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October 23, 1992

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Attn: Section 8(e) Coordinator
Office of Toxic Substances
U.S. Environmental Protection Agency
East Tower NEG004, Mail Stop 790
401 M Street, S.W.
Washington, D.C. 20460

COMPANY SANITIZED

CONFIDENTIAL INFORMATION NOTED IN BRACKETS

RE: TSCA 8EHQ-0492-5142; PMN# P89-632; DCN: 50-891003208

Dear Document Control Officer:

On April 6, 1992 the [ ], submitted a TSCA Section 8(e) report of preliminary findings from a subchronic study on the following substance:

> 1,3-Propanediamine, N,N''-1,2-ethanediylbis, polymer with 2,4,6-trichloro-1,3,5-triazine, reaction products with N-butyl-2,2,6,6-tetramethyl-4-piperidinamine
> CAS# 120498-03-5.

Supplemental information regarding this submission was filed on June 25, 1992.

The subject chemical is covered by a TSCA Section 5(e) Consent Order DCN: 50-891003208. Pursuant to this Consent Order, the complete study report was filed with EPA's Document Control Officer on October 22, 1992. I am therefore filing with this letter the summary report (without attachments) in order to complete the TSCA Section 8(e) file. If any additional information is desired from the complete report, or you would like to discuss this submission, please do not hesitate to call.

Sincerely,

Robert J. Fensterheim

1616 P Street, NW • Suite 412 • Washington, DC 20036
202-939-3444 • Fax: 202-939-3445

Bio/dynamics, Inc.

PROJECT NO. 90-3589

A SUBCHRONIC ORAL TOXICITY STUDY OF TABANOL IN THE RAT VIA ORAL GAVAGE ADMINISTRATION WITH A 4-WEEK RECOVERY PERIOD

Final Report

VOLUME I OF II

Date: October 9, 1992

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Bio/dynamics, Inc.

PROJECT NO. 90-3589

A SUBCHRONIC ORAL TOXICITY STUDY OF TABANOL IN THE RAT

VIA ORAL GAVAGE ADMINISTRATION WITH A 4-WEEK RECOVERY PERIOD

ABSTRACT

This study was designed to assess the potential subchronic toxicity of TABANOL when administered orally, via gastric intubation to 80 Sprague-Dawley CD® rats [CD®-Crl: CD® (SD)BR] (Groups II and III - 10/sex/group and Group IV - 20/sex) at dose levels of 25, 75, and 250 mg/kg/day. Control animals (20/sex) received the vehicle (i.e., 0.5% methylcellulose) at the same dose volume as administered to the treated animals. Physical observations, ophthalmoscopic examinations, body weight and food consumption measurements were done on all animals pretest and on all survivors at selected intervals during the study. Hematology, clinical chemistry, and urinalyses were performed on all survivors at selected intervals during the treatment and recovery periods. After at least 3 months of treatment, up to 10 animals/sex/group were sacrificed. Ten animals/sex/group in the control and high-dose groups were retained for a 4-week recovery period and sacrificed. Selected organs were weighed and organ/body and organ/brain weight ratios calculated at each sacrifice interval. Complete gross postmortem examinations were performed on all animals. Histopathological evaluations of selected tissues were conducted on all animals in the control and high-dose groups at terminal sacrifice. In addition, evaluations were performed on the lungs, liver, kidneys and lymph nodes for all animals in Groups II and III. Microscopic examination of the lungs and lymph nodes from the control and high-dose animals sacrificed at the recovery interval was also performed.

Analysis of weekly dose suspension preparations confirmed that the test material concentrations were within the tolerances accepted for this study.

There were no treatment-related effects seen in the mortality, in-life physical observations and urinalysis values evaluated.

Administration of TABANOL to rats for 90 days at a dose of 250 mg/kg/day produced transient decreases in body weight gains (males), reversible increases in numbers of segmented neutrophils and elevated absolute and relative lung weights which persisted in males through termination of the recovery period. Microscopic changes (granulomas and other evidence of foreign body reactions) in the lungs, mediastinal and mesenteric lymph nodes and nasal passages were also seen in animals in this group. Effects at the 75 mg/kg/day dose level consisted of elevated lung weights and the presence of microgranulomas in the lungs and

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lymph nodes. The only effect at the 25 mg/kg/day dose level was the presence of granulomas in the lungs and lymph nodes. No treatment-related effects were seen in the progression of sperm development nor in the testes and epididymides in the male animals in this study. No other treatment-related pathologic findings were seen in any of the other tissues examined.

Based on these observations, a no effect level for oral administration of TABANOL to rats was not established in this study.

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I. INTRODUCTION:

This study was designed to assess the potential subchronic toxicity of TABANOL when administered orally, via gastric intubation, to Sprague-Dawley CD® rats for 3 months and to evaluate reversibility of any effects during a 4-week recovery period.

This study was designed to meet or exceed the requirements of TSCA (Toxic Substance Control Act) of the U.S. Environmental Protection Agency, 40 CFR, Part 798.2650, Subchronic Oral Toxicity.

This study was also conducted in compliance with FDA, Part 58 of 21 CFR principles of Good Laboratory Practice and EPA Good Laboratory Practice Regulations - TSCA, Part 792 of 40 CFR.

Species and strain of test animal, method and route of test substance administration and dose levels were determined by the sponsor. This study was conducted at Bio/dynamics, Inc., Mettlers Road, East Millstone, New Jersey 08875. All raw data, specimens, the original study protocol, the original final report and a sample of the test substance and vehicle are stored in the Archives of Bio/dynamics, Inc.

II. MATERIALS AND METHODS:

A. Study Dates:

Study Initiation Date: (Date Study Director Signs Protocol)	10 May 1991
Experimental Start Date: (First Dose)	23 July 1991
Study Completion Date:	Date final report is signed by Study Director.

II. MATERIALS AND METHODS (cont.):

B. Test Substance: TABANOL

Lot No.:	03/A/0
Concentration:	98% Active Ingredient
Description:	Off-white powder
Dates Received:	2 August 1990 17 August 1990 14 January 1991
Expiration Date:	July 1992
Analysis:	The identity, strength, purity and composition; and synthesis, fabrication, and/or derivation of the test substance is the responsibility of the sponsor.
Stability:	The stability of the test substance is the responsibility of the sponsor.
Storage:	Room temperature, in a temperature monitored room.
Sampling:	An archival sample of approximately 10 grams of the test substance is stored in the Archives of Bio/dynamics, Inc.
Disposition:	All remaining containers of the test substance will be returned to the sponsor after completion of the study.

II. MATERIALS AND METHODS (cont.):

C. Vehicle:	Methylcellulose (prepared as a 0.5% aqueous suspension).
Supplier:	Dow Chemical Midland, Michigan 48640
Description:	Fine white powder.
Date Received:	27 July 1984
Lot No.:	MM83092611A
Storage:	Room temperature, keep dry.
Sampling:	An archival sample of approximately 10 grams of the vehicle is stored in the Archives of Bio/dynamics, Inc.
D. Test Animals:	Albino Rats (outbred)
Strain:	CD® (Sprague-Dawley derived) [CD® - Crl: CD® (SD)BR]
Justification for Animal Selection:	The rat is a rodent animal model commonly utilized in toxicity studies as recommended in the referenced guidelines. In addition, a historical data base is available for comparative evaluation.
Number of Animals:	
Received:	155 total (77 males, 78 females)
Placed on Test:	120 total (60 males, 60 females)
Supplier:	Charles River Breeding Laboratories, Inc. Kingston, New York 12484

II. MATERIALS AND METHODS (cont.):

D. Test Animals (cont.):

Date Received: 8 July 1991

Age at Receipt: 28 days old

Age at Initiation of Treatment: 43 days old

Weight at Initiation of Treatment (grams):

	Mean	Range
Males:	260	234-288
Females:	182	164-199

Acclimation Period: Animals were acclimated for 14 days (8 to 22 July 1991). All animals were examined by the staff veterinarian during the acclimation period.

E. Selection:

More animals than required for the study were purchased and equilibrated. Animals considered unsuitable for the study on the basis of pretest physical examinations, outlying body weight data and/or ophthalmoscopic examinations were eliminated prior to random selection for group assignment.

F. Group Assignment:

Animals considered suitable for study were first distributed into 6 groups of 10 animals/group by a computerized random sort program so that body weight means for each group were comparable. Those groups were then randomly combined to form the four permanent dose groups (i.e., Groups I and IV - 20/sex/group and Groups II and III - 10/sex/group). Individual weights of animals placed on test did not exceed 20% of the mean weight for each sex.

G. Animal Identification:

Each rat was identified with a metal ear tag bearing its unique Bio/dynamics, Inc. animal number. If the tag was lost, it was replaced. In addition, each cage was provided with a cage card which was color coded for dose level identification and contained the project number, animal number, sex and dose-group information.

II. MATERIALS AND METHODS (cont.):

H. Experimental Outline:

Group	Test Substance	Dose Level (mg/kg/day)	Number of Animals: Total M	Total F	Clinical Laboratory Studies[b] (Termination) M	(Termination) F	(Recovery) M	(Recovery) F	Necropsy[c] (Termination) M	(Termination) F	(Recovery) M	(Recovery) F	Histopathology[d] M	F
I	Control[a]	0	20	20	10	10	9	9	10	10	9	9	10	10
II	TABANOL	25	10	10	10	10	-	-	10	10	-	-	10	10
III	TABANOL	75	10	10	10	10	-	-	10	10	-	-	10	10
IV	TABANOL	250	20	20	9	10	10	10	9	10	10	10	10	10

[a]Control animals received the vehicle (0.5% methylcellulose) at the same dose volume administered to the test animals.
[b]Hematology, clinical chemistry and urinalysis were performed on the first 10 animals/sex/group which survived to the termination of dosing and on all surviving animals in Groups I and IV at the recovery sacrifice.
[c]Gross necropsy examinations were performed on all animals, including those animals which died prior to their scheduled sacrifice.
[d]Histopathological examinations of selected tissues were performed on all animals in the control and high-dose groups which were scheduled for sacrifice at termination of dosing (includes one Group IV male which died prior to sacrifice). In addition, the lungs, liver, kidneys and lymph nodes were examined for all animals in Groups II and III. Microscopic examination of the lungs and lymph nodes from the control and high-dose animals sacrificed at the recovery interval was also performed.

I. Husbandry:

Housing: Animals were doubly housed in elevated stainless steel wire mesh cages during the first week of the acclimation period and individually housed thereafter.

Food: ad libitum; standard laboratory diet (Purina Certified Rodent Chow® Brand Animal Diet #5002 - mash-type). Fresh food presented weekly.

Analysis of Feed: Analysis of each feed lot used during this study was performed by Purina Mills, Inc. prior to receipt at Bio/dynamics, Inc. Results are maintained on file at Bio/dynamics.

II. MATERIALS AND METHODS (cont.):

I. Husbandry (cont.):

Water:	ad libitum; by automated watering system (Elizabethtown Water Company).
Analysis of Water:	Water analysis was provided by Elizabethtown Water Company, Westfield New Jersey (Raritan-East Millstone Plant). Results are maintained on file at Bio/dynamics.
Environmental Conditions:	12 hour light/dark cycle (7 AM to 7 PM and 7 PM to 7 AM) via automatic timer; temperature was monitored and recorded twice daily, humidity was monitored and recorded once daily.
Temperature:	Desired: 67-76°F (19-24°C) Actual: 67-75°F (19-24°C)
Humidity:	Desired: 40-60% Actual: 32-84%

J. Test Substance Administration:

Route:	Oral, via intubation (oral gavage).
Justification of Route of Administration:	The oral route is one of the potential routes of human exposure to this test substance and is the route specified in the referenced guidelines.
Analyses of Dose Suspensions:	Analyses to determine stability, homogeneity and concentration of the test substance with a carrier under the conditions of this study were performed by the Metabolism and Analytical Chemistry Department at Bio/dynamics, Inc. Results of these analyses are presented in Appendix K.

II. MATERIALS AND METHODS (cont.):

J. Test Substance Administration (cont.):

Method:	Appropriate amounts of test substance were suspended in the vehicle weekly to yield dose levels of 25, 75, and 250 mg/kg/day (which are concentrations of 5, 15 and 50 mg/ml, respectively) at a constant dose volume of 5 ml/kg/dose. Individual doses were adjusted by most recent weekly body weight. Control animals were administered the vehicle at the same dose volume as the treated animals.
Dose Volume:	5 ml/kg/dose
Frequency:	Once daily (7 days per week) through the day prior to necropsy.
Duration:	90 or 91 days (depending on day of sacrifice).
Dates of Treatment:	23 July to 20 or 21 October 1991 (depending on day of sacrifice).

K. Recovery Period:

Duration:	28 days
Dates of Recovery:	22 October to 18 November 1991

L. Observations:

For Mortality and Gross Signs of Toxicologic or Pharmacologic Effects:	Twice daily, once in the morning and once in the afternoon.
Detailed Physical Examination for Signs of Local or Systemic Toxicity, Pharmacologic Effects and Palpation for Tissue Masses:	(Methodology and References, Appendix A) Pretest and weekly thereafter.

II. MATERIALS AND METHODS (cont.):

M. Ophthalmoscopic Examination: (Methodology and References, Appendix A)

Time Intervals

Pretest: 12 July 1991
Termination: 17 October 1991
Recovery: 15 November 1991

N. Body Weight: (Methodology and References, Appendix A)

Twice pretest, weekly during the study period and terminally (after fasting).

O. Food Consumption: (Methodology and References, Appendix A)

Once pretest and weekly throughout the study.

P. Laboratory Studies: (Methodology and References, Appendix A)

Blood was obtained via venipuncture of the orbital sinus (retrobulbar venous plexus) while animals were lightly anesthetized with a mixture of carbon dioxide and oxygen. Rats were fasted overnight prior to blood collections.

Number of Animals: Performed on up to 10 animals/sex/group at terminal sacrifice and on all remaining animals (up to 10 animals/sex/group) in Groups I and IV at the recovery sacrifice.

Parameters Evaluated:

Hematology:

Time Intervals

Termination: 21, 22 October 1991
Recovery: 18 November 1991

hemoglobin concentration
hematocrit
erythrocyte count
reticulocyte count
platelet count
mean corpuscular volume
mean corpuscular hemoglobin
mean corpuscular hemoglobin concentration
prothrombin time
activated partial thromboplastin time
total and differential leukocyte counts
erythrocyte morphology

II. MATERIALS AND METHODS (cont.):

P. Laboratory Studies (cont.):

Parameters Evaluated (cont.):

Clinical Chemistry:	Time Intervals
aspartate aminotransferase	Termination: 21, 22 October 1991
alanine aminotransferase	Recovery: 18 November 1991
alkaline phosphatase	
blood urea nitrogen	
creatinine	
blood urea nitrogen/ creatinine ratio (calculated)	
fasting glucose	
cholesterol	
triglycerides	
total protein	
albumin	
globulin (calculated)	
A/G ratio (calculated)	
total bilirubin	
sodium	
potassium	
chloride	
calcium	
inorganic phosphorus	
gamma glutamyl transpeptidase	

Urinalysis:	Time Intervals
gross appearance	Termination: 17, 18 October 1991
specific gravity	Recovery: 15 November 1991
pH	
protein	
nitrite	
glucose	
ketones	
bilirubin	
occult blood	
urobilinogen	
16-hour volume	
microscopic analysis	

II. MATERIALS AND METHODS (cont.):

Q. Postmortem:

Animals Found Dead or Killed at Scheduled Sacrifice Intervals:	Complete gross postmortem examinations were performed on all animals. External surface, all orifices, the cranial cavity, carcass, the external surfaces of the brain and spinal cord, the thoracic, abdominal and pelvic cavities and their viscera and cervical tissues and organs were examined for all animals. Animals were fasted prior to scheduled sacrifices.
Terminal Sacrifice:	21 and 22 October 1991
Number of Animals:	79 animals total
Recovery Sacrifice:	18 November 1991
Number of Animals:	38 animals total
Sacrifice Method:	Exsanguination under ethyl ether anesthesia.
Organs Weighed and Organ/Body Weight, Organ/Brain Weight Ratios Calculated:	(Methodology and References, Appendix A) The following organs were weighed for all animals at the scheduled sacrifice intervals. Paired organs were weighed together. adrenals brain heart kidneys liver lungs pituitary spleen testes with epididymides thymus thyroid/parathyroids ovaries

II. MATERIALS AND METHODS (cont.):

Q. Postmortem (cont.):

Tissues Preserved:[1]

adrenals (2)
aorta (thoracic)
bone (sternum)
bone marrow (sternum)
brain (medulla/pons, cerebrum and cerebellum)
epididymides (2)
esophagus
eyes with optic nerve (2)
femur (including articular surface)
heart
intestine
- cecum
- colon
- duodenum
- ileum
- jejunum
- rectum

kidneys (2)
lacrimal gland (2)
liver (2 lobes)
lungs (with mainstem bronchi - 2)
lymph nodes (mesenteric, mediastinal)
mammary gland
nasopharyngeal (4)
nerve (sciatic)
ovaries (10 sections/ovary)
pancreas
pituitary
prostate
salivary gland (mandibular)
seminal vesicles (2)
skeletal muscle (<u>biceps femoris</u>)
skin
spinal cord (cervical, thoracic, lumbar)
spleen
stomach (3)
testes (2 sections/testis)
thymus
thyroid/parathyroids (2)
trachea
urinary bladder
uterus (body/horns) with cervix
gross lesions

[1]Number in parentheses indicates number of organs/sections preserved.

II. MATERIALS AND METHODS (cont.):

Q. Postmortem (cont.):

Tissues Examined Histopathologically:[2]

All tissues listed below and on the following page were examined for all animals in the control and high-dose groups which were scheduled for sacrifice at termination of dosing (includes one Group IV male which died prior to sacrifice). In addition, the lungs, liver, kidneys and lymph nodes were examined for all animals in Groups II and III. Microscopic examination of the lungs and lymph nodes from the control and high-dose animals sacrificed at the recovery interval was also performed.

adrenals (2)
aorta (thoracic)
bone (sternum)
bone marrow (sternum)
brain (medulla/pons, cerebrum and cerebellum)
epididymides (2)
esophagus
eyes with optic nerve (2)
femur (including articular surface)
heart
intestine
- cecum
- colon
- duodenum
- ileum
- jejunum
- rectum

kidneys (2)
lacrimal gland (2)
liver (2 lobes)
lungs (with mainstem bronchi - 2)
lymph nodes (mesenteric, mediastinal)
mammary gland
nasopharyngeal (4)
nerve (sciatic)
ovaries (10 sections/ovary)
pancreas
pituitary
prostate
salivary gland (mandibular)

[2]Number in parentheses indicates number of organs/sections examined.

II. MATERIALS AND METHODS (cont.):

Q. Postmortem (cont.):

Tissues Examined Histopathologically (cont.):[2]	seminal vesicles (2) skeletal muscle (biceps femoris) skin spinal cord (cervical, thoracic, lumbar) spleen stomach (3) testes (2 sections/testis) thymus thyroid/parathyroids (2) trachea urinary bladder uterus (body/horns) with cervix gross lesions
Preservatives:	10% neutral buffered formalin (eyes, testes and epididymides were initially placed in Bouin's solution, transferred to 70% Synosol®, and then preserved in formalin).
Stain:	(Methodology and References, Appendix A) Hematoxylin and Eosin

R. Statistical Analysis: (Methodology and References, Appendix A)

Body weight, body weight change (week to week), body weight change from Week 0, food consumption, hematology and clinical chemistry parameters, terminal organ and body weights and organ/body and organ/brain weight ratios were analyzed. Mean values of all dose groups were compared to control at each time interval. Statistically significant differences from control are indicated on mean tables of appendices.

[2]Number in parentheses indicates number of organs/sections examined.

II. MATERIALS AND METHODS (cont.):

S. Protocol Deviations:

The following protocol deviations occurred during the study period. These deviations were not considered to have had an adverse effect on the study purpose or results.

1. Humidity values were outside of the desired range on several occasions.

2. Due to a calculation error at Week 9, control Female No. 1503 received 1.4 ml/day rather than 1.3 ml/day and high-dose Male No. 4006 received 2.4 ml/day (approximately 261 mg/kg/day) rather than 2.3 ml/day (250 mg/kg/day) during this week.

III. RESULTS AND DISCUSSION:

A. Mortality (Appendix B):

In the treatment phase of this study, the only death was a high-dose (Group IV) male in Week 2. Based on the results of gross and microscopic evaluations, this death can not be clearly attributed to the test material. During the recovery phase of this study two control animals (one male and one female) died.

B. In-Life Physical Observations (Appendix C):

All of the noted observations are common to laboratory rats and not test material-related.

C. Ophthalmoscopic Examinations (Appendix D):

There were no indications of treatment-related effects in the eyes.

D. Body Weights (Appendix E):

The body weight values of the low- and mid-dose groups (II and III) and high-dose (Group IV) females were similar to the control group. Body weight gains for Group IV males were statistically significantly decreased compared to values for the control group from Week 3 to 8 and tended to remain decreased during the remainder of the dosing period. However, mean weights for this group were within two percent of the control mean at study termination, and Group IV males had body weight gains similar to or greater than the control group during the recovery period.

III. RESULTS AND DISCUSSION (cont.):

E. Food Consumption (Appendix E):

The high-dose (Group IV) and occasionally the mid-dose (Group III) food consumption values were statistically significantly greater than the control group values. Though these differences appear to be test material-related, increased food consumption values are generally not considered to be an adverse effect. This difference was not seen in the recovery animals.

F. Hematology (Appendices F and G):

At termination, there was a treatment-related increase in the white blood cell counts in the high-dose (Group IV) animals when compared to the control group; this effect was more evident in the females. The increases were due to an increase in the segmented neutrophil portion of the white blood cell population. Although these differences appear to represent an effect of test material administration, white blood cell counts in all of the groups were within the range of Bio/dynamics' normal control values. This effect was not evident at the end of the recovery period.

G. Clinical Chemistry (Appendix H):

Slight, statistically significant, elevations in serum alanine aminotransferase (SGPT) values and decreases in total protein and serum albumin values were seen in high-dose males at study termination. SGPT values for mid- and high-dose females were also slightly higher than control values, but differences were not statistically significant. Similar differences were not evident at termination of the recovery period. Most individual values were within Bio/dynamics' historical control ranges and, in the absence of microscopic liver pathology, these slight, reversible differences are considered to be of questionable toxicological significance.

III. RESULTS AND DISCUSSION (cont.):

H. Urinalysis (Appendix I):

There were no treatment-related effects evident in the urinalysis values.

I. Terminal Organ and Body Weight, Organ/Body Weight and Organ/Brain Weight Ratios (Appendix J):

Lung weights and/or lung/body and lung/brain weight ratios tended to increase with increasing dose and the increases were greatest in the mid- and high-dose females. This treatment-related increase was consistent with microscopic observations of granuloma formation and edema in the lungs of treated animals. This effect persisted through the recovery period in the high-dose group males, but not in the females.

J. Analyses of Dosing Suspensions (Appendix K):

The analysis results confirmed that the test material dosing suspensions were homogeneous and stable during the dosing period. Weekly analyses confirmed that the dosing solutions were prepared within acceptable tolerances.

K. Pathology (Appendix L, Volume II):

Macroscopic examination revealed changes which occurred sporadically, or otherwise showed similar incidences between the control and the treated groups.

Microscopic examination revealed microgranulomas in the lungs, mediastinal lymph nodes and mesenteric lymph nodes of treated animals killed at the end of the study (males and females, Groups II, III and IV) and high-dose animals killed after a 4-week recovery period (males and females, Group IV).

III. RESULTS AND DISCUSSION (cont.):

K. Pathology (cont.):

Incidence is tabulated below. Severity was similar in all three dose groups, including the high-dose recovery group.

Incidence of Microgranulomas in the Lung and Lymph Nodes
(N = 10 for all observations)

Group	Dose (mg/kg/day)	LUNGS M	LUNGS E	LYMPH NODES Mesenteric M	LYMPH NODES Mesenteric E	LYMPH NODES Mediastinal M	LYMPH NODES Mediastinal E
Termination							
I	0	0	0	0	0	0	0
II	25	4	1	7	6	2	0
III	75	8	7	8	10	7	2
IV	250	6	7	8	10	3	4
Recovery							
I	0	0	0	0	0	0	0
IV	250	7	3	10	10	5	2

Acute inflammation, purulent exudate, proteinaceous exudate and hyperplasia or squamous metaplasia of the respiratory mucosa were seen in the nasal turbinates of the high-dose males and females at study termination (these tissues were not examined for the low- or mid-dose group or the recovery animals).

The changes in the lungs and nasal turbinates were believed to have been induced by inadvertent aspiration of the test material during the dosing process or by excretion of the test material by the respiratory system. The test material probably provoked an acute inflammatory reaction in the lungs and nasal turbinates, which, in time, became chronic and predominantly granulomatous in the lungs. Prolonged irritation of the respiratory mucosa in the nasal passages apparently led to hyperplasia or metaplastic change in the squamous

III. RESULTS AND DISCUSSION (cont.):

K. Pathology (cont.):

epithelium. Drainage of the inhaled test material from the lungs may have caused the formation of the microgranulomas in the mediastinal and, perhaps, the mesenteric lymph nodes. Absorption of the test material through the gastrointestinal tract probably produced the granulomatous reaction in the mesenteric lymph nodes.

No compound-related effects were seen in the progression of sperm development, nor were there any abnormalities in the testes and epididymides in most of the animals in this study. The notable findings in two low-dose males were incidental to treatment. No other treatment-related pathologic findings were seen in any of the other tissues examined.

IV. CONCLUSION:

Oral administration of TABANOL to rats for 90 days at doses of 25, 75 and 250 mg/kg/day was associated with granulomas in the lungs and lymph nodes of animals in all dose groups; no recovery was evident in the high-dose recovery group. Elevated lung weights were also seen, primarily in mid- and high-dose animals. Other signs of toxicity were seen in the high-dose group only. However, based on the presence of lung and lymph node microgranulomas at the lowest dose administered, a no effect level was not established in this study.

John M Mitchell — 10/9/92

John M. Mitchell, M.S.
Study Director
Toxicologist

Date

Ira W. Daly — 10/9/92

Ira W. Daly, Ph.D., D.A.B.T.
Senior Vice-President and
Director of Toxicology

Date