5-18-84

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

003832

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: FAP #1H5283. Review of the rat chronic feeding/ oncogenicity, mouse oncogenicity and rat reproduction studies with sumithrin.

Tox Chem. No. 652B

TO: T. A. Gardner, PM #17
Registration Division (TS-767)

THRU: William Burnam, Branch Chief
Toxicology Branch, HED (TS-769)

Albin B. Kocialski
acting Section Head
Section II 5/18/84

FROM: John D. Doherty 5/18/84
Toxicology Branch, HED (TS-769)

Background:

The McLaughlin Gormley King Co. (Minneapolis, MN) has submitted a rat chronic feeding/oncogenicity, a mouse oncogenicity, and a rat reproduction study for review in support of FAP #1H5283.

The studies submitted were reviewed (see below). It was noted that these studies were initiated and conducted at the IBT facility in Illinois but that in 1977 at the time of closure of this laboratory, the records, tissues and slides were sent to JAPAN. The Sumitomo Co. completed the study and made the report as it was submitted to EPA.

In a letter from the Sumitomo Chemical America, Inc (see letter from E.J. Goldberg dated March 18, 1983) to Mr. F.D.R. Gee of EPA, the agency was advised that certain studies that were conducted at the IBT facility in Illinois were to be repeated. In addition, the letter listed other studies which will be used to support the tolerances and registrations were in progress and that they should be completed in 1985.

17

The details of PAP #1H5283 were not included in the submission package but were sent to TB previously (refer to J. Doherty memo dated June 23, 1982, for this petition). In the earlier request it was indicated that a tolerance of 0.1 ppm in foods resulting from the use of this pesticide in food handling areas was sought.

Comments:

1. All three studies were reviewed and determined to be SUPPLEMENTARY. See the individual reviews for the basis for this classification.

It is TOXICOLOGY BRANCH's understanding that an additional rat chronic feeding/oncogenicity, mouse oncogenicity and rat reproduction studies are currently being conducted to replace the studies conducted at the IBT facility. See letter from E.J. Goldberg attached.

2. The registrant should be advised that several other studies must be submitted, reviewed and foun acceptable before this tolerance can be favorably recommended. These required studies include:

a. teratology - two species
b. 1 year or longer dog chronic dosing study
c. mutagenicity studies (three types)
   i. point mutation
   ii. structural chromosomal aberrations
   iii. direct DNA damage and repair
d. metabolism in rats

TB is also aware of a neurotoxicity study with d-Phenothrin (sumithrin) in rats and requests that this study and any other neurotoxicity data be submitted for review (refer to the list of studies sent to RD with the June 23, 1982.

3. TOXICOLOGY BRANCH requests that the registrant be advised that when the second rat and mouse oncogenicity studies are submitted that the report should contain individual animal histopathology sheets which show the gross necropsy and microscopic findings on the same page(s). Also the gross necropsy and histopathology summary tables must specify the number of animals actually evaluated visually or microscopically for each tissue type together with the number of animals having each lesion type.

003832

Studies Reviewed

Study	Result	Core Classification
Rat chronic feeding/ oncogenicity Research Dept. Sumitomo Chem. Co. #ET-90-0041 February 19, 1980 EPA Accession No. 248339	Chronic Feeding: NOEL=2000 ppm LEL=6000ppm body weight and organ weight changes Oncogenicity= Conclusions Pending	SUPPLEMENTARY (Chronic feeding NOEL is tentative)
Mouse oncogenicity Research Dept. Sumitomo Chem. Co. #ET-90-0042 February 19, 1980 EPA Accession No. 248340	No evidence of oncogenic effects at up to including 3000 ppm. Systemic effects: NOEL=300 ppm. LEL=1000 ppm increases in lung amyloidosis LEL=3000 ppm increases in liver weight	SUPPLEMENTARY
Rat reproduction Research Dept. Sumitomo Chem. Co. #ET-90-0043 February 20, 1980 EPA Accession No. 248339	NOEL=2000 ppm. (HDT) no effects	SUPPLEMENTARY

SUMITOMO CHEMICAL AMERICA, INC.
345 PARK AVENUE
NEW YORK, N.Y. 10154

003832
401/116864

PHONE
-8600
-3813

Please reply to:
1330 Dillon Heights Avenue
Baltimore, Maryland 21228

March 18, 1983

Mr. Franklin D.R. Gee (PM-17)
OPTS-RD (TS767C)
U.S. Environmental Protection Agency
Washington, D.C. 20460

Subject: Sumithrin (EPA Reg. No. 10308-6)
Toxicology Studies

Dear Mr. Gee,

For your information, please note that we are conducting 2 replacement (for IBT studies) and 3 additional studies upon Sumithrin toxicology. These are:

1.) Dog Feeding - 6 months
2.) Rats long-term feeding and oncogenicity study
3.) Mice long-term feeding and oncogenicity study
4.) Rats reproduction study
5.) Rats teratology study

These studies should be completed in 1985.

Sincerely yours,

SUMITOMO CHEMICAL AMERICA, INC.

Eugene J. Gerberg, Ph.D.
Technical Advisor

EJG:cw

A: Two-year chronic toxicity study of S2539 in rats

Research Dept. Sumitomo Chem. Co., ET-90-0041, February 19, 1980. EPA Accession No. 248339.

[Note: The in-life phase of this study was conducted at the IBT facilities in the State of Illinois. The report states that after termination of the feeding all the raw data were transported to Japan where this study was concluded.]

B. The test material was S2539. Three lots of the test material were used: Lot #S-3 (90.5% pure), lot #ME202 (95.5% pure) and lot #60105 (92.7% pure). Purities were stated by the sponsor.

C. The test animals used were Charles River (CD strain) obtained from the Wilmington, Mass., facility. They were five weeks of age at the start of dosing. Five groups of 50 male and 50 female rats were dosed as either 0, 200, 600, 2,000 or 6,000 ppm of the test material in the diet. Each rat was housed individually.

D. Fresh diets were prepared each week. A 5% premix of the test material was made and blended with rat ration to obtain the desired dietary levels. No periodic analyses of the diet were made to assure that the desired dietary levels were attained.

E. Survival and clinical reaction. Survival was very poor for this study. 50% of the males died by about week 68, and 50% of the females died by about week 80. No evidence was available to indicate that the poor survival was related to ingestion of the test material. There were 5 (10%), 7 (14%), 12 (24%), 6 (12%), and 9 (18%) male survivors and 12 (24%), 14 (28%), 10 (20%), 13 (26%) and 14 (28%) female survivors among the control, low, mid levels, and high dose groups. For both sexes, the frequency of deaths increased after the 44th week. Many of the rats that died had pneumonia.

There were no abnormal clinical reactions reported as being related to ingestion of the test material. There was no table or summary which indicated the periodic examination of the test animals.

F. Body weight. The high-dose male group showed an initial lower rate of body weight gain, but by the 5th month this group was only slightly lower than the controls. At termination, the high dose group was higher in weight (+11%). No statistically significant body weight differences were noted for the females, although at termination the high-dose group was lower in weight (14.7%), but the group dosed with 2,000 ppm was higher (+5%) than the controls.

Food consumption data were provided and occasional (but not consistent) differences were noted.

A NOEL of 2,000 ppm is assigned for body weight changes. At 6,000 ppm there are noted some decreases in body weight gain.

For sections G and H below, samples of blood were taken from the suborbital sinus at 3, 6, 12, 18, and 24 months from 10 rats per sex (or all survivors) for the control and 6000 ppm groups. At termination, 10 rats (or all survivors) from the low and middle groups were also sampled.

G. Hematology. The following parameters were investigated: total leukocytes, erythrocyte count, hemoglobin concentration, hematocrit value, neutrophils, lymphocytes monocytes, eosinophils and basophils.

* The total leucocyte level was decreased for the the high dose group males; for the females the high-dose group was increased slightly (+14%) at 3 mos. and decreased slightly at 12 mos. In the absence of other supporting data the effect in the males is not considered to be related to the test material.

NOEL for hematological changes = 6,000 ppm (HDT)

H. Clinical biochemistry. The following parameters were investigated: Fasting blood glucose, BUN, serum alkaline phosphatase, serum glutamic pyruric transaminase, bilirubin Na+, K+, Cl-, total protein, albumin, alpha, beta and gamma globulin and albumin/globulin ratio.

Of these several parameters, serum glutamic pyruvic transaminase was elevated in the high-dose test group (males only) but not in the lower test groups. Na+ was lower and the albumin/globulin ratio was also elevated.

The NOEL for changes in clinical biochemistries is set at 2,000 ppm. At 6,000 ppm (LEL) serum glutamic pyruvic transaminase is elevated. Na+ and albumin/globulin elevations are less definite effects of the test material at the high dose level.

I. Urinalyses. There were no test chemical related changes noted in the urine in glucose, albumin pH, specific gravity, bilirubin, leukocytes, erythrocytes, or "crystals."

NOEL for changes in urinalysis = 6,000 ppm (HDT)

J. Gross pathology. The report summary states that there were no gross necropsy changes related to ingestion of the test material. No summary table demonstrating this result was presented. The gross necropsy findings are in a table

occupying some 42 pages which lists the animal numbers and only those organs which had a macroscopic lesion and a description of that lesion. The table also listed those organs for which autolysis precluded an analysis.

K. Organ weights. Note the numbers in the parentheses represent the value for the relative weight of the high dose test group (numerator) and the control group (denominator) usually. Adrenals (0.0122/0.0157, = -23%), brain (.3716/.4508, =-18%), brain-females (.5485/.4800= +14%), gonads-males (.4863/.4869), females (0.0198/0.0166 = +19%), heart (.3599/.3855, = -7% kidneys (.7266/.7325), liver (males 2.494/2.7452, -11%), l ver (females 3.1477/ 2.3971, +31%),* spleen (.1766/.2964, -41%), and thyroid (.0074/.0059 +25%).

* Of these organs only the liver was statistically significantly different for females. Organ to body wt. ratio was increased, however organ to brain wt. ratio was not significantly different from controls.

Although differences for the other organs were noted as indicated, the intermediate dose groups did not show dose responses for weight changes consistent with the effects noted in the high-dose test group.

Because there was some evidence (or at least suggestion) of weight changes, the liver, spleen, thyroid and adrenals should be carefully evaluated for histopathological changes.

The NOEL for organ weight changes is set at 2,000 ppm. At 6,000 ppm there is a definite increase in female liver weight, based on organ wt. to body wt. ratio. Brain to organ wt. ratio was comparable to controls.

L. Histopathology. The rats in the control and 6,000 ppm dose groups received the most extensive microscopic examination. Some 28 basic organs/tissues plus any gross lesions were reportedly prepared and examined for these groups if they were sacrificed at termination. The rats that died intercurrently in these groups received a limited microscopic evaluation which included the lung, trachea, heart, lymph node, liver, spleen, pancreas, kidney, testes or ovary, uterus and any gross lesions. The rats in the groups dosed with 200, 600, or 2,000 ppm received a microscopic evaluation which consisted of only the lung, lymph node, liver, spleen, kidney and any gross lesions.

Overall oncogenic response: The following table indicates

the total number of rats effected with tumors.

Test group	Males	Females
Control	8/50*	27/49
200 ppm	2/49	14/50
600 ppm	3/50	15/48
2,000 ppm	8/48	22/49
6,000 ppm	11/49	33/48

* Number of rats with tumors of any kind/number of rats available in each group. Note: not all available tissues for all rats were examined.
The low number of rats with tumors in the low and two middle dose groups is because not all tissues of all rats were examined.

Comparision of the control and high-dose test groups indicates a possible increase in incidences of neoplasm in both the males and females, because for both sexes the net rats affected with tumors is higher for the high-dose group than for the controls.

Individual organ discussions:

1. The liver. The liver showed increased weight gain (organ wt/body wt.) and SGPT was elevated. There were eight incidences of neoplasms in the male livers. Of these there was a single incidence of hepatocellular carcinoma (high-dose group), two incidences of neoplastic nodules (control and 2,000 ppm group), one incidence of cyst adenoma (2,000 ppm group), one incidence of hemangioma (600 ppm group). The other neoplasms were lymphomas and sarcomas.

   Among the females, there were 12 incidences of neoplasms in the liver; 8 of these were sarcoma or lymphomas. There were 4 incidences of neoplastic nodules (3 in the 2,000 ppm group and one in the high-dose group).

   A variety of nonneoplastic lesions were noted but none of these showed evidence of being related to the presence of sumithrin in the diet. The liver tissue was also examined by electron microscopy to determine if there were increases in the smooth endoplasmic reticulum. There were no remarkable increases.

2. The spleen The spleen showed a decrease in weight.

There were no dose-related increases in lesions in the spleen. The neoplasms in the spleen were lymphomas and these were in the controls at the same frequency as in the test groups.

3. The thyroid. The thyroid showed a slight increase in weight. There were very few nonneoplastic lesions. There were three adenomas among the females (two in the controls, one in the 2,000 ppm group). There were two adenomas in the males (both in the high-dose group). Note: Only the control and high-dose animals were routinely examined for lesions in the thyroid.

4. The adrenals. The adrenals showed a slight decrease in weight. Among the females there is evidence of a possibility of an increased incidence of "hematocyst bilateral." For example, there were 11, 5, 1, 4 and 20 incidences among the control, low, middle and high-dose test groups. [Note: The exact number of rats examined was not provided.] There were two adenomas among both the males and the females (both in the control groups).

5. The lung. The lung has been indicated as a target organ for a neoplastic effect for other pyrethroids. There was a single incidence of a lung carcinoma among the males (high-dose group). There were no adenomas. There were no primary lung tumors among the females. Both the males and females (all groups) showed evidence of pneumonia, but there was no definite relationship to the presence of the test material. There were no indications of dose related increases in amyloidosis.

6. The testis. In the study with sumithrin, there was only a single incidence of an adenoma (in the 2,000 ppm group).

7. Rare neoplasms. There were no unusual neoplasms which were considered to be rare by this reviewer.

8. Systemic neoplasms (lymphomas and sarcomas). These types of neoplasms were present but affected only a few individuals in each group. There were no indications of increased incidence with the dose level.

9. Mammary gland. Among the females, the mammary gland

accounted for many of the tumors. There were 19, 16, 11, 14 and 11 incidences of fibroadenoma among the controls, low, middle and high-dose groups. [Note: The exact number of rats examined was not provided.]* There were 3 incidences of adenocarcinomas among the females (high-dose group only).

10. Pituitary gland. Among the females, the pituitary gland accounted for many of the tumors. There were 10, 6, 6, 12, and 17 incidences among the control, low, middle and high-dose test groups. [Note: The exact number of rats examined was not provided.]

11. Sciatic nerve. Pyrethroids have been indicated as causing a characteristic lesion in the sciatic and other nerves when given in high-doses. No special staining techniques were employed to try to determine if there were lesions present. There were no indications of lesions noted with the staining and examination technique employed. (The optic nerve and "peripheral nerve" were reported to have been examined.)

M. Special studies- N/A

N. Conclusion.

1. CORE Classification of this study is SUPPLEMENTARY. The reasons for this classification include the poor survival rate among males and the incompleteness or lack of thoroughness of the microscopic evaluations.

2. NOEL for systemic effects on the basis of available information is set at 2,000 ppm. The LEL is 6,000 ppm. At this level there are body weight losses and organ weight (liver) changes.

3. No conclusions related to the oncogenic potential were drawn from this study.

[Note: It is Toxicology Branch's understanding that a second chronic feeding oncogenicity study with sumithrin will be conducted. The NOEL and oncogenic potential (if any will be determined based on this study if it is found acceptable by the agency.]

A. Eighteen-month chronic oral toxicity and tumorigenicity study of S-2539 in mice.

Research Dept., Sumitomo Chem. Co. #ET-90-0042, February 19, 1980. EPA Accession No. 248340.

Note: The in-life phase (feeding phase) was conducted at the IBT facility (Illinois). It was stated in the report that after termination of the feeding all of the records of observations as well as all tissues and slides for microscopic examination were transported to Japan where the slides were examined and the report was written.

B. The test material was S-2539 which was stated as being 95.5% pure and from lot ME-202.

C. The test animals were Charles River CD-1 strain mice. The mice were grouped as 50 of each sex into four groups and dosed with either 0, 300, 1,000 or 3,000 ppm of test material. The mice were housed 2 males per cage and 10 females per cage and were 5-7 weeks old at the initiation of the study. The mice were dosed for 18 months (78 weeks).

D. No data were presented which showed that samples of the diet were periodically analyzed to ascertain that the desired dose levels were attained.

E. Survival and Clinical/Behavioral Reactions.

The number of mice surviving at the end of 78 weeks is shown in the following table.

Dose Level	Males	Females
Control	22 (44)*	37 (74)
Low	11 (22)	39 (78)
Mid	11 (22)	38 (76)
High	14 (28)	34 (68)

* The actual number of mice available at termination followed by the percent of 50 in parentheses. One male mouse each from the low and mid dose test groups were lost ("escaped") from their cages.

Survival was especially poor among the males. The latest time when 50% of the mice were alive for all male groups were between weeks 68-72. There was, however, no clear test chemical effect on survival, although it is noted that the male group with the highest number of survivors was the control group.

The results section of the report states that there were no clinical behavioral signs noted for the test mice. There were no tables which showed the frequency of observation.

F. Body weight. Body weight gain was only slightly affected for the male group and this was noted only during months 10-14 when the body weight of the high-dose group males was about

7-8% lower. Final body weights among the males were essentially equal. No effects were noted on the body weight of females.

Food and water consumption were not recorded.

[Note: For sections G and H below the mice were bled after 18 months of feeding the test diets. 10 mice/sex/group were bled by cardiac puncture.]

G. Hematology. The following parameters were investigated: total leucocyte count, erythrocyte count, hemoglobin concentration, hematocrit, differential leukocyte counts (lymphocytes, neutrophils, eosinophils, basophils, and bands) were also determined and no effects of the test material were noted.

H. Clinical Biochemistry. The following parameters were investigated: serum glutamic-pyruvic transaminase*, serum alkaline phosphatase, BUN, and glucose.

*The female levels of SGPT were apparently elevated at all dose levels but because of a lack of supporting data (no pathology) and, because there was no dose response between the low, mid and high-test dose groups, this effect is not considered to be definitely a response to treatment.

I. No urinalyses were made.

J. Gross necropsy. No table summarizing the gross necropsy findings as incidences per group was presented. The gross necropsy findings are presented for each mouse in a table occupying some 30 pages. The study summary states that there were no abnormal lesions indicative of an effect of S-2.

K. Organ weights. The absolute organ weights and organ weights relative to body weight and to brain weights were determined for the following organ: kidneys (1.86/1.85)*, lung (.84/.78), liver (for males (7.94/5.57, +43%, N.S., for females 9.23/5/12, +80% significant P<.01), spleen (.53/.43), brain (1.24/1.27), heart (.64/.65) and both gonads (for males .63/.62, for females ( )6 /.08).

Only the high-dose group female liver was statistically significantly higher in weight.

* The numerical value of the high-dose group males (females indicated)/the numerical value of the control group. The percent difference follows the comma.

L. Pathology. Some 29 tissue types were routinely prepared for microscopic examination for all mice when available. Tissue masses and any apparently abnormal tissues were also prepared.

According to the study results there was no evidence of an oncogenic response to the test material and the only chemical-related nonneoplastic response was amyloidosis.

The following table presents the findings regarding the mice affected with primary tumors.

Test group	Males	Females
Control	8	5
300 ppm	7	3
1000 ppm	6	8
3000 ppm	1	2

This table shows no evidence of oncogenic effects.

Thi able shows only primary tumors, and mice affected with any .. the various systemic tumors are not included.

There is no obvious dose-related increase in primary tumors.

Individual organ discussions

1. Lungs. Among the males there were 5, 4, 2, and 0 incidences and among the females there were 2, 1, 4 and 0 incidences of adenomas among the control, low, mid and high-dose test groups respectively. There was a total of 3 incidences of adenocarcinoma in the males (2 in mid-dose group and 1 in the control group), none in the females.

Other neoplastic findings in the lungs were related to systemic sarcomas. There is no evidence based on the data in this study to suggest that the lung is a target organ for a neoplastic effect of sumithrin.

There were dose-related increased incidences of amyloidosis in the lungs of both males and females as shown in the following table.

	Amyloidosis Incidences	
Dose level	Males	Females
Control	3/48*	2/50
300 ppm	5/46	4/47
1000 ppm	10/48	7/44
3000 ppm	14/48	13/46

*incidences/number of mice examined.

The testing laboratory assigned a NOEL for induction of amyloidosis at 300 ppm in lung and eventually assigned this level as the NOEL for the study. See the separate discussion of amyloidosis below.

2. The liver. Female liver weight was increased. There were infrequent incidences of liver tumors. Hepatoma (one control male); hemangioma (one low dose female); and hemangioendothelioma (2 low-dose and one high-dose group males and low-dose group female).

Although the levels of SGPT were reported to be elevated, there was no evidence of pathological lesions in the liver to indicate liver damage.

Amyloidoses was also slightly higher in the mid and high-dose group males and high-dose group females (see 4 below).

3. Systemic tumors. There were a variety of systemic tumors including myelosarcoma, reticulum cell sarcoma, fibrosarcoma, lymphosarcoma, hemangiosarcoma and hemangioendothelioma. There was no evidence that the high dose groups had more individual mice affected than the controls. There were about 5 males and 8 females control mice affected with these types of tumors. The dosed groups did not have many more individuals affected. For example, only the low-dose male group had 6 mice affected.

4. Amyloidosis. Many of the tissues showed amyloidoses specially the lung. The liver showed higher incidences for the high-dose than for the controls. Other tissues such as the heart (26-41%), spleen (34-43%) small intestine (28-39%), kidney (18-35%), testis (17-25%), thyroid (15-36%), adrenal (36-46%) and salivary gland (20-26%) and the ovary (37-41%) also showed amyloidosis. The numbers in parentheses represent the low to high number of incidences for the males. The incidence ranges for the females for these tissues were quantitatively similiar. In all of the organs except the lung and liver there was no real dose response.

Amyloidosis is considered by this reviewer to be a spontaneous occurring condition in mice that increases with age that is some times aggravated by the presence of xenobiotics. The high incidence of amyloidosis is recognized by TB, but only in the case of lung and liver is there clear evidence of increased incidences of amyloidosis with increase in the dose-level.

M. Special Studies-N/A

N. Conclusions

1. This study is SUPPLEMENTARY. The survival to termination for the male groups prevents assignment to higher classification.

2. The NOEL for this study is 300 ppm. At 1,000 ppm and above there is an increase in amyloidoses in the lung and liver. The NOEL of 300 ppm was also assigned by the testing laboratory. The only other test chemical-related effect was an increase in female liver weight at the highest dose level tested.

3. There was no evidence of an oncogenic effect up to and including 3,000 ppm, the highest level tested.

A. Three Generation Reproduction Study of S-2539 in rats.

Research Dept., Sumitomo Chem. Co., #ET-90-0043, Feb. 20, 1980. EPA Acc. No. 248339.

Note: The in-life phase of this study was conduted at IBT facilities in Northbrook, Il. It was stated in the report that following termination of the in-life phase all the records of observations, as well as tissue samples (slide preparation, paraffin block, the remaining wet tissues fixed in formalin) were transported to Japan, where they were processed and examined.

B. The test material used for this study was S-2539 and was from lot ME-202 and was stated as being of 97.1% purity. No data were presented to verify that the desired dose levels of test material in the diet were attained.

C. The test animals used were Charles River albino rats obtained from the Charles River Breeding Laboratories, Wilmington, Mass. The study consisted of 4 groups of 8 males and 16 females per group. The test dose levels used were 0, 200, 600 and 2,000 ppm. The F_0 parental rats were bred twice to produce the $F1_a$ and $F1_b$ generations. The $F1_b$ rat pups were culled to produce the $F2_a$ and $F2_b$ progeny. $F3_a$ and $F3_b$ generations were produced using the $F2_b$ litters as parents. The rats were first mated when they were 100 days of age and each male was housed with two females. The reproductive performance, health, and viability of the pups were assessed. The assessment included gross pathology and histopathology of parents and pups.

D. Effects on the parents. No adverse effect on the reproductive performances of either the males or the females for any of these parental groups resulted. The specific parameters investigated were mating index, fecundity index, male fertility index, female fertility index and incidence of parturition. There were some fluctuations in body and organ weights, but these were not consistent throughout the three parental groups. There were no dose-related gross necropsy or histopathological lesions in the adult rats used for parents for any generation.

E. Effects on the pups. No test chemical-related adverse effects on the rat pups were noted that were consistent among the six sets of progeny bred. The specific parameters investigated included live birth index, 24-hour survival index, 4-day survival index, 12-day survival index, and 21-day survival index.

There were no gross or histopathological lesions noted in the pups that could be attributed to the test material.

F. Conclusion. This study is SUPPLEMENTARY. The study shows that there are no effects on the reproductive performance of rats at dose levels up to and including 2,000 ppm. This study is deficient in that only 8 males and 16 females were employed for each dose group for parental generation. The ideal number is at least 20 males and a sufficient number of females to yield at least 20 pregnant females at or near term. However, the ratio of 10 males to 20 pregnant females would also be acceptable.