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Division of Biology and Safety Evaluation

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PROJECT NO. 79-7342

A DOMINANT-LETHAL INHALATION STUDY

WITH BENZENE IN RATS

Final Report

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PROJECT NO. 79-7342

A DOMINANT-LETHAL INHALATION STUDY

WITH BENZENE IN RATS

ABSTRACT

This study was conducted for the Chemical Manufacturers Association and American Petroleum Institute to assess the mutagenic potential of Benzene in male rats using the dominant-lethal test. Benzene was administered by inhalation at dose levels of 1, 10, 30 and 300 ppm. Male Charles River CD rats (20 males/group) of proven fertility were exposed 6 hours/day, five days/week for a ten-week treatment period.

Dominant-Lethal mutagenicity was evaluated over a two-week post-treatment mating period. On the last day of dosing, each male was caged with two virgin, untreated females for seven consecutive days. At the end of this interval, these females were removed and replaced with another two untreated females. All females exposed to males were sacrificed 19 days after the first day of exposure to the males. Females were scored for corpora lutea and uterine implantation data. The latter were distinguished as viable fetuses and dead implants.

Parameters evaluated include: male mortality, physical in-life observations and body weight data (treatment, mating and post-mating periods). Each male was given a gross postmortem examination and testes/epididymides were preserved in formalin, and histological evaluations of these tissues were performed for all control and high-dose males. Mutagenicity was evaluated on the basis of pre-implantation loss (implantation efficiency ratio) and post-implantation loss (mean number of dead implants and mutagenic ratio, i.e. no. dead implants/ total implants). Pregnancy rate data were also evaluated.

No treatment-related effects were evident in male mortality, in-life physical observations or body weight data.

Pregnancy rates of females exposed to treated males showed no statistically significant changes at Weeks 1 or 2.

Implantation efficiency ratios (indications of pre-implantation loss) were comparable between the control and treated groups for both weeks of the mating period.

The mean number of dead implants and mutagenic ratios were comparable between the control and treated groups II, III and IV (1, 10 and 30 ppm, respectively) at Week 1. At Week 2, the mean number of dead implants and mean mutagenic ratio data in these same treated groups were slightly higher than control, but comparable to historical control data for these same parameters. Control group data for this interval was considered unusually low.

In the high dose group (300 ppm), the mean number of dead implants and mean mutagenic ratio values were higher than control for each week of the post-treatment mating period. These differences were not statistically significant. The increases in mean number of dead implants and mutagenic ratio were largely attributed to data for females exposed to a single high-dose male. This male impregnated both females each week and each female had a high number of dead implants.

Following a 10-week post-mating interval, males were sacrificed and given a gross postmortem examination. These examinations showed several males in each of the treated groups with hepatic pallor and accentuation of lobular pattern of the liver. Microscopic evaluation of testes/epididymides revealed two high-dose males with testicular lesions.

Thus, Benzene exposure at dose levels of 1, 10 and 30 ppm did not effect male reproduction performance or have a demonstrable dominant-lethal mutagenic effect. In the high-dose group (300 ppm) the observed increase in mean number of dead implants and mean mutagenic ratio were primarily related to the performance of a single male. It is unclear if these effects were related to benzene exposure as the increase in group values for mean dead implants and mutagenic ratio were not statistically significant. No gross or histopathologic lesions were noted during the evaluations of the testes in this same high-dose male.

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I. INTRODUCTION

This study, conducted for the Chemical Manufacturers Association and the American Petroleum Institute, was designed to assess the mutagenic potential on male rats of benzene at dose levels of 1, 10, 30 and 300 ppm. Test substance was administered via inhalation for 6 hours per day, 5 days a week for 10 consecutive weeks. Mutagenic potential was evaluated by the dominant-lethal test.

Species and strain of test animals, dose levels and route of administration were established by the sponsors. Testing was conducted at Bio/dynamics, Inc., Mettlers Road, East Millstone, New Jersey 08873. All specimens, raw data and final report are maintained in the Bio/dynamics archives.

II. MATERIALS

A. Test Substance:	Benzene
Supplier:	Chemical Manufacturers Association
Description:	Clear colorless liquid with characteristic odor.
Date Received:	November 13, 1979
Lot No.:	API-CMA Benzene Lot No. 1 (Sample withdrawal date 11/13/79)
Stability:	Benzene was analyzed for purity at four intervals during the study, i.e. Pre-test, prior to initiation of Treatment, Week 6 of the Treatment Period and at Termination of treatment. (See Appendix G).
Storage:	Amber glass bottles at room temperature

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II. MATERIALS (cont.):

B. Test Animals:

Species: Rat

Strain: CD® (Sprague-Dawley derived)

Number of Animals:

Purchased:

Males: 140

Females: 267 (pre-treatment mating period)
459 (post-treatment mating period)

Placed on Test:

Males: Pre-Treatment Mating Period-total 123 males
Initiation of Treatment - total 100 males
(20/group)

Females: Pre-treatment mating period: 2 females/male;
total 246.
Post-treatment mating period: 2 females/
male/week; total 396.

Age:

Males: 10 weeks at initiation of pre-treatment
mating period.

Females: Virgin; at least 200 grams at initiation
of mating (pre- and post-treatment periods).

Supplier: Charles River Breeding Laboratories
Wilmington, Massachusetts 01887

Justification for
Animal Selection: Generally recognized standard laboratory
rat

Dates Received:

Males: 29 November 1979

Females: 29 November 1979 (pre-treatment mating
period)
6 March 1980 (post-treatment mating period)

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III. EXPERIMENTAL OUTLINE:

Group	Exposure Treatment ^a	Males	No. of Rats	
			Pre-treatment Mating Period	Post-treatment Mating Period
I	Control-Chamber-Exposed	20	40	80
II	Benzene - 1 ppm	20	40	76 ¹
III	Benzene - 10 ppm	20	40	80
IV	Benzene - 30 ppm	20	40	80
V	Benzene - 300 ppm	20	40	80

^aTreatment schedule - 6 hours/day, 5 days/week for 10 consecutive weeks.

¹One Group II male died during the treatment period reducing the number of females exposed to males to 38 per week (2/male; 19 males) for a total of 76 for this group.

A sufficient number of males were acquired to insure that enough proven fertile males were available to start on treatment. Male fertility was evaluated during a one week pre-treatment mating period; males were considered fertile if they impregnated at least one female.

Dominant lethal mutagenicity was evaluated on the basis of pre-implantation loss (i.e. implantation efficiency ratio) and post-implantation loss (i.e. mean number of dead implants, mutagenic ratio) during a two week post-treatment period.

IV. METHODS:

A. In-Life:

Husbandry:

Lights: 12 hours on/12 hours off

Temperature: Recorded twice daily.

During Exposure Period:

Housing: Paired in stainless steel wire mesh cages in chamber

IV. METHODS (cont.)

A. In-Life (cont.)

Food: None

Water: None

Humidity: Relative humidity recorded during the daily exposure intervals (at least three distinct intervals daily). Initiated during Week 1 of the treatment period.

During Non-Exposure Period:

Housing: Individual, except during mating, in suspended wire mesh cages; during mating housed with two females in these same cages.

Food: Purina Rodent Laboratory Chow 5002 (Certified) Mash; ad libitum. See Appendix F

Humidity: 40-60% recorded twice daily; morning and afternoon. Humidity was recorded on 231 days for the duration of the study. It was found to be out of range approximately 10% of the time. In chambers humidity was found to be out of range approximately 18%-25% of the time.

Water: Tap - Elizabeth Water Co. automatic watering system - ad libitum; analyzed for contaminants on a monthly basis. Special water analyses (Appendix H) were done at two intervals during the study - during the 10-week treatment period and near the termination of the study. Analysis included:

Heavy metals: Cd, As, Pb, Hg, Se, Be, Sb
PCB's
Organic Phosphate Pesticides-Malathion
Chlorinated hydrocarbons including lindane, heptachlor, DDT and Dieldrin
Benzene
Carbamate pesticide screen

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IV. METHODS (cont.):

A. In-Life (cont.):

**Identification of
Animals:**

Each male and female were identified with a metal ear tag bearing its animal number. This number plus the Bio/dynamics project number comprised a unique identification number.

Assignment to Groups: Males of proven fertility (pre-treatment mating period) were assigned to groups so as to equalize pre-test body weight.

**Benzene Administra-
tion:**

Route: Inhalation

Chamber Operation: See Appendix B

Frequency: 6 hours/day for Group I and test substance-treated groups.

**Duration: (Dates
of Treatment):** Five days (Monday-Friday)/week, for 10 consecutive weeks (14 January 1980 - 21 March 1980).

**Atmospheric
Sampling:** See Appendix B

**Observations for Signs
of Pharmacologic or
Toxicologic Effects
and Mortality:** Twice daily (morning, afternoon)

**Detailed Physical
Examination Including
Palpation for Tissue
Masses:** Males - weekly throughout the study. During the treatment period the detailed physical examinations were given following the exposure period.

Body Weights: Males - weekly throughout the study.

IV. METHODS (cont.):

A. In-Life (cont.):

Mating Design and
Mating Period:
Pre-treatment Mating
Period:

Fertility of each male used in this study was determined on the basis of performance during a one week pre-treatment mating period.

During this interval each male was caged continuously with two untreated, virgin females for seven consecutive days. At the end of this period females were removed, housed individually and sacrificed 18 days after the first day of caging with males. Corpora lutea and uterine implantation data were recorded. Males were considered of proven fertility if they impregnated at least one female during the pre-treatment interval. Corpora lutea and implantation data for females mated to control and treated group males during the pre-treatment mating period are presented in Appendix A.

Duration of the pre-treatment mating period-
23 December 1979 - 30 December 1979.

Post-treatment Mating
Period:

On the last day of treatment at least two hours after termination of exposure each male was caged with two untreated, virgin females for seven consecutive days. At completion of this interval these females were removed and replaced with another two untreated, virgin females for a second seven day interval.

Duration of post-treatment mating period -
Week 1 - 21 March 1980 - 28 March 1980
Week 2 - 28 March 1980 - 4 April 1980

B. Postmortem:

Sacrifice:

Males - sacrificed at completion of the study following sacrifice of the last females. Gross postmortem examination performed. Males sacrificed - 12 June 1980

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IV. METHODS (cont.):

B. - Postmortem (cont.):

Females:

Pre-Treatment
Mating Period:

Sacrificed 18 days after the first day of caging with the males, resulting in a gestation period of 11-18 days. Ovaries evaluated for the number of corpora lutea; uterine implantation data recorded. The latter were distinguished as viable fetuses or dead implants.

Date of Sacrifice: January 10, 1980

Post-Treatment
Mating Period:

Sacrificed 19 days after the first day of caging with males, resulting in a gestation period of 12-19 days. Ovaries and uterus were evaluated:

Date of Sacrifice: Week 1, 9 April, 1980.
Week 2, 16 April, 1980.

Sacrifice Method:

Lethal exposure to ether.

Uterine Implantation
Data (Post-Treatment
Mating Period):

The abdominal cavity of each female was opened and the uterus with ovaries attached dissected free and removed. Immediately, the uterus was evaluated grossly for implantation sites (i.e., criteria for pregnancy). Uteri with implantations were further dissected along the antimesometrial margin to better reveal the implants. The number of implantation sites (both horns) was recorded and each implant further distinguished as:

1. Viable fetus: the amnion was dissected, the fetus observed and viability was determined on the basis of one of the following criteria: fetal movements; beating heart (observed through the transparent thoracic cavity); or general size and vascular development.

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IV. METHODS (cont.):

B. Postmortem (cont.):

Uterine Implantation

2. Dead implants:

Dead implants were identified either as an implant that elicited a decidual response but no fetus was evident or a fetus that by size and/or viability criteria (i.e. movement of the head and extremities, beating heart or vascularity) was not considered viable.

Ovaries - the ovaries were dissected free from the uterine horns and evaluated grossly for the presence and number of corpora lutea.

The uteri and ovaries from all females (pregnant and non-pregnant) were appropriately identified and preserved intact in a 10% neutral buffered formalin solution.

Male Reproductive System:

Tissues Preserved: Testes and Epididymides were saved from all males (testes were fixed for 48 hours in Bouin's solution, rinsed in tap water and stored in 10% neutral buffered formalin); epididymides saved in 10% formalin.

Tissues Examined Histopathologically:

Testes and Epididymides (all control and high-dose animals).

C. Statistical Analysis: See Appendix I.

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V. RESULTS AND DISCUSSION:

A. Mortality:

No mortality occurred in control group or treated Groups III, IV or V (10, 30 and 300 ppm) throughout the study. In Group II (1 ppm) male No. 300 died during Week 8 of the treatment period and male No. 316 died during Week 2 of the post-mating interval. Gross postmortem observations for each of these males are presented in Appendix D.

B. Body Weight Data:

Individual male body weight data during the treatment, mating and post-mating intervals are presented in Appendix C. Mean body weight data during the study are summarized in Table 1 (page 15-16).

Mean weekly body weights during the treatment period and mean weight gain during this same interval were comparable between the control and treated groups. Likewise, mean body weights during the mating period and 10-week post-mating interval were comparable between all groups.

No treatment effect on body weight data was evident.

C. Physical In-Life Observation Data:

A slight increase in the incidence of males exhibiting lacrimation was noted in Groups III, IV and V (10, 30 and 300 ppm, respectively) during the first three weeks of the treatment period. During this interval, lacrimation was noted in 3 control, 3 Group II (1ppm), 7 Group III, 9 Group IV and 13 Group V males; this represents an incidence of 15%, 15%, 35%, 45%, and 65% of the animals in each group, respectively. For the remainder of the study the incidence of males with lacrimation observations was similar between the control and treated groups.

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During the mating period several control and treated males were noted with a swollen cervical area. This observation is typical of sialodacryoadenitis (SDA) viral infection. The observation of "swollen cervical area" was transient in nature and occurred in both control and treated males; no treatment effect was indicated.

Other observations noted during the physical in-life evaluations were noted with similar frequency between the control and treated groups.

D. Male Impregnating Indices and Pregnancy Rates:

Male impregnating indices and pregnancy rates for each week of the post-treatment mating period are presented in Table 2 (page 17). These indices are summarized from reproduction data presented in Appendix C.

Male impregnating indices for each week of the post-treatment mating period were comparable between the control and treated group. Every control and treated male impregnated at least one female during the total two-week mating period.

Pregnancy rates during Week 1 of the post-treatment mating period were lower than control in Groups II, III and IV (1, 10 and 30 ppm, respectively); these differences were not statistically significant. Pregnancy rates for the high-dose group (300 ppm) at Week 1 were comparable to control. In the absence of an effect on pregnancy rate at the highest dose level (300 ppm) at Week 1, this decline in pregnancy rates at the lower dose levels was not considered indicative of a treatment effect.

During Week 2 of the post-treatment mating period pregnancy rates were comparable between the control and treated groups.

E. Corpora Lutea, Implantation and Implantation Efficiency Data:

Corpora lutea and implantation data and implantation efficiency values (representative of pre-implantation loss) for individual females during the post-treatment mating period are presented in Appendix E. These data are summarized in Table 3 (page 18).

The mean number of corpora lutea were comparable between the control and treated groups for each week of the post-treatment mating period. The mean number of implantation sites at Week 1 was comparable between the control and Groups II, IV and V (1, 30 and 300 ppm, respectively). In Group III (10 ppm), a slight decrease in mean number of implants was noted at Week 1; this difference was not statistically significant and was, in part, attributed to a reduced ovulation rate (i.e. decreases in number of corpora lutea) for this group at this same interval. The mean number of implantation sites during Week 2 of the post-treatment mating period was comparable between the control and treated groups.

Mean implantation efficiency values (indicative of pre-implantation loss) were comparable between the control and treated groups for each week of the post-treatment mating period.

F. Uterine Implantation Data Amplified - Mean Number of Viable Fetuses and Dead Implants:

Uterine implantation data for individual females during each week of the post-treatment mating period are presented in Appendix E. Mean implantation data distinguished as to number of implants, viable fetuses and dead implants are presented in Table 4 (page 19).

At Week 1 of the post-treatment mating period, the mean number of dead implants was comparable between the control and treated Groups II, III and IV (1, 10 and 30 ppm) and slightly higher than control in Group V (300 ppm); however, this difference between the control and high-dose groups was not statistically significant.

During Week 2, the mean number of dead implants was slightly higher than control at each dose level; however, these differences were not statistically significant. The mean number of dead implants in the control group at Week 2 was considered unusually low. Historically, the mean number of dead implants recorded for control groups in studies of this type (inhalation

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dominant lethal studies) range from 0.3-1.4 with a weekly mean of 0.7 over 22 weekly intervals (three separate studies). In respect to historical control data and concurrent control data at Week 1, the increase in mean number of dead implants for treated Groups II, III and IV (1, 10, 30 ppm) at Week 2 was not considered unusually high.

The slight increase in mean number of dead implants in Group V (300 ppm) for each week of the post-treatment mating period was, in part, attributed to an increase in dead implants in females mated to a single high-dose male (No. 913). During Week 1, the two females mated to this male had a total of 24 implants of which 16 (66.7%) were dead. In Week 2, the two females mated to male No. 913 had a total of 28 implants of which 16 (57%) were dead.

The mean number of viable fetuses was considered comparable between the control and treated groups for each week of the post-treatment mating period.

G. Mutagenic Ratio Data:

Mutagenic ratio data for individual females during Weeks 1 and 2 of the post-treatment mating period are presented in Appendix E. Mean mutagenic ratio data are summarized in Table 4 (page 19).

During Week 1 of the post-treatment mating period the mean mutagenic ratios were considered comparable between the females mated to control males and the females mated to treated males in Groups II, III and IV (1, 10 and 30 ppm, respectively). The mean mutagenic ratio for the females mated to the high-dose males (Group V, 300 ppm) was higher than control; however, this difference was not statistically significant. Within the high-dose group, the increase in mean mutagenic ratio was largely attributed to three females. Two of these females (Nos. 1026 & 1027) were mated to a single high-dose male (No. 913); female No. 1026 had 14 implants of which nine were dead (a mutagenic ratio of 64.3%) and female No. 1027 had 10 implants

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of which seven were dead (a mutagenic ratio of 70.0%). The third female with a high mutagenic ratio resulting from an increase in dead implants, was female No. 1024 (mated to high-dose male No. 912); this female had 15 implants of which nine were dead (a mutagenic ratio of 60.0%). The second female mated to male No. 913 during Week 1 had 12 implants and all were viable.

During Week 2, mean mutagenic ratios for females exposed to the treated males were all slightly higher than the control group value. This was attributed to unusually low values for the control during this interval (i.e. a mean mutagenic ratio of 4.4%). Historically, using this strain of rat a mean mutagenic ratio of 7.0% has been observed (this represents 20 weekly intervals for three dominant lethal inhalation studies with a range in weekly values of 4.0-11.0%). The mean mutagenic ratio for treated Groups II, III and IV (1, 10 and 30 ppm, respectively) fall within this historical control range. As was the case with Week 1 of the post-treatment mating period, the mutagenic ratio for the high-dose group (300 ppm) was higher (i.e. 11.7%) than the concurrent control and was just outside the range of values noted historically (i.e. 4.0-11.0%). During Week 2, the higher mutagenic ratio was again attributed to the two females (Nos. 1066, 1067) that mated with male No. 913. Female No. 1066 had 16 implants and eight were dead (a mutagenic ratio of 50.0%); female No. 1067 had 12 implants and eight were dead (a mutagenic ratio of 66.7%).

H. Gross Postmortem Observations (Appendix D):

Males were sacrificed after a 10-week post-mating interval and given a gross postmortem evaluation. These postmortem evaluations revealed an increased incidence of males with hepatic pallor and accentuation of the lobular pattern of the liver among the treated group animals. Other morphologic findings occurred sporadically in the treated and/or control animals and were not considered to be related to treatment.

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I. Histopathological-Evaluations (Appendix E):

The testes and epididymides of rats from the control and high-dose groups were evaluated histopathologically.

In high-dose male No. 908, the testes revealed moderate tubular degeneration and atrophy characterized by multifocal depletion of spermatogenic epithelium as well as thickening of the basement membrane. During the post-treatment, mating period this male impregnated both females during Week 1 and one female during Week 2. No effect was indicated in implantation efficiency values or mutagenic ratio values for females impregnated by this male.

In high-dose male No. 900, one testis revealed focal disarray and syncital transformation of spermatogenic epithelium. This male impregnated both females each week of the post-treatment mating period. During Week 2 one female (No. 1041) had an unusually low implantation efficiency value (indicative of pre-implantation loss) and for Week 1 both females (Nos. 1000 and 1001) had high mutagenic ratios.

In summary, microscopic evaluation of the testes and epididymides of control and high-dose rats revealed two high-dose males with lesions; no such lesions were noted in the control animals. Concerning the lesions noted in the high-dose group, there was no conclusive evidence indicating a compound-related injury.

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Table 1
A Dominant-Lethal Inhalation Study
With Benzene in Rats

Mean Male Body Weights - grams													
Group ppm	Week:	Initial	Treatment Period										Wt. Gains
			1	2	3	4	5	6	7	8	9	10	1-10
I 0 (Chamber- exposed Control)	Mean	398	406	411	423	438	455	464	476	487	500	500	94
	S.D.	35	31	28	28	30	32	31	34	37	39	40	20
	N	20	20	20	20	20	20	20	20	20	20	20	20
II 1	Mean	407	406	412	425	441	460	465	471	477	491	491	88
	S.D.	27	27	31	35	37	39	39	36	39	39	40	21
	N	20	20	20	20	20	20	20	20	19	19	19	19
III 10	Mean	407	409	413	430	444	464	471	481	493	505	505	96
	S.D.	38	41	42	44	47	51	52	48	54	56	54	18
	N	20	20	20	20	20	20	20	20	20	20	20	20
IV 30	Mean	406	409	412	426	440	459	464	476	484	495	498	90
	S.D.	37	36	37	40	40	43	42	43	41	42	42	20
	N	20	20	20	20	20	20	20	20	20	20	20	20
V 300	Mean	409	411	412	424	439	458	468	481	492	502	505	95
	S.D.	38	34	34	35	39	40	42	43	45	45	46	18
	N	20	20	20	20	20	20	20	20	20	20	20	20

No statistically significant differences from control.

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Table 1 (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

Mean Male Body Weights - grams (cont.)

Group ppm	Week:	Post-Treatment Mating Period		Post-Mating Interval									
		<u>1</u>	<u>2</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>10</u>	
I 0 (Chamber- exposed Control)	Mean	505	521	538	550	554	568	575	590	599	602	616	
	S.D.	40	41	45	47	49	51	51	51	52	54	59	
	N	20	20	20	20	20	20	20	20	20	20	20	
II 1	Mean	498	518	534	551	556	571	581	595	608	612	630	
	S.D.	34	36	42	45	48	48	49	48	49	49	49	
	N	19	19	19	18	18	18	18	18	18	18	18	
III 10	Mean	511	526	544	558	563	579	586	596	608	606	630	
	S.D.	54	57	63	67	66	71	72	72	71	75	74	
	N	20	20	20	20	20	20	20	20	20	20	20	
IV 30	Mean	502	519	537	551	560	578	581	591	606	605	624	
	S.D.	45	46	48	48	49	49	48	50	53	51	52	
	N	20	20	20	20	20	20	20	20	20	20	20	
V 300	Mean	509	524	544	559	564	579	587	603	611	610	629	
	S.D.	48	47	46	48	49	48	50	52	50	49	53	
	N	20	20	20	20	20	20	20	20	20	20	20	

No statistically significant differences from control.

Table 2
A Dominant-Lethal Inhalation Study
With Benzene in Rats

Male Impregnating Indices and Pregnancy Rates
Post-Treatment Mating Period

Group ppm	Male Impregnating Index ^a		Pregnancy Rate ^b	
	No.	%	No.	%
	<u>Week 1</u>			
I (0)	20/20	100.0	36/40	90.0
II (1)	19/19	100.0	30/38	78.9
III (10)	19/20	95.0	30/40	75.0
IV (30)	19/20	95.0	29/40	72.5
V (300)	20/20	100.0	37/40	92.5
	<u>Week 2</u>			
I (0)	20/20	100.0	36/40	90.0
II (1)	19/19	100.0	32/38	84.2
III (10)	20/20	100.0	32/40	80.0
IV (30)	19/20	95.0	35/40	87.5
V (300)	19/20	95.0	36/40	90.0

No statistically significant differences from control.

^aMale impregnating index = No. of males impregnating at least one female/No. of males caged with females.

^bPregnancy rate = No. of pregnant females/No. of females exposed to males.

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A Dominant-Lethal Inhalation Study
With Benzene in Rats

Corpora Lutea, Implantation and Implantation Efficiency Data
Post-Treatment Mating Period

Group ppm	Mean No./Pregnant Female		Mean Implantation Efficiency Values ^a %
	Corpora Lutea	Implantation Sites	
	<u>Week 1</u>		
I (0),	A+F 14.6	K+ 13.8	V- 92.7
II (1)	15.3	14.3	92.7
III (10)	13.5	12.0	85.7
IV (30)	14.6	13.1	89.4
V (300)	14.2	13.1	91.1
	<u>Week 2</u>		
I (0)	A- 14.7	K- 13.4	V- 91.4
II (1)	14.7	12.7	85.1
III (10)	14.2	12.8	89.0
IV (30)	14.7	14.2	95.2
V (300)	14.9	14.0	93.3

For explanation of statistical symbols (i.e. A+, A-, F, K+, K-, V-) see Appendix I-5.

No statistically significant differences from control.

^aIndividual female values presented in Appendix C.

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Table 4
A Dominant-Lethal Inhalation Study
With Benzene in Rats

Bio/dynamics Inc.

Uterine Implantation Data Amplified and
Mean Mutagenic Ratio Values

Group ppm	Mean No./Pregnant Females			Mean Mutagenic Ratio ^a %
	Implantation Sites	Dead Implants	Viable Fetuses	
	<u>Week 1</u>			
I (0),	K+ 13.8	K- 1.1	K+J 12.7	V- 7.8
II (1)	14.3	0.7	13.5	6.0
III (10)	12.0	0.7	11.3	7.1
IV (30)	13.1	1.3	11.8	11.6
V (300)	13.1	1.6	11.5	14.9
	<u>Week 2</u>			
I (0)	K- 13.4	K- 0.4	K- 13.0	V- 4.4
II (1)	12.7	1.0	11.7	10.3
III (10)	12.8	0.8	12.1	7.3
IV (30)	14.2	1.0	13.2	8.2
V (300)	14.0	1.5	12.6	11.7

For explanation of statistical symbols (i.e. J, K+, K-, V-) see Appendix I-5.

^aMutagenic ratios for individual females are presented in Appendix E. Mutagenic Ratio = $\frac{\text{No. of Dead Implants}}{\text{No. of Implantation Sites}}$; a mutagenic ratio is calculated for each pregnant female. See Appendix I.

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Appendix A
A Dominant-Lethal Inhalation Study
With Benzene in Rats

Pregnancy, Corpora Lutea and Implantation Data - Pre-treatment Mating Period

Preface

Corp. Lut.	=	Corpora Lutea
Impl.	=	Implantations
VFS	=	Viable Fetuses

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Appendix A (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats
Pregnancy, Corpora Lutea and Implantation Data

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Pre-Treatment Mating Period^a - Group I - Chamber-exposed Control

Male No.	Female No.	Corp. Lvt.	Impl.	Number of Dead Implants	WFS	Male No.	Female No.	Corp. Lvt.	Impl.	Number of Dead Implants	WFS
100	1308 1310	10 16	6 14	0 0	6 14	111	1492 1493	15 14	15 14	0 1	15 13
101	1331 1332	Not pregnant.		0	12	112	1494 1495	Not pregnant.		0	14
102	1333 1334	13 16	13 13	0 0	13 13	113	1496 1497	Not pregnant.		0	14
103	1335 1336	17 14	16 13	0 0	16 13	114	1509 1510	Not pregnant.		0	15
104	1389 1390	10 13	2 12	0 0	2 12	115	1515 1516	17 Not pregnant.	17	4	13
105	1408 1410	13 16	12 17	1 2	11 15	116	1539 1540	Not pregnant.		1	12
106	1419 1420	19 15	19 15	0 0	19 15	117	1551 1552	15 Not pregnant.	14	0	14
107	1423 1424	14 19	14 16	0 0	14 16	118	1560 1561	19 Not pregnant.	18	1	17
108	1453 1454	Not pregnant.		1	11	119	1564 1565	Not pregnant.		0	13
109	1466 1469	21 18	17 15	0 0	17 15	Total:		458	411	11	400
110	1480 1481	15 15	13 13	0 0	13 13	Mean:		15.3	13.7	0.4	13.3
						S.D.:		2.7	3.3	0.9	3.2
						N:		30	30	30	30

^aData not analyzed statistically.

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Appendix A (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats
Pregnancy, Corpora Lutea and Implantation Data

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Pre-Treatment Mating Period^a - Group II - (1 ppm)

Male No.	Female No.	Corp. Lut.	Impl.	Number of Dead Implants	VFS	Male No.	Female No.	Corp. Lut.	Impl.	Number of Dead Implants	VFS		
300	1326 1327	Not pregnant. 17	16	0	16	311	1433 1434	Not pregnant. 15	15	0	15		
301	1341 1342	16 16	16 14	0 0	16 14	312	1447 1448	14 14	14 14	2 0	12 14		
302	1343 1344	14 15	14 15	0 0	14 15	313	1457 1458	13 Not pregnant.	13	7	6		
303	1347 1348	18 14	18 13	0 0	18 13	314	1490 1491	15 13	14 10	1 0	13 10		
304	1377 1378	13 17	13 17	0 3	13 14	315	1517 1518	15 14	15 14	0 2	15 12		
305	1385 1386	12 Not pregnant.	12	0	12	316	1519 1520	Not pregnant. 17	17	1	16		
306	1391 1395	17 16	7 6	0 0	7 6	317	1525 1526	14 14	12 13	1 0	11 13		
307	1402 1403	19 22	16 15	0 0	16 15	318	1541 1542	12 13	12 12	1 0	11 12		
308	1404 1405	13 16	13 13	0 1	13 12	319	1547 1548	Not pregnant. 14	14	0	14		
309	1406 1407	14 Not pregnant.	14	0	14	Total: Mean: S.D.: N:		483	435	20	415		
310	1415 1416	Not pregnant. 17	14	1	13			15.1	13.6	0.6	13.0		
								2.2	2.5	1.4	2.8		
								32	32	32	32		

^aData not analyzed statistically.

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Appendix A (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats
Pregnancy, Corpora Lutea and Implantation Data

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Pre-Treatment Mating Period^a - Group III - (10 ppm)

Male No.	Female No.	Corp. Lut.	Impl.	Number of Dead Implants	VS	Male No.	Female No.	Corp. Lut.	Impl.	Number of Dead Implants	VS
500	1320 1322	14 15	14 14	0 0	14 14	511	1461 1463	9 Not pregnant.	2	0	2
501	1355 1356	13 17	13 14	1 0	12 14	512	1498 1499	16 Not pregnant.	16	0	16
502	1361 1362	18 16	14 14	1 0	13 14	513	1500 1501	16 Not pregnant.	13	0	13
503	1363 1364	11 10	4 7	0 2	4 5	514	1511 1512	13 10	13 4	1 0	12 4
504	1383 1384	4 13	4 13	0 0	4 13	515	1521 1522	14 Not pregnant.	14	0	14
505	1387 1388	Not pregnant. 15	15	0	15	516	1531 1532	11 13	3 13	0 1	3 12
506	1398 1399	14 20	13 17	0 0	13 17	517	1537 1538	15 Not pregnant.	15	0	15
507	1400 1401	Not pregnant. 18	15	0	15	518	1549 1550	16 14	16 14	0 2	16 12
508	1413 1414	15 16	15 16	1 1	14 15	519	1556 1556	17 18	17 8	1 5	16 3
509	1417 1418	16 15	14 15	0 0	14 15						
510	1449 1450	17 17	17 17	1 0	16 17						
							Total:	476	413	17	396
							Mean:	14.4	12.5	0.5	12.0
							S.D.:	3.2	4.5	1.0	4.7
							N:	33	33	33	33

^aData not analyzed statistically.

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Appendix A (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats
Pregnancy, Corpora Lutea and Implantation Data

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Pre-Treatment Mating Period^a - Group IV - (30 ppm)

Male No.	Female No.	Corp. Lut.	Impl.	Number of Dead Implants	VFS	Male No.	Female No.	Corp. Lut.	Impl.	Number of Dead Implants	VFS
700	1303 1304	16 12	16 12	0 1	16 11	711	1455 1456	15 Not pregnant.	15	3	12
701	1317 1319	Not pregnant. 19	14	0	14	712	1474 1475	18 17	15 17	0 0	15 17
702	1353 1354	14 14	14 14	0 0	14 14	713	1486 1487	6 18	1 17	0 0	1 17
703	1357 1358	15 15	14 15	1 0	13 15	714	1504 1505	13 14	13 13	0 0	13 13
704	1365 1366	16 15	16 10	2 0	14 10	715	1523 1524	15 17	15 11	0 4	15 7
705	1369 1370	Not pregnant. 15	14	4	10	716	1527 1528	Not pregnant. 14	14	1	13
706	1375 1376	13 12	13 12	1 0	12 12	717	1543 1544	12 Not pregnant.	12	1	11
707	1379 1380	21 17	15 14	2 1	13 13	718	1545 1546	14 14	14 14	0 1	14 13
708	1381 1382	6 Not pregnant.	1	0	1	719	1562 1563	16 15	16 6	0 0	16 6
709	1421 1422	16 Not pregnant.	16	0	16	Total:		487	430	23	407
						Mean:		14.8	13.0	0.7	12.3
						S.D.:		3.0	3.8	1.1	3.8
						N:		33	33	33	33
710	1438 1439	15 18	14 13	0 1	14 12						

^aData not analyzed statistically.

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Appendix A (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats
Pregnancy, Corpora Lutea and Implantation Data

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Pre-Treatment Mating Period^a - Group V - (300 ppm)

Male No.	Female No.	Corp. Lut.	Impl.	Number of Dead Implants	VFS	Male No.	Female No.	Corp. Lut.	Impl.	Number of Dead Implants	VFS
900	1313 1314	15 Not pregnant.	10	0	10	911	1440 1441	16 Not pregnant.	16	1	15
901	1337 1338	Not pregnant. 10	8	1	7	912	1442 1443	Not pregnant. 5	2	0	2
902	1345 1346	12 14	10 14	0 0	10 14	913	1472 1473	15 Not pregnant.	15	0	15
903	1349 1350	17 16	16 16	1 0	15 16	914	1478 1479	16 14	15 14	0 0	15 14
904	1351 1352	16 Not pregnant.	14	0	14	915	1482 1483	16 14	16 14	0 1	16 13
905	1359 1360	11 15	11 15	1 0	10 15	916	1484 1485	18 18	16 16	1 0	15 16
906	1373 1374	15 13	11 11	1 0	10 11	917	1488 1489	Not pregnant. 14	13	0	13
907	1411 1412	17 15	15 15	0 0	15 15	918	1502 1503	15 Not pregnant.	14	0	14
908	1427 1428	Not pregnant. 10	10	2	8	919	1553 1554	16 15	16 15	2 0	14 15
909	1431 1432	12 12	4 3	0 0	4 3	Total:		455	394	12	382
910	1436 1437	17 26	15 14	0 1	15 13	Mean:		14.7	12.7	0.4	12.3
						S.D.:		3.4	3.9	0.6	3.9
						N:		31	31	31	31

^aData not analyzed statistically.

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Appendix B
A Dominant-Lethal Inhalation Study in Rats
with Benzene

Inhalation Report

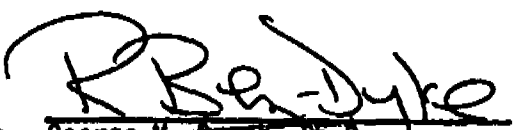
SUMMARY

Four groups of 20 male rats were exposed to vapors of benzene six hours per day, five days per week for ten consecutive weeks. A sham air exposed control group was also included. Each male, following this exposure interval, was mated with two untreated females per week for two consecutive weeks.

Air samples from each chamber were analyzed by infra-red spectroscopy six times during each exposure. The variable background interference of the infra-red technique, due to the presence of animals in the exposure chamber, was significant at the two lower levels and in part accounts for the greater fluctuations in chamber concentration at these levels.

Mean levels and ranges (as determined analytically) on samples of chamber atmospheres (expressed in ppm) were as follows:

Group			
II	III	IV	V
1.0 (0.3-3.5)	9.8 (7.4-12.4)	30.3 (28.5-33.3)	299 (275-319)

pp 
George M. Rusch, Ph.D.
Director, Inhalation Technology

12/2/80
Date

Report Preparation: Cecelia A. Bozak, B.A.
Study Monitor, Inhalation

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Appendix B (cont.)
A Dominant-Lethal Inhalation Study in Rats
with Benzene

Inhalation Report

INTRODUCTION

This study was designed to assess the mutagenic potential of a test material when administered to male rats by inhalation for 6 hours/day, 5 days/week for ten consecutive weeks. Males of proven mating and re-productive capacity were used for exposure. Each male, following the treatment period, was mated with two untreated females per week for two consecutive weeks. The females were then scored for pregnancy and total number of implants and fetal deaths. Adverse effects on those parameters were considered indications of a dominant-lethal mutagenic effect in the males.

In this report, the infrared calibration curve and nominal and actual concentrations are presented from initiation (January 14, 1980) through termination (March 21, 1980) of the study.

EXPERIMENTAL DESIGN

Group	Exposure Treatment ¹ (target concentration - ppm)	Males	No. of Rats	
			Females (untreated)	
			Pre-treatment Mating Period	Post-treatment Mating Period
I	Control - Chamber exposed	20	40	80
II	Benzene - 1 ppm	20	40	76
III	Benzene - 10 ppm	20	40	80
IV	Benzene - 30 ppm	20	40	80
V	Benzene - 300 ppm	20	40	80

¹Treatment schedule - 6 hours/day; 5 days/week for 10 consecutive weeks.

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Appendix B (cont.)
A Dominant-Lethal Inhalation Study in Rats
with Benzene

Inhalation Report

Test Material Administration

Benzene vapor concentrations were generated into one cubic meter stainless steel and glass chambers using a flash-evaporation generating system. Liquid benzene was pumped into a heated 3-neck flask through a 3-inch length of 1/8-inch diameter teflon tubing from a glass syringe fitted with a 16 gauge stainless steel needle. Flask temperature was maintained at 50°C in Groups II, III, and IV and 80°C in Group V. These temperatures were selected as the minimum required to achieve complete volatilization of the test material. The 3-neck flask was heated using a Glas-Col heating mantle and temperature was measured using a Glas-Col laboratory pyrometer. The benzene was pumped using Sage Instruments Model 220 and 341 syringe pumps. Adjustments in chamber concentration were made by adjusting pump flow rates (ml/hr) or chamber air flow (lpm). Air flow was determined by measuring the change in pressure (ΔP , cm H₂O) over a one inch orifice plate using a Dwyer magnehelic pressure gauge. Airflows were maintained between 150 and 250 lpm for the duration of the six hour exposures.

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Appendix B (cont.)
A Dominant Lethal Inhalation Study in Rats
with Benzene

Miran/dyn micron Inc.

Inhalation Report

Chamber Operation

The stainless steel and glass exposure chambers in which the animals were exposed had a total volume of one cubic meter with an effective volume of 760 liters. They were operated dynamically at an air flow between 155 and 245 liters per minute, providing one air change in from 6.5 to 4.1 minutes and a 99% equilibration time (t₉₉) from 29.9 to 18.9 minutes.

Daily Nominal Concentration

Nominal exposure concentrations were calculated daily using the following equation:

$$\text{Nominal Conc. (ppm)} = \frac{\Delta \text{wt (g)} \times 1000 \text{ mg/g}}{\Delta t \text{ (min)} \times \text{chamber air flow (lpm)}} \times 307.78 \text{ mg/ul}$$

Daily nominal concentrations are presented for Groups II-V in Table 4.

Chamber Atmospheric Concentration

One sample per hour (at about 0.5, 1.5, 2.5, 3.5, 4.5 and 5.5 hours) was drawn from each exposure chamber using a Wilks Instrument Company, Miran Long Pathlength Infrared Analyzer Model IA (In-house identification numbers "L" and "4")². The exposure levels were determined by comparing the observed absorbance of these samples to a previously determined standard curve generated using the test material under the same instrumental settings. The calibration curves for this test material are presented on pages 9-17 of this appendix.

²Miran L was used from Day 1 (1/14/80) through Day 59 (3/12/80) of the study. Miran 4 replaced Miran L on Day 60 (3/13/80) and was used through termination of the study (Day 68 - 3/21/80). Therefore, calibration curves were generated for each phase of the study, the first set corresponding to Miran L (1/14/80 - 3/12/80) and the second set corresponding to Miran 4 (3/13/80 - 3/21/80).

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Appendix B (cont.)
A Dominant-Lethal Inhalation Study in Rats
with Benzene

Inhalation Report ..

Calculation of Chamber Concentrations

Upon initiation of the study, it was observed that the presence of the animals in the chamber created a background interference in the infrared monitoring procedure used to analyze the benzene exposure concentration. This interference was negligible for the Group IV (30 ppm) and Group V (300 ppm) exposure groups but if uncorrected, could have resulted in a significant overstatement of the concentration in the Group II (1.0 ppm) and Group III (10 ppm) exposure groups. Using the first few weeks of data a correction factor was calculated, based on measurements of the background infrared absorption in the control chamber.

An attempt was made to adjust the measurements using the control chamber data on a point-for-point basis. However, since the animals were exposed in a separate room, this approach did not produce a good correlation; therefore, a correction procedure was developed using the average measured absorbance in the control chamber. This procedure involved the calculation of the average measured interference in the control chamber and then correcting each individual measurement in the Group II and Group III chambers by subtracting this average background reading from the observed exposure chamber absorbance measurement.

Monitoring for this background interference during the first two weeks of the study in the control chamber led to a correction factor of 0.007 absorbance units for Groups II and III. It was also observed that the first one or two samples of the day had higher absorbances than the remaining samples in both the control and low level exposure groups. This was attributed to the increased activity of the animals following loading of the chamber.

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Appendix B (cont.)
A Dominant-Lethal Inhalation Study in Rats
with Benzene

bio/dynamics Inc.

Inhalation Report

Calculation of Chamber Concentrations (cont.)

At the conclusion of the study, samples collected at each sampling interval (ie. 1/2 hr, 1-1/2 hr, 2-1/2 hr, 3-1/2 hr, 4-1/2 hr and 5-1/2 hr) were separately averaged and then statistically compared to one another.³ Where possible, separate calculations were performed for each phase of the study. When it was found that a particular interval possessed a unique correction factor, either by being statistically different, or in the case of the smaller sample groups, by appearing to be unique, this factor was applied to all absorbance measurements taken at that sample interval, for that period. These values have been used to calculate the corrected individual exposure concentrations. The statistical comparison is presented in Table 1 and the actual correction factors are presented in Table 2.

³F-test and Student's t-test (modified using Cochran's approximation [t] when variances differ). Snedecor G.S., and W.G. Cochran, Statistical Methods 6th ed., Iowa State University Press, Ames, 1967, pp 104-106, 114-119.

Appendix B (cont.)
Table 1
A Dominant Lethal Inhalation Study in Rats
with Benzene

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Inhalation Report
Statistical Calculation of Correction Factors Used for
Determination of Exposure Concentrations for Groups II and III

Time Interval	Exposure Nos.	Mean Background Absorbances (Group I)						
			Sample Intervals:					
			<u>1/2 hr</u>	<u>1-1/2 hr</u>	<u>2-1/2 hr</u>	<u>3-1/2 hr</u>	<u>4-1/2 hr</u>	<u>5-1/2 hr</u>
1/14/80 - 3/12/80	1-43	Mean	0.0128 ⁺	0.0081 ⁺	0.0068	0.0066	0.0061	0.0061
		S.D.	0.0030	0.0027	0.0022	0.0021	0.0015	0.0021
		N	43	43	43	43	42	43
3/13/80 - 3/21/80	44-50	Mean	0.0115 ^a	0.0090	0.0088	0.0087	0.0084	0.0085
		S.D.	0.0042	0.0048	0.0044	0.0034	0.0035	0.0034
		N	7	7	7	7	7	7

⁺Significantly different from succeeding values ($p \leq 0.05$).

^aDifferent from succeeding values ($p > 0.05$).

Appendix B (cont.)
 Table 2
 A Dominant Lethal Inhalation Study in Rats
 with Benzene

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Inhalation Report
 Correction Factors Applied to Measured Absorbance
 For Groups II and III

Time Interval	Exposure Nos.	Correction Factors					
		Sample Intervals:					
		<u>1/2 hr</u>	<u>1-1/2 hr</u>	<u>2-1/2 hr</u>	<u>3-1/2 hr</u>	<u>4-1/2 hr</u>	<u>5-1/2 hr</u>
1/14/80 - 3/12/80	1-43	0.013	0.008	0.006	0.006	0.006	0.006
3/13/80 - 3/21/80	44-50	0.012	0.009	0.009	0.009	0.009	0.009

Appendix B (cont.)
A Dominant Lethal Inhalation Study in Rats
with Benzene

Inhalation Report

Infrared Analysis of Benzene

CALIBRATION FOR: Benzene
Molecular Weight: 78.11 amu
Density: 0.878 g/ml

MIRAN SETTINGS:

Wavelength: 3.3 u - optimized to 3.28 u
Pathlength: 21.75 m (14.0 dial reading)
Range: 0.1 Å (Groups I, II, III) 1.0 Å (Groups IV, V)
Slit Width: 1 mm
Meter Response Time: 1 second
Coarse Zero: x 1

STANDARD: Measured volumes of benzene were injected into a closed loop circulation system in order to generate atmospheres inside the Miran of known concentration levels. The closed loop system, including the Miran, measures 5.64 liters in volume.

Appendix B (cont.)
A Dominant Lethal Inhalation Study in Rats
with Benzene

Inhalation Report
Miran Ambient Air Analyzer
Closed Loop Calibrations
Miran L (1/14/80 - 3/12/80)

Range	Injection Volume (ul)	Concentration (ppm)	Absorbance			
			A1	A2	A3	A4
0.1 Å	0.01	0.5	0.001	0.001	0.001	0.001
	0.02	1.0	0.003	0.002	0.003	0.002
	0.03	1.4	0.004	0.003	0.005	0.003
	0.05	2.4	0.007	0.006	0.007	0.006
	0.10	4.8	0.015	0.014	0.012	0.014
	0.15	7.2	0.023	0.022	0.019	0.021
	0.19	9.1	0.029	0.029	0.024	0.027
	0.21	10.1	0.032	0.032	0.026	0.030
	0.23	11.0	0.034	0.035	0.028	0.033
	0.30	14.4	0.045	0.046	0.038	0.043
	0.50	24.0	0.075	0.077	0.065	0.074
	0.60	28.8	0.091	0.092	0.079	0.088
1.0 Å	0.50	24.0	0.075	0.070	0.070	0.075
	0.60	28.8	0.09	0.090	0.080	0.090
	0.63	30.2	0.10	0.095	0.090	0.095
	0.65	31.1	0.10	0.10	0.090	0.095
	0.70	33.5	0.11	0.11	0.10	0.10
	1.00	47.9	0.15	0.15	0.14	0.15
	2.00	95.8	0.30	0.30	0.28	0.29
	3.00	143.7	0.44	0.43	0.41	0.43
	4.00	191.6	0.56	0.56	0.53	0.55
	5.00	239.6	0.68	0.68	0.64	0.66
	6.00	287.5	0.79	0.79	0.74	0.76
	6.20	297.0	0.81	0.81	0.76	0.78
	6.30	301.8	0.82	0.82	0.77	0.79
	6.50	311.4	0.84	0.84	0.79	0.81
	7.00	335.4	0.89	0.89	0.83	0.85
	7.50	359.3	0.94	0.94	0.87	0.89
	8.00	383.3	0.99	0.99	0.91	0.94

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Appendix B (Cont.)

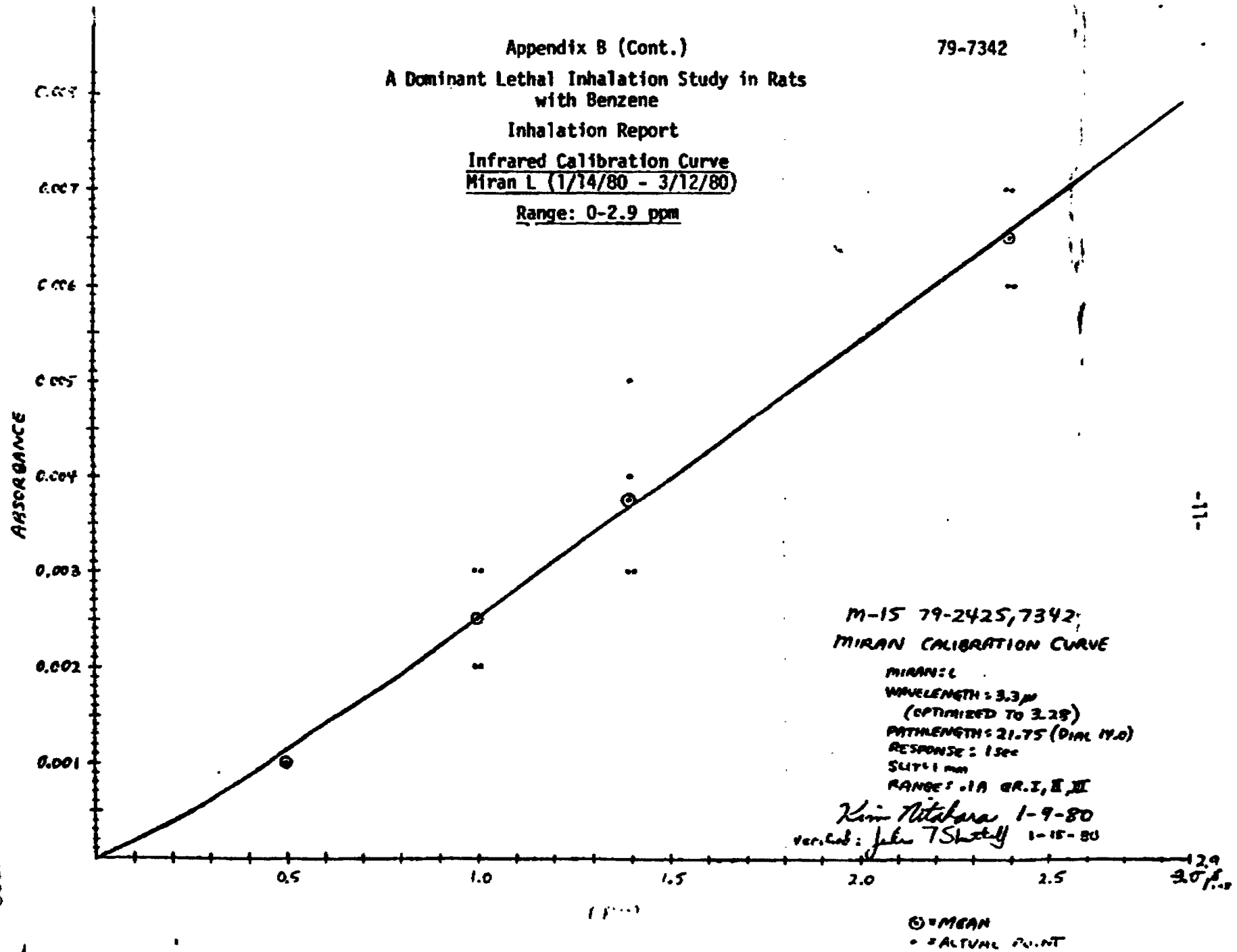
79-7342

A Dominant Lethal Inhalation Study in Rats
with Benzene

Inhalation Report

Infrared Calibration Curve
Miran L (1/14/80 - 3/12/80)

Range: 0-2.9 ppm



Appendix B (Cont.)

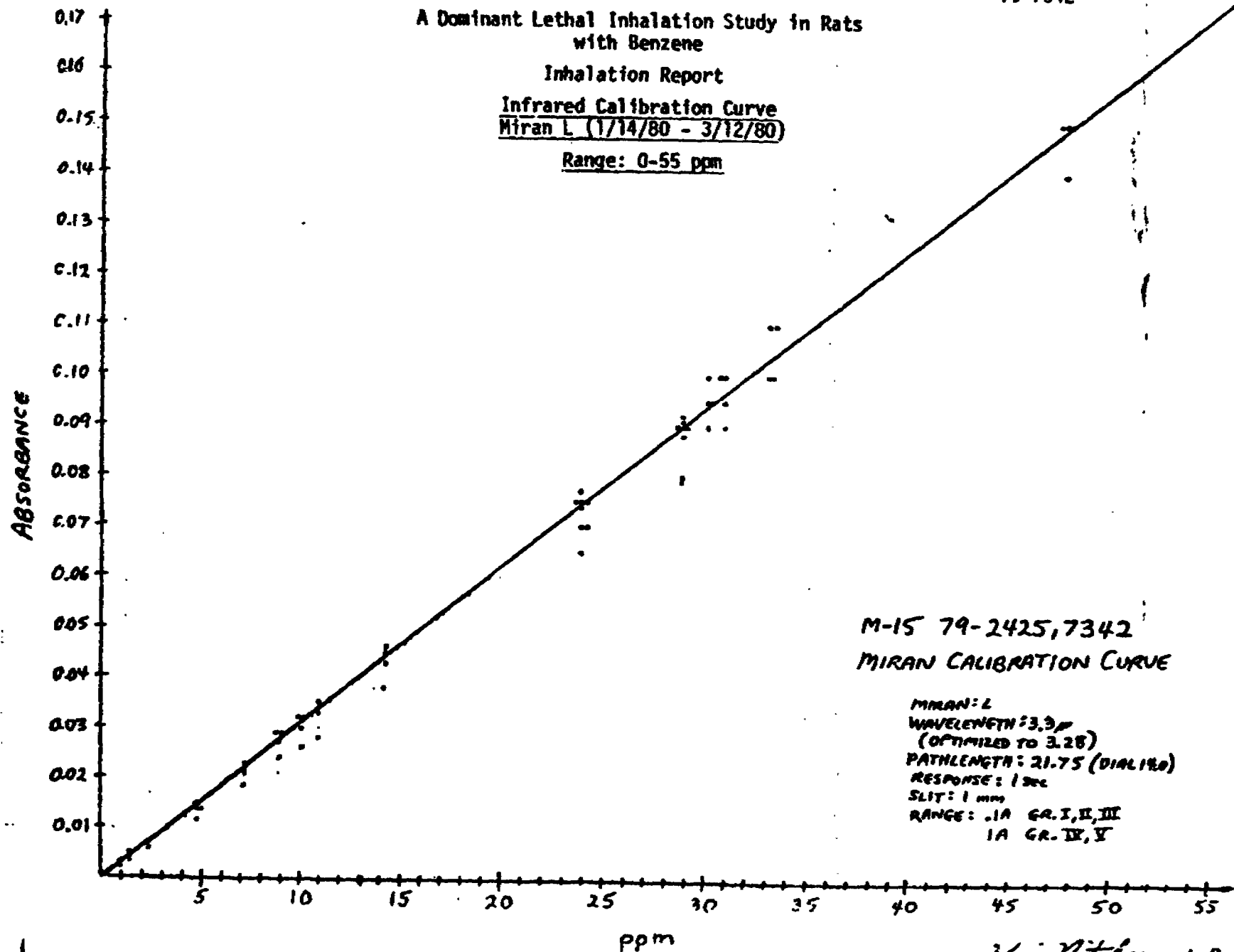
79-7342

A Dominant Lethal Inhalation Study in Rats
with Benzene

Inhalation Report

Infrared Calibration Curve
Miran L (1/14/80 - 3/12/80)

Range: 0-55 ppm

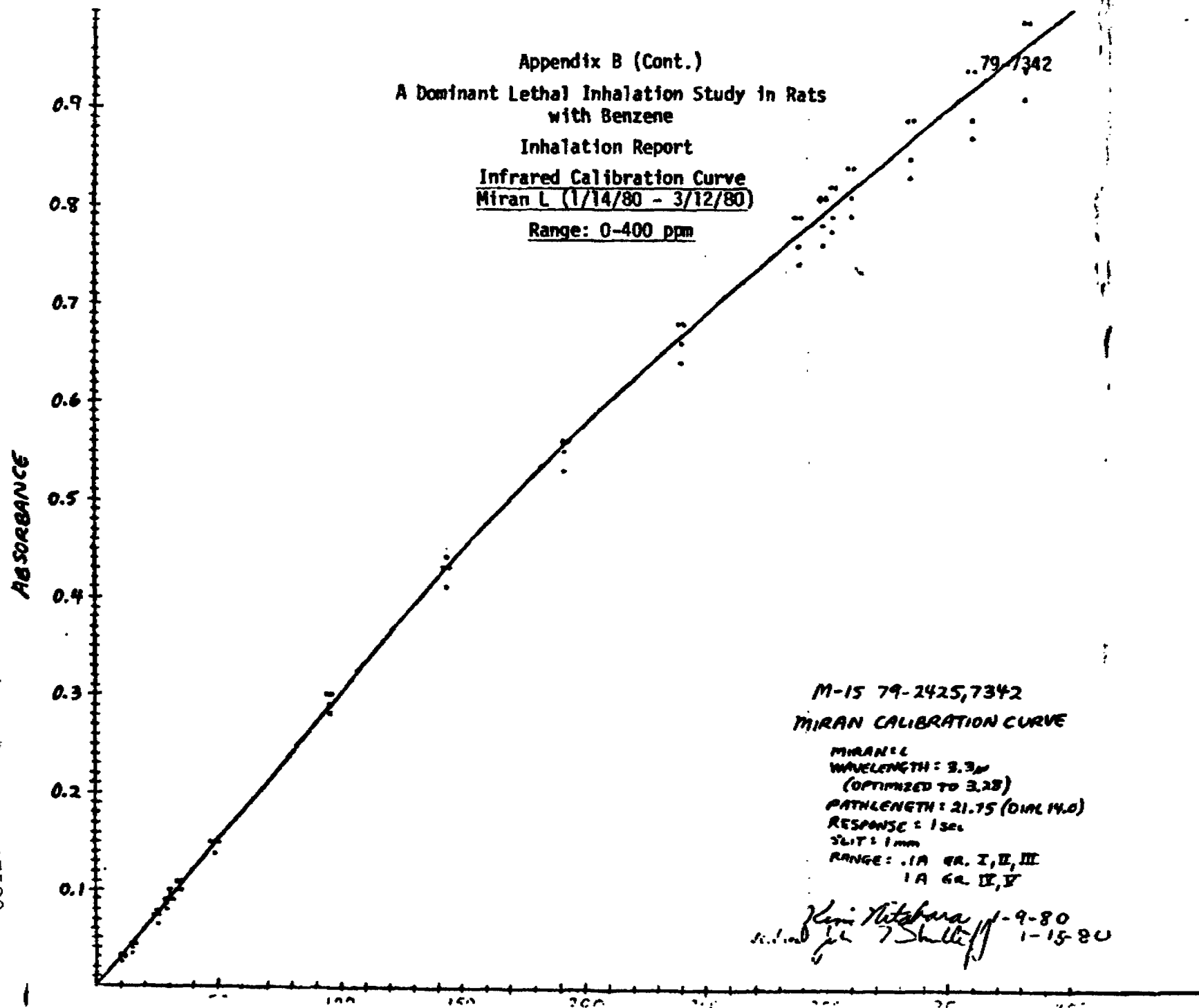


M-15 79-2425,7342
MIRAN CALIBRATION CURVE

MIRAN: L
WAVELENGTH: 3.3 μ
(OPTIMIZED TO 3.28)
PATHLENGTH: 21.75 (DIAL 100)
RESPONSE: 1 sec
SLIT: 1 mm
RANGE: .1A GR. I, II, III
1A GR. IV, V

Kim Nitchman 1-9-80

Appendix B (Cont.)
 A Dominant Lethal Inhalation Study in Rats
 with Benzene
 Inhalation Report
 Infrared Calibration Curve
 Miran L (1/14/80 - 3/12/80)
 Range: 0-400 ppm



M-15 79-2425,7342
 MIRAN CALIBRATION CURVE
 MIRAN L
 WAVELENGTH: 3.3μ
 (OPTIMIZED TO 3.28)
 PATHLENGTH: 21.75 (DIAL 14.0)
 RESPONSE: 1 sec
 SLIT: 1 mm
 RANGE: .1A GR. I, II, III
 1A GR. IV, V

Kimi Nishihara 1-9-80
7 Shultz 1-15-80

DO 067530
 CONFIDENTIAL

YZ0083093

Appendix B (cont.)
A Dominant Lethal Inhalation Study in Rats
with Benzene

Inhalation Report
Miran Ambient Air Analyzer
Closed Loop Calibrations
Miran 04 (3/13/80 - 3/21/80)

Range	Injection Volume (ul)	Concentration (ppm)	Absorbance			
			A ₁	A ₂	A ₃	A ₄
0.1 Å	0.01	0.5	0.001	0.001	0.002	0.000
	0.02	1.0	0.002	0.002	0.003	0.001
	0.03	1.4	0.002	0.004	0.005	0.002
	0.05	2.4	0.005	0.007	0.008	0.003
	0.10	4.8	0.012	0.014	0.016	0.009
	0.15	7.2	0.018	0.022	0.023	0.015
	0.19	9.1	0.024	0.027	0.029	0.020
	0.21	10.1	0.026	0.030	0.032	0.022
	0.23	11.0	0.029	0.034	0.036	0.025
	0.30	14.4	0.039	0.044	0.046	0.033
	0.50	24.0	0.068	0.072	0.074	0.062
	0.60	28.8	0.081	0.086	0.088	0.074
1.0 Å	0.50	24.0	0.07	0.07	0.07	0.07
	0.60	28.8	0.09	0.08	0.08	0.08
	0.63	30.2	0.09	0.09	0.09	0.09
	0.65	31.1	0.10	0.09	0.09	0.09
	0.70	33.5	0.10	0.10	0.10	0.10
	1.00	47.9	0.14	0.14	0.14	0.14
	2.00	95.8	0.27	0.26	0.26	0.25
	3.00	143.7	0.38	0.38	0.37	0.37
	4.00	191.6	0.48	0.48	0.46	0.46
	5.00	239.6	0.57	0.58	0.55	0.55
	6.00	287.5	0.65	0.66	0.62	0.62
	6.20	297.0	0.66	0.68	0.63	0.63
	6.30	301.8	0.67	0.68	0.64	0.64
	6.50	311.4	0.68	0.70	0.65	0.65
	7.00	335.4	0.71	0.73	0.68	0.69
	7.50	359.3	0.75	0.76	0.71	0.72
	8.00	383.3	0.77	0.79	0.75	0.75

DO 067531
CONFIDENTIAL

YZ0083094

Appendix B (Cont.)

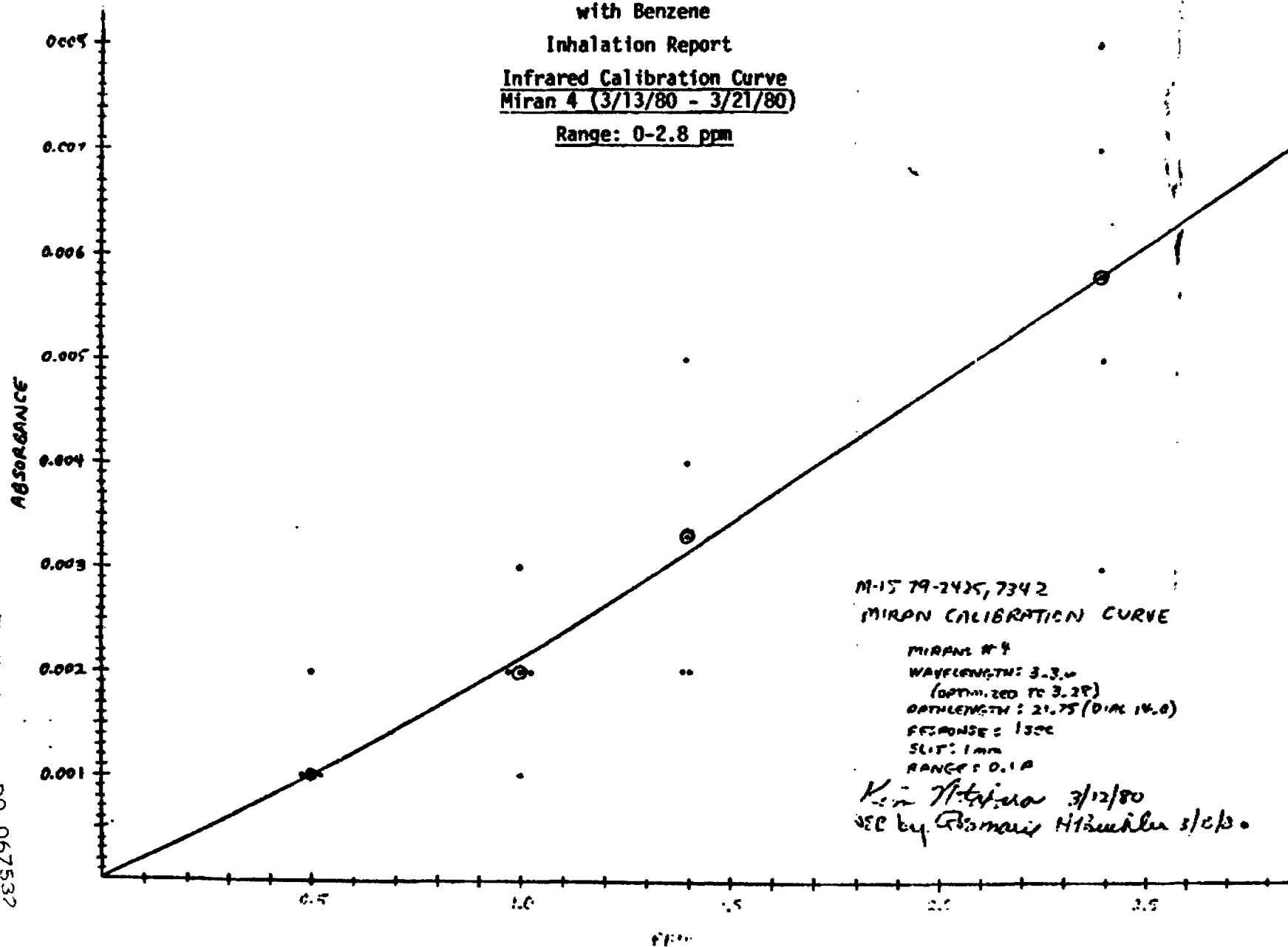
79-7342

A Dominant Lethal Inhalation Study in Rats
with Benzene

Inhalation Report

Infrared Calibration Curve
Miran 4 (3/13/80 - 3/21/80)

Range: 0-2.8 ppm



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DO 067537
CONFIDENTIAL

YZ0083095

Appendix B (Cont.)

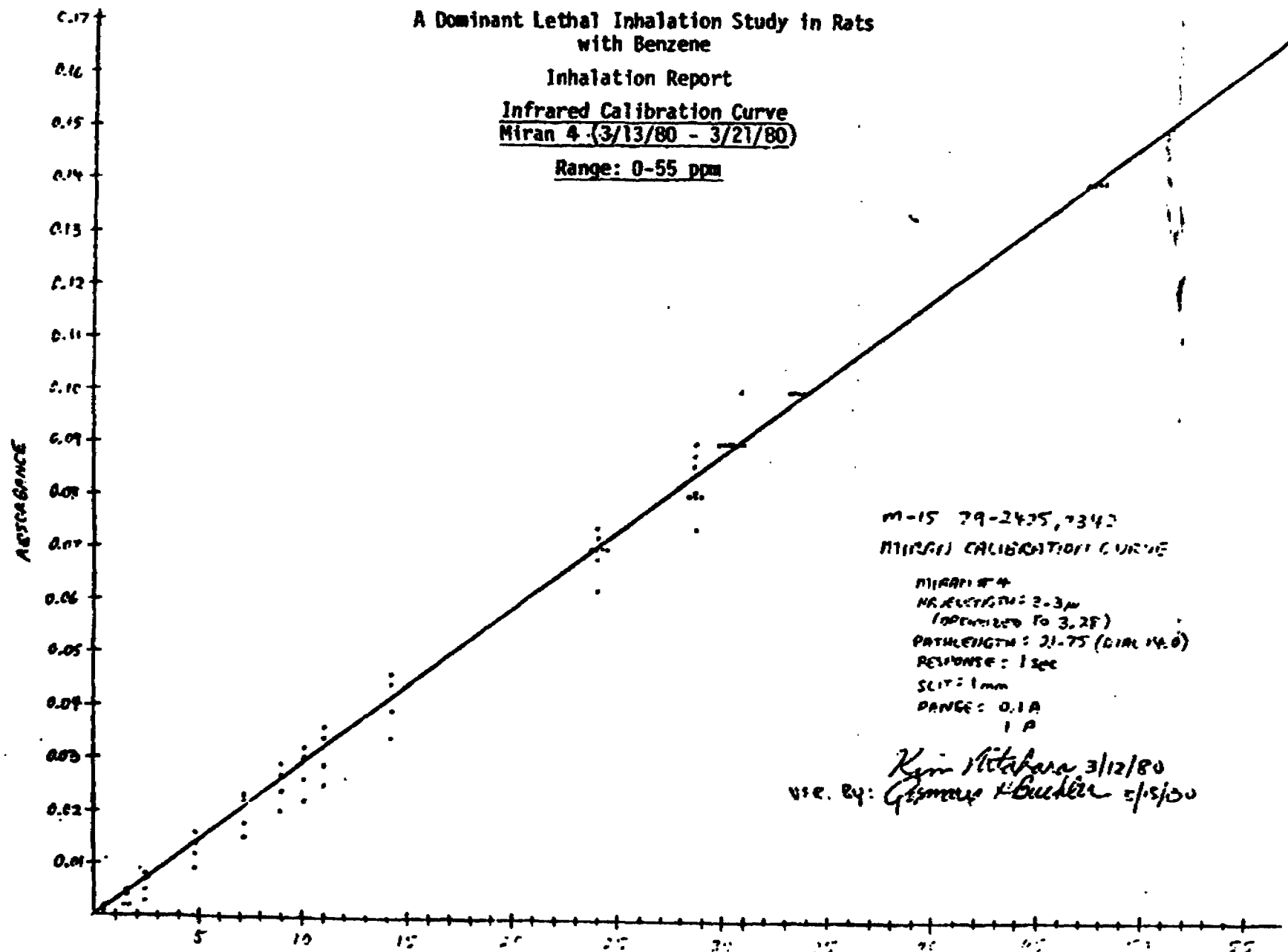
79-7342

A Dominant Lethal Inhalation Study in Rats
with Benzene

Inhalation Report

Infrared Calibration Curve
Miran 4 (3/13/80 - 3/21/80)

Range: 0-55 ppm



M-15 79-2425, 7342

MIRAN CALIBRATION CURVE

MIRAN 4

WAVELENGTH: 2.3 μ

(ADJUSTED TO 3.25)

PATHLENGTH: 21.75 (GAL 14.0)

RESPONSE: 1 sec

SPLIT: 1 mm

RANGE: 0.1 A

1 A

Kim Nishikawa 3/12/80
V.E. By: *Germa E. Buckler 3/15/80*

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DO 067533
CONFIDENTIAL

YZ0083096

Appendix u (Cont.)

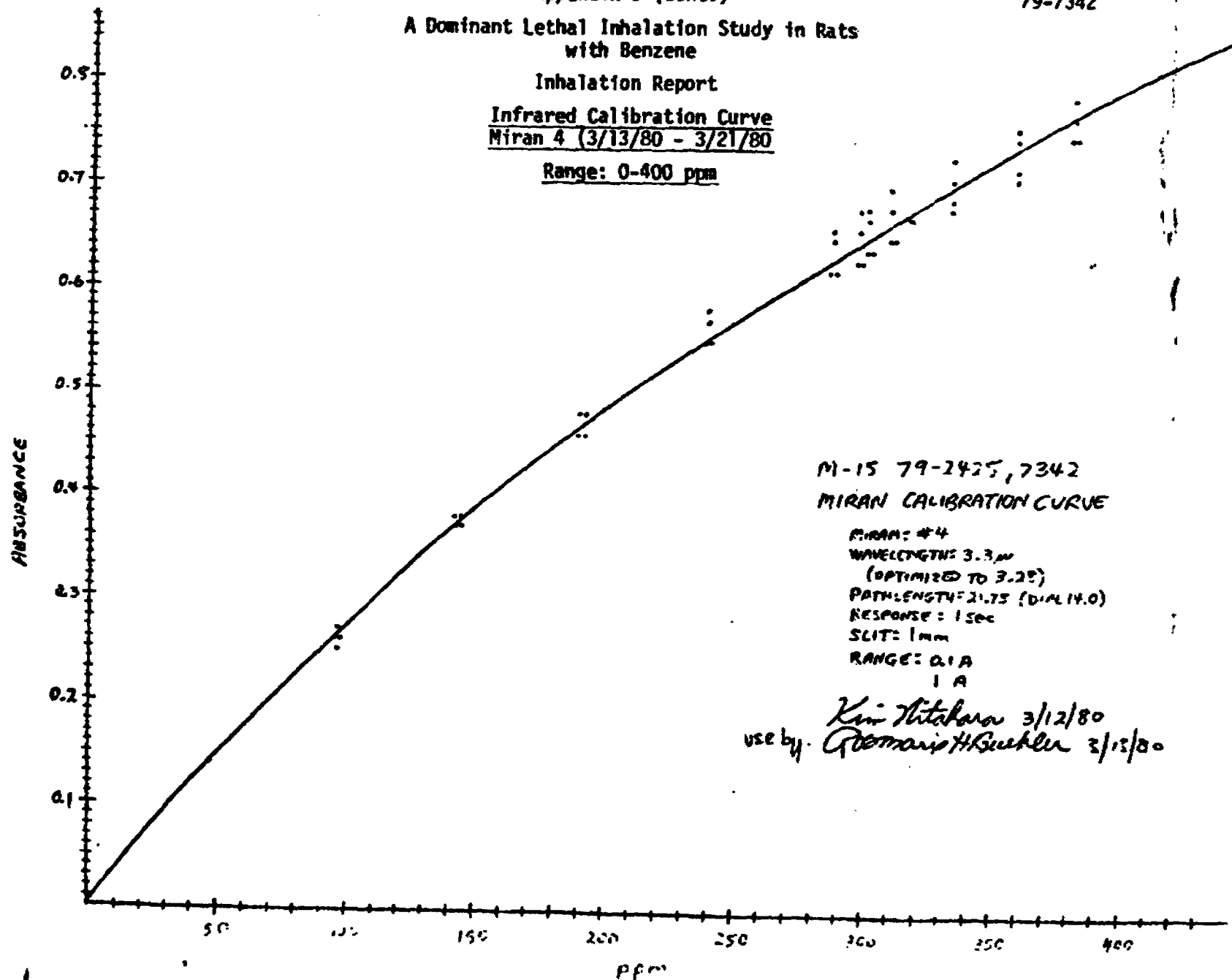
79-7342

A Dominant Lethal Inhalation Study in Rats
with Benzene

Inhalation Report

Infrared Calibration Curve
Miran 4 (3/13/80 - 3/21/80)

Range: 0-400 ppm



M-15 79-2425, 7342

MIRAN CALIBRATION CURVE

MIRAN: #4
WAVELENGTH: 3.3 μ
(OPTIMIZED TO 3.2 μ)
PATHLENGTH: 21.75 (DIAL 14.0)
RESPONSE: 1 sec
SLIT: 1 mm
RANGE: 0.1 A
1 A

use by *Kim Hatakara* 3/12/80
German H. Guebler 3/13/80

DO 067534
CONFIDENTIAL

YZ0083097

Appendix B (cont.)
 Table 3
 A Dominant Lethal Inhalation Study in Rats
 with Benzene

Inhalation Report
 Cumulative Exposure Record
 Group II - 1 ppm

Date	Test Day	Exposure Number	Mean Daily Exposure Concentration	SD	Daily Exposure Hours	Daily Concentration Hours	Total Exposure Hours	Total Concentration Hours	Cumulative Integrated Mean Concentration
1/14/80	1	1	0.5	0.4	6	3.0	6	3.0	0.5
1/15/80	2	2	0.3	0.4	6	1.8	12	4.8	0.4
1/16/80	3	3	0.8	0.6	6	4.8	18	9.6	0.5
1/17/80	4	4	0.5	0.5	6	3.0	24	12.6	0.5
1/18/80	5	5	0.5	0.3	6	3.0	30	15.6	0.5
1/21/80	8	6	1.1	0.7	6	6.6	36	22.2	0.6
1/22/80	9	7	1.0	0.6	6	6.0	42	28.2	0.7
1/23/80	10	8	0.9	0.6	6	5.4	48	33.6	0.7
1/24/80	11	9	1.6	0.5	6	9.6	54	43.2	0.8
1/25/80	12	10	1.2	0.6	6	7.2	60	50.4	0.8
1/28/80	15	11	1.2	0.6	6	7.2	66	57.6	0.9
1/29/80	16	12	1.4	0.4	6	8.4	72	66.0	0.9
1/30/80	17	13	0.9	0.5	6	5.4	78	71.4	0.9
1/31/80	18	14	1.3	0.4	6	7.8	84	79.2	0.9
2/1/80	19	15	1.1	0.4	6	6.6	90	85.8	1.0
2/4/80	22	16	1.5	0.9	6	9.0	96	94.8	1.0
2/5/80	23	17	1.2	0.4	6	7.2	102	102.0	1.0
2/6/80	24	18	0.7	0.5	6	4.2	108	106.2	1.0
2/7/80	25	19	1.5	0.7	6	9.0	114	115.2	1.0
2/8/80	26	20	0.7	0.3	6	4.2	120	119.4	1.0
2/11/80	29	21	0.4	0.4	6	2.4	126	121.8	1.0
2/12/80	30	22	0.8	0.3	6	4.8	132	126.6	1.0
2/13/80	31	23	0.9	0.6	6	5.4	138	132.0	1.0
2/14/80	32	24	0.7	0.9	6	4.2	144	136.2	0.9
2/15/80	33	25	1.1	1.2	6	6.6	150	142.8	1.0
2/18/80	36	26	1.5	0.4	6	9.0	156	151.8	1.0
2/19/80	37	27	0.5	0.6	6	3.0	162	154.8	1.0
2/20/80	38	28	1.2	0.5	6	7.2	168	162.0	1.0

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YZ0083098

Appendix B (cont.)
 Table 3 (cont.)
 A Dominant Lethal Inhalation Study in Rats
 with Benzene

Inhalation Report
 Cumulative Exposure Record
 Group II - 1 ppm (cont.)

Date	Test Day	Exposure Number	Mean Daily Exposure Concentration	SD	Daily Exposure Hours	Daily Concentration Hours	Total Exposure Hours	Total Concentration Hours	Cumulative Integrated Mean Concentration
2/21/80	39	29	1.2	0.3	6	7.2	174	169.2	1.0
2/22/80	40	30	0.9	0.3	6	5.4	180	174.6	1.0
2/25/80	43	31	1.0	0.4	6	6.0	186	180.6	1.0
2/26/80	44	32	0.8	0.6	6	4.8	192	185.4	1.0
2/27/80	45	33	0.8	0.7	6	4.8	198	190.2	1.0
2/28/80	46	34	1.1	0.4	6	6.6	204	196.8	1.0
2/29/80	47	35	3.5	4.9	6	21.0	210	217.8	1.0
3/3/80	50	36	1.3	0.7	6	7.8	216	225.6	1.0
3/4/80	51	37	1.0	0.4	6	6.0	222	231.6	1.0
3/5/80	52	38	0.8	0.3	6	4.8	228	236.4	1.0
3/6/80	53	39	1.4	0.3	6	8.4	234	244.8	1.0
3/7/80	54	40	0.9	0.8	6	5.4	240	250.2	1.0
3/10/80	57	41	1.1	0.7	6	6.6	246	256.8	1.0
3/11/80	58	42	1.2	0.5	6	7.2	252	264.0	1.0
3/12/80	59	43	1.0	0.4	6	6.0	258	270.0	1.0
3/13/80	60	44	0.8	1.1	6	4.8	264	274.8	1.0
3/14/80	61	45	0.3	0.4	6	1.8	270	276.6	1.0
3/17/80	64	46	0.3	0.4	6	1.8	276	278.4	1.0
3/18/80	65	47	1.4	0.6	6	8.4	282	286.8	1.0
3/19/80	66	48	0.4	0.4	6	2.4	288	289.2	1.0
3/20/80	67	49	0.4	0.6	6	2.4	294	291.6	1.0
3/21/80	68	50	0.0	0.0	6	0.0	300	291.6	1.0

Standard deviation of Cumulative Integrated Mean concentration for Group II is 0.2 for entire study.

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YZ0083099

Appendix B (cont.)
 Table 3 (cont.)
 A Dominant Lethal Inhalation Study in Rats
 with Benzene

Inhalation Report
 Cumulative Exposure Record
 Group III - 10 ppm

Date	Test Day	Exposure Number	Mean Daily Exposure Concentration	SD	Daily Exposure Hours	Daily Concentration Hours	Total Exposure Hours	Total Concentration Hours	Cumulative Integrated Mean Concentration
1/14/80	1	1	8.6	0.8	6	51.6	6	51.6	8.6
1/15/80	2	2	8.7	0.7	6	52.2	12	103.8	8.7
1/16/80	3	3	9.2	0.6	6	55.2	18	159.0	8.8
1/17/80	4	4	7.4	0.4	6	44.4	24	203.4	8.5
1/18/80	5	5	8.6	0.5	6	51.6	30	255.0	8.5
1/21/80	8	6	9.6	0.3	6	57.6	36	312.6	8.7
1/22/80	9	7	8.9	0.4	6	53.4	42	366.0	8.7
1/23/80	10	8	8.5	0.7	6	51.0	48	417.0	8.7
1/24/80	11	9	9.7	0.4	6	58.2	54	475.2	8.8
1/25/80	12	10	11.5	0.7	6	69.0	60	544.2	9.1
1/28/80	15	11	12.4	1.6	6	74.4	66	618.6	9.4
1/29/80	16	12	10.4	1.4	6	62.4	72	681.0	9.5
1/30/80	17	13	10.1	1.1	6	60.6	78	741.6	9.5
1/31/80	18	14	9.8	2.1	6	58.8	84	800.4	9.5
2/1/80	19	15	9.3	1.6	6	55.8	90	856.2	9.5
2/4/80	22	16	10.2	3.4	6	61.2	96	917.4	9.6
2/5/80	23	17	12.7	2.6	6	76.2	102	993.6	9.7
2/6/80	24	18	8.6	0.9	6	51.6	108	1045.2	9.7
2/7/80	25	19	9.5	0.8	6	57.0	114	1102.2	9.7
2/8/80	26	20	10.0	1.4	6	60.0	120	1162.2	9.7
2/11/80	29	21	9.4	1.0	6	56.4	126	1218.6	9.7
2/12/80	30	22	8.5	2.9	6	51.0	132	1269.6	9.6
2/13/80	31	23	11.3	2.3	6	67.8	138	1337.4	9.7
2/14/80	32	24	9.6	1.1	6	57.6	144	1395.0	9.7
2/15/80	33	25	10.4	1.6	6	62.4	150	1457.4	9.7

DO 067537
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YZ0083100

Appendix B (cont.)
 Table 3 (cont.)
 A Dominant Lethal Inhalation Study in Rats
 with Benzene

Inhalation Report
 Cumulative Exposure Record
 Group III - 10 ppm (cont.)

Date	Test Day	Exposure Number	Mean Daily Exposure Concentration	SD	Daily Exposure Hours	Daily Concentration Hours	Total Exposure Hours	Total Concentration Hours	Cumulative Integrated Mean Concentration
2/18/80	36	26	10.6	1.3	6	63.6	156	1521.0	9.8
2/19/80	37	27	8.9	0.6	6	53.4	162	1574.4	9.7
2/20/80	38	28	10.5	1.3	6	63.0	168	1637.4	9.7
2/21/80	39	29	11.2	1.2	6	67.2	174	1704.6	9.8
2/22/80	40	30	9.7	1.3	6	58.2	180	1762.8	9.8
2/25/80	43	31	10.1	0.7	6	60.6	186	1823.4	9.8
2/26/80	44	32	10.2	1.6	6	61.2	192	1884.6	9.8
2/27/80	45	33	10.3	0.7	6	61.8	198	1946.4	9.8
2/28/80	46	34	10.4	0.8	6	62.4	204	2008.8	9.8
2/29/80	47	35	8.1	4.0	6	48.6	210	2057.4	9.8
3/3/80	50	36	10.2	1.2	6	61.2	216	2118.6	9.8
3/4/80	51	37	10.4	0.6	6	62.4	222	2181.0	9.8
3/5/80	52	38	10.6	1.5	6	63.6	228	2244.6	9.8
3/6/80	53	39	10.6	0.7	6	63.6	234	2308.2	9.9
3/7/80	54	40	10.4	1.0	6	62.4	240	2370.6	9.9
3/10/80	57	41	9.4	0.7	6	56.4	246	2427.0	9.9
3/11/80	58	42	11.4	1.4	6	68.4	252	2495.4	9.9
3/12/80	59	43	9.6	0.6	6	57.6	258	2553.0	9.9
3/13/80	60	44	10.3	1.0	6	61.8	264	2614.8	9.9
3/14/80	61	45	9.3	0.9	6	55.8	270	2670.6	9.9
3/17/80	64	46	9.1	0.6	6	54.6	276	2725.2	9.9
3/18/80	65	47	9.5	0.8	6	57.0	282	2782.2	9.9
3/19/80	66	48	9.3	1.2	6	55.8	288	2838.0	9.9
3/20/80	67	49	9.3	2.1	6	55.8	294	2893.8	9.8
3/21/80	68	50	8.9	1.6	6	53.4	300	2947.2	9.8

Standard deviation of Cumulative Integrated Mean concentration for Group III is 0.4 for entire study.

DO 067538
 CONFIDENTIAL

YZ0083101

Appendix B (cont.)
 Table 3 (cont.)
 A Dominant Lethal Inhalation Study in Rats
 with Benzene

Inhalation Report
 Cumulative Exposure Record
 Group IV - 30 ppm

Date	Test Day	Exposure Number	Mean Daily Exposure Concentration	SD	Daily Exposure Hours	Daily Concentration Hours	Total Exposure Hours	Total Concentration Hours	Cumulative Integrated Mean Concentration
1/14/80	1	1	32.7	2.4	6	196.2	6	196.2	32.7
1/15/80	2	2	32.2	2.0	6	193.2	12	389.4	32.5
1/16/80	3	3	28.5	6.8	6	171.0	18	560.4	31.1
1/17/80	4	4	30.6	2.7	6	183.6	24	744.0	31.0
1/18/80	5	5	30.1	2.6	6	180.6	30	924.6	30.8
1/21/80	8	6	29.0	6.7	6	174.0	36	1098.6	30.5
1/22/80	9	7	29.3	2.2	6	175.8	42	1274.6	30.3
1/23/80	10	8	29.5	2.4	6	177.0	48	1451.4	30.2
1/24/80	11	9	29.5	1.3	6	177.0	54	1628.4	30.2
1/25/80	12	10	29.5	1.3	6	177.0	60	1805.4	30.1
1/28/80	15	11	32.2	2.0	6	193.2	66	1998.6	30.3
1/29/80	16	12	32.8	3.2	6	196.8	72	2195.4	30.5
1/30/80	17	13	29.0	2.9	6	174.0	78	2369.4	30.4
1/31/80	18	14	30.6	4.0	6	183.6	84	2553.0	30.4
2/1/80	19	15	32.2	2.0	6	193.2	90	2746.2	30.5
2/4/80	22	16	33.3	4.8	6	199.8	96	2946.0	30.7
2/5/80	23	17	32.2	0.0	6	193.2	102	3139.2	30.8
2/6/80	24	18	31.7	1.3	6	190.2	108	3329.4	30.8
2/7/80	25	19	30.1	1.7	6	180.6	114	3510.0	30.8
2/8/80	26	20	30.6	1.8	6	183.6	120	3693.6	30.8
2/11/80	29	21	29.5	1.3	6	177.0	126	3870.6	30.7
2/12/80	30	22	31.1	2.6	6	186.6	132	4057.2	30.7
2/13/80	31	23	30.6	3.4	6	183.6	138	4240.8	30.7
2/14/80	32	24	29.0	2.1	6	174.0	144	4414.8	30.7
2/15/80	33	25	29.5	1.3	6	177.0	150	4591.8	30.6

DO 067539
 CONFIDENTIAL

YZ0083102

Appendix B (cont.)
 Table 3 (cont.)
 A Dominant Lethal Inhalation Study in Rats
 with Benzene

Inhalation Report
 Cumulative Exposure Record
 Group IV - 30 ppm (cont.)

Date	Test Day	Exposure Number	Mean Daily Exposure Concentration	SD	Daily Exposure Hours	Daily Concentration Hours	Total Exposure Hours	Total Concentration Hours	Cumulative Integrated Mean Concentration
2/18/80	36	26	29.5	1.3	6	177.0	156	4768.8	30.6
2/19/80	37	27	29.5	1.3	6	177.0	162	4945.8	30.5
2/20/80	38	28	29.5	1.3	6	177.0	168	5122.8	30.5
2/21/80	39	29	30.1	2.6	6	180.6	174	5303.4	30.5
2/22/80	40	30	29.5	1.3	6	177.0	180	5480.4	30.4
2/25/80	43	31	29.5	1.3	6	177.0	186	5657.4	30.4
2/26/80	44	32	29.5	2.4	6	177.0	192	5834.4	30.4
2/27/80	45	33	29.0	2.1	6	174.0	198	6008.4	30.3
2/28/80	46	34	30.1	1.7	6	180.6	204	6189.0	30.3
2/29/80	47	35	28.5	1.3	6	171.0	210	6360.0	30.3
3/3/80	50	36	30.6	2.7	6	183.6	216	6543.6	30.3
3/4/80	51	37	30.1	1.7	6	180.6	222	6724.2	30.3
3/5/80	52	38	29.5	1.3	6	177.0	228	6901.2	30.3
3/6/80	53	39	30.1	1.7	6	180.6	234	7081.8	30.3
3/7/80	54	40	29.5	1.3	6	177.0	240	7258.8	30.2
3/10/80	57	41	29.0	2.1	6	174.0	246	7432.8	30.2
3/11/80	58	42	29.5	1.3	6	177.0	252	7609.8	30.2
3/12/80	59	43	30.1	3.3	6	180.6	258	7790.4	30.2
3/13/80	60	44	30.1	1.4	6	180.6	264	7971.0	30.2
3/14/80	61	45	30.7	2.2	6	184.2	270	8155.2	30.2
3/17/80	64	46	33.0	1.8	6	198.0	276	8353.2	30.3
3/18/80	65	47	30.7	3.1	6	184.2	282	8537.4	30.3
3/19/80	66	48	30.7	2.2	6	184.2	288	8721.6	30.3
3/20/80	67	49	31.9	2.8	6	191.4	294	8913.0	30.3
3/21/80	68	50	30.2	2.6	6	181.2	300	9094.2	30.3

Standard deviation of Cumulative Integrated Mean concentration for Group IV is 0.5 for entire study.

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YZ0083103

Appendix B (cont.)
 Table 3 (cont.)
 A Dominant Lethal Inhalation Study in Rats
 with Benzene

Inhalation Report
 Cumulative Exposure Record
 Group V - 300 ppm

Date	Test Day	Exposure Number	Mean Daily Exposure Concentration	SD	Daily Exposure Hours	Daily Concentration Hours	Total Exposure Hours	Total Concentration Hours	Cumulative Integrated Mean Concentration
1/14/80	1	1	292	25	6	1752	6	1,752	292
1/15/80	2	2	275	3	6	1650	12	3,402	284
1/16/80	3	3	300	22	6	1800	18	5,202	289
1/17/80	4	4	294	22	6	1764	24	6,966	290
1/18/80	5	5	293	15	6	1758	30	8,724	291
1/21/80	8	6	296	8	6	1776	36	10,500	292
1/22/80	9	7	296	14	6	1776	42	12,276	292
1/23/80	10	8	284	12	6	1704	48	13,980	291
1/24/80	11	9	285	12	6	1710	54	15,690	291
1/25/80	12	10	305	3	6	1830	60	17,520	292
1/28/80	15	11	295	7	6	1770	66	19,290	292
1/29/80	16	12	303	6	6	1818	72	21,108	293
1/30/80	17	13	303	16	6	1818	78	22,926	294
1/31/80	18	14	304	19	6	1824	84	24,750	295
2/1/80	19	15	306	5	6	1836	90	26,586	295
2/4/80	22	16	303	29	6	1818	96	28,404	296
2/5/80	23	17	302	3	6	1812	102	30,216	296
2/6/80	24	18	299	13	6	1794	108	32,010	296
2/7/80	25	19	303	4	6	1818	114	33,828	297
2/8/80	26	20	304	6	6	1824	120	35,652	297
2/11/80	29	21	299	11	6	1794	126	37,446	297
2/12/80	30	22	300	5	6	1800	132	39,246	297
2/13/80	31	23	300	12	6	1800	138	41,046	297
2/14/80	32	24	300	3	6	1800	144	42,846	298
2/15/80	33	25	301	12	6	1806	150	44,652	298

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Appendix B (cont.)

Table 3 (cont.)

A Dominant Lethal Inhalation Study in Rats
with BenzeneInhalation Report
Cumulative Exposure Record
Group V - 300 ppm (cont.)

Date	Test Day	Exposure Number	Mean Daily Exposure Concentration	SD	Daily Exposure Hours	Daily Concentration Hours	Total Exposure Hours	Total Concentration Hours	Cumulative Integrated Mean Concentration
2/18/80	36	26	301	6	6	1806	156	46,458	298
2/19/80	37	27	299	5	6	1794	162	48,252	298
2/20/80	38	28	301	8	6	1806	168	50,058	298
2/21/80	39	29	298	7	6	1788	174	51,846	298
2/22/80	40	30	301	8	6	1806	180	53,652	298
2/25/80	43	31	299	4	6	1794	186	55,446	298
2/26/80	44	32	299	17	6	1794	192	57,240	298
2/27/80	45	33	302	12	6	1812	198	59,052	298
2/28/80	46	34	303	4	6	1818	204	60,870	298
2/29/80	47	35	294	11	6	1764	210	62,634	298
3/3/80	50	36	311	42	6	1866	216	64,500	299
3/4/80	51	37	301	5	6	1806	222	66,306	299
3/5/80	52	38	299	11	6	1794	228	68,100	299
3/6/80	53	39	300	14	6	1800	234	69,900	299
3/7/80	54	40	300	5	6	1800	240	71,700	299
3/10/80	57	41	303	20	6	1818	246	73,518	299
3/11/80	58	42	310	22	6	1860	252	75,378	299
3/12/80	59	43	297	25	6	1782	258	77,160	299
3/13/80	60	44	291	18	6	1746	264	78,906	299
3/14/80	61	45	300	32	6	1800	270	80,706	299
3/17/80	64	46	293	18	6	1758	276	82,464	299
3/18/80	65	47	302	32	6	1812	282	84,276	299
3/19/80	66	48	303	31	6	1818	288	86,094	299
3/20/80	67	49	319	51	6	1914	294	88,008	299
3/21/80	68	50	302	23	6	1812	300	89,820	299

Standard deviation of Cumulative Integrated Mean concentration for Group V is 4.0 for entire study.

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YZ0083105

Appendix B (cont.)
 Table 4
 A Dominant Lethal Inhalation Study in Rats
 with Benzene

Inhalation Report
 Daily Nominal Concentrations

<u>Date</u>	<u>Test Day</u>	<u>Exposure Number</u>	<u>Nominal Concentration (ppm)</u>			
			<u>Group II</u>	<u>Group III</u>	<u>Group IV</u>	<u>Group V</u>
Miran L						
1/14/80	1	1	0.7	8.1	29.8	316
1/15/80	2	2	0.7	8.1	30.7	305
1/16/80	3	3	1.0	8.5	29.0	337
1/17/80	4	4	0.9	8.4	28.5	302
1/18/80	5	5	1.3	8.2	30.6	307
1/21/80	8	6	1.3	8.2	28.9	321
1/22/80	9	7	1.4	8.2	27.9	310
1/23/80	10	8	1.4	8.0	28.2	290
1/24/80	11	9	1.5	8.8	30.7	300
1/25/80	12	10	1.4	10.9	31.4	300
1/28/80	15	11	1.5	6.1	25.9	299
1/29/80	16	12	1.3	10.6	32.7	290
1/30/80	17	13	0.7	10.7	31.3	317
1/31/80	18	14	1.6	10.4	31.3	312
2/1/80	19	15	1.4	10.2	29.5	317
2/4/80	22	16	1.4	5.1	25.2	302
2/5/80	23	17	1.3	9.9	30.2	312
2/6/80	24	18	1.5	8.5	29.8	320
2/7/80	25	19	1.8	9.0	30.2	324
2/8/80	26	20	2.0	11.5	30.6	319
2/11/80	29	21	a	a	23.5	308
2/12/80	30	22	1.0	9.1	30.3	319
2/13/80	31	23	0.8	9.1	31.1	314
2/14/80	32	24	1.9	12.7	30.9	329
2/15/80	33	25	0.8	10.4	28.6	321

^aNominal concentration suspect due to possible weighing error, not included in mean calculation.

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YZ0083106

Appendix B (cont.)
 Table 4 (cont.)
 A Dominant Lethal Inhalation Study in Rats
 with Benzene

Inhalation Report
 Daily Nominal Concentrations (cont.)

Date	Test Day	Exposure Number	Nominal Concentration (ppm)			
			Group II	Group III	Group IV	Group V
Miran L (cont.)						
2/18/80	36	26	1.2	11.3	30.0	325
2/19/80	37	27	1.3	10.3	29.7	317
2/20/80	38	28	1.1	10.1	28.7	326
2/21/80	39	29	1.1	9.5	28.3	315
2/22/80	40	30	1.1	10.6	29.1	320
2/25/80	43	31	1.0	10.5	29.3	318
2/26/80	44	32	a	10.0	30.1	324
2/27/80	45	33	1.1	12.1	30.5	325
2/28/80	46	34	1.9	10.4	30.3	319
2/29/80	47	35	1.3	8.3	29.4	314
3/3/80	50	36	1.4	10.3	32.5	318
3/4/80	51	37	1.2	10.8	31.0	321
3/5/80	52	38	1.2	10.2	30.4	337
3/6/80	53	39	1.4	10.9	30.3	338
3/7/80	54	40	1.2	10.4	30.4	343
3/10/80	57	41	1.3	11.3	30.6	344
3/11/80	58	42	1.0	10.5	32.4	361
3/12/80	59	43	1.3	10.7	31.3	338
Miran 04						
3/13/80	60	44	1.2	11.9	35.9	352
3/14/80	61	45	1.5	11.0	32.9	362
3/17/80	64	46	1.9	6.9	32.0	321
3/18/80	65	47	0.8	9.9	34.5	375
3/19/80	66	48	0.9	10.3	34.7	355
3/20/80	67	49	1.0	11.3	32.4	343
3/21/80	68	50	1.0	10.4	34.4	363
Mean			1.3	9.8	30.4	323
S.D.			0.3	1.5	2.2	19
N			48	49	50	50

^aNominal concentration suspect due to possible weighing error, not included in mean calculation.

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Appendix B (cont.)
 Table 5
 A Dominant Lethal Inhalation Study in Rats
 with Benzene

Inhalation Report
 Mean Daily Nominal Concentration VS. Mean Daily Actual (IR) Concentrations¹

<u>Group</u>		<u>Nominal Conc.</u> (ppm)	<u>Actual Conc.</u> (ppm)
II	Mean	1.3	1.0**
	S.D.	0.3	0.5
	N	48	50
III	Mean	9.8	9.8
	S.D.	1.5	1.0
	N	49	50
IV	Mean	30.4	30.3
	S.D.	2.2	1.2
	N	50	50
V	Mean	323	299**
	S.D.	19	7
	N	50	50

Significantly different from nominal concentration: ** $p < 0.01$.
¹Mean daily actual (IR) concentrations were compared to mean daily nominal concentrations by the F-test and Students' t-test. When variances differed significantly (F-test), Students' t-test was appropriately modified using Cochran's approximation (t'). Snedecor, G.S., and W.G. Cochran, Statistical Methods, 6th ed., Iowa State University Press, Ames, 1967, pp. 104-106, 114-119.

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Appendix C
A Dominant-Lethal Inhalation Study
With Benzene in Rats

79-7342

Individual Male Body Weights (grams)
Group 1 (Chamber-Exposed Control - 0 ppm)

An. No.	Treatment Period											Change in Body Wt. 1-10
	Initial	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	
100	A-	A-	A-	A-	A-	A-	A-	A-	A-	A-	A-	A-
101	416	420	433	448	465	480	485	489	504	515	520	100
102	364	364	368	383	400	410	422	431	435	446	447	83
103	402	403	404	420	436	458	461	472	486	491	500	97
104	423	419	417	426	438	464	479	512	519	538	538	119
105	371	377	386	403	420	425	440	455	460	476	477	100
106	389	384	386	396	402	417	431	442	456	464	453	69
107	485	497	487	492	519	531	541	557	580	597	598	101
108	386	386	396	406	423	432	446	457	466	483	486	100
109	321	432	437	447	468	484	498	507	526	539	548	116
110	409	410	412	418	424	441	449	460	473	480	477	67
111	412	411	416	431	448	464	472	487	497	506	501	90
112	440	437	443	454	471	498	506	517	532	546	540	103
113	408	412	423	441	449	466	477	489	502	519	508	96
114	367	362	370	383	398	417	426	434	438	451	455	93
115	414	418	398	408	432	452	462	472	477	494	488	70
116	364	370	388	391	398	412	418	423	439	446	444	74
117	410	417	428	440	455	469	480	494	508	526	521	104
118	385	389	402	420	440	473	481	494	513	528	534	145
119	385	390	394	403	423	430	436	445	451	461	466	76
119	424	422	433	446	460	467	471	482	486	486	489	67
Mean	398	406	411	423	438	455	464	476	487	500	500	94
S.D.	35	31	28	28	30	32	31	34	37	39	40	20
N	20	20	20	20	20	20	20	20	20	20	20	20

For explanation of statistical symbol: A-; see Appendix I.

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Appendix C (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

79-7342

Individual Male Body Weights (grams)
Group II (1 ppm)

An. No.	Treatment Period											Change in Body Wt. 1-10
	Initial	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	
300 ^a	455	452	471	490	506	532	539	468	-	-	-	-
301	419	416	426	447	461	479	473	485	419	454	494	78
302	393	395	401	414	430	442	452	459	465	485	474	79
303	455	463	468	491	510	533	535	541	548	567	569	106
304	417	405	402	412	434	452	445	467	489	499	487	82
305	411	399	401	419	439	455	454	466	484	495	495	96
306	432	425	428	445	449	472	482	502	514	527	538	113
307	415	415	436	457	476	495	503	515	530	533	546	131
308	415	398	424	435	449	466	464	473	481	483	481	83
309	401	391	385	388	393	409	409	421	437	443	451	60
310	410	407	408	428	446	474	481	484	454	498	481	74
311	351	345	342	357	373	385	400	404	418	425	433	88
312	395	397	406	418	434	459	466	472	482	499	504	107
313	371	370	370	370	380	394	394	398	407	419	410	40
314	385	395	402	408	421	446	451	465	479	488	493	98
315	379	396	407	410	434	444	453	467	473	488	493	97
316	394	390	404	421	436	456	459	474	492	501	456	66
317	391	402	403	418	431	454	465	476	484	494	500	96
318	445	451	463	473	498	516	521	533	533	555	548	97
319	398	400	393	404	423	444	447	458	465	476	471	71
Mean	407	406	412	425	441	460	465	471	477	491	491	88
S.D.	27	27	31	35	37	39	39	36	39	39	40	21
N	20	20	20	20	20	20	20	20	19	19	19	19

No statistically significant differences from control.
^aAnimal found dead during Week 8 of the treatment period.

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YZ0083110

Appendix C (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

79-7342

Individual Male Body Weights (grams)
Group III (10 ppm)

An. No.	Initial	Treatment Period										Change in Body Wt. 1-10
		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	
500	406	398	400	411	423	462	463	478	492	505	504	106
501	409	419	420	436	451	467	478	482	487	507	498	79
502	440	451	445	462	479	500	517	527	536	548	556	105
503	416	428	430	451	471	482	488	505	522	526	527	99
504	349	340	351	365	380	386	393	396	410	419	421	81
505	415	408	412	434	446	470	471	480	494	503	513	105
506	455	466	480	501	522	545	550	568	578	587	587	121
507	381	385	397	414	427	445	456	466	471	481	487	102
508	414	414	400	430	449	476	492	498	511	533	533	119
509	415	420	431	449	465	485	496	504	509	524	527	107
510	379	375	368	377	388	403	413	429	441	444	438	63
511	404	403	410	417	431	457	457	471	478	486	471	68
512	378	392	396	407	417	437	452	463	476	484	482	90
513	404	403	412	423	428	440	452	466	474	486	490	87
514	379	384	397	416	425	444	451	467	480	488	499	115
515	404	400	406	419	437	469	476	485	491	513	510	110
516	525	534	540	561	582	609	616	597	646	664	647	113
517	354	354	357	369	379	392	387	400	408	416	419	65
518	415	418	426	443	461	484	488	503	510	525	522	104
519	391	384	391	405	414	418	429	443	449	455	463	79
Mean	407	409	413	430	444	464	471	481	493	505	505	96
S.D.	38	41	42	44	47	51	52	48	54	56	54	18
N	20	20	20	20	20	20	20	20	20	20	20	20

No statistically significant differences from control.

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YZ0083111

Appendix C (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

79-7342

Individual Male Body Weights (grams)
Group IV (30 ppm)

An. No.	Treatment Period											Change in Body Wt. 1-10
	Initial	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	
700	381	388	388	393	391	408	412	416	421	431	432	44
701	428	428	427	431	435	457	457	473	483	497	503	75
702	419	420	406	421	433	450	464	480	496	514	515	96
703	343	352	362	371	386	405	417	431	437	447	454	102
704	362	363	367	381	393	414	417	431	442	454	446	83
705	419	414	408	423	449	474	479	494	504	519	524	110
706	365	363	366	373	392	401	407	420	436	442	440	77
707	385	391	397	404	418	448	452	457	457	463	461	70
708	369	372	381	388	414	418	424	442	455	459	479	107
709	421	420	422	443	449	474	483	494	510	521	518	98
710	430	419	413	435	438	460	461	470	480	491	488	69
711	486	482	497	508	526	545	552	563	566	572	565	83
712	379	372	377	401	415	431	444	461	482	487	503	131
713	400	412	419	446	455	477	480	497	475	487	502	90
714	445	453	456	474	496	520	524	540	525	562	568	115
715	365	377	382	397	409	418	426	433	444	461	461	84
716	437	442	444	457	472	488	494	503	513	522	526	84
717	401	410	414	422	437	459	461	468	476	479	493	83
718	454	456	477	499	511	536	536	552	571	567	575	119
719	430	440	428	462	471	489	492	502	501	516	514	74
Mean	406	409	412	426	440	459	464	476	484	495	498	90
S.D.	37	36	37	40	40	43	42	43	41	42	42	20
N	20	20	20	20	20	20	20	20	20	20	20	20

No statistically significant differences from control.

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YZ0083112

Appendix C (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

79-7342

Individual Male Body Weights (grams)
Group V (300 ppm)

An. No.	Treatment Period											Change in Body Wt. 1-10
	Initial	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	
900	494	477	452	469	489	524	531	548	561	568	569	92
901	436	430	438	453	472	492	494	506	516	518	512	82
902	431	434	436	461	475	483	496	511	514	525	533	99
903	425	420	432	441	462	475	493	513	522	539	549	129
904	374	377	386	396	401	437	437	438	453	466	462	85
905	376	388	389	399	424	441	453	467	484	491	495	107
906	414	412	417	434	439	462	468	480	491	496	500	88
907	413	410	405	416	427	446	454	472	482	499	511	101
908	394	407	416	427	440	459	465	478	479	495	493	86
909	445	438	450	471	489	509	521	528	538	557	561	123
910	381	380	386	408	416	439	444	465	474	477	478	98
911	353	363	366	375	387	403	411	424	432	442	450	87
912	444	451	448	448	470	473	499	513	541	544	559	108
913	409	407	411	416	433	442	455	461	478	485	491	84
914	389	400	398	415	420	436	450	463	478	487	481	81
915	360	360	340	352	357	367	373	387	391	401	403	43
916	391	409	412	426	440	454	462	477	481	502	513	104
917	401	398	391	401	420	448	458	466	483	491	493	100
918	481	482	485	491	516	542	556	569	587	597	590	108
919	371	375	378	387	405	427	435	446	454	459	461	86
Mean	409	411	412	424	439	458	468	481	492	502	505	95
S.D.	38	34	34	35	39	40	42	43	45	45	46	18
N	20	20	20	20	20	20	20	20	20	20	20	20

No statistically significant differences from control.

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Appendix C (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

79-7342

Individual Male Body Weights (grams)
Group 1 (Chamber-Exposed Control - 0 ppm)

Animal No.	Mating Period		Post-Mating Period								
	Week 1	Week 2	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 10
	A-	A-	A-	A-	A-	A-	A-	A-	A-	A-	A-
100	512	536	572	590	597	604	612	618	634	637	653
101	447	461	477	482	486	497	511	529	538	533	549
102	516	541	562	579	581	599	608	614	637	628	641
103	542	557	574	595	588	615	622	643	656	668	690
104	476	486	503	516	521	537	537	553	557	557	569
105	456	468	485	500	502	516	528	547	551	553	557
106	600	614	641	656	663	692	700	722	723	739	773
107	489	509	527	534	530	546	555	566	581	585	591
108	556	574	592	603	619	630	640	654	671	674	699
109	474	485	498	512	520	543	552	568	574	583	599
110	519	526	538	542	538	562	574	588	593	597	612
111	545	574	595	607	619	629	632	644	652	641	666
112	522	537	554	575	586	597	599	607	616	614	626
113	460	473	486	498	500	511	515	538	539	543	557
114	497	523	539	554	547	547	573	583	601	602	619
115	459	480	490	503	496	512	511	527	537	541	557
116	521	535	544	552	564	573	575	586	594	599	599
117	539	547	567	574	577	586	598	619	624	626	634
118	465	472	481	486	490	502	507	522	532	534	540
119	496	522	536	546	553	563	557	568	575	580	597
Mean	505	521	538	550	554	568	575	590	599	602	616
S.D.	40	41	45	47	49	51	51	51	52	54	59
N	20	20	20	20	20	20	20	20	20	20	20

For explanation of statistical symbol: A-; see Appendix 1.

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YZ0083114

Appendix C (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

79-7342

Individual Male Body Weights (grams)
Group II (7 ppm)

Animal No.	Mating Period		Post-Mating Period								
	Week 1	Week 2	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 10
300 ^a	-	-	-	-	-	-	-	-	-	-	-
301	523	551	576	592	588	608	615	637	651	654	676
302	475	496	511	527	533	550	555	576	585	583	604
303	537	581	600	616	621	641	652	665	679	676	696
304	494	509	529	555	557	568	582	593	607	597	614
305	511	525	544	557	557	591	591	609	624	637	648
306	525	540	569	592	601	615	633	642	659	667	682
307	554	566	593	608	615	636	649	663	679	686	705
308	504	529	546	571	579	593	601	621	630	630	642
309	455	476	482	497	508	526	539	556	564	565	591
310	496	525	546	556	570	579	593	611	612	617	621
311	438	460	466	476	481	492	502	513	521	534	553
312	518	541	555	584	588	606	617	629	642	651	670
313	415	431	442	455	438	455	469	490	504	509	525
314	504	516	536	552	548	565	579	588	603	609	625
315	504	512	529	535	542	563	566	576	587	602	618
316 ^b	490	524	511	-	-	-	-	-	-	-	-
317	503	509	512	530	538	547	555	572	589	591	608
318	531	553	577	594	605	606	620	620	639	640	673
319	484	496	516	529	530	537	538	556	563	561	581
Mean	498	518	534	551	556	571	581	595	608	612	630
S.D.	34	36	42	45	48	48	49	48	49	49	49
N	19	19	19	18	18	18	18	18	18	18	18

No statistically significant differences from control.
^aAnimal found dead during Week 8 of the treatment period.
^bAnimal found dead Week 2 of the post-mating period.

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YZ0083115

Appendix C (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

79-7342

Individual Male Body Weights (grams)
Group III (10 ppm)

Animal No.	Mating Period		Post-Mating Period								
	Week 1	Week 2	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 10
500	513	523	541	566	570	585	602	591	619	623	647
501	502	513	542	563	576	589	605	617	626	634	661
502	554	575	602	619	620	639	647	652	659	669	712
503	537	552	570	580	589	602	613	634	650	652	671
504	431	439	454	468	475	493	497	510	514	524	526
505	520	527	538	557	560	576	583	596	616	616	638
506	599	606	627	639	642	655	665	664	697	700	726
507	496	517	538	544	538	556	567	582	593	590	612
508	540	551	566	584	591	613	626	626	649	638	677
509	528	542	553	575	576	591	589	592	611	603	621
510	446	461	473	480	485	498	498	520	516	528	539
511	476	491	507	509	519	534	550	556	567	560	583
512	486	489	497	509	518	523	519	540	554	556	579
513	496	519	537	542	545	556	550	570	583	521	597
514	514	536	547	555	569	583	594	603	617	624	654
515	509	522	534	544	555	574	578	591	597	590	607
516	657	692	736	758	764	802	806	830	811	826	823
517	429	451	466	474	479	490	498	506	512	515	525
518	529	551	575	593	591	611	619	621	643	632	656
519	456	471	484	492	492	508	517	519	528	527	543
Mean	511	526	544	558	563	579	586	596	608	606	630
S.D.	54	57	63	67	66	71	72	72	71	75	74
N	20	20	20	20	20	20	20	20	20	20	20

No statistically significant differences from control.

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Appendix C (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

79-7342

Individual Male Body Weights (grams)
Group IV (30 ppm)

Animal No.	Mating Period		Post-Mating Period								
	Week 1	Week 2	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 10
700	440	449	465	483	492	506	512	518	531	537	555
701	515	536	548	559	564	577	590	597	610	613	616
702	520	536	568	590	600	614	621	631	644	648	656
703	456	476	491	507	514	524	529	548	561	567	592
704	436	450	463	480	487	502	501	512	524	518	530
705	534	551	555	568	575	596	594	597	605	607	625
706	444	463	472	490	501	517	517	528	536	540	556
707	456	489	516	528	529	553	555	569	573	568	574
708	498	506	521	527	539	562	564	571	584	580	615
709	526	540	565	576	595	616	626	632	658	654	674
710	494	524	551	558	569	597	601	600	622	621	648
711	579	602	617	631	638	664	655	672	691	684	709
712	496	506	528	546	556	578	581	606	625	623	656
713	514	542	561	577	577	589	594	589	611	611	630
714	580	585	611	633	639	659	658	677	690	691	703
715	470	479	486	495	502	523	527	541	544	550	566
716	495	518	541	553	559	581	580	581	602	608	630
717	488	514	531	548	548	572	571	585	592	593	609
718	584	609	633	643	656	656	662	682	701	689	710
719	514	499	524	537	550	567	576	591	616	607	629
Mean	502	519	537	551	560	578	581	591	606	605	624
S.D.	45	46	48	48	49	49	48	50	53	51	52
N	20	20	20	20	20	20	20	20	20	20	20

No statistically significant differences from control.

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YZ0083117

Appendix C (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

79-7342

Individual Male Body Weights (grams)
Group V (300 ppm)

Animal No.	Mating Period		Post-Mating Period								
	Week 1	Week 2	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 10
900	575	605	616	637	640	649	667	683	701	681	717
901	508	532	548	560	563	581	586	607	614	614	633
902	532	547	573	591	599	620	625	634	643	650	657
903	549	560	580	602	616	621	637	641	664	673	686
904	474	489	509	520	518	531	531	540	544	551	571
905	497	515	541	558	576	588	595	613	621	611	649
906	512	502	518	530	534	553	557	573	591	592	610
907	513	522	549	569	575	587	604	615	626	631	634
908	504	524	536	558	562	576	579	597	600	601	624
909	568	589	603	617	625	644	645	671	676	680	697
910	472	482	509	530	531	549	562	577	585	565	590
911	475	449	475	491	491	508	512	515	535	543	561
912	555	575	606	631	617	643	651	683	664	658	709
913	502	517	539	549	559	570	583	590	609	610	619
914	489	517	524	529	538	543	549	568	574	573	589
915	419	436	455	468	476	498	507	525	533	539	544
916	516	526	551	565	575	583	593	623	613	608	624
917	502	516	536	554	551	578	588	600	604	608	618
918	606	608	622	628	646	651	662	668	681	681	698
919	463	469	483	496	496	511	515	531	539	539	555
Mean	509	524	544	559	564	579	587	603	611	610	629
S.D.	48	47	46	48	49	48	50	52	50	49	53
N	20	20	20	20	20	20	20	20	20	20	20

No statistically significant differences from control.

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YZ0083118

D-1

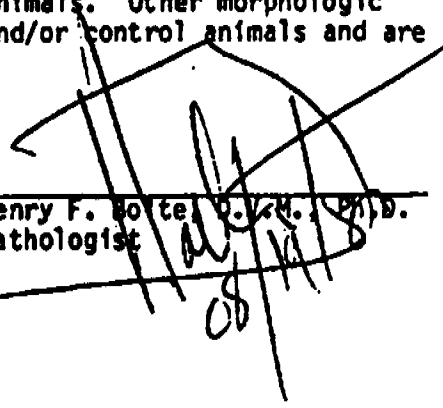
79-7342

Appendix D
A Dominant-Lethal Inhalation Study
With Benzene in Rats

Gross Postmortem Observations - Males

Preface

Hepatic pallor and an increased incidence of accentuation of the lobular pattern of the liver were seen in the treated animals. Other morphologic findings occurred sporadically in the treated and/or control animals and are not considered to be compound-related.


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Pathologist

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YZ0083119

Appendix D (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

Gross Postmortem Observations - Males

Group ppm	Animal Number	Type of Death ^a	Observation(s) ^b
I 0	100	T	N.O.A.
	101	T	<u>Lungs</u> : few scattered red foci on all surfaces of all lobes.
	102	T	N.O.A.
	103	T	<u>Lungs</u> : few scattered tan foci on all lobes.
	104	T	<u>Lungs</u> : dark red areas (0.3 cm. in diam.) on left lobe. <u>Liver</u> : accentuated lobular pattern.
	105	T	N.O.A.
	106	T	N.O.A.
	107	T	N.O.A.
	108	T	N.O.A.
	109	T	N.O.A.
	110	T	N.O.A.
	111	T	N.O.A.
	112	T	<u>Lungs</u> : scattered red foci on all lobes and surfaces. <u>Ear (Right)</u> : scab at eartag (0.2 cm.).
	113	T	<u>Ear (Right)</u> : scab.
	114	T	N.O.A.
	115	T	N.O.A.
	116	T	N.O.A.

^aT = Terminal.^bN.O.A. = No observable abnormalities.

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Appendix D (cont.)
 - A Dominant-Lethal Inhalation Study
 With Benzene in Rats

Gross Postmortem Observations - Males

<u>Group</u> <u>ppm</u>	<u>Animal</u> <u>Number</u>	<u>Type of</u> <u>Death^a</u>	<u>Observation(s)^b</u>
I 0 (cont.)	117	T	<u>Lungs</u> : scattered tan foci on all lobes and surfaces. <u>Ear (Right)</u> : scab (0.2 cm. in diam.)
	118	T	N.O.A.
	119	T	N.O.A.
II 1	300	S.D.	<u>Liver</u> : accentuated lobular pattern of all lobes and surfaces; slightly enlarged. <u>Lungs</u> : all lobes and surfaces not collapsed; multiple white to tan areas (0.1 - 0.4 cm.); areas confluent; white areas extend beneath surface; found throughout tissue. <u>Brain</u> : cerebrum highly vascularized.
	301	T	<u>Lungs</u> : left lobe adhered to thoracic wall. Raised, irregular tan areas (0.1 - 0.3 cm.) with gray centers on all lobes.
	302	T	<u>Lungs</u> : multiple scattered gray foci on all lobes.
	303	T	<u>Kidneys (Both)</u> : pale tan. <u>Lungs</u> : red focus on right posterior lobe.
	304	T	N.O.A.
	305	T	N.O.A.
	306	T	<u>Lungs</u> : scattered tan and gray foci on all lobes and surfaces.
	307	T	<u>Kidneys (Both)</u> : pale brown. <u>Liver</u> : all lobes pale brown with extremely accentuated lobular pattern. <u>Lungs</u> : multiple scattered red and gray foci on all lobes.

^aT = Terminal; S.D. = Spontaneous Death.

^bN.O.A. = No observable abnormalities.

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YZ0083121

Appendix D (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

Gross Postmortem Observations - Males

<u>Group</u> <u>ppm</u>	<u>Animal</u> <u>Number</u>	<u>Type of</u> <u>Death^a</u>	<u>Observation(s)^b</u>
II 1 (cont.)	308	T	<u>Lungs</u> multiple scattered gray foci on all lobes.
	309	T	<u>Liver</u> all lobes pale brown. <u>Lungs</u> all lobes mottled pink and tan. Slight gray color at left lung and bronchiole junction. Nodules embedded in edge of posterior lobe. Proliferation of 0.1 cm., light green-tan, solid nodules.
	310	T	<u>Ear (Right)</u> : torn with scab at eartag. <u>Kidneys (Both)</u> scattered tan foci. <u>Liver</u> all lobes pale tan. <u>Lungs</u> : all lobes dark red with scattered gray, tan and red foci.
	311	T	<u>Lungs</u> : few scattered gray foci on all lobes.
	312	T	<u>Kidneys (Both)</u> : mottled red. <u>Lungs</u> : few scattered red foci on all lobes.
	313	T	N.O.A.
	314	T	N.O.A.
	315	T	<u>Lungs</u> scattered red foci on all lobes and surfaces.
	316	S.D.	<u>Seminal vesicles</u> : 2-3 x larger than normal with surrounding edema (clear). <u>Urinary bladder</u> large (3.2 x 1.8 cm.); red, tan, firm, filled with extreme amount of thin red fluid and calculi (0.1 - 0.3 cm. in diam.). <u>Kidneys (Both)</u> pale brown with distended renal pelvis (0.8 x 0.4 cm.). Surrounding adipose tissue containing moderate amount of clear edema. <u>Thoracic cavity</u> : moderate amount of thin, red hydra-pleura.

^aT = Terminal; S.D. = Spontaneous Death.
^bN.O.A. = No observable abnormalities.

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YZ0083122

Appendix D (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

Gross Postmortem Observations - Males

Group ppm	Animal Number	Type of Death ^a	Observation(s) ^b
II 1 (cont.)	316 (cont.)	S.D.	<u>Lungs</u> : all lobes adhered to thoracic wall and diaphragm with dark red and tan mottling, scattered with white areas (0.1 - 0.4 cm. in diam.).
	317	T	<u>Kidneys (Both)</u> multiple clustered tan foci. <u>Liver</u> : all lobes pale tan; accentuated lobular pattern. <u>Lungs</u> : few scattered tan foci on all lobes.
	318	T	N.O.A.
	319	T	N.O.A.
III 10	500	T	<u>Liver</u> : accentuated lobular patterns of all lobes.
	501	T	N.O.A.
	502	T	<u>Lungs</u> : scattered red foci on all lobes.
	503	T	<u>Lungs</u> : few scattered tan foci on all lobes and surfaces. <u>Liver</u> : all lobes and surfaces slightly pale tan; accentuated lobular pattern.
	504	T	N.O.A.
	505	T	<u>Ear (R)</u> : torn at eartag. <u>Liver</u> : all lobes pale tan; moderately accentuated lobular pattern.
	506	T	<u>Liver</u> accentuated lobular pattern of all lobes.
	507	T	N.O.A.
	508	T	N.O.A.

^aT = Terminal; S.D. = Spontaneous Death.

^bN.O.A. = No observable abnormalities.

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Appendix D (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

Gross Postmortem Observations - Males

Group ppm	Animal Number	Type of Death ^a	Observation(s) ^b
III 10 (cont.)	509	T	<u>Lungs</u> : scattered red foci on all lobes and surfaces.
	510	T	<u>Liver</u> : accentuated lobular pattern of all lobes. <u>Lungs</u> : all lobes slightly red; white discoloration (0.4 cm. in diam.) on dorsal surface of right lobe.
	511	T	<u>Incisors (both; upper)</u> : missing.
	512	T	N.O.A.
	513	T	N.O.A.
	514	T	N.O.A.
	515	T	<u>Liver</u> : all lobes and surfaces slightly pale; accentuated lobular pattern. <u>Ear (Right)</u> : scab (0.3 cm.).
	516	T	N.O.A.
	517	T	N.O.A.
	518	T	<u>Kidneys (Both)</u> : few scattered tan foci. <u>Lungs</u> : few scattered tan foci on all lobes.
	519	T	<u>Testes (Both)</u> : slightly reddened. <u>Kidneys (Both)</u> : mottled red. <u>Lungs</u> : red focus on right median lobe.
IV 30	700	T	N.O.A.
	701	T	N.O.A.
	702	T	<u>Liver</u> : all lobes and surfaces slightly pale tan; accentuated lobular pattern.

^aT = Terminal.

^bN.O.A. = No observable abnormalities.

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Appendix D (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

Gross Postmortem Observations - Males

Group ppm	Animal Number	Type of Death ^a	Observation(s) ^b
IV 30 (cont.)	703	T	<u>Testis (Right)</u> : not developed; small; 1/8 normal size.
	704	T	<u>Lungs</u> : few scattered tan foci on all lobes.
	705	T	N.O.A.
	706	T	<u>Liver</u> : slightly pale red-brown; extremely accentuated lobular pattern.
	707	T	N.O.A.
	708	T	<u>Liver</u> : slightly accentuated lobular pattern of all lobes <u>Forelimbs (Both)</u> : moderate hair loss.
	709	T	N.O.A.
	710	T	N.O.A.
	711	T	<u>Liver</u> : accentuated lobular pattern of all lobes and surfaces. <u>Lungs</u> : few scattered dark red foci on all lobes and surfaces.
	712	T	<u>Liver</u> : all lobes pale tan; extremely accen- tuated lobular pattern. <u>Lungs</u> : few scattered tan foci.
	713	T	<u>Lungs</u> : multiple clustered, raised tan areas (up to 0.3 cm. in diam.) on all lobes. <u>Ear (Right)</u> : slight scab.
	714	T	<u>Liver</u> : all lobes and surfaces slightly pale tan; accentuated. <u>Lungs</u> : scattered red foci on all lobes and surfaces. <u>Kidneys (Both)</u> : few depressions (<0.2 cm.).

^aT = Terminal.

^bN.O.A. = No observable abnormalities.

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Appendix D (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

Gross Postmortem Observations - Males

Group ppm	Animal Number	Type of Death ^a	Observation(s) ^b
IV 30 (cont.)	715	T	<u>Liver</u> : slightly accentuated lobular pattern of all lobes.
	716	T	<u>Incisors (upper)</u> : maloccluded. <u>Lungs</u> : scattered gray foci on all lobes.
	717	T	N.O.A.
	718	T	<u>Liver</u> : all lobes pale tan; extremely accentuated lobular pattern. <u>Kidneys (Both)</u> : extremely pale tan. <u>Lungs</u> : few scattered tan foci on all lobes.
	719	T	N.O.A.
V 300	900	T	<u>Lungs</u> : moderate scattered gray foci on all lobes and surfaces.
	901	T	<u>Lungs</u> : few scattered red foci on all lobes.
	902	T	<u>Liver</u> : all lobes and surfaces slightly pale tan; accentuated lobular pattern. <u>Lungs</u> : scattered tan and red foci on all lobes and surfaces.
	903	T	<u>Kidney (Right)</u> : embedded cyst (0.4 cm. in diam.) near hilus; containing clear, thin fluid. <u>Kidneys (Both)</u> : pale brown.
	904	T	N.O.A.
	905	T	N.O.A.
	906	T	<u>Testis (Left)</u> : slightly reddened. <u>Lungs</u> : red focus on ventral surface of left lobe. <u>Liver</u> : slightly accentuated lobular pattern of all lobes.

^aT = Terminal.^bN.O.A. = No observable abnormalities.

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Appendix D (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

Gross Postmortem Observations - Males

Group ppm	Animal Number	Type of Death ^a	Observation(s) ^b
V 300 (cont.)	907	T	<u>Liver</u> : all lobes pale tan; extremely accentuated lobular pattern. <u>Lungs</u> : few tan scattered foci on all lobes.
	908	T	N.O.A.
	909	T	<u>Lungs</u> : scattered tan foci on all lobes and surfaces. <u>Liver</u> : accentuated lobular pattern of all lobes and surfaces.
	910	T	N.O.A.
	911	T	<u>Liver</u> : slightly accentuated lobular pattern of all lobes.
	912	T	<u>Lungs</u> : scattered tan and green foci on all lobes and surfaces.
	913	T	N.O.A.
	914	T	N.O.A.
	915	T	N.O.A.
	916	T	<u>Kidneys (Both)</u> : mottled red; depressed area (left) - (0.5 x 1.0 cm.). <u>Liver</u> : slightly accentuated lobular pattern of all lobes. <u>Lungs</u> : red area (0.2 cm.) on dorsal surface of right median lobe; red focus of right anterior lobe. <u>Ear (Right)</u> : scab at eartag.
	917	T	N.O.A.
	918	T	<u>Liver</u> : red areas (0.4 - 0.8 cm. in diam.) over surfaces of all lobes; moderately accentuated lobular pattern.

^aT = Terminal.

^bN.O.A. = No observable abnormalities.

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Appendix D (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

Gross Postmortem Observations - Males

<u>Group</u> ppm	<u>Animal</u> <u>Number</u>	<u>Type of</u> <u>Death</u> ^a	<u>Observation(s)</u> ^b
V 300	919	T	<u>Kidney (Right):</u> renal calculi. <u>Lungs:</u> scattered gray foci on all lobes. <u>Eye (Left):</u> 20% opacity.

^aT = Terminal.

^bN.O.A. = No observable abnormalities.

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Appendix E

A Dominant-Lethal Inhalation Study
With Benzene in Rats

Pregnancy and Implantation Data - Post-Treatment Mating Period

Preface

Corp. Lut.	=	Corpora Lutea
Impl.	=	Implantations
VFS	=	Viable Fetuses
M.R.	=	Mutagenic Ratio (for definition see Methodology and Reference; Appendix I)
I.E.	=	Implantation Efficiency (for definition see Methodology and Reference; Appendix I)

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Appendix E (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats
Pregnancy, Corpora Lutea and Implantation Data

79-7342

Post-Treatment Mating Period (Week 1) - Group 1 - Chamber-Exposed Control

Male No.	Female No.	Corp. Lut.	Impl.	I.E. $\times 10^{-2}$	Number of Dead Implants		M.R. $\times 10^{-2}$	Male No.	Female No.	Corp. Lut.	Impl.	I.E. $\times 10^{-2}$	Number of Dead Implants		M.R. $\times 10^{-2}$
		A+F	K+	V-	K-	K+J	V-						VFS		
100	200	14	13	92.9	0	13	1.9	111	222	16	15	93.8	1	14	6.7
	201	20	19	95.0	2	17	10.5		223	12	12	97.9	1	11	8.3
101	202	16	15	93.8	1	14	6.7	112	224	13	13	98.1	2	11	15.4
	203	15	15	98.3	0	15	1.7		225	13	13	98.1	1	12	7.7
102	204	18	17	94.4	0	17	1.5	113	226	9	8	88.9	1	7	12.5
	205	Not pregnant.							227	13	9	69.2	0	9	2.8
103	206	13	13	98.1	0	13	1.9	114	228	13	13	98.1	0	13	1.9
	207	20	15	75.0	1	14	6.7		229	15	14	93.3	1	13	7.1
104	208	Not pregnant.						115	230	Not pregnant.					
	209	15	14	93.3	2	12	14.3		231	14	14	98.2	2	12	14.3
105	210	Not pregnant.						116	232	12	4	33.3	0	4	6.3
	211	15	14	93.3	1	13	7.1		233	14	14	98.2	0	14	1.8
106	212	19	17	89.5	3	14	17.6	117	234	13	13	98.1	1	12	7.7
	213 ^a	13	14	-	1	13	7.1		235	14	14	98.2	1	13	7.1
107	214	15	15	98.3	1	14	6.7	118	236	18	18	98.6	1	17	5.6
	215	12	12	97.9	0	12	2.1		237	16	15	93.8	0	15	1.7
108	216	15	14	93.3	0	14	1.8	119	238	13	13	98.1	0	13	1.9
	217	15	15	98.3	1	14	6.7		239	12	12	97.9	0	12	2.1
109	218	12	11	91.7	0	11	2.3	Total:		524	496	3151.5	38	458	280.7
	219	16	16	98.4	3	13	18.8	Mean:		14.6	13.8	92.7	1.1	12.7	7.8
								S.D.:		2.4	2.8	12.3	1.8	2.6	9.1
110	220	14	14	98.2	0	14	1.8	N:		36	36	34	36	36	36
	221 ^a	17	19	-	10	9	52.6								

For explanation of statistical symbols: A+F, K+, K-, K+J, V-; see Appendix I.

^aTotal number of implants greater than total number of corpora lutea; data excluded from calculations of implantation efficiency.

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Appendix E (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats
Pregnancy, Corpora Lutea and Implantation Data

79-7342

Post-Treatment Mating Period (Week 1) - Group II - (1 ppm)

Male No.	Female No.	Corp. Lut.	Impl.	I.E. x 10 ⁻²	Number of Dead Implants			Male No.	Female No.	Corp. Lut.	Impl.	I.E. x 10 ⁻²	Number of Dead Implants			
					VFS	M.R. x 10 ⁻²							VFS	M.R. x 10 ⁻²		
300 ^a	400 401	- -	- -	- -		- -	- -	311	422 423	Not pregnant. 16	12	- 75.0	- 1	11	- 8.3	
301	402 403	16 17	16 16	98.4 94.1	1 0	15 16	6.3 1.6	312	424 425	15 17	15 17	98.3 98.5	2 0	13 17	13.3 1.5	
302	404 405	14 19	13 14	92.9 73.7	1 1	12 13	7.7 7.1	313	426 427	13 14	13 14	98.1 98.2	4 2	9 12	30.8 14.3	
303	406 407	18 12	18 12	98.6 97.9	1 0	17 12	5.6 2.1	314	428 429	Not pregnant. 17	15	- 88.2	0	15	1.7	
304	408 409	15 15	15 15	98.3 98.3	0 2	15 13	1.7 13.3	315	430 431	18 Not pregnant.	17	94.4	3	14	17.6	
305	410 411	17 13	15 12	88.2 92.3	0 0	15 12	1.7 2.1	316	432 433	Not pregnant. 18	13	- 72.2	1	12	7.7	
306	412 413	Not pregnant. 15	- 15	- 98.3	- 0	- 15	- 1.7	317	434 435	Not pregnant. 15	15	- 98.3	1	14	6.7	
307	414 415	14 16	14 16	98.2 98.4	0 1	14 15	1.8 6.3	318	436 437	13 14	12 14	92.3 98.2	0 0	12 14	2.1 1.8	
308	416 417	15 Not pregnant.	13 -	86.7 -	0	13	1.9	319	438 439	15 Not pregnant.	13	86.7	0	13	1.9	
309	418 419	16 16	16 15	98.4 93.8	1 0	15 15	6.3 1.7	Total:			459	428	2779.9	22	406	181.0
								Mean:			15.3	14.3	92.7	0.7	13.5	6.0
								S.D.:			1.8	1.8	8.2	1.0	1.9	6.5
310	420 421	13 13	10 13	76.9 98.1	0 0	10 13	2.5 1.9	N:			30	30	30	30	30	30

^aMale No. 300 found dead during Week 8 of treatment period.

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YZ0083131

Appendix E (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats
Pregnancy, Corpora Lutea and Implantation Data

79-7342

Post-Treatment Mating Period (Week 1) - Group III - (10 ppm)

Male No.	Female No.	Corp. Lut.	Impl.	I.E. ₂ x10 ⁻²	Number of Dead Implants	VFS	M.R. x10 ⁻²	Male No.	Female No.	Corp. Lut.	Impl.	I.E. ₂ x10 ⁻²	Number of Dead Implants	VFS	M.R. x10 ⁻²
500	600	13	13	98.1	1	12	7.7	511	622	13	3	23.1	0	3	8.3
	601	13	12	92.3	2	10	16.7		623	11	6	54.5	0	6	4.2
501	602	12	12	97.9	1	11	8.3	512	624	11	11	97.7	1	10	9.1
	603	Not pregnant.							625	12	12	97.9	0	12	2.1
502	604	Not pregnant.						513	626	16	14	87.5	0	14	1.8
	605	10	9	90.0	0	9	2.8		627	Not pregnant.					
503	606 ^a	14	15	-	1	14	6.7	514	628	15	14	93.3	0	14	1.8
	607	10	6	60.0	2	4	33.3		629	13	11	84.6	1	10	9.1
504	608	15	14	93.3	0	14	1.8	515	630	15	13	86.7	2	11	15.4
	609	14	14	98.2	1	13	7.1		631	Not pregnant.					
505	610 ^a	16	17	-	1	16	5.9	516	632	13	13	98.1	0	13	1.9
	611	Not pregnant.							633	17	17	98.5	0	17	1.5
506	612	Not pregnant.						517	634	Not pregnant.					
	613	Not pregnant.							635	17	13	76.5	0	13	1.9
507	614	Not pregnant.						518	636	11	10	90.9	0	10	2.5
	615	18	18	98.6	2	16	11.1		637	15	15	98.3	1	14	6.7
508	616	12	12	97.9	0	12	2.1	519	638	12	12	97.9	2	10	16.7
	617	16	16	98.4	1	15	6.3		639	13	13	98.1	0	13	1.9
509	618	12	12	97.9	0	12	2.1	Total: 405 360 2400.2 20 340 205.1							
	619	14	12	85.7	1	11	8.3	Mean: 13.5 12.0 85.7 0.7 11.3 7.1							
								S.D.: 2.1 3.9 22.8 0.8 3.8 6.8							
510	620	12	1	8.3	0	1	(25.0)	N: 30 30 28 30 30 29							
	621	Not pregnant.													

^aTotal number of implants greater than total number of corpora lutea; data excluded from calculation of implantation efficiency.

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Appendix E (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats
Pregnancy, Corpora Lutea and Implantation Data

79-7342

Post-Treatment Mating Period (Week 1) - Group IV - (30 ppm)

Male No.	Female No.	Corp. Lut.	Impl.	I.E. ₂ x10 ⁻²	Number of			Male No.	Female No.	Corp. Lut.	Impl.	I.E. ₂ x10 ⁻²	Number of			
					Dead Implants	VFS	M.R. x10 ⁻²						Dead Implants	VFS	M.R. x10 ⁻²	
700	800	14	14	98.2	1	13	7.1	711	822	Not pregnant.						
	801	12	10	83.3	3	7	30.0		823	Not pregnant.						
701	802	14	13	92.9	1	12	7.7	712	824	16	15	93.8	1	14	6.7	
	803	Not pregnant.							825	11	11	97.7	2	9	18.2	
702	804	Not pregnant.						713	826	14	14	98.2	0	14	1.8	
	805	14	10	71.4	3	7	30.0		827	Not pregnant.						
703	806	13	12	92.3	0	12	2.1	714	828	14	14	98.2	0	14	1.8	
	807	Not pregnant.							829	Not pregnant.						
704	808	12	10	83.3	1	9	10.0	715	830	14	14	98.2	0	14	1.8	
	809	12	12	97.9	1	11	8.3		831	14	13	92.9	0	13	1.9	
705	810	14	5	35.7	1	4	20.0	716	832	16	16	98.4	2	14	12.5	
	811	16	15	93.8	2	13	13.3		833	16	14	87.5	1	13	7.1	
706	812	13	13	98.1	0	13	1.9	717	834	14	14	98.2	0	14	1.8	
	813	14	12	85.7	1	11	8.3		835	Not pregnant.						
707	814	Not pregnant.						718	836	Not pregnant.						
	815	15	13	86.7	1	12	7.7		837	18	16	88.9	2	14	12.5	
708	816	17	16	94.1	8	8	50.0	719	838	17	17	98.5	0	17	1.5	
	817	17	10	58.8	5	5	50.0		839	Not pregnant.						
709	818	16	16	98.4	1	15	6.3	Total:			423	381	2594.0	39	342	336.8
	819	16	13	81.3	1	12	7.7	Mean:			14.6	13.1	89.4	1.3	11.8	11.6
								S.D.:			1.7	2.5	13.8	1.7	3.1	13.1
710	820	15	15	98.3	0	15	1.7	N:			29	29	29	29	29	29
	821	15	14	93.3	1	13	7.1									

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Appendix E (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats
Pregnancy, Corpora Lutea and Implantation Data

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Post-Treatment Mating Period (Week 1) - Group V - (300 ppm)

Male No.	Female No.	Corp. Lut.	Impl.	I.E., x10 ⁻²	Number of Dead Implants			Male No.	Female No.	Corp. Lut.	Impl.	I.E., x10 ⁻²	Number of Dead Implants						
					VFS		M.R., x10 ⁻²						VFS		M.R., x10 ⁻²				
900	1000	15	14	93.3		3	11	21.4	911	1022	12	11	94.7		0	11	2.3		
	1001	11	10	90.9		2	8	20.0		1023	13	13	98.1		1	12	7.7		
901	1002 ^a	19	20	-		1	19	5.0	912	1024	15	15	98.3		9	6	60.0		
	1003	18	17	94.4		0	17	1.5		1025	12	12	97.9		0	12	2.1		
902	1004	13	12	92.3		0	12	2.1	913	1026	15	14	93.3		9	5	64.3		
	1005	12	12	97.9		0	12	2.1		1027	11	10	90.9		7	3	70.0		
903	1006	17	17	98.5		0	17	1.5	914	1028	Not pregnant.								
	1007	16	14	87.5		0	14	1.8		1029	16	16	98.4		1	15	6.3		
904	1008	16	16	98.4		2	14	12.5	915	1030	14	13	92.9		2	11	15.4		
	1009	12	12	97.9		4	8	33.3		1031	Not pregnant.								
905	1010	11	8	72.7		1	7	12.5	916	1032	16	15	93.8		0	15	1.7		
	1011	13	13	98.1		0	13	1.9		1033	15	14	93.3		0	14	1.8		
906	1012	12	12	97.9		1	11	8.3	917	1034	18	15	83.3		0	15	1.7		
	1013	Not pregnant.								1035	23	11	47.8		0	11	2.3		
907	1014	13	13	98.1		1	12	7.7	918	1036	14	14	98.2		3	11	21.4		
	1015	14	13	92.9		0	13	1.9		1037	12	12	97.9		3	9	25.0		
908	1016	14	14	98.2		0	14	1.8	919	1038	17	17	98.5		1	16	5.9		
	1017	13	13	98.1		0	13	1.9		1039	14	14	98.2		4	10	28.6		
909	1018	13	11	84.6		0	11	2.3											
	1019	10	2	20.0		2	0	87.5	Total: 524							58	426	552.9	
									Mean: 14.2							1.6	11.5	14.9	
									S.D.: 2.7							2.4	3.9	21.6	
910	1020	11	11	97.7		0	11	2.3	N: 37							37	37	37	
	1021	14	14	98.2		1	13	7.1											

^aTotal number of implants greater than total number of corpora lutea; data excluded from calculation of implantation efficiency.

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Appendix E (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats
Pregnancy, Corpora Lutea and Implantation Data

79-7342

Post-Treatment Mating Period (Week 2) - Group I - Chamber-Exposed Control

Male No.	Female No.	Corp. Lut.	Impl.	I.E. x10 ⁻²	Number of Dead Implants			Male No.	Female No.	Corp. Lut.	Impl.	I.E. x10 ⁻²	Number of Dead Implants		
						VFS	M.R. x10 ⁻²							VFS	M.R. x10 ⁻²
100	240 241	A- 13 17	K- 13 16	V- 98.1 94.1	K- 0 1	K- 13 15	V- 1.9 6.3	111	262 263	15 11	12 11	80.0 97.7	0 0	12 11	2.1 2.3
101	242 243	14 20	14 14	98.2 70.0	2 1	12 13	14.3 7.1	112	264 265	19 16	16 13	84.2 81.3	2 0	14 13	12.5 1.9
102	244 245	12 Not pregnant.	12	97.9	1	11	8.3	113	266 267	8 16	7 16	87.5 98.4	0 1	7 15	3.6 6.3
103	246 247	11 15	11 13	97.7 86.7	0 0	11 13	2.3 1.9	114	268 269	14 16	13 14	92.9 87.5	0 0	13 14	1.9 1.8
104	248 249	15 13	14 11	93.3 84.6	0 0	14 11	1.8 2.3	115	270 271	Not pregnant. 22	15	68.2	0	15	1.7
105	250 251	14 14	14 14	98.2 98.2	0 0	14 14	1.8 1.8	116	272 273	12 16	12 16	97.9 98.4	0 0	12 16	2.1 1.6
106	252 253	15 15	15 15	98.3 98.3	0 1	15 14	1.7 6.7	117	274 275	14 12	14 12	98.2 97.9	0 2	14 10	1.8 16.7
107	254 255	15 Not pregnant.	13	86.7	0	13	1.9	118	276 277	21 16	14 15	66.7 93.8	1 1	13 14	7.1 6.7
108	256 257	Not pregnant. 18	14	77.8	1	13	7.1	119	278 279	13 12	13 11	98.1 91.7	0 0	13 11	1.9 2.3
109	258 259	13 14	13 14	98.1 98.2	0 1	13 13	1.9 7.1	Total: 530 483 3291.3							
								Mean: 14.7 13.4 91.4							0.4 13.0 4.4
								S.D.: 2.8 1.8 9.4							0.7 1.7 3.8
110	260 261	14 15	14 15	98.2 98.3	0 1	14 14	1.8 6.7	N: 36 36 36							36 36 36

For explanation of statistical symbols: A-, K-, V-; see Appendix I.

Appendix E (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats
Pregnancy, Corpora Lutea and Implantation Data

79-7342

Post-Treatment Mating Period (Week 2) - Group II - (1 ppm)

Male No.	Female No.	Corp. Lut.	Impl.	I.E. x10 ⁻²	Number of Dead Implants	YFS	M.R. x10 ⁻²	Male No.	Female No.	Corp. Lut.	Impl.	I.E. x10 ⁻²	Number of Dead Implants	YFS	M.R. x10 ⁻²
300 ^b	440	-	-	-	-	-	-	311	462	15	14	93.3	0	14	1.8
	441	-	-	-	-	-	-		463	13	13	98.1	1	12	7.7
301	442	12	11	91.7	1	10	9.1	312	464	11	11	97.7	0	11	2.3
	443	Not pregnant.							465	16	15	93.8	1	14	6.7
302	444	15	15	98.3	0	15	1.7	313	466	19	15	78.9	5	10	33.3
	445	Not pregnant.							467	12	12	97.9	5	7	41.7
303	446	Not pregnant.						314	468	10	10	97.5	0	10	2.5
	447	16	15	93.8	1	14	6.7		469	15	15	98.3	2	13	13.3
304	448	14	12	85.7	0	12	2.1	315	470	11	5	45.5	0	5	5.0
	449	13	12	92.3	1	11	8.3		471	11	1	9.1	1	0	(75.0)
305	450	18	16	88.9	0	16	1.6	316	472	16	15	93.8	0	15	1.7
	451	12	2	16.7	2	0	87.5		473	Not pregnant.					
306	452	14	13	92.9	0	13	1.9	317	474	16	15	93.8	0	15	1.7
	453	16	16	98.4	3	13	18.8		475	14	14	98.2	0	14	1.8
307	454	24	15	62.5	1	14	6.7	318	476	Not pregnant.					
	455	14	13	92.9	1	12	7.7		477	13	13	98.1	0	13	1.9
308	456	16	14	87.5	0	14	1.8	319	478	17	17	98.5	1	16	5.9
	457	15	15	98.3	2	13	13.3		479	14	14	98.2	1	13	7.1
309	458	Not pregnant.						Total: 469			405	2724.2	31	374	321.1
	459	14	14	98.2	2	12	14.3	Mean: 14.7			12.7	85.1	1.0	11.7	10.3
								S.D.: 2.8			3.9	23.3	1.3	4.0	17.0
310	460	15	7	46.7	0	7	3.6	N: 32			32	32	32	32	31
	461	18	16	88.9	0	16	1.6								

^bMale No. 300 found dead during Week 8 of treatment.

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Appendix E (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats
Pregnancy, Corpora Lutea and Implantation Data

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Post-Treatment Mating Period (Week 2) - Group III - (10 ppm)

Male No.	Female No.	Corp. Lut.	Impl.	I.F. $\times 10^{-2}$	Number of Dead Implants	VFS	M.R. $\times 10^{-2}$	Male No.	Female No.	Corp. Lut.	Impl.	I.F. $\times 10^{-2}$	Number of Dead Implants	VFS	M.R. $\times 10^{-2}$
500	640	12	12	97.9	0	12	2.1	511	662	17	4	23.5	0	14	6.3
	641	17	17	98.5	1	16	5.9		663	10	5	50.0	0	5	5.0
501	642	14	13	92.9	1	12	7.7	512	664	19	17	89.5	0	17	1.5
	643	Not pregnant.							665	15	15	98.3	0	19	1.7
502	644	17	16	94.1	1	15	6.3	513	666	16	15	93.8	1	14	6.7
	645	Not pregnant.							667	Not pregnant.					
503	646	11	9	81.8	4	5	44.4	514	668	Not pregnant.					
	647	13	5	38.5	1	4	20.0		669	14	14	98.2	0	14	1.8
504	648	11	11	97.7	1	10	9.1	515	670	13	13	98.1	0	13	1.9
	649	11	11	97.7	1	10	9.1		671	16	16	98.4	0	16	1.6
505	650	16	16	98.4	1	15	6.3	516	672	Not pregnant.					
	651	Not pregnant.							673	13	13	98.1	1	12	7.7
506	652	Not pregnant.						517	674	14	14	98.2	0	14	1.8
	653	14	14	98.2	0	14	1.8		675	15	14	93.3	1	13	7.1
507	654	Not pregnant.						518	676	15	15	98.3	1	14	6.7
	655	13	12	92.3	0	12	2.1		677	20	17	85.0	1	16	5.9
508	656	17	17	98.5	2	15	11.8	519	678	13	13	98.1	0	13	1.9
	657	12	12	97.9	0	12	2.1		679	14	14	98.2	1	13	7.1
509	658	11	6	54.5	0	6	4.2	Total: 455 411 2847.5 24 387 233.9							
	659	15	14	93.3	2	12	14.3	Mean: 14.2 12.8 89.0 0.8 12.1 7.3							
								S.D.: 2.4 3.6 19.1 0.9 3.6 8.1							
510	660	13	13	98.1	1	12	7.7	N: 32 32 32 32 32 32							
	661	14	14	98.2	2	12	14.3								

Appendix E (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats
Pregnancy, Corpora Lutea and Implantation Data

79-7342

Post-Treatment Mating Period (Week 2) - Group IV - (30 ppm)

Male No.	Female No.	Corp. Lut.	Impl.	I.E. ₁ x10 ⁻²	Number of Dead Implants	VFS	M.R. x10 ⁻²	Male No.	Female No.	Corp. Lut.	Impl.	I.E. ₂ x10 ⁻²	Number of Dead Implants	VFS	M.R. x10 ⁻²
700	840	18	18	98.6	1	17	5.6	711	862	14	13	92.9	0	13	1.9
	841	13	13	98.1	1	12	7.7		863	15	15	98.3	0	15	1.7
701	842	15	14	93.3	2	12	14.3	712	864	13	13	98.1	1	12	7.7
	843	14	13	92.9	0	13	1.9		865	13	13	98.1	1	12	7.7
702	844 ^a	15	16	-	2	14	12.5	713	866	13	13	98.1	0	13	1.9
	845	14	12	85.7	0	12	2.1		867	15	14	93.3	5	9	35.7
703	846	14	14	98.2	1	13	7.1	714	868	14	14	98.2	1	13	7.1
	847	Not pregnant.							869	13	13	98.1	0	13	1.9
704	848	15	15	98.3	0	15	1.7	715	870	16	14	87.5	1	13	7.1
	849	15	14	93.3	0	14	1.8		871	16	15	93.8	3	12	20.0
705	850	11	11	97.7	0	11	2.3	716	872	14	14	98.2	0	14	1.8
	851	15	15	98.3	0	15	1.7		873	Not pregnant.					
706	852	14	14	98.2	1	13	7.1	717	874	13	13	98.1	2	11	15.4
	853	14	14	98.2	0	14	1.8		875	15	13	86.7	1	12	7.7
707	854	13	9	69.2	5	4	55.6	718	876	Not pregnant.					
	855	12	12	97.9	1	11	8.3		877	19	19	98.7	1	18	5.3
708	856	15	14	93.3	0	14	1.8	719	878	17	16	94.1	1	15	6.3
	857	15	15	98.3	0	15	1.7		879	15	15	98.3	1	14	6.7
709	858	18	18	98.6	1	17	5.6	Total: 513 496 3237.2 35 461 287.6							
	859	18	18	98.6	2	16	11.1	Mean: 14.7 14.2 95.2 1.0 13.2 8.2							
								S.D.: 1.8 2.0 5.9 1.3 2.5 10.6							
								N: 35 35 34 35 35 35							
710	860	Not pregnant.													
	861	Not pregnant.													

^aTotal number of implants greater than total number of corpora lutea; data excluded from calculation of implantation efficiency.

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Appendix E (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats
Pregnancy, Corpora Lutea and Implantation Data

79-7342

Post-Treatment Mating Period (Week 2) - Group V - (300 ppm)

Male No.	Female No.	Corp. Lut.	Impl.	I.E. $\times 10^{-2}$	Number of Dead Implants	VFS	M.R. $\times 10^{-2}$	Male No.	Female No.	Corp. Lut.	Impl.	I.E. $\times 10^{-2}$	Number of Dead Implants	VFS	M.R. $\times 10^{-2}$
900	1040	16	16	96.4	1	15	6.3	911	1062	17	17	98.5	4	13	23.5
	1041	16	8	50.0	0	8	3.1		1063	13	12	92.3	1	11	8.3
901	1042	Not pregnant.						912	1064	15	15	98.3	1	14	6.7
	1043	Not pregnant.							1065	Not pregnant.					
902	1044	15	13	86.7	1	12	7.7	913	1066	16	16	98.4	8	8	50.0
	1045	16	16	98.4	3	13	18.8		1067	13	12	92.3	8	4	66.7
903	1046	13	13	96.1	0	13	1.9	914	1068	15	14	93.3	0	14	1.8
	1047	13	13	98.1	0	13	1.9		1069	12	12	97.9	2	10	16.7
904	1048	14	14	96.2	0	14	1.8	915	1070	15	15	98.3	2	13	13.3
	1049	20	16	80.0	0	16	1.6		1071	20	8	40.0	5	3	62.5
905	1050	16	16	98.4	0	16	1.6	916	1072	16	16	98.4	0	16	1.6
	1051	15	14	93.3	3	11	21.4		1073	17	16	94.1	1	15	6.3
906	1052	14	14	98.2	0	14	1.8	917	1074	15	15	98.3	1	14	6.7
	1053	15	15	98.3	1	14	6.7		1075	13	13	98.1	1	12	7.7
907	1054	13	13	96.1	0	13	1.9	918	1076*	12	13	-	1	12	7.7
	1055	15	15	96.3	2	13	13.3		1077	11	11	97.7	0	11	2.3
908	1056	16	16	98.4	1	15	6.3	919	1078	16	16	98.4	0	16	1.6
	1057	Not pregnant.							1079	14	12	85.7	1	11	8.3
909	1058	14	14	96.2	2	12	14.3	Total: 537 505 3264.1							
	1059	14	14	96.2	0	14	1.8	Mean: 14.9 14.0 93.3							
								S.D.: 1.9 2.2 12.9							
910	1060	15	15	96.3	1	14	6.7	N: 36 36 35							
	1061	17	17	98.5	2	15	11.8								

*Total number of implants greater than total number of corpora lutea; data excluded from calculation of implantation efficiency.

Appendix F
A Dominant-Lethal Inhalation Study
With Benzene in Rats

Certified Feed Information^a

Week of Study	Interval	Date	Lot. No.
1	Acclimation	12/11/79	Oct 03792B
2	Acclimation	12/18/79	Oct 03792B
3	Pre-Treatment Mating Period	12/24/79	Oct 22791D
4	Pre-Treatment Mating Period	12/31/79	Oct 22791D
5	Female Sacrifices (Pre-Treatment)	1/8/80	Oct 22791C
6	Treatment Period	1/15/80	Oct 22791C
7	Treatment Period	1/22/80	Dec 6791A
8	Treatment Period	1/29/80	Dec 06791A
9	Treatment Period	2/5/80	Dec 06791A
10	Treatment Period	2/12/80	Dec 20791C
11	Treatment Period	2/19/80	Dec 20791C
12	Treatment Period	2/26/80	Dec 06791E
13	Treatment Period	3/4/80	Dec 27792C
14	Treatment Period	3/11/80	Dec 27792C
15	Treatment Period	3/18/80	Jan 04801C
16	Post-Treatment Mating Period-Week 1	3/25/80	Feb 14801E
17	Post-Treatment Mating Period-Week 2	4/1/80	Jan 31801B
18	Female Sacrifice (Week 1)	4/8/80	Feb 14801C
19	Female Sacrifice (Week 2)	4/15/80	Feb 14801C
20	Post-Mating Interval	4/22/80	Feb 14801C
21	Post-Mating Interval	4/29/80	Feb 28801F
22	Post-Mating Interval	5/6/80	Feb 14801A
23	Post-Mating Interval	5/13/80	Feb 14801A
24	Post-Mating Interval	5/20/80	Mar 06801E
25	Post-Mating Interval	5/27/80	Mar 26801E
26	Post-Mating Interval	6/3/80	Mar 19802F
27	Post-Mating Interval	6/10/80	Mar 19802F

^aPurina Laboratory Chow 5002 (Certified Feed) mash; ad libitum.

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Appendix G
A Dominant-Lethal Inhalation Study
with Benzene in Rats

79-7342

Analysis of Benzene

	Study Interval			
	<u>Pre-test</u>	<u>Prior to initiation of treatment</u>	<u>Week 6 of the Treatment Period</u>	<u>Completion of Treatment</u>
Date Collected:	12/3/1979	1/14/1980	2/18/1980	3/21/1980
Freezing Point (°C)	5.5064	5.5084	5.5188	5.5291
Purity (%)	99.96	99.97	99.98	100.00
Specific Gravity	0.8845	0.8845	0.8843	0.8844
Total Sulfur by Microcoulometry - ppm	<1.0	<1.0	<1.0	<1.0
Sats ppm	42	42	28	45
Toluene ppm	28	28	5	26
Acetone ppm	2	2	0.3	-

^aAnalyses were performed at the Exxon Research and Engineering Company Linden, N.J.

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Appendix H
A Dominant-Lethal Inhalation Study
With benzene in Rats

DETERMINATION OF POLLUTANTS IN DRINKING WATER GIVEN
TO ANIMALS FOR STUDIES NO. 79-2425 AND 79-7342

Report No.: 80023

Sponsor: Chemical Manufacturers' Association and
American Petroleum Institute
Washington, D.C.

Prepared by: James C. Eschbach

Date: September 3, 1980

Issued by: Bio/dynamics Inc.
Department of Metabolism and Analytical Chemistry
Environmental Sciences
P.O. Box 43
Mettlers Road
East Millstone, New Jersey 08873

SUMMARY

The drinking water given to rats for Studies No. 79-2425 and 79-7342 was sampled and assayed for residues which could interfere with the studies. The compounds assayed included benzene, trace metals, pesticides and PCBs. The samples were assayed according to E.P.A. proposed and established pesticide procedures using mass spectrometry, atomic absorption spectrometry and gas chromatography.

The results obtained illustrate that < 1.0 ppb of benzene, < 10 ppb trace metals assayed, < 1.0 ppb chlorinated pesticides, < 4.0 ppb carbamates and < 2.0 ppb of PCBs were determined in the drinking water samples collected from the animal rooms.

Joseph S. O'Grodnick 9-3-80
Joseph S. O'Grodnick, Ph.D.
Director
Department of Metabolism and
Analytical Chemistry

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1.0 INTRODUCTION

Drinking water samples were collected at two intervals from the rooms in which the animals for Studies No. 79-2425 and 79-7342 were housed. These samples were assayed for compounds which could have adverse effects on the studies if they were present in the drinking water. The samples were assayed for benzene, trace metals, pesticides and PCBs at the beginning and end of the studies.

2.0 EXPERIMENTAL

Water samples were collected and composited since they were from the same water source. An aliquot was taken for benzene for assay according to Method 624 for volatile organic compounds by purge and trap prior to g.c./mass spectrometry. This sample was collected in an air-tight container to prevent volatilization prior to assay. Additional aliquots were collected for the analyses of pesticides, metals and PCBs. The assays were performed according to proposed or approved E.P.A. methodology.

3.0 RESULTS

The data obtained illustrate that < 1.0 ppb of benzene, < 10 ppb trace metals, <1.0 ppb of chlorinated and <4.0 ppb carbamate pesticides and <2.0 ppb of PCBs were determined in the water samples assayed. Table I summarizes the data obtained in this study.

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Appendix H (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

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4.0 ACKNOWLEDGEMENT

This study was supported by both the Chemical Manufacturers' Association and the American Petroleum Institute.

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Appendix H (cont.)
A Dominant-Lethal Inhalation Study
With Benzene in Rats

80023

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TABLE I. RESULTS OF DRINKING WATER ASSAYS FOR STUDIES
NO. 79-2425 AND 79-7342

<u>METALS</u>	<u>Assayed</u> <u>3/17/80</u> <u>ppb</u>	<u>Assayed</u> <u>6/12/80</u> <u>ppb</u>
Antimony	< 1.3	< 6.7 ^b
Beryllium	< 1.0	< 1.0
Cadmium	< 1.0	< 1.0
Arsenic	< 0.5 ^a	< 1.0 ^a
Lead	< 1.0	1.2
Mercury	< 0.5 ^a	< 0.5
Selenium	< 1.0 ^a	< 8.3 ^a
 <u>PESTICIDES</u>		
Lindane	< 1.0	< 1.0
Heptachlor	< 1.0	< 1.0
DDT	< 1.0	< 1.0
Dieldrin	< 1.0	< 1.0
Malathion	< 1.0	< 1.0
Carbamate	< 1.0	< 1.0
PCB	< 1.0	< 2.0
<u>BENZENE</u>	< 1.0	< 1.0

a. Level of detection high because graphite method of analysis used instead of hydride method of analysis.

b. Level of detection higher because of possible loss in lamp efficiency.

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Appendix I
A Dominant-Lethal Inhalation Study
with Benzene in Rats

79-7342

Methodology and References

Parameter	Method
Body Weight (Pre-mating Treatment Mating and Post mating periods)	Torbal Torsion Balance.

Statistical Analysis of Data

Results of analyses by the indicated statistical procedures were reported for the following:

Parameter	Method
1. Male Body Weights - Treatment Period, Mating Period and Post- Mating Period.	A
2. Male Body Weight Gain - Treatment Period.	A

Corpora Lutea and Implantation Data - Post-Treatment Mating Period

1. Number of corpora lutea	A
2. Number of implantations	A
3. Number of dead implants	A
4. Total number of dead implants	A
5. Viable fetuses	A
6. Implantation efficiency (pre-implantation loss)	C
7. Mutagenic ratio (post-implantation loss)	C
8. Pregnancy rate	B
9. Male Impregnating Index	B

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Appendix I (cont.)

A Dominant-Lethal Inhalation Study
with Benzene in Rats

Methodology and References (cont.)

Statistical Analysis of Data (cont.)Method A^a:

Statistical evaluation of equality of means was made by the appropriate one-way analysis of variance technique, followed by a multiple comparison procedure if needed. First, Bartlett's test was performed to determine if groups had equal variances. If the variances were equal, parametric procedures were used; if not, nonparametric procedures were used. The parametric procedures were the standard one-way ANOVA using the F-distribution to assess significance. If significant differences among the means were indicated, Dunnett's test was used to determine which means were significantly different from the control. If a nonparametric procedure for testing equality of means was needed, the Kruskal-Wallis test was used, and if differences were indicated a summed rank test (Dunn) was used to determine which treatments differed from control.

A statistical test for trend in the dose level was also performed. In the parametric case (i.e. equal variance), standard regression techniques with a test for trend and lack of fit were used. In the nonparametric case, Jonckheere's test for monotonic trend was used.

The test for equal variance (Bartlett's) was conducted at the 1%, two-sided risk level. All other statistical tests were conducted at the 5% and 1% two-sided risk levels.

^aSnedecor, G.W., and Cochran, W.G., Statistical Methods, 6th ed., Iowa State Univ. Press (1967), Hollander and Wolfe, Nonparametric Statistical Methods, John Wiley and Sons, New York (1973), Dunnett, C.W., J. Am. Sta. Assn., Vol. 50 (1955) and Biometrics, Vol. 20 (1964).

Bartlett's Test	pp. 296-298	S&C
ANOVA	pp. 277-279	S&C
Dunnett's Test	pp. 1096-1121, 482	D
Kruskal-Wallis	pp. 114-116	H&W
Summed Rank Test (Dunn)	pp. 131	H&W
Regression Analysis		
Trend	pp. 149-152	S&C
Lack of Fit	pp. 160-164	S&C
Jonckheere's Statistic	pp. 120-123	H&W

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Appendix I (cont.)
A Dominant-Lethal Inhalation Study
with Benzene in Rats

Methodology and References (cont.)

Statistical Analysis of Data (cont.)

Method B^b:

Statistical analysis of incidence data was performed using contingency tables. First, a standard chi-square analysis was performed to determine if the proportion of incidences differed between the groups tested. In keeping with standard statistical practice, if any one cell had an expected value of less than 5, this step was not reported. Next, each treatment group was compared to the control group using a 2x2 Fisher Exact test and the significance level was corrected via the Bonferroni inequality to assure an overall test of the stated significance level. Thirdly, Armitage's test for linear trend in the dosage groups was performed.

-
- ^bChi-square: Snedecor, G.W., and Cochran, W.G., Statistical Methods, 6th ed., Iowa State Univ. Press, Ames, Iowa, 1971, pp. 250-253.
Fisher Exact Test: Bradley, J.V., Distribution Free Statistical Tests, Prentice Hall Englewood Cliffs, N.J., 1968, pp. 195-203.
Bonferroni Inequality: Miller, R.G., Jr., Simultaneous Statistical Inference McGraw-Hill Book Co., N.Y. 1966, p. 15.
Armitage's Test: Armitage, P., "Tests for Linear Trends in Proportions and Frequencies", Biometrics, Sept. 1955, pp. 375-386.

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Statistical Analysis

Method C

Analysis for dominant-lethal studies based on corpora lutea and implantation characteristics will be as follows. The number of corpora lutea, implants (total) and dead implants will be determined for each female in the study, females with fewer than two implants will be excluded from the analysis. The mutagenic ratio or ratio of the number of dead implants to the total number of implants will be computed. The implantation efficiency or ratio of the number of implants to the number of corpora lutea will be computed (if the result is greater than unity, the ratio for that female will be ignored).

The mutagenic ratio and implantation efficiency will be modified by Bartlett's transformation (Snedecor and Cochran, page 328), then transformed by the inverse sine transformation (Snedecor and Cochran, page 327). The two ratios will be analyzed using a standard nested design with the females nested within males nested within treatments (Gill, pages 201-210). Statistical significance of the treatment differences will be based on the F ratio of "treatment mean square" to "male mean square" in the nested design. If the treatment differences are statistically different ($p < .05$, or $p < .01$), statistical significance among individual transformed means will be determined by the least significant differences technique (Snedecor and Cochran, page 272). Untransformed mean ratios will be presented.

All tests were reported at the 5% and 1% level of significance.

References:

Snedecor, G.W. and Cochran, W., Statistical Methods, 6th edition, Iowa State University Press, Ames, Iowa, 1971.

Gill, J.L. Design and Analysis of Experiments in the Animal and Medical Sciences, Vol. I., Iowa State University Press, Ames, Iowa, 1978.

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Appendix I (cont.)
A Dominant-Lethal Inhalation Study
with Benzene in Rats

79-7342

Methodology and References (cont.)

Statistical Analysis of Data (cont.)

Statistical Notations

<u>Symbol</u>			<u>Statistical Statement</u>
<u>No Sig</u>	<u>p<0.05</u>	<u>p<0.01</u>	<u>Absolute Data</u>
A-			No statistical differences among the means (parametric ANOVA).
	A+		The means differ significantly (parametric ANOVA).
	*	**	Significantly different from control (Dunnett's).
K-			No statistical differences among the means (Kruskal-Wallis, nonparametric).
	K+		The means differ significantly (Kruskal-Wallis, nonparametric).
	L		The response is linearly related to the dose levels.
	J		There is an ordered response to dosage.
	F		Lack of fit.
	V-		F-test
			<u>Incidence Data</u>
	+	++	Significantly different from control (Fisher Exact Test).

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Appendix J
A Dominant Lethal Inhalation
Study in Rats with Benzene

Histopathology Report

Bio/Dynamics Project Number
M15, 79-7342

Submitted to: Dr. A. L. Knezevich
Director, Pathology Dept
Bio/Dynamics Inc.
East Millstone, N. J.

DO 067588
CONFIDENTIAL

YZ0083151

**A Dominant Lethal Inhalation
Study in Rats with Benzene**

Histopathology Report

Table of Contents

- 1. Introduction**
- 2. Materials and Methods**
- 3. Results and Discussion**
- 4. Summary**

**Table I - Microscopic Findings
Control Rats**

**Table II - Microscopic Findings
Exposed Rats**

**Table III - Summary of Microscopic
Findings**

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A Dominant Lethal Inhalation
Study in Rats with Benzene

Histopathology Report

1. Introduction

A study was designed and performed to assess the mutagenic potential of a test compound administered by inhalation to Charles River rats. This report denotes and discusses the results obtained from microscopic evaluation of testes and epididymides of rats in the high dose group.

2. Materials and Methods

The experimental design is detailed in the protocol (Bi / Dynamics Project No. M-15, 79-7342). Five groups, each consisting of twenty male rats were exposed for 6 hours a day, 5 days a week, for 10 consecutive weeks. Group I animals received unmedicated chamber air. Groups II, III, IV and V animals were administered Benzene by inhalation at doses of 1 ppm, 10 ppm, 30 ppm and 300 ppm respectively. At the end of the study all animals were sacrificed and necropsied.

The testes and epididymides were collected and preserved for 48 hours in Bouin's fixative and transferred into 10% neutral buffered formalin. After fixation, the specimens from Groups I and V were embedded in paraffin, sectioned at a thickness of approximately 6 microns and stained with hematoxylin and eosin for evaluation by light microscopy.

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3. Results and Discussion

The microscopic findings are presented in Tables I and II and summarized in Table III. Microscopic findings were denoted as follows:

- N = Within normal histologic limits
- 2 = Mild degree of indicated change
- 3 = Moderate degree of indicated change
- * = Tissue absent
- U = Tissue inadequate (fragmented, etc.)

In animal 908 (Group V, High Dose) the testes revealed moderate tubular degeneration and atrophy characterized by multifocal depletion of spermatogenic epithelium as well as thickening of the basement membrane. In animal 900 (Group V, High Dose) one testis revealed focal disarray and syncytial transformation of spermatogenic epithelium. The changes thus described occurred only in testes of treated animals. However the single occurrences are judged to be much too sporadic to be associated with the experimental inhalation administration of Benzene.

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A Dominant Lethal Inhalation
Study in Rats with Benzene

Histopathology Report

4. Summary

A study was designed and performed to assess the mutagenic potential of Benzene administered by inhalation to Charles River male rats.

Microscopic evaluation of the testes and epididymides of control and treated rats (High Dose Group) revealed few lesions in treated rats. However there was no conclusive evidence indicating compound related injury.

 8/11/90

N. Jonathan Nosu, D.V.M., Ph.D.
Consulting Pathologist

DO 067592
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Table I

A Dominant Lethal Inhalation Study
in Rats with Benzene

Control Rats

Microscopic Findings

Animal Number	100	101	102	103	104	105	106	107	108	109
Sex	M	M	M	M	M	M	M	M	M	M
Pathology Number	80-3707	3708	3709	3710	3711	3712	3713	3714	3715	3716
Group	I	I	I	I	I	I	I	I	I	I
Testes	N	N	N	N	N	N	N	N	N	N
Epididymides	N	N	N	*	N	N	N	N	N	N

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Table I

A Dominant Lethal Inhalation Study
in Rats with Benzene

Control Rats

Microscopic Findings

Animal Number	110	111	112	113	114	115	116	117	118	119
Sex	M	M	M	M	M	M	M	M	M	M
Pathology Number	80-3717	3718	3719	3720	3721	3722	3723	3724	3725	3726
Group	I	I	I	I	I	I	I	I	I	I
Testes	N	N	N	N	N	N	N	N	N	N
Epididymides	*	N	N	N	N	N	N	N	N	N

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Table II

**A Dominant Lethal Inhalation Study
in Rats with Benzene**

Exposed Rats

Microscopic Findings

Animal Number	900	901	902	903	904	905	906	907	908	909
Sex	M	M	M	M	M	M	M	M	M	M
Pathology Number 80-	3727	3728	3729	3730	3731	3732	3733	3734	3735	3736
Group	V	V	V	V	V	V	V	V	V	V
Testes		N	N	N	N	N	N	N		N
- seminiferous tubules, degeneration									3	
- focal syncitial cell formation	2									
Epididymides		N	N	N	*	N	N	N	*	N
- globular/syncitial cell formation	2									

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Table II

A Dominant Lethal Inhalation Study
in Rats with Benzene

Exposed Rats

Microscopic Findings

Animal Number	910	911	912	913	914	915	916	917	918	919
Sex	M	M	M	M	M	M	M	M	M	M
Pathology Number	80-3737	3738	3739	3740	3741	3742	3743	3744	3745	3746
Group	V	V	V	V	V	V	V	V	V	V
Testes	U	N	N	N	N	N	N	U	N	N
Epididymides	N	N	N	N	N	*	N	N	*	N

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Table III

A Dominant Lethal Inhalation
Study in Rats with Benzene

Summary of Microscopic Findings

Organ/Microscopic Finding	Group	I	V
Testes			
- seminiferous tubules, degeneration			1/18
- focal syncytial cell formation			1/18
Epididymides			
- globular/syncytial cell formation			1/16

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Appendix K
A Dominant-Lethal Inhalation Study
with Benzene in Rats

79-7342

PERSONNEL

DEPARTMENT/TITLE	NAME	DEGREE
STUDY DIRECTOR	Raymond E. Schroeder	M.S.
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Appendix K (cont.)
A Dominant-Lethal Inhalation Study
with Benzene in Rats

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