.39±0.00	0.40±0.01	0.38±0.01	0.39±0.01	0.37±0.01*
78 Weeks	0.36±0.01	0.35±0.00	0.35±0.02	0.35±0.01	0.33±0.01*
104 Weeks	0.36±0.01	0.34±0.01	0.38±0.01	0.36±0.00	0.33±0.00*
Leukocytes (giga/L)[c]					
52 Weeks	4.5±0.15	4.3±0.16	5.1±0.33	4.9±0.28	5.0±0.15*
78 Weeks	4.4±0.21	4.9±0.35	4.3±0.13	4.4±0.14	5.6±0.37**
104 Weeks	4.0±0.23	5.6±0.86	4.7±0.43	4.9±0.36*	5.0±0.31*

[a]Group = Nine to ten rats/group.

[b]10^{12} cells/L.

[c]10^{9} cells/L.

*Significantly different from control at $p < 0.05$.

**Significantly different from control at $p < 0.01$.

At week 78, males in the high dose group had a significant ($p < 0.05$) increase in leukocytes (Table 4) and a higher incidence of neutrophilic polymorphonuclear granulocytes starting from week 52 and continuing to week 104. No differences in leukocyte counts were noted in the lower dose (1, 5, and 25 ppm) groups.

Females in the high-dose (100 ppm) group had significant ($p < 0.01$ or 0.05) increases in leukocyte counts (Table 5) at weeks 52-104; females in the 25 ppm dose group at week 104 also showed significantly ($p < 0.05$) higher leukocyte counts. No differences in white cell counts were noted in the lower dose (1 and 5 ppm) groups.

b. Clinical Chemistry

	Electrolytes
X	Calcium†
X	Chloride†
	Magnesium†
X	Phosphorus†
X	Potassium†
X	Sodium†
	Enzymes
X	Alkaline phosphatase (ALP)
X	Cholinesterase (Plasma, RBC and Brain)
	Creatinine phosphokinase†
X	Lactic acid dehydrogenase
X	Serum alanine aminotransferase (SGPT)†
X	Serum aspartate aminotransferase (SGOT)†
	Gamma glutamyltransferase (GGT)

	Other
X	Albumin†
	Albumin/globulin ratio
X	Blood creatinine†
X	Blood urea nitrogen†
X	Cholesterol†
X	Globulins
X	Glucose†
X	Total bilirubin†
X	Total protein†
X	Triglycerides
X	Direct bilirubin

Results: Cholinesterase activities are summarized in Tables 6 and 7.

When compared to control groups, plasma and erythrocyte cholinesterase activity were significantly ($p < 0.01$) decreased in both high-dose (100 ppm) male and female rats, from weeks 1 through 104 of study. With the exception of weeks 52 and 78 in males and week 78 in females, erythrocyte cholinesterase activity was also decreased ($p < 0.01$) in the 25 ppm dose groups. In the 5 ppm dose group, males at week 104 and females at weeks 13, 26, and 52 also showed significant ($p < 0.01$) decreases in erythrocyte cholinesterase activity. Plasma cholinesterase levels were comparable to control values in all animals at doses $\leq$25 ppm. No changes in plasma or erythrocyte cholinesterase were noted in the 1 ppm dose groups at any test interval.

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†Recommended by Subdivision F (October 1982) Guidelines.

TABLE 6. Results of Cholinesterase Activity in Male Rats Fed Dimethoate for 2 Years

Parameter/Intervals	Dose Group[a] (ppm)/Mean ± SE (Percent of Control)				
	0	1	5	25	100
Plasma (µKat/L)[c]					
Week 0	13.0±0.48	13.1±0.57(101)[b]	12.8±0.51(98)	12.8±0.43(98)	12.3±0.40(95)
4	9.6±0.70	9.8±0.76(102	9.3±0.57(97)	8.4±0.40(88)	4.4±0.28**(46)
13	12.6±1.30	13.0±1.08(103)	11.8±0.71(94)	10.3±0.53(83)	5.7±0.43**(44)
26	12.5±1.26	14.8±1.17(118)	12.9±0.33(103)	12.6±0.82(101)	6.6±0.40**(53)
52	15.9±1.55	16.6±1.29(104)	15.5±0.86(97)	13.8±0.97(86)	7.5±0.45**(47)
78	14.7±1.51	17.1±0.93(116)	15.7±0.68(107)	13.3±0.54(90)	6.8±0.69**(46)
104	14.5±1.12	17.5±1.19(121)	17.3±0.49*(119)	15.2±1.67(105)	7.6±1.63**(52)
Erythrocyte (µKat/L)					
Week 0	8.1±1.25	7.6±0.79(94)	9.5±1.61(117)	9.3±2.52(115)	9.1±1.66(112)
4	23.0±1.19	24.0±0.56(104)	20.5±0.60(89)	14.0±0.59**(61)	4.7±0.24**(20)
13	21.0±2.16	25.8±1.20(123)	17.9±2.04(85)	13.6±0.50**(65)	4.5±0.29**(21)
26	19.7±1.55	22.8±0.92(116)	19.4±0.62(98)	13.4±0.76**(68)	5.6±0.31**(28)
52	20.4±2.51	23.5±1.33(115)	20.7±1.78(101)	15.3±1.25(75)	5.1±0.32**(25)
78	16.0±1.82	13.9±0.80(87)	17.1±1.76(107)	12.2±1.22(76)	6.0±0.22**(38)
104	27.3±0.65	28.0±0.71(103)	22.5±1.14**(82)	16.3±1.14**(60)	5.3±0.42**(19)
Brain (µKat/g protein)					
Week 104	0.48±0.04	0.44±0.02(92)	0.37±0.01*(77)	0.33±0.03**(69)	0.18±0.01**(38)

[a]Group = Nine to ten rats/group.

[b]The values in parentheses are percent of control.

[c]uKat = not defined.

*Significantly different from control at $p < 0.05$.

**Significantly different from control at $p < 0.01$.

TABLE 7. Results of Cholinesterase Activity in Female Rats Fed Dimethoate for Two-Years

Parameter/Intervals	Dose Group[a] (ppm)/Mean ± SE (Percent of Control)				
	0	1	5	25	100
Plasma (µKat/L)[c]					
Week 0	15.5±0.93	15.6±0.76(101)[b]	15.8±0.68(102)	14.8±0.74(95)	16.1±0.79(104)
4	32.2±1.08	33.8±2.32(105)	34.1±1.52(106)	27.8±1.37*(86)	15.5±1.12**(48)
13	43.6±2.35	45.4±2.50(104)	46.4±3.55(106)	39.2±3.31(90)	20.3±2.00**(47)
26	48.6±2.06	54.0±3.40(111)	54.9±3.46(113)	50.6±3.45(104)	30.3±1.97**(62)
52	53.5±2.35	50.9±2.59(95)	52.8±1.86(99)	50.2±2.07(94)	24.0±1.46**(45)
78	30.7±2.76	35.7±3.25(116)	39.9±3.52(130)	30.7±4.07(100)	14.2±1.60**(46)
104	29.1±2.54	26.6±3.92(91)	31.3±1.70(108)	25.6±3.22(88)	12.9±0.84**(44)
Erythrocyte (µKat/L)					
Week 0	17.4±2.08	19.0±1.03(109)	17.2±1.08(99)	15.8±1.53(91)	19.3±2.21(111)
4	25.4±1.78	24.5±1.59(96)	19.3±1.58*(76)	15.0±0.52**(59)	5.6±0.42**(22)
13	27.4±0.98	25.6±1.66(93)	20.7±1.33**(76)	16.1±0.83**(59)	6.4±0.41**(23)
26	24.6±1.17	25.0±0.84(102)	19.8±1.13**(80)	14.1±0.38**(57)	5.8±0.34**(24)
52	27.3±2.14	28.8±1.92(105)	18.0±1.57**(66)	13.8±1.72**(51)	12.0±1.96**(44)
78	16.4±1.71	15.7±2.17(96)	15.7±1.46(96)	12.9±1.04(79)	5.8±0.43**(35)
104	24.8±0.73	23.6±2.19(95)	22.4±1.49(90)	17.9±0.77**(72)	6.0±0.21**(24)
Brain (µKat/g protein)					
Week 104	0.50±0.02	0.50±0.03(100)	0.45±0.03(90)	0.30±0.01**(60)	0.19±0.01**(38)

[a]Group = Nine to ten rats/group.

[b]The values in parentheses are percent of control.

[c]µKat = Not defined.

*Significantly different from control at $p < 0.05$.

**Significantly different from control at $p < 0.01$.

At week 104, brain cholinesterase was assessed. There were significant ($p < 0.01$) decreases in both male and female rats receiving 25 or 100 ppm of the test material; a slight, but significant ($p < 0.05$) decrease (77% of control) was noted in the 5 ppm male dose group. No changes from controls were observed in female rats dosed at 1 or 5 ppm or in male rats at 1 ppm.

The authors did not consider the decreases in cholinesterase activities in the 5 ppm groups to be of biological significance because according to Gage,[2] "an inhibition of cholinesterase activity up to 30% below the control value should be regarded as a biological threshold limit for both plasma and erythrocyte cholinesterase." The percents of inhibition below the control for erythrocyte cholinesterase activity were 18% for males at week 104 and 24, 24, 20, and 34% for females at weeks 4, 13, 26, and 52, respectively. The brain cholinesterase inhibition in males was 23%. These findings were considered to be within normal biological variation.

Other chemistry parameter changes (see Table 8) considered to be compound related were, a significant decrease in total protein in high-dose males at week 78 ($p < 0.05$) and at week 104 ($p < 0.01$), and an increase in SGPT in high-dose females at week 78 ($p < 0.01$) and week 104 ($p < 0.05$). Females dosed with 25 and 100 ppm of the test material had significantly decreased potassium levels ($p < 0.05$ and $p < 0.01$, respectively) at week 104. The authors stated that these clinical chemistry changes were of marginal significance based on comparison to historical control data and since they only occurred in one sex.

6. Urinalysis: The CHECKED (X) parameters were examined.

	Appearance†	X	Glucose†
	Volume†	X	Ketones†
	Specific gravity†	X	Bilirubin†
X	pH	X	Blood†
X	Sediment (microscopic)†	X	Nitrate
X	Protein†	X	Urobilinogen

Results: Urinalysis results for the dosed animals were comparable to controls.

7. Sacrifice and Pathology: All animals that died or were sacrificed on schedule were subject to gross pathological examination, and the CHECKED (X) tissues of animals in the main groups were collected for histological examination. In addition, these tissues

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[2]Gage, J. C. The significance of blood cholinesterase activity measurements. Residue Reviews (1967): 18, p. 158.

†Recommended by Subdivision F (October 1982) Guidelines.

TABLE 8. Selected Blood Chemistry Results from Rats Fed Dimethoate for 2 Years

Dose Group (ppm)	Week	Males/Total Protein (g/L) 78	104
0		68.028±1.141	67.803±0.534
100		65.021±0.762*	64.398±0.928**

Dose Group (ppm)	Week	Females/SGPT (μKat/L) 78	104	Females/Potassium (mmol/L) 104
0		0.830±0.046	0.701±0.029*	5.776±0.178
25		--[a]	--[a]	5.222±0.159*
100		1.104±0.081*	1.040±0.127*	5.129±0.106**

[a]Data not applicable and omitted by reviewers.

*Significantly different from control at $p < 0.05$.

**Significantly different from control at $p < 0.01$.

were also examined histologically for animals in the satellite groups that died. The (XX) organs from all surviving animals in the main study groups were weighed.

	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue		Aorta†	XX	Brain†
X	Salivary glands†	XX	Heart†	X	Peripheral nerve (sciatic nerve)†
X	Esophagus†	X	Bone marrow†	X	Spinal cord (3 levels)
X	Stomach†	X	Lymph nodes†	X	Pituitary†
X	Duodenum†	XX	Spleen†	X	Eyes (optic nerve)†
X	Jejunum†	X	Thymus†		
X	Ileum†				Glandular
X	Cecum†		Urogenital	XX	Adrenals†
X	Colon†	XX	Kidneys†		Lacrimal gland
X	Rectum†	X	Urinary bladder†	X	Mammary gland†
XX	Liver†	XX	Testes†		Parathyroids†
	Gall bladder†		Epididymides	X	Thyroids†
X	Pancreas†	X	Prostate	X	Harderian glands
			Seminal vesicle		
	Respiratory	XX	Ovaries		Other
X	Trachea†	X	Uterus†	X	Bone (sternum)†
X	Lung†				Skeletal muscle†
				X	Skin
				X	All gross lesions and masses
				X	Musculature
				XX	Animal's body after exsanguination
				X	Head (nasal cavity)

Results:

a. Organ Weights: Selected organ weights, organ-to-body weight, and organ-to-brain weight ratios are presented in Tables 9 and 10.

In the male high-dose (100 ppm) group, the absolute spleen weight, spleen-to-body and spleen-to-brain weight ratios were significantly ($p < 0.01$ or 0.05) increased over the control group. Absolute adrenal weights and adrenal-to-brain weight ratio were significantly ($p < 0.05$) increased in the 25 and 100 ppm dose groups. The authors stated that there were no correlated histopathological findings; hence, the significance of the increased spleen weights was not obvious. The authors interpreted the increased adrenal findings as incidental because the increases were more pronounced in the 25 ppm group than in the 100 ppm dose group.

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†Recommended by Subdivision F (October 1982) Guidelines.

TABLE 9. Terminal Mean[a] Body and Brain Weights; Selected Organ Weights; Organ/Body and Brain Weight Ratios for Male Rats Fed Dimethoate for 2 Years

	Dose Group (ppm)/Mean ± SD			
	0	5	25	100
Body Weight (g)	647.7±87.5	662.8±92.6	655.0±102.3	668.9±79.2
Brain Weight (g)	2.199±0.090	2.182±0.087	2.205±0.098	2.200±0.084
Spleen (g)				
Absolute Wt. (g)	1.115±0.249	1.176±0.332	1.140±0.211	1.317±0.321**
g/g Body Wt.	0.174±0.040	0.178±0.046	0.175±0.028	0.197±0.044*
g/100 g Brain Wt.	0.506±0.108	0.539±0.161	0.517±0.097	0.599±0.141**
Adrenal Gland				
Absolute Wt.	0.0935±0.0198	0.0966±0.0181	0.1043±0.0154*	0.1011±0.0206
Relative/Body Wt.	0.0146±0.0033	0.0147±0.0027	0.0158±0.0024	0.0151±0.0030
Relative/Brain Wt.	0.0426±0.0091	0.0444±0.0084	0.0472±0.0074*	0.0460±0.0090*

[a]Mean based on all surviving animals (main study groups) at termination of study.

*Significantly different from control at $p < 0.05$.

**Significantly different from control at $p < 0.01$.

TABLE 10. Terminal Mean[a] Body Weights; Selected Organ Weight; Organ/Body and Brain Weight Ratios for Female Rats Fed Dimethoate for 2 Years

	Dose Group (ppm)/Mean ± SD			
	0	5	25	100
Body Weight (g)	358.2±56.0	382.7±64.4	377.4±63.6	405.48±83.4**
Brain (g)				
Absolute Wt. (g)	1.975±0.076	1.939±0.0106	1.963±0.106	1.988±0.077
Relative/Body Wt. (g/100 g)	0.563±0.081	0.519±0.080	0.530±0.066	0.508±0.094**
Heart (g)				
Absolute Wt.	1.34±0.15	1.39±0.16	1.39±0.27	1.55±0.20**
Relative/Body Wt.	0.38±0.45	0.37±0.05	0.37±0.07	0.39±0.06
Relative/Brain Wt.	0.68±0.07	0.72±0.09	0.70±0.12	0.78±0.09**
Liver (g)				
Absolute Wt.	12.21±2.05	12.89±2.66	12.59±2.51	14.10±2.98**
Relative/Body Wt.	3.41±0.52	3.37±0.46	3.35±0.53	3.49±0.50
Relative/Brain Wt.	6.16±0.99	6.65±1.38	6.40±1.13	7.07±1.37**
Spleen (g)				
Absolute Wt.	0.745±0.224	0.807±0.248	0.771±0.246	0.885±0.296*
Relative/Body Wt.	0.208±0.055	0.214±0.072	0.203±0.051	0.220±0.060
Relative/Brain Wt.	0.377±0.112	0.416±0.125	0.391±0.117	0.444±0.144*
Ovaries (g)				
Absolute Wt.	0.0731±0.0240	0.0856±0.0315	0.0706±0.0282	0.0513±0.0101*
Relative/Body Wt.	0.0197±0.0066	0.0223±0.0076	0.0191±0.0072	0.0126±0.0037**
Relative/Brain Wt.	0.0367±0.0127	0.0444±0.0167	0.0356±0.0139	0.0258±0.0056*

[a]Mean based on all surviving animals (main study groups) at termination of study.

*Significantly different from control at $p < 0.05$.

**Significantly different from control at $p < 0.01$.

When compared to the control group, the body weight of the female high-dose (100 ppm) group was significantly ($p < 0.01$) increased and the brain-to-body weight ratio was decreased ($p < 0.01$). No significant changes were noted in the absolute brain weight. There were significant ($p < 0.01$) increases in the absolute heart, liver, and spleen weights with significant ($p < 0.05$ or 0.01) increases in the organ-to-brain weight ratios. The relative organ-to-body weight ratios were comparable to the control group. The absolute ovary weight, ovary-to-body and ovary-to-brain weight ratios were significantly ($p < 0.05$-0.01) decreased in the high-dose females. The authors reported that the increases in the heart and liver weights and the decrease in the brain-to-body weight ratio, coincided with the significant body weight increases in the female high-dose group. The increased spleen weights noted in both the high-dose males and females had no correlating histopathological findings. Similarly, the significant decreases observed in the ovary weights had no correlating gross or histopathological findings.

b. Gross Pathology: Selected findings are presented in Table 11.

The authors reported that the gross pathological findings were evaluated solely on the basis of the histopathological diagnoses, and that the distribution of gross findings were uniform throughout all groups. There were no indications of compound or dose-related changes.

c. Microscopic Pathology:

1) Nonneoplastic: Table 12 presents representative nonneoplastic histologic findings.

A significant increase in the incidence of medullary hyperplasia in the adrenal medulla was observed in the male 5-ppm dose group. The authors did not consider the increase to be a compound-related alteration because there was no dose-response relationship. All other nonneoplastic lesions observed in the dose groups were of the same type, incidence, and severity of those found in the control animals.

2) Neoplastic: Table 13 summarizes neoplastic findings. There was a nonsignificant ($p > 0.05$) increase in islet cell adenomas in the pancreas of males receiving 25 or 100 ppm when compared to concurrent controls. Exocrine adenomas of the pancreas were increased in males receiving 100 ppm, but there was no dose-response and the increase was not significant ($p > 0.05$).

There was an increase in hemangiosarcomas in the spleen and mesenteric lymph nodes of males receiving 5, 25, or

TABLE 11. Selected Gross Pathology Findings in Rats Fed Dimethoate for 2 Years

Organ/Finding	Males/Dose Group (ppm)					Females/Dose Group (ppm)				
	0	1	5	25	100	0	1	5	25	100
Spleen	(65)[a]	(20)	(65)	(65)	(65)	(65)	(20)	(65)	(65)	(65)
Enlarged	2	1	6	6	9	5	2	7	3	4
Pancreas										
Increase in circumference/ nodules	1	0	4	5	7	1	0	0	7	4
Skin										
Hair loss	1	0	0	1	3	3	0	8	6	13
Decubitus	6	3	12	10	16	0	0	0	0	2
Increase in circumference/ tumors; nodules	2	3	4	8	5	1	0	1	2	3
Tail										
Skin lesion	0	0	1	0	10	0	0	0	2	2

[a]The numbers in parentheses are the number of animals examined.

TABLE 12. Representative Nonneoplastic Histologic Findings in Rats Fed Dimethoate for 2 Years

Organ/Findings	Males/Dose Group (ppm) 0	1	5	25	100	Females/Dose Group (ppm) 0	1	5	25	100
Liver	(55)[a]	(8)	(51)	(56)	(56)	(53)	(6)	(54)	(51)	(55)
Fatty Infiltration	30	6	31	34	31	11	1	11	12	14
Lymphoid Cell Infiltration	23	2	19	18	28	5	0	1	4	2
Bile Duct Proliferation	7	2	6	6	10	8	0	7	0	4
Biliary Cyst(s)	7	0	2	8	5	8	0	9	12	13
Cell Hypertrophy	7	7	6	7	12	13	4	8	11	17
Necrosis	1	2	4	5	3	5	0	4	3	8
Mixed Cell Focus	2	0	5	1	0	1	0	6	2	7
Clear Cell Focus	16	1	8	10	8	4	0	3	1	0
Hepatocyte Nodule	7	0	4	7	5	8	0	4	1	2
Pancreas	(55)	(8)	(51)	(56)	(56)	(53)	(6)	(54)	(51)	(55)
Lymphoid Cell Infiltration	4	0	3	9	10	3	0	5	1	6
Acinar Atrophy	6	0	4	6	4	3	0	3	5	2
Inflammation	0	0	0	0	0	1	1	1	4	6
Kidney	(55)	(7)	(51)	(56)	(56)	(53)	(6)	(54)	(51)	(55)
Lymphoid Cell Infiltration	14	3	14	20	17	3	0	4	4	0
Chronic Nephropathy	17	1	20	20	16	14	1	12	15	22
Calcification, Pelv.	8	2	6	13	10	22	2	25	23	27
Urothel. Hyperplasia	5	0	6	9	11	5	2	15	8	11
Heart	(55)	(8)	(51)	(56)	(56)	(53)	(6)	(54)	(51)	(55)
Myofibrosis	26	4	21	34	26	21	3	21	16	22
Spleen	(55)	(7)	(51)	(56)	(56)	(53)	(6)	(54)	(51)	(55)
Hematopoiesis	22	2	19	18	24	21	3	24	17	25
Lymphatic Hyperplasia	5	0	4	4	2	0	0	1	4	4
Brain	(55)	(8)	(51)	(56)	(56)	(53)	(5)	(54)	(51)	(55)
Compression, Focal	0	1	2	1	2	16	3	11	11	19
Adrenal--Cortex	(55)	(7)	(51)	(56)	(54)	(53)	(6)	(54)	(51)	(54)
Congestion	7	2	9	10	9	3	3	7	11	15
Adrenal--Medulla	(55)	(8)	(51)	(56)	(55)	(53)	(6)	(44)	(41)	(51)
Medullary Hyperplasia	3	1	10*	8	7	2	0	4	7	5

(Continued)

*Significantly different than control value ($p < 0.05$).

TABLE 12. Representative Nonneoplastic Histologic Findings in Rats Fed Dimethoate for 2 Years (continued)

Organ/Findings	Males/Dose Group (ppm) 0	1	5	25	100	Females/Dose Group (ppm) 0	1	5	25	100
Testes	(55)	(8)	(51)	(56)	(56)					
Tubular Atrophy	22	5	27	21	20					
Leydig Cell Hyperplasia	27	2	25	27	30					
Ovaries						(53)	(6)	(54)	(51)	(55)
Cystic Bursa Ovarica						7	2	8	6	8
Cyst(s)						21	1	19	12	22
Skin	(55)	(0)	(51)	(56)	(56)	(53)	(0)	(54)	(51)	(55)
Abscess	0	--	3	3	2	0	--	0	0	2
Inflammation	6	--	11	9	16	3	--	4	2	10
Ulceration	2	--	0	2	8	0	--	1	2	5
Eschar Formation	0	--	1	3	2	0	--	0	0	0
Mammary Glands	(30)	(5)	(39)	(41)	(56)	(49)	(6)	(53)	(39)	(54)
Lacteal Cyst(s)	2	1	4	2	3	29	1	24	34	45

(Concluded)

[a]The numbers in parentheses are the number of tissues examined histologically.

TABLE 13. Representative Neoplastic Histologic Findings in Rats Fed Dimethoate for 2 Years[a]

Organ/Finding	Males/Dose Group (ppm) 0	1	5	25	100	Females/Dose Group (ppm) 0	1	5	25	100
Pancreas	(55)	(8)	(51)	(56)	(56)	(53)	(6)	(54)	(51)	(55)
Islet-Cell Adenoma	1	0	0	3	4[b]	0	0	0	0	0
Exocrine Adenoma	4	1	4	1	8	0	0	0	0	1
Exocrine Carcinoma	0	0	1	0	0	0	0	1	1	0
Spleen	(55)	(7)	(51)	(56)	(56)	(53)	(6)	(54)	(51)	(55)
Hemangiosarcoma	1	0	3	2	6[e]	3	0	1	0	2
Hemangioma	0	1	0	0	0	0	0	0	0	0
Mesenteric Lymph Node	(55)	(6)	(51)	(55)	(55)	(52)	(5)	(51)	(50)	(53)
Hemangioma	1	1	4	6	3	1	0	1	1	1
Hemangiosarcoma	0	0	4[c]	3	3	2	0	1	0	1
Hemangioma/hemangiosarcoma[d]	1	1	8*	9*	6	3	0	2	1	2
Metastatic Carcinoma	0	0	0	0	0	0	0	1	0	0
Metastatic Sarcoma	0	0	0	1	0	0	0	0	0	0
Kidney	(55)	(7)	(51)	(56)	(56)	(53)	(6)	(54)	(51)	(55)
Adenoma	0	0	0	0	0	0	1	0	0	1
Carcinoma	0	0	0	0	0	1	0	0	0	0
Hemangioma	0	0	0	0	0	0	0	0	1	0
Hemangiosarcoma	0	0	0	1	0	0	0	0	0	0
Lipomatous tumor	0	0	0	1	0	0	0	0	1	0
Skin	(55)	(8)	(51)	(56)	(56)	(53)	(6)	(54)	(51)	(55)
Fibroma	0	1	0	1	2	0	0	0	0	0
Malignant Schwannoma	0	1	2	2	1	0	0	0	0	3
Hemangiosarcoma	1	0	0	0	0	0	0	0	0	0
Adrenal-Medulla	(55)	(0)	(51)	(56)	(55)	(53)	(0)	(53)	(50)	(51)
Pheochromocytoma	1	--	5*	7*	3	4	--	6	2	3
Mammary Gland	(28)	(5)	(39)	(41)	(44)	(49)	(6)	(53)	(51)	(45)
Adenoma	0	0	0	0	0	4	0	1	4	1
Fibroma	0	0	0	0	0	0	0	0	1	0
Fibroadenoma	0	0	0	0	0	7	2	11	11	13
Carcinoma	0	0	0	0	0	2	0	2	1	5

*Statistically significant ($p \leq 0.05$) by Fisher's exact test; analysis by report authors.

[a]This table combines the animals in the main groups and those that died and were examined histologically in the satellite groups. The numbers of tissues examined histologically are in parentheses.

[b]One tumor was found in the six animals that died in the satellite group.

[c]Significantly different from control ($p = 0.0503$), analysis by our reviewers.

[d]Significantly different from control ($p < 0.01$), analysis by our reviewers.

[e]$p = 0.059$, Fisher exact test; $p < 0.05$ Cochran-Armitage trend test.

100 ppm, but the increases were reported not to be significant ($p \geq 0.05$) when compared to controls. The authors combined angiogenic tumors (hemangiomas and hemangiosarcomas) at all sites (lymph node, spleen, kidney, and skin) and statistically analyzed the data. The incidence in all dosed groups of males, 12/50, 11/50, and 10/50 at dosage levels of 5, 25, and 100 ppm was significantly increased ($p \leq 0.05$) when compared to controls (3/50).

The authors stated that the increase in angiogenic tumors observed was primarily due to an unusually low incidence of hemangiomas/hemangiosarcomas in control males. They reported BASF historical incidence of 29/250 (11.6%) in male Wistar rats. However, the laboratory performing the histopathology was Inveresk Research International. Their laboratory control incidence was available but was not used by the study authors for evaluation of the angiogenic tumors (see Section 14, Reviewers' Discussion).

There was a significant increase of pheochromocytomas in male rats receiving 5 and 25 ppm dimethoate but no effect in the males receiving 100 ppm. There was a significant trend for malignant schwannoma of the skin in females receiving 100 ppm; however, it was reported that when the overall incidence of malignant schwannomas was analyzed there was no significant difference between control and dosed females. Mammary fibroadenomas were increased in dosed females and adenocarcinomas of the mammary gland were increased in females receiving 100 ppm, but it was reported that the increased incidence in either tumor type was not significant nor was the overall incidence of epithelial mammary tumors significantly increased.

D. STUDY AUTHORS' CONCLUSIONS:

The study authors concluded that dimethoate administered at 1, 5, 25, and 100 ppm in the diet for 2 years was not oncogenic in male or female rats. Decreases in body weight gain were observed in both male and female high-dose groups during the first year of study. Mortality was slightly increased in the female high-dose group. Throughout the study there was a biologically significant inhibition of plasma cholinesterase activity in all high-dose animals; in addition, erythrocyte cholinesterase in both male and female rats receiving 25 or 100 ppm of the test material was significantly decreased. Brain cholinesterase analyzed at study termination was also reduced in both sexes in the two high dose groups.

The authors concluded that although there were significant decreases ($p < 0.01$ or 0.05) observed in erythrocyte cholinesterase activity in the 5 ppm male and female dose groups and reduced brain cholinesterase activity in the male dose (5 ppm) group, the decreases were not considered biologically significant. Signs of anemia were observed

in the high-dose animals and increased leukocyte counts were noted in both sexes of the high-dose groups. Other alterations in clinical chemistry parameters were noted; included were decreased total protein in high-dose males, increased SGPT in high-dose females, and decreased potassium levels in the 25 and 100 ppm female dose groups. These changes occurred between weeks 78 and 104. Organ weight differences were observed in all high-dose rats at termination; however, the changes did not correlate with any histopathological findings.

E. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS:

It is our assessment that dimethoate was carcinogenic in Wistar-Han rats; it induced a significant increase in hemangiomas and hemangiosarcomas; the incidence was significantly increased in all groups. The study authors attributed this increase to a lower than normal incidence of these angiogenic tumors in concurrent controls. However, they based this conclusion on BASF laboratory data and on published data by Deering et al. (1980) for Wistar-Han rats. Laboratory data for the laboratory performing the histopathology (Inveresk Research International) were available for review; however, these data were not used by the study authors.

The study by Deering et al. was a longevity study on 320 rats of each sex. At the end of 4 years 73.4% of the male rats had developed "lymphoangioma" of the mesenteric lymph nodes. However, at the end of 2 years when 40 of the 320 males had died, 12 rats had the tumor or 0.3% of the rats on study. Since the study design did not follow the typical protocol of a chronic feeding study, these data should not be used for comparison.

Table 14 presents the laboratory historical incidence of hemangioma and hemangiosarcoma in Wistar-Han male rats. There is an increase in hemangiomas or hemangiosarcomas in dosed males in the present study when compared to this historical incidence.

We reanalyzed the statistics for hemangiomas and hemangiosarcomas in males using a trend analysis and Fisher exact test for pairwise comparison (Table 15). There was no significant trend for hemangioma or hemangiosarcoma singly or combined in mesenteric lymph node, spleen, or all sites combined. Using pairwise comparison, the p values for hemangiosarcomas in the mesenteric lymph node in males receiving 5 ppm was 0.0503 and the p value for hemangioma/hemangiosarcoma in males receiving 5 or 25 ppm was <0.01. For hemangioma/hemangiosarcoma at all sites the p value was <0.015 in males receiving 5, 25, or 100 ppm dimethoate.

The study authors noted a significant increase in pheochromocytoma in male rats receiving 5 and 25 ppm. They reported that since there was no dose-response (insignificant by the trend test) this effect was related to an unexpectedly low incidence of pheochromocytomas in concurrent control males. The concurrent control incidence (1.8%), however, compares with laboratory control incidence ranging from 0.5-0.9% (mean 0.7% for 552 males). Therefore these data suggest an oncogenic response.

Dimethoate toxicology review

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TABLE 15. Analysis of Hemangiomas/Hemangiosarcomas at all Sites in Male Rats Fed Dimethoate for 2 Years[a]

	Dose Group (ppm)			
	0	5	25	100
Incidence	3/55	11/51	12/56	12/56
p value[b]		0.014	0.012	0.012

[a]Includes all animals examined histologically in the main groups as well as those in the satellite groups that died and were examined histologically. The tumors are counted hierarchically for spleen, kidney, lymph node, and skin. The numerator is the number of animals with either neoplasm, not the number of neoplasms.

[b]Fisher exact test.

Our reviewers reanalyzed the incidence of islet cell adenomas in the pancreas of males including one adenoma found in a high-dose satellite group male; there was no significant increase ($p > 0.05$). We assess that there was no carcinogenic response in females. The concurrent control incidence of fibroadenoma and carcinoma of the mammary gland, 14 and 4%, respectively, was comparable to those found historically (18.7 and 4.5%).

We agree with the study authors' assessment that the decreases in erythrocyte and brain cholinesterase activity in males receiving 5 ppm and in erythrocyte cholinesterase of females receiving 5 ppm were not of biological significance. The other alterations in clinical chemistry parameters and changes in organ weights were of marginal toxicologic importance.

Based on cholinesterase activity inhibition, on decreased weight gain, and finding of anemia in males, 100 ppm (highest dose tested) was an MTD. Based on cholinesterase activity inhibition, the NOEL was 5 ppm, equivalent to approximately 0.25 mg/kg/day.