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

005942

JUN 16 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Dimethoate: Review of Two Mutagenicity Studies
EPA Reg. No. 241-75. Record No. #162367.
Accession No. 259921.

TO: William H. Miller, PM #16
Registration Division (TS-767)

FROM: Karen L. Hamernik, Ph.D., Pharmacologist KLH 6/16/87
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769)

THRU: Albin B. Kocialski, Ph.D., Supervisory Pharmacologist
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769) ABK 6/16/87

Tox Chem File No. 358

The two mutagenicity studies listed below, were reviewed by the Dynamac contractor and were then secondarily reviewed by Irving Mauer, Ph.D., Toxicology Branch geneticist. The final versions of the study reviews are attached.

1. In vivo Bone Marrow Cytogenetics Rat Metaphase Analysis. Dimethoate Technical. Pharmakon Research Int. Inc., Waverly, PA, PH 315-AC-001-84, August 29, 1985. Accession No. 259921. The study was found to be acceptable.

2. Dominant Lethal Study with Dimethoate Technical in the Mouse. RCC Research and Consulting Company AG, Itingen, Switzerland, Study No. 039003, July 24, 1985. Accession No. 259921. The study was found to be acceptable.

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OK J. Mauer 5-1-87

EPA: 68-02-4225
DYNAMAC No.: 262-C1
March 19, 1987

005942

DATA EVALUATION RECORD

DIMETHOATE

Mutagenicity--Dominant Lethal Assay in Mice

STUDY IDENTIFICATION: Becker, H. and Schafroth, P. Dominant lethal study with Dimethoate technical in the mouse. (Unpublished study No. 039003 prepared by RCC Research and Consulting Company AG; Itingen, Switzerland for Dimethoate Task Force, Farmoplant, Milano, Italy; dated July 24, 1985.) Accession No. 259921.

APPROVED BY:

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

Signature: I. Cecil Felkner

Date: 3-19-87

1. CHEMICAL: Dimethoate Technical.

2. TEST MATERIAL: Dimethoate technical, batch No. 611A, was described as a white crystalline solid with a purity of 96.89%. The test material was stored at 4°C in the dark.

3. STUDY/ACTION TYPE: Mutagenicity--Dominant lethal assay in mice.

4. STUDY IDENTIFICATION: Becker, H. and Schafroth, P. Dominant lethal study with Dimethoate technical in the mouse. (Unpublished study No. 039003 prepared by RCC Research and Consulting Company AG; Itingen, Switzerland for Dimethoate Task Force, Farmoplant, Milano, Italy; dated July 24, 1985.) Accession No. 259921.

5. REVIEWED BY:

Brenda Worthy, M.T.
Principal Reviewer
Dynamac Corporation

Signature: Brenda Worthy
Date: 3-19-87

Nancy E. McCarroll, B.S.
Independent Reviewer
Dynamac Corporation

Signature: Nancy E. McCarroll
Date: 3-19-87

6. APPROVED BY:

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

Signature: I. Cecil Felkner
Date: 3-19-87

Karen Hamernik, Ph.D.
EPA Reviewer

Signature: KBK for KH
Date: 6/16/87

Albin Kocialski, Ph.D.
EPA Section Head

Signature: A. Kocialski
Date: 6/16/87

7. CONCLUSIONS:

A. Under the conditions of this assay, the oral administration by gavage of 5, 10, and 20 mg/kg dimethoate for 5 consecutive days did not elicit a dominant lethal effect in the offspring of male mice (15/group) which were sequentially mated (2 females/mating) for 8 weeks. The dose-related decrease in body weight gain observed at the conclusion of dosing suggests that dimethoate was assayed up to an appropriate concentration.[1]

B. The study is acceptable.

Items 8 through 10--see footnote 2.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. Test Material: Dimethoate technical, batch No. 611A, was described as a white crystalline solid with a purity of 96.89%, and was stored at 4°C in the dark. The test material was dissolved in distilled water and was reported to be stable in the solvent for 1 day.

2. Test Animals:

a. Source: Seven-week-old male and female, NMRI Han. KFM, outbred, SPF, mice, obtained from KFM, Kleintierfarm Madoerin AG, Fuellinsdorf, Switzerland, were used on study. Shipments of female mice were obtained at each mating period so that all females were 8 weeks old when mated.

b. Maintenance: Animals, identified by coded color spots, were acclimated to laboratory conditions for at least 1 week and housed in an air conditioned room controlled for air exchange (10-15 air changes/hour), temperature (22±2°C), relative humidity (55±10%), and light (12 hour light/dark cycle) with 8 hours of music/light period. The mice were fed standard Kliba 343 pelleted diet, and tapwater was available ad libitum.

c. Group Assignment: Fifteen male mice were assigned to each of the test material, solvent or positive control groups by a randomization algorithm.

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[1] Green, S., Auletta, A., Fabricant, J., Kapp, R., Manandhar, M., Shea, C., Springer, J., and Whitfield, B. Current status of bioassays in genetic toxicology--the dominant lethal assay. Mutat. Res. 154(1985): 49-67.

[2] Only items appropriate to this DER have been included.

3. Dose Selection: Dose selection was made by the sponsor based on an acute LD_{50} (the route of administration was not reported but was assumed to be oral) study in mice performed by RCC (project 038981). The LD_{50} results showed that there was 0% mortality at 10, 20, 40, and 80 mg/kg; 50% mortality at 160 mg/kg; and 100% mortality at 320 mg/kg. The 20 mg/kg dose caused sedation, dyspnea and curved body position.

   Based on these findings, the doses selected for the dominant lethal assay were 5, 10, and 20 mg/kg body weight.

4. Test Compound Administration: Fifteen males per group were administered the appropriate dose of the test material or solvent control at a volume of 10 mL/kg by oral gavage for 5 consecutive days. The last dose was received on the initial day of mating. The positive control, methylmethane sulfonate (MMS) at 80 mg/kg, was administered ip on the initial day of mating at a volume of 5 mL/kg.

5. Dominant Lethal Assay

   a. Mating: Each dosed male was housed with two randomly selected untreated virgin females for 7 days. At the end of each mating interval, the females were removed and replaced with two untreated virgin females. Mating was repeated for 8 consecutive weeks. After the last mating interval, males were sacrificed by cervical dislocation and discarded.

   b. Animal Observations: Mated females were examined daily for vaginal plugs. The day the plug was observed was designated as day 0 of gestation.

      All animals were observed twice daily for abnormalities and mortality. The body weights of males were recorded prior to dosing and weekly after the last dose was administered.

   c. Scoring Progeny: Females were sacrificed by cervical dislocation on day 14 after mating. The uteri were examined for the number of live and dead embryos. Uteri without visible implants were examined for early embryonic resorptions using a solution of ammonium sulphide. Fertility indexes, mating, pregnancy, implantation rate and number and percentages of live and dead embryos were calculated for each week. Additionally, the percentage of the dominant lethal factors (FL%) was calculated weekly using the formula of Ehling et al.[3]

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[3] Ehling, U. H., Machema, L., Buselmaier, W., Dycka, J., Frohberg, H., Kratochvilova, J., Lang, R., Lorke, D., Muller, D., Peh, J., Rohrborn, G., Roll, R., Schulze-Schencking, M., and Wiemann, H. Standard protocol for the dominant lethal test on male mice set up by the work group "Dominant Lethal Mutations of the ad hoc Committee Chemogenetics." Arch. Toxicol. 39(1978): 173-185.

6. Statistical Evaluation: Dunnett's test was used to evaluate the body weight data of the males. The proportion of live and dead embryos at each mating interval was analyzed by Fisher's exact test; significance was judged at $p = <0.01$.

B. Protocol: See Appendix A.

12. REPORTED RESULTS:

A. Male mice were dosed orally for 5 consecutive days with 5, 10, and 20 mg/kg of dimethoate. The body weight gains for the low- and mid-dose groups were comparable to the control. The mean body weight of the high-dose group on day 5 of dosing (35 ± 2 g) was significantly lower than on day 1 of dosing, as compared to an increase in body weight gain over the 5 days in the control group (38 ± 2 g).

No other signs of toxicity were noted during the entire study.

No adverse effects were noted at any dose in mating frequency, pregnancy rates or implantation ratios. The number of dead embryos for all doses were comparable to the controls at all intervals. By contrast, the positive control MMS at 80 mg/kg caused statistically significant effects on the preimplantation loss and an increase in embryonic deaths at the first and second mating periods; thereby demonstrating dominant lethal induction.

Representative results are presented in Table 1.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The authors concluded that "The oral administration of Dimethoate technical to sexually mature male mice did not adversely affect the mating ratio of the paired mice, or the pregnancy and implantation rates of the female mice. No detectable dominant lethal mutations were noted in subsequent test matings under the described conditions of this study."

B. A quality assurance statement was signed and dated September 12, 1985.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

We assess that the study was conducted appropriately, and that the authors interpreted their data correctly. At the doses tested (5, 10, and 20 mg/kg) Dimethoate did not cause an increase in the number of embryonic deaths per female. It was concluded that the decrease in body weight gain noted in the high-dose group, during the 5-day

TABLE I. Representative Results from Selected Mating Weeks of the Dominant Lethal Assay in Mice Exposed to Dimethoate

Mating Week	Substance (mg/kg)	Fertility Index (%)[a]	Total Implants	Live Implants	Live Implants/ Female	Embryonic Deaths	% Deaths	% Dominant Lethal Factor[b]
1	Distilled water	29/29(100)	424	402	13.9	22	5.2	—
	Methylmethane sulfonate	24/29 (85.7)	243	157*	6.5	86	35.4*	53.2*
	Dimethoate[c]							
	5	25/30 (83.3)	345	320	12.8	25	7.2	7.9
	10	25/30 (83.3)	363	348	13.9	15	4.1	0
	20[d]	24/28 (85.7)	316	284	11.8	32	10.1	15.1
2	Distilled water	29/30 (96.7)	369	351	12.1	18	4.9	--
	Methylmethane sulfonate	25/29 (86.2)	232	88*	3.5	144	62.1*	71.1*
	Dimethoate							
	5	26/27 (96.3)	349	327	12.6	22	6.3	4.1
	10	27/30 (90.0)	376	353	13.1	23	6.1	8.3
	20	29/30 (96.7)	383	349	12.0	34	8.9	0.8
3	Distilled water	28/29 (96.6)	346	321	11.4	25	7.2	—
	Methylmethane sulfonate	28/29 (96.6)	332	308	11.0	24	7.2	4.3
	Dimethoate							
	5	24/28 (85.7)	280	262	11.4	18	6.4	0.9
	10	29/30 (96.7)	414	391	13.5	23	5.6	17.4
	20	29/29(100)	349	337	11.6	12	3.4	0.9

[a] $\text{Fertility Index} = \frac{\text{No. of Pregnant Females}}{\text{No. of Females Mated}} \times 100.$

[b] $\text{\% Dominant Lethal Factor} = 1 - \frac{\text{Live Implants/Females in Test Group}}{\text{Live Implants/Females in Control Group}} \times 100.$

[c] Oral gavage, five consecutive administrations.

[d] Significant decreases in body weight gain on the last day of treatment compared to the control by Dunnett's test; decreases in body weight gain also observed in 5 and 10 mg/kg group.

*Significantly different from control at $p < 0.05$ by Fisher's test.

Note: Results from Mating Periods 4–8 were comparable to the solvent control; data were therefore not presented.

dosing interval, was sufficient evidence in this test system that a maximum tolerated dose was achieved.[4] Response by the positive control, MMS, demonstrated the sensitivity of the assay to detect clastogenicity.

Item 15--see footnote 2.

16. CBI APPENDIX: Appendix A, Materials and Methods, CBI pp. 11-16.

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[4] Green, S. et al., Mutat. Res. 154(1985): 49-67.

APPENDIX A

(Materials and Methods)

Dimethoate toxicology review

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Pages 10 through 15 are not included in this copy.

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___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

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EPA: 68-02-4225
DYNAMAC No. 262-C2
March 19, 1987

005942

DATA EVALUATION RECORD

DIMETHOATE

Mutagenicity--Cytogenetic Assay in Rat Bone Marrow

STUDY IDENTIFICATION: San Sebastion, J. R, Naismith, R. W., and Matthews, R. J. In vivo bone marrow cytogenetics rat metaphase analysis: Dimethoate CL 12,880. (Unpublished study No. PH 315-AC-001-84 prepared by Pharmakon Research Int. Inc., Waverly, PA, submitted by the Dimethoate Task Force, Farmoplant, S.p.A. Registration Dept., Milano, Italy; dated August 29, 1985.) Accession No. 259921.

APPROVED BY:

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

Signature: I. Cecil Felkner

Date: 3-19-87

1. CHEMICAL: Dimethoate; O,O-dimethyl S-, (methyl carbamoyl) methyl phosphate.

2. TEST MATERIAL: Dimethoate, CL 12,880, lot No. 611A, was described as a white crystalline solid with a purity of 96.89%.

3. STUDY/ACTION TYPE: Mutagenicity--cytogenetic assay in rat bone marrow.

4. STUDY IDENTIFICATION: San Sebastion, J. R, Naismith, R. W., and Matthews, R. J. In vivo bone marrow cytogenetics rat metaphase analysis: Dimethoate CL 12,880. (Unpublished study No. PH 315-AC-001-84 prepared by Pharmakon Research Int. Inc., Waverly, PA, submitted by the Dimethoate Task Force, Farmoplant, S.p.A. Registration Dept., Milano, Italy; dated August 29, 1985.) Accession No. 259921.

5. REVIEWED BY:

Brenda Worthy, M.T.
Principal Reviewer
Dynamac Corporation

Signature: Brenda Worthy
Date: 3-19-87

Nancy E. McCarroll, B.S.
Independent Reviewer
Dynamac Corporation

Signature: Nancy E. McCarroll
Date: 3-19-87

6. APPROVED BY:

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

Signature: I. Cecil Felkner
Date: 3-19-87

Karen Hamernik, Ph.D.
EPA Reviewer

Signature: KBK for KH
Date: 6/16/87

Albin Kocialski, Ph.D.
EPA Section Head

Signature: A. Kocialski
Date: 6/16/87

7. CONCLUSIONS:

A. Under the conditions of the assay, Dimethoate tested at 15, 75, and 150 mg/kg ip did not cause a clastogenic response in the bone marrow of male or female rats harvested 6, 16, and 24 hours after treatment. Mitomycin C the positive control at 5 mg/kg, demonstrated the sensitivity of the assay system to detect a clastogenic effect.

B. The study is acceptable.

Items 8-10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. Test Material: Dimethoate, CL 12,880, lot No. 611A, was described as a crystalline solid with a purity of 96.89% and was stored in the dark at 4°C. The test material was dissolved in 0.9% saline, the solvent control.

2. Test Animals: Sixty-five male (178-201 g) and 65 female (141-165 g) Sprague-Dawley rats, obtained from Blue Spruce Farms Inc., Atatamont, NY, were randomized by body weight, assigned to treatment group and ear tagged on day 6 of a 13-day acclimation period. Animals were individually housed in stainless steel cages in an environmentally controlled room (22±3°C temperature and 30-70% humidity) on a 12-hour light/dark cycle. Food and water were available ad libitum.

3. Dose Selection: Based on a preliminary range-finding study, that assessed the effects of the test material on the animal (toxicity) and target cell (bone marrow), the doses selected for the cytogenetic assay were 15, 75, and 150 mg/kg.

4. Treatment Groups: Ten animals (five/sex/group/sampling interval) were assigned to each test material, positive control (Mitomycin C at 5 mg/kg) and solvent control (0.9% saline) group.

5. Compound Administration: Dosing solutions were prepared just prior to administration. The test material and solvent control groups received a single i.p. dose at a volume of 10 mL/kg of body weight; the positive control dose was administered at 5 mL/kg of body weight. Two and one-half hours before sacrifice, each animal received a single i.p. injection of colchicine (0.4 mg/kg) at a volume of 10 mL/kg. Animals were observed for toxic signs immediately after dosing and prior to colchicine administration.

6. Animal Sacrifice/Bone Marrow Harvest and Slide Preparation:

a. Animal Sacrifice: Animals in the test material and solvent control groups were sacrificed at 6, 16, and 24 hours after dimethoate or saline administration by CO_2 inhalation. The positive control group was sacrificed by CO_2 inhalation 24 hours after receiving Mitomycin C.

b. Bone Marrow Harvest: Bone marrow was harvested from both femurs of each animal by aspiration in prewarmed (37°) phosphate buffered saline (PBS) pH 7.0. Cells were centrifuged, resuspended in prewarmed hypotonic KCl, and recentrifuged. The marrow pellet was fixed in methanol:glacial acetic acid (3:1) and resuspended. Cells were refrigerated overnight.

c. Slide Preparation: Cells were resuspended in fresh fixative, and a drop of the cell suspension was placed on a glass slide. Slides were stained in 3% Giemsa, rinsed, air dried, mounted, and randomly coded.

7. Cytogenetic Analysis: If possible, five-hundred metaphase cells per treatment group (50/animal) were scored for the presence of chromosome aberrations. See Appendix A for characterization of chromosomal aberrations.

8. Statistical Analysis: The proportion of aberrant versus normal metaphases was analyzed by Chi-square ($p \leq 0.05$) analysis. Mean breaks/cell/rat were analyzed by a one way analysis of variance (ANOVA) at $p < 0.05$. To determine the significance ($p < 0.05$) of the positive control, a t-test was performed.

B. Protocol: See Appendix A.

12. REPORTED RESULTS:

A. Preliminary Range-Finder Study:

1. Dimethoate was administered ip at doses of 16.5, 32.5, 75, and 150 mg/kg to two male and two female Sprague-Dawley rats/group. Two to three hours after dosing, each animal received an ip injection of colchicine. Animals were sacrificed at 24 hours after dose administration.

Animal Observation: Animals in the two lower dose groups did not show any toxic signs after test material dosing or prior to receiving colchicine.

The mid-dose (75 mg/kg) rats showed no toxic effects after test material dosing; however, prior to the colchicine injection, one male exhibited piloerection.

Immediately after test material dosing, animals in the high dose group exhibited decreased body tone and activity; two rats exhibited piloerection prior to colchicine administration.

2. Two groups of rats (2 rats/sex/group) were administered ip 75 mg/kg of the test material and received an ip dose of colchicine two hours after dosing. Groups of animals were sacrificed at 6 hours or 16 hours post treatment.

   Animal Observation: No toxic signs were observed in the animals at the 16 hour sacrifice. All animals at the 6 hour sacrifice exhibited decreased body tone and activity and slight tremors prior to receiving colchicine. No animals died on study.

   To determine the cytotoxic effect of the test material, bone marrow slides were prepared. One thousand cells/animal were examined for metaphases, and the mitotic index was calculated. The test material did not produce a cytotoxic effect on the target cell at any dose level at the 24 hour harvest. No cytotoxic effects were observed in the 75 mg/kg dose group at the 16 hour harvest. Results for the 75 mg/kg dose group at the 6 hour harvest were not available because of poor slide quality; cells were not scorable. Representative results of the mitotic indexes are presented in Table 1. Dimethoate was insoluble at 200 and 300 mg/mL; therefore, it was not assessed at a dose higher than 150 mg/kg.

   Based on this preliminary data, doses selected for the cytogenetic assay were 15, 75, and 150 mg/kg.

B. Cytogenetic Assay:

   1. Animal Observation:

      a. Six Hour Sacrifice: No toxic signs were observed in the low dose group. Decreased body tone and activity was observed in all animals of the mid-dose prior to colchicine administration and in the high-dose group immediately after test material dosing and prior to colchicine administration. In addition, slight tremors were noted in 3/5 males and 4/5 females, and salivation was noted in 3/5 males and 1/5 females of the high-dose groups.

      b. Sixteen hour sacrifice: No toxic signs were observed in the low-or mid-dose groups. Prior to receiving colchicine all animals, in the high dose groups, exhibited poor grooming, salivation and decreased body tone and activity. Tremors in 1/5 males and chromodacryorrhea in 1/5 males were also noted.

TABLE 1. Representative Results from the Preliminary Range Finding Study with Dimethoate

Substance	Dose (mg/kg)	Harvest Time (Hrs.)	No. Rats[a]	No. Cells Scored	No. Metaphases	Mitotic Index (%)
Negative Control						
Untreated Cells	0	24	4	4000	93	2.3
Solvent Control						
0.9% Saline	10mL	24	4	4000	51	1.3
Test Material						
Dimethoate	150[b]	24	4	4000	70	1.8
	75	6[c]	-	--	--	--
		16	4	4000	71	1.8
		24	4	4000	77	1.9

[a]Number of rats = 2 males and 2 females/group

[b]Highest dose soluble in 0.9% NaCL; results for lower doses (16.5, 32.5, and 75 mg/kg) were comparable to the negative control.

[c]Due to the poor quality of the slides, cells harvested at 6 hrs. were not scored.

c. Twenty-Four Hour Sacrifice: No toxic signs were noted in the low dose groups or in the females in the mid-dose group; however, the males in the mid-dose group exhibited poor grooming before receiving colchicine. At the high-dose, salivation, decreased body tone, and activity were noted in 4/5 males and in 4/5 females prior to receiving colchicine.

In the positive control group 1/5 males showed decreased body tone and activity prior to colchicine administration. The remaining animals showed no toxic effects.

d. Post Mortem Observation: Spasmodic twiching of the extremities and muscles were observed in the animals of the high-dose groups at all sacrifice intervals. The intensity seemed to depend upon the recovery time from treatment at 6, 16, and 24 hours.

2. Bone Marrow Results: No statistically significant increases in the proportion of aberrant versus normal metaphases for the dosed groups compared to controls were seen. No statistically significant increases in mean breaks/cell were noted in the test material groups when compared to controls. Representative results are presented in Table 2.

The positive control, Mitomycin C was significantly ($p = < 0.05$) increased over the solvent control.

13. STUDY AUTHORS' CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The study authors concluded that "Based on the results of this assay Dimethoate is judged negative in the In Vivo Bone Marrow Cytogenetics Rat Metaphase Analysis Assay under the conditions of this laboratory."

B. A quality assurance statement was signed and dated May 23, 1985.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

A. We assess that the study authors interpreted the data correctly, and that Dimethoate at 3 doses ranging from 15 to 150 mg/kg did not cause an increase in chromosomal aberrations in the bone marrow of male or female rats.

Although, the test material did not demonstrate a cytotoxic effect in the target cells, there were toxic effects noted in the high-dose group. The test material was assayed to its limit of solubility, therefore, the doses selected were adequate.

TABLE 2. Representative Results from the Cytogenetic Assay in Rat Bone Marrow with Dimethoate

Substance	Dose (mg/kg)	Harvest Time (Hrs.)	No. Rats[a]	No. Metaphases Scored	No. Cells with one or more Aberrations	Mean Proportion Aberrant Cells ± SD	% Aberrant Cells	Total Breaks	Mean Breaks/Cell[b] ± SD
Solvent control									
0.9% Saline	10 mg/mL	6	10	500	6	0.012 ± 0.013	1.2	6	0.012 ± 0.013
		16	10	500	6	0.012 ± 0.016	1.2	6	0.012 ± 0.016
		24	10	500	1	0.002 ± 0.006	0.2	1	0.002 ± 0.006
Positive Control									
Mitomycin C	5	24	10	475[c]	360	0.766 ± 0.117	76.6*	1782	3.78 ±1.624**
Test Material									
Dimethoate	150[b]	6	10	468[e]	0	0.000 ± 0.000	0.0	0	0.000 ± 0.000
		16	10	500	3	0.006 ± 0.009	0.6	3	0.006 ± 0.009
		24	10	500	6	0.012 ± 0.013	1.2	6	0.012 ± 0.013

[a]No. rats = 5 males and 5 females/group.

[b]Mean breaks/cell was calculated from mean breaks/cell/animal.

[c]One animal had only 25 scorable cells.

[d]Highest dose tested; lower dose (15, and 75 mg/kg) results were comparable to the solvent control.

[e]One animal had only 18 scorable cells.

*Significant at $p \leq 0.05$ by Chi-Square analysis.

**Significant at $p \leq 0.05$ by t-test method.

The positive control (Mitomycin C at 5 mg/kg) demonstrated the sensitivity of the assay to detect a clastogenic effect.

Item 15 see--footnote 1.

16. CBI APPENDIX: Appendix A: Protocol: Materials and Methods for Range Finder CBI pp. 1-3 and Cytogenetics Assay CBI pp. 2-8 and 14.

APPENDIX A

(Protocol)

Dimethoate toxicology review

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Pages 26 through 36 are not included in this copy.

The material not included contains the following type of information:

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