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

002262

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Date: NOV 24 1981

Subject: EPA Registration No. 476-2107. Review of a 13-Week Inhalation Toxicity Study and Reproduction-Fertility Study of R-4572 in the Rat.
Tox. Chem. No. 444
EPA Acc. No. 241965

From: Thomas S.S. Mao, Ph.D. Thomas S.S. Mao
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Thru: William L. Burnam
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Toxicology Branch/HED (TS-769)

Applicant: Stauffer Chemical Company
400 Farmington Avenue
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Action Requested:

Review of the results of a 13-week inhalation toxicity study and reproduction-fertility study of R-4572 in the rat was requested by the Registration Division for inclusion in the file for Ordram.

Comments:

1. The 13-week inhalation toxicity study is considered Core minimum data. The reproduction-fertility study of R-4572 in the rat was reasonably carried out and reported. The results of both studies are acceptable in support of the registration of Ordram.

2. The results of these two inhalation studies clearly indicated that technical Ordram has the adverse effects on the testes (particularly decrease in size), and abnormality (morphological change) and population (decrease in numbers) of spermatoza in male rats at the relatively low dose levels tested. Also, under review at present are oral antifertility studies in rabbits, mice and rats with technical Ordram. When the reviews are completed, Toxicology Branch will discuss in details about Ordram effects in the testes and spermatoza, which are of potentially serious concerns to any human exposure, in a separate memorandum. In the interim, Toxicology Branch recommends that Registration Division not register any further

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uses of either technical or formulation products of Ordram in order to avoid any possibly additional field worker exposure to this chemical.

Review of the Submitted Experiments

I. A 13-Week Inhalation Toxicity Study (By Raymond E. Schroeder, George M. Rusch and William E. Rinehart of Bio/dynamics Inc., Division of Biology and Safety Evaluation, East Millstone, New Jersey 08873; Project No. 7153 of December 13, 1979.)

A. Experimental

(1) A clear dark brown liquid product of Stauffer Chemical Company (Ordram Technical R-4572, Lot WRC 4921-8-5, GGB-1802) was used as the test material. Eighty rats (10/sex/group) of Sprague-Dawley CD(R) species, purchased from Charles River Breeding Labs., Wilmington, Mass., were used as the test animals. The age of the rats at initial exposure was 56 days. The mean body weight immediately prior to exposure was 263 (237-290) grams for males and 180 (163-206) grams for females.

(2) Eighty rats (40 males and 40 females) were equally divided males and females into 4 groups for exposure to four concentrations of test material including none (control), 2 mg, 10 mg and 50 mg/m^3 in this experiment as follows:

			Number of Animals[1]					
				Lab Test				
Group[2]	Concentration	Exposure Time	Exposure	P.E.[3]	Week 5	Terminal	Necropsy	Histo-Pathology
I	None (Control)	6 Hr/Day 5 Day/Wk 3 Months	20	10	10	A.S.[4]	20	20
II	2 mg/m^3	6 Hr/Day 5 Day/Wk 3 Months	20	10	10	A.S.	20	20
III	10 mg/m^3	6 Hr/Day 5 Day/Wk 3 Months	20	10	10	A.S.	20	20
IV	50 mg/m^3	6 Hr/Day 5 Day/Wk 3 Months	20	10	10	A.S.	20	20
		TOTALS:	80	40	40		80	80

[1]Equally divided males and females.
[2]These animals were simultaneously exposed with the animals for Bio/dynamics project no. 78-2346.
[3]P.E. = Pre-exposure.
[4]A.S. = All survivors.

(3) For the Group II exposures, the test material was placed in a 1 cubic centimeter glass syringe attached to a Sage syringe pump Model 352. The test material was dripped down the side of a four-neck flask heated by a heating mantel and a variable transformer to achieve complete volatization. However, the test material was placed in the 20 cubic centimeter glass syringes and Sage syringe pump models 352 and 341 and variable transformers were used for Groups III and IV, respectively. The feed rate of the test material was varied in order to provide the final exposure concentrations for the test groups. The glass and stainless steel exposure chambers in which the animals were exposed were operated dynamically at a flow rate of 245 liters per minute. This flow rate provided one air change every 4.1 minutes and a 99% equilibrium (t_{99}) of 18.9 minutes.

(4) Three samples per day were drawn from each exposure chamber using Porapak-Q adsorption tubes. The amount of test material trapped on each tube was determined by extraction followed by gas chromatographic analysis.

The concentration of test material in the chamber was calculated from the volume of chamber air sampled and the amount of test material collected. Furthermore, one sample was drawn per day from each exposure chamber using a high efficiency filter so that it would be analyzed for the possible presence of an aerosol in the chamber during the first week of experiment. The particle size was then analyzed using the Rayco Portable Particle Monitor, Model 218, for measuring particles between 0.5 and 10.0 micrometers in diameter. Two additional samples were drawn simultaneously from each exposure chamber once a week, one from above and one from below the test animals, in order to measure the distribution of the test material.

(5) The animals were observed daily for abnormal signs. Individual body weights were recorded weekly from eight days prior to exposure through termination. Opthalmoscopic exmination was carried out on all survivors (10/sex/group) during the week 13.

(6) Laboratory studies, including hematology (hemoglobin, red and white cell counts, etc.), blood chemistry (serum enzymes, protein, minerals, etc.) and cholinesterase determinations (plasma, RBC and brain) were carried out accordingly and in details.

(7) Examinations of postmortem were carried out with post-exposure necropsy, weights of essential organs, histological examination of tissues (heart, kidneys, liver, lungs, lymph nodes, bone narrow smear, brains, eyes, etc.).

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(8) Body weights, hematology and clinical chemistry parameters, cholinesterase levels, organ weights and organ/body weight ratios were statistically evaluated. Mean values for all treatment groups were compared to the control group for significant differences.

B. Results

(1) The rats in Groups II (low-level), III (mid-level) and IV (high-level) received exposure to cumulative mean exposure concentrations (CMEC) of 2.2, 11.1 and 42 mg/m^3 respectively, based on gas chromatographic analysis of the test material collected on Porapak-Q adsorption tubes. The optical particle size distribution was calculated for the measurements obtained on a selected five days in the high-level chamber. The median diameter of an average count from these analyses was 0.96 micrometers with a median standard deviation of 1.9 based on these values. The aerosol concentration was in the neighborhood of 2.82 mg/m^3 which represented 7% of the CMEC for this study.

In the mid-level chamber, the aerosal concentration was 0.78 mg/m^3 which corresponded to a 7% of CMEC. In the case of the low-level chamber, the aerosol concentration was 0.63 mg/m^3 which represented 29% of CMEC for the study.

(2) All animals survived the 13-week study and were sacrificed at the terminal of test. The mean body weight values for the male and female rats in Group II (low-level) and Group III (mid-level) were comparable to the mean body weight values for the male and female rats in Group I (control) during 13-week study period. However, the Group IV (high-level) male rats showed a significant decrease in the week 1 mean body weight value ($P \leq 0.05$) when compared to the control. The mean male body weights were also significantly decreased ($P \leq 0.01$) from week 2 through week 13. The female rats in the same group (high-level) showed significantly decreased mean body weights ($P \leq 0.01$) when compared to the control from week 1 through week 13 of the test. The decreases of weight gaining in rats of both sexes of Group IV appeared to be dose-related to the test material taken.

(3) The physical conditions of the rats in each group were fully assessed once a week for 13 weeks. The rats in Group I (control) exhibited dry rales (11 of 20 rats), corneal opacities (2 of 20 rats), and mucoid nasal discharge, moist rales, red nasal discharge, chromodacryarrhea, excessive lacrimation, hair loss and exophthalmia during thirteen weekly observations. These signs were scattered in appearance. The rats in Group II (low-level) and Group III (mid-level) also exhibited the aforementioned physical conditions. In general, these signs were comparable to those observed in the control group.

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The rats in Group IV (high-level) exhibited dry rales (11 of 20 rats), mucoid nasal discharge (13 of 20 rats), excessive lacrimation (7 of 20 rats), hair loss (2 of 20 rats), and red nasal discharge, moist rales, and chromodacryarrhea (1 of 20 rats, each) as did the rats in the control group. However, aggressive behavior and rapid breathing (2 of 20 rats, each) and labored breathing, excessive salivation, and yellow staining of the ano-genital fur (1 of 20 rats, each) were observed in the Group IV rats. The increased incidences of mucoid nasal discharge and excessive lacrimation and the appearance of aggressive behavior and labored and rapid breathing in this particular group might be considered as test-material related.

(4) Hematology parameters, which were examined pretest and during weeks 5 and 13, included hemoglobin, hematocrit, total erythrocytes, total and differential leukocytes, and reticulocytes. All pretest mean hematology values for both males and females in three experimental groups were comparable to the control. The mean erythrocyte values of Group III (mid-level) males during weeks 5 and 13 were significantly increased ($P \leq 0.05$) as was the mean erythrocyte value of Group IV (high-level) females during week 13. The mean reticulocyte value for the females in Group III was significantly decreased ($P < 0.01$) compared to the control during week 13, while the males of the same group showed significantly decreased ($P \leq 0.05$) leukocyte values during week 5. The female rats of Group IV (high-level) showed significantly decreased ($P < 0.01$) leukocyte values during week 13. Therefore, both increased erythrocyte values and decreased leukocyte values may have been a result of the test-material exposure.

(5) All the clinical chemistry tests specified were performed pretest and during experimental weeks 5 and 13. Among the clinical chemistry parameters evaluated pretest, the mean alkaline phosphatase value of males in the Group III (mid-level) and the mean glucose value of males in the Group IV (high-level) showed significant increases ($p \leq 0.05$ and $p \leq 0.01$, respectively) compared to the control. In the case of females, the mean glucose value and the mean albumin/globulin ratio value were significantly increased ($p \leq 0.05$) in Group IV, the mean calcium value was significantly increased ($p \leq 0.05$) in Group III, the mean lactic dehydrogenase value was signficantly decreased ($p \leq 0.05$) in Group IV, and the mean globulin value was significantly decreased ($p \leq 0.01$) in Group IV compared to the control.

The mean potassium value was significantly decreased ($p \leq 0.01$) in the Group IV males and females during week 5 and the Group IV males during week 13 compared to the control. These values

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were also significantly decreased ($p \leq 0.05$) in the females of Group III during week 5 and in the females of Group IV during week 13. The mean serum glutamic oxalacetic transaminase value was significantly increased ($p \leq 0.05$) in the Group II males during week 5, significantly decreased ($p \leq 0.05$) in the Group IV females during week 13, and significantly decreased ($p \leq 0.01$) in the Group IV males during weeks 5 and 13 when compared to the control. The mean lactic dehydrogenase value was significantly decreased ($p \leq 0.01$) in Group IV males and females during weeks 5 and 13 and was also significantly decreased ($p \leq 0.05$) in the Group III males during week 13.

The mean blood urea nitrogen value was significantly increased ($p \leq 0.01$) during week 5 in the Group IV males and was significantly increased ($p \leq 0.05$) in the Group IV males and females during week 13. The mean calcium value was significantly decreased ($p \leq 0.05$) in the Group IV males during week 5 and in the Group IV females during week 13. The mean globulin values were significantly decreased in the Group III and IV males ($p \leq 0.01$ and $p \leq 0.05$, respectively) during week 5 when compared to the control. The albumin/ globulin ratio was significantly increased in the Group III males ($p \leq 0.05$) during week 5. The mean T4 value (thyroxin) was significantly increased ($p \leq 0.05$) during week 13 in the Group IV males.

The decreased potassium and lactic dehydrogenase values for the males and females in Group IV during weeks 5 and 13 appeared to be test material related. Furthermore, the decreased serum glutamic oxalacetic transaminase and increased blood urea nitrogen in the males and females during week 13 and the decreased serum glutamic oxalacetic transaminase as well as the increased blood urea nitrogen value in the males during week 5 may be a result of exposures to the test material administered.

(6) The plasma cholinesterase activities were also specifically measured. Its mean level was significantly increased ($p \leq 0.05$) in the Group III males and significantly decreased ($p \leq 0.01$) in the Group IV females during week 8 compared to the control. This enzyme activity was not affected in the Group II (low level) test animals.

During week 13, the plasma cholinesterase level was also significantly decreased ($p \leq 0.01$) in the Group IV (high-level) females while this decrease did not occur in the Group IV (high-level) males. The brain cholinesterase levels were significantly decreased ($p \leq 0.05$) in the Group III males and significantly decreased ($p \leq 0.01$) in the Group IV males and females during week 13. Since this brain enzyme value in Group

II (low-level) animals was unaffected, the decrease in brain cholinesterase values appeared to be a response to the test material exposure.

(7) The mean terminal body weights in the Group IV (high-level) males and females were significantly decreased ($p \leq 0.01$) when compared to the control. All other mean terminal body weights were comparable to the control mean values.

The mean brain weights of the Group IV (high-level) females and the mean testes and heart weights of the Group IV males were significantly decreased ($p \leq 0.05$). Significant decreases ($p \leq 0.01$) were observed in the mean lung, spleen, and pituitary weights of the Group IV males and in the mean heart, spleen, lung, and pituitary weights of the Group IV females compared to the control. The mean adrenal and thyroid weights of the Group III (mid-level) males were significantly increased ($p \leq 0.05$) and the mean adrenal weights in the Group IV males and females and the mean thyroid weight of the Group IV females were significantly increased ($p \leq 0.01$).

Significant increases ($p \leq 0.05$) in the Group IV females brain/body weight ratios, the Group III female adrenal/body weight ratios, and the Group III male thyroid/body weight ratios were noted compared to the control. Significantly increased ($p \leq 0.01$) brain-, adrenal-, left kidney-, and right kidney/body ratios were noted in the Group IV males; significantly increased ($p \leq 0.01$) adrenal-, left kidney-, right kidney-, liver-, and thyroid/body weight ratios were shown in the Group IV females. Also, significantly increased ($p \leq 0.01$) adrenal/body weight ratios were noted in the Group III males.

It can be concluded that the increased adrenal weights in the Groups III and IV males and the Group IV females, the decreased pituitary weights in the Group IV males and females, and the increased thyroid weights in the Group IV females appeared to be results of the test material exposure.

(8) There was no dose-related ocular change in the rats of all groups exposed to the test compound (R-4572).

(9) The gross pathology examinations were also undertaken. The testes of three rats which received the highest dose level (Group IV) were smaller than the normal. This decrease in size is considered to be treatment related.

Microscopic examination revealed the occurrence of testicular degeneration in eight high-dose, three mid-dose and four low-dose male rats, while the control rats were not affected at all. In high-dose rats this lesion was even more severe and

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extensive. Significant numbers of abnormal spermatoza were observed in the epididymides of all high-dose, one mid-dose and two low-dose rats. The population of spermatoza was also significantly decreased in six high-dose and one low-dose male rats. The aforementioned testicular degeneration and abnormal population of spermatoza in the treated rats are considered to be test material related.

C. Conclusion

Ordam Technical R-4572 produced a variety of toxicities but of different degrees depending on the dose-levels of this compound administered and the kind of parameters located in the animals. All animals survived the duration of the 13-week study. A few profound toxicities, which appeared to be dose-level related, are herewith summarized.

(1) In-life observations of the high level exposure group IV, increased incidences of mucoid nasal discharge and excessive lacrimation as well as observations of aggressive behavior and labored and rapid breathing were recorded.

(2) The decreases of body weight gaining in rats of both sexes of Group IV.

(3) Significant decreases in the mean reticulocyte values for the females during week 13 and leukocyte values for the males during week 5, both of Group III; also significant decrease in leukocyte values for the female rats of Group IV during week 13.

(4) The decreased potassium and lactic dehydrogenase values for the males and females in Group IV during weeks 5 and 15; decreased serum glutamic oxalacetic transaminase and increased blood urea nitrogen in the males and females during week 13, and in the males during week 5, all of Group IV.

(5) Significant decrease in brain cholinesterase levels in Group III males and Group IV males and females during week 13.

(6.) Increased adrenal weights in the Group III and IV males and the Group IV females; decreased pituitary weights in the Group IV males and females; and increased thyroid weights in the Group IV females.

(7) Decreased population of spermatozoa and testicular degeneration in the treated rats have been described in detail in point (9) under Results. No NOEL was established for the effects on the testicular degeneration, and abnormality and population of spermatoza in this study.

Core Classification: Minimum data.

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II. Reproduction - Fertility Study of R-4572 in the Rat (by Raymond E. Schroeder, George M. Rusch, and William E. Rinehart of Bio/dynamics, Inc., Division of Biology and Safety Evaluation, East Millstone, New Jersey 08873; Project No. 78-2346 of December 13, 1979).

A. Experimental

The same animals [Sprague-Dawley (CD(R)) rats] were treated by the same test material (R-4572) in the same way (chamber inhalation) simultaneously with animals of the 13-week inhalation toxicity study (Project No. 78-7153) described in the foregoing Part I. This reproduction-fertility study was conducted to evaluate the effects of daily inhalation exposure of R-4572, six hours/day, five days/week, on the fertility of male rats. It was intended to distinguish the absence or presence in male rats of the antifertility effect previously observed in chronic and subchronic feeding studies.

1. Experimental design:

Group[1]	Concentration	Exposure Time	No. of Males	No. of Females Exposed to Males				Necropsy Males
				Mating Interval				
				Treatment Period		Post-Recovery		
				One-Month	Three-Month	One Month	Three Month	
IB	None-Chamber Control	6 hrs/day 5 days/wk 3 months	10	20	20	20	20	10
IIB	2 mg/m^3	6 hrs/day 5 days/wk 3 months	10	20	20	20	20	10
IIIB	10 mg/m^3	6 hrs/day 5 days/wk 3 months	10	20	20	20	20	10
IVB	50 mg/m^3	6 hrs/day 5 days/wk 3 months	10	20	20	20	20	10

[1]The animals were simultaneously exposed with the animals in Bio/dynamics Project No. 78-7153 (Repeated (3 month) Inhalation Study of R-4572 in the Rat).

(2) Four mating intervals were used in this reproduction-fertility study:

a. One-month interval mating period - following one-month exposure to test material (R-4572). Each male rat was caged with two unexposed females nightly for 10 consecutive days.

b. Three-month interval mating period - involving the last 10 days of the treatment period. Each male was caged with two unexposed females nightly for the last 10 consecutive days of the treatment (exposure) period.

c. One-month post-recovery mating period - initiated one month following the last day of exposure to test material. Each male was caged with two unexposed females nightly for 10 consecutive days.

d. Three-month post-recovery mating period - initiated three months following the last day of treatment of test material. Each male was caged with two unexposed females nightly for 10 consecutive days.

(3) Observation for signs of pharmacological and toxicological effects and mortality: Twice daily (males and females).

(4) Detailed hysical examination, including palpation for tissue masses: males - weekly; females - not observed.

(5) Body Weights: Males - weekly during treatment and post-treatment intervals through completion of the post-treatment recovery period; females - not recorded.

(6) Postmortem procedures: Animals were killed by an overdose of ether at the appropriate intervals.

a. Males - a gross postmortem examination was performed at completion of three-month post-recovery mating period. The testes were taken, weighed, and preserved in 10% neutral buffered formalin.

b. Females were sacrified on day 19 of gestation (Day 19 post-mortem).

(i) Uterus (number in each horn was recorded): fetuses, late resorptions, early resorptions, and implantation sites.

(ii) Ovaries: Corpora lutea were counted for each ovary and number was recorded.

(7) Statistical analysis

a. Body weight and testes weight data were analyzed by the Dunnett's test.

b. Uterine implantation data (i.e., implantations, resorptions and fetuses) and corpora lutea data were analyzed by the F-test and Student's t-test.

c. Incidence data (mating and fertility indices and pregnancy rates) were analyzed by the chi-square test.

B. Results

(1) Chamber concentration of test material: Refer to part I (13-week inhalation toxicity study).

(2) There was no mortality of male rats in the control, mid- or high-dose groups. One male rat in the low-dose group was killed in a moribund condition during mating of the three-month post-treatment recovery period.

(3) Body weight data - treatment and post-treatment recovery period:

The significantly decreased mean body weights occurred only in the high-dose group at weeks 1 and 4-12 of the treatment period. The mean weight gain during the treatment period was significantly lower than control, also only in the high-dose group.

During the recovery period, mean body weights for the high-dose group continued to be lower than the control. Mean weight gain during the recovery period was higher than control in each of the treated groups, but only in the mid- and high-dose groups were these differences from control statistically significant.

(4) In-life physical observations:

The types and incidences of the in-life physical conditions observed in the low- and mid-dose groups were generally similar to observations noted in the control group during both the treatment and recovery periods. An increase in the incidence of closed eyes (eyelids partially closed) was observed only in the high-dose group during the last four weeks of the treatment period.

(5) Mating, pregnancy and fertility indices:

a. Mating at the one-month treatment interval: Mating indices were comparable between the control and treated males. The pregnancy indices were lower than the control in each of the female groups exposed to treated males; however, only in the mid- and high-dose groups were these differences from control statistically significant. Male fertility indices were considered comparable between the control and low-dose group and lower than control in the mid- and high-dose groups (only in the latter group was this difference from control statistically significant).

b. Mating at the three-month treatment interval: Male mating indices were comparable between control and treated groups. Pregnancy rates for females exposed to low-dose males were comparable to control and lower than control at the mid-dose level. However, none of the mated females were pregnant at the high-dose level. Male fertility indices were comparable between the control and low-dose group and lower than control in the mid-dose group. The fertility index for the high-dose males was zero; none of these males impregnated a female.

c. Mating at the one-month post-treatment recovery interval:

Mating indices were comparable between the control and treated group males. Pregnancy indices were comparable between the control, low- and mid-dose groups and significantly lower than control at the high-dose level. Male fertility indices were comparable between the control, low- and mid-dose groups, and slightly lower than control at the high-dose level.

d. Mating at the three-month post-treatment recovery interval:

Mating, pregnancy and fertility indices were comparable between the control and all treated groups.

(6) Uterine implantation for the treatment and post-treatment periods:

a. Mating at one-month treatment interval: The mean number of implantations was significantly lower ($p \leq 0.01$) than control in each of the female groups exposed to treated males. An obvious dose-relationship was shown as the mean number of implants decreased with increasing dose levels. The mean number of fetuses in the low- and mid-dose groups was significantly lower than control. In the high dose group all the implantations noted were resorptions; no viable fetuses were observed The mean number of resorptions in females exposed to the high-dose males was significantly higher($p \leq 0.01$) than control data.

b. Mating at the three-month treatment interval: The mean numbers of implantations and fetuses in females exposed to low- and mid-dose males were significantly lower than control. The mean number of resorptions was comparable between the control and the same treated groups. None of the females exposed to the high-dose males were pregnant.

c. Mating at the one-month post-treatment recovery interval: Mean numbers of implantations, resorptions and fetuses were considered comparable between the female groups exposed to control and treated group males.

d. Mating at the three-month post-treatment recovery interval. Mean numbers of implantations, resorptions and fetuses were comparable between the female group exposed to control and treated males.

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(7) Terminal body weights and testes weight data: Mean terminal body weights were comparable between the control and mid-dose group, slightly higher than control in the low-dose group, and lower than control in the high-dose group. Mean testes weights were comparable between control, low- and mid-dose groups, and significantly lower than control in the high-dose group.

(8) Gross postmortem observations in the males: A few gross lesions in lungs, liver and testes were observed in both control and treated groups. The findings are considered to be incidental and unrelated to the Ordram treatment.

(9) The adverse effects of Ordram on the testes were observed at all dose levels, but no detailed histopathological examination was performed on this particularly affected organ.

C. Conclusion

No mortality occurred in the control and treated groups, except one male was killed in a moribund condition during mating of three-month post-treatment recovery period. The following adverse effects appeared to be test material exposure related:

(1) An increase in the incidence of closed eyes was noted only in the highdose group.

(2) Mating, pregnancy and fertility indices:

a. Mating at the one-month treatment interval - Statistically significant decrease in the pregnancy indices in the female groups exposed to treated males of mid- and high-dose groups. Male fertility indices were significantly decreased in the high-dose group.

b. Mating at the three-month treatment interval - No pregnancy was observed in the females exposed to the high-dose males. The male fertility index for the high-dose males was zero; none of these males inpregnated a female.

c. Mating at the one-month post-treatment recovery interval - Pregnancy indices were significantly decreased in the females exposed to the high-dose males.

(3) Uterine implantation for the treatment and post-treatment period.

a. Mating at one-month treatment interval - The mean number of implantations was significantly lower than the control in each of the females exposed to the treated males. A clear dose relationship was shown as the mean number of implants decreased with increasing dose levels. No viable fetuses were observed in the females exposed to the high-dose males.

b. Mating at the three-month treatment interval - The mean numbers of implantations and fetuses in females exposed to low-and mid-dose males were significantly lower than the control. None of the females exposed to the high-dose males were pregnant.

(4) Terminal body weights and testes weight data: Mean terminal body weights were lower than the control in the high dose males. Mean testes weights were also significantly lower than the control in the high-dose males.

(5) No NOEL for the significant decrease in implantation and fetuses, etc., was establisned in this study.