

8EHQ - 0396-13607

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March 13, 1996

Document Processing Center (TS-790)
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U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460
ATTN: 8(e) Coordinator

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Dear Sir:

**SUBJECT: NECROSIS OF OLFACTORY EPITHELIUM IN RAT NASAL PASSAGES
FOLLOWING EXPOSURE TO N-BUTYL ACETATE**

The following information is submitted under TSCA 8(e).

Following inhalation exposure of rats for 6 hours/day, 5 days/week, for 13 weeks to vapor concentrations of 0, 500, 1500, or 3000 ppm N-butyl acetate (CASN 123-86-4), necrosis of the olfactory epithelium of the nasal cavity was reported after exposure at the 1500 and 3000 ppm dose levels. No lesions were observed in the nasal passages of the 500 ppm group. The voluntary study was conducted by the Eastman Kodak Company Toxicological Sciences Laboratory for the Chemical Manufacturers Association Oxo Process Panel.

n-Butyl acetate is a solvent used in commercial products by Shell Chemical Company. Shell became aware of the information during technical review of the draft report of the study. A copy of the abstract to the draft report is attached. A copy of the final report will be provided when it is available.

Relevance of these findings to humans is unclear, since n-butyl acetate occurs naturally among numerous other propionates and butyrates in bananas and other fruit, and is used as a flavoring agent and solvent. It should also be noted that, since the study evaluated repeated daily exposures and demonstrated decreasing intensity of the effect with decreasing vapor concentration, it is unlikely that a single, brief exposure to low vapor concentrations of n-butyl acetate would produce adverse effects to the nasal cavity of humans. Moreover, the OSHA PEL TWA for n-butyl acetate is 150 ppm compared with a NOAEL for nasal effects in the 13-week study of 500 ppm.

This report is filed to provide information EPA may find useful. In no way is it intended as a waiver of any rights or privileges belonging to Shell Chemical Company as the reporting corporation, its agents or employees. The reporting corporation, its agents and employees,

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reserve the right to object to this report's use or admissibility in any subsequent judicial or administrative proceeding against the corporation, its agents or employees.

This report has been compiled based on information available as of the date of filing. The corporation, its agents and employees reserve the right to supplement the data contained in this report, and to revise and amend any conclusions drawn therefrom.

This report contains no confidential business information.

The following person should be contacted if you have questions or a need for discussion.

J. C. Willett
Manager, Product Safety and Compliance
Shell Chemical Company
P.O. Box 4320
Houston, TX 77210
Telephone No. 713-241-6958
Fax. 713-241-3325

Very truly yours,

A handwritten signature in black ink, appearing to read "J. C. Willett", written in a cursive style.

Attachment

THG/

and minimal to mild for the 1500 ppm group. No lesions were observed in the nasal passages of the 500 ppm group. A few (3/10) 3000 ppm female rats had inflammation of the stomach mucosa (glandular or forestomach). The severity was minimal to mild. No effects to the stomach mucosa were seen in the low- and mid-concentration groups.

Summary/Conclusion. Repeated exposure to 1500 and 3000 ppm n-butyl acetate vapor produced necrosis of the olfactory epithelium in rat nasal passages. To the best of my knowledge, this effect has not previously been reported for n-butyl acetate. A related ester, n-butyl propionate, has also produced olfactory epithelium necrosis following repeated inhalation exposure (SHR-324-95-06).

STUDY TITLE

n-BUTYL ACETATE

**A THIRTEEN-WEEK SUBCHRONIC INHALATION
TOXICITY STUDY IN THE RAT**

HAEL NO. 94-0305 KAN 900710
CAS NO. 000123-86-4

DRAFT REPORT

AUTHORS

Lisa G. Bernard, B.S.
Raymond M. David, Ph.D., D.A.B.T.

PERFORMING LABORATORY

Toxicological Sciences Laboratory
Health and Environment Laboratories
Eastman Kodak Company
Rochester, New York 14652-6272
USA

LABORATORY PROJECT ID

940305I7

STUDY SPONSOR

Oxo Process Panel
Chemical Manufacturers Association
2501 M Street, NW
Washington, DC 20037

CMA REFERENCE NUMBER

OXO-17.0-BA-KODAK

STUDY COMPLETION DATE



Shell Chemical Company
Interoffice Memorandum

February 26, 1996

FROM: M.I. Banton
TO: T.H. Gardiner, ON-SITE-COORDINATOR
SUBJECT: **SUSPECT HAZARD REPORT FOR n-BUTYL ACETATE**

This memorandum is intended to provide documentation for the n-butyl acetate suspect hazard report.

Background. n-Butyl acetate was recently the subject of a 13-week subchronic inhalation toxicity study conducted by the Eastman Kodak Company Toxicological Sciences Laboratory. The purpose of this study was to evaluate the potential toxicity of this material to rats following 13-week repeated inhalation exposure. This study was conducted voluntarily by the Chemical Manufacturers Association Oxo Process Panel in parallel with a subchronic neurotoxicity study that was conducted under a consent agreement with the U.S. Environmental Protection Agency. The subchronic inhalation study is now complete and a draft report has been released to member companies for review.

Experimental Design. Male and female Sprague-Dawley rats were exposed to concentrations of 0, 500, 1500 or 3000 ppm of n-butyl acetate for 6 hours per day, 5 days per week for 13 consecutive weeks. During and/or after the exposure period, animals were evaluated for effects on mortality, body weight, feed consumption, ophthalmology, hematologic parameters, clinical chemistry parameters, organ weights, and gross and microscopic pathology.

Study Results. No spontaneous mortality occurred during the study. Animals exposed to 1500 and 3000 ppm n-butyl acetate displayed acute, transient signs of reduced activity levels during exposure. The 1500 ppm and 3000 ppm treatments also produced decreased body weight and feed consumption throughout much of the exposure period. The 500 ppm treatment resulted in reductions in feed consumption at a few time periods, however, this was not accompanied by a corresponding statistically significant reductions in body weight. No treatment-related ophthalmologic changes were observed in the treated animals. Effects on hematology, clinical chemistry and organ weights were unremarkable. Gross necropsy observations were limited to signs of irritation to the glandular stomach and necrosis in the non-glandular stomach in two 3000 ppm female rats. Microscopic examination of the tissues revealed exposure-related changes in the nasal passages and stomach of 1500 and 3000 ppm rats. All male and female 3000 ppm rats and 4/10 male and 6/10 female 1500 ppm rats had necrosis of the olfactory epithelium. The severity of the olfactory lesion was mild to moderate for the 3000 ppm group

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ABSTRACT

Male and female Sprague-Dawley (SD) rats were exposed to concentrations of 0, 500, 1500, or 3000 ppm of n-butyl acetate for 6 hours per day, 5 days per week for 13 consecutive weeks. The time-weighted average analytical concentrations were within 10% of the target concentrations. The daily mean temperatures and relative humidity inside the chambers during exposure were 21.1 - 24.7°C and 36.7 - 68.7%, respectively.

No spontaneous mortality occurred during the study. Animals were observed for signs of toxicity prior to exposure, once per hour during exposure, and 30 minutes to one hour after exposure. Animals exposed to 3000 ppm had reduced activity levels which were of generally minor severity during exposure. Signs of sialorrhea and red discoloration on the chin hair were also observed. Animals exposed to 1500 ppm exhibited reduced activity of generally minimal severity. Control and 500 ppm animals appeared normal during exposure. After exposure, animals in all groups had porphyrin nasal discharges and dried porphyrin stains around the nose. These clinical signs were occasionally seen during the morning examination before exposure.

Mean body weights for the 3000 ppm group were significantly ($p \leq 0.05$) lower than the control group for male rats on Days 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, and 91, and for female rats on Days 14, 21, 28, 35, 42, 56, 63, 70, 77, 84, and 91. Mean feed consumption for the 3000 ppm groups were significantly lower ($p \leq 0.05$) than for the control group throughout the study for male rats and at all intervals except Days 84 and 91 for female rats. Mean body weights for the male 1500 ppm group were significantly ($p \leq 0.05$) lower than the control group on Days 42, 49, 56, 63, 70, 77, 84, and 91. Mean body weights for the female 1500 ppm group were significantly ($p \leq 0.05$) lower than the control group on Days 14, 21, 28, 35, 42, 56, 63, 70, 77, 84, and 91. Mean feed consumption values for the 1500 ppm groups were significantly lower ($p \leq 0.05$) than for the control group on Days 35, 42, 49, 56, 63, 70, 77, and 84 for male rats and at all intervals except Day 91 for female rats. Mean body weights for the 500 ppm groups were comparable to the control group throughout the study, and no statistically significant differences were noted. However, mean feed consumption values for the 500 ppm groups were significantly lower ($p \leq 0.05$) than for the control group on Days 35, 42, 63, and 70, for male rats and on Days 7 and 14 for female rats.

Blood was collected from 5 animals per group after 30 days of exposure, and from 10 animals per group at termination. No significant differences in hematologic parameters were

seen after 30 days of exposure, and slight hemoconcentration was observed for the 3000 ppm male and female rats after 90 days on test. None of the differences were considered biologically significant, however. Evaluation of blood cell morphology did not suggest any compound-related effects. After 30 days of exposure, slight but significantly ($p \leq 0.05$) lower mean sodium concentrations were observed for the male and female 3000 ppm groups compared with the control groups, and significantly lower ($p \leq 0.05$) mean chloride concentration for the 1500 ppm male group compared with the control groups. No other differences in blood chemistries were seen among groups. After 90 days of exposure, minor but statistically significant changes were observed for mean albumin and total protein concentrations for the 3000 ppm female group, and mean sorbitol dehydrogenase activity for the 1500 ppm male group. These changes were not considered to be toxicologically meaningful, and no other differences in serum chemistry were observed among groups.

No treatment-related ophthalmologic changes were observed. Mean terminal body weights were significantly lower ($p \leq 0.05$) for the 1500 and 3000 ppm male and female groups compared with the control group. Mean absolute weights of the liver, kidneys, and spleen were significantly lower ($p \leq 0.05$), but relative organ weights (to body weight) were not significantly different except for the mean spleen-to-body weight ratio for the 3000 ppm male group which was significantly lower than for the control group. Reduced body weight was also reflected in the significantly lower ($p \leq 0.05$) mean absolute brain weight for the 3000 ppm male group and significantly higher ($p \leq 0.05$) mean brain-to-body weight for the 1500 ppm female and 3000 ppm male groups compared with their respective control groups. In addition, mean testes-to-body weights for the 1500 and 3000 ppm male groups and the mean relative lung (to body weight) weight for the 3000 ppm male group were significantly higher ($p \leq 0.05$) than for the control group. Mean adrenal gland-to-body weight ratios for the 1500 ppm female and 3000 ppm male and female groups were significantly higher ($p \leq 0.05$) than for the respective control groups.

Signs of irritation of the glandular stomach and necrosis in the non-glandular stomach were observed in two 3000 ppm female rats. No compound-related changes were detected on necropsy examination of male or female rats exposed to the test substance. Signs of irritation were also seen microscopically in the nasal passages (necrosis of the olfactory epithelium) of some 1500 and all 3000 ppm rats. No lesions were observed in the nasal passages of 500 ppm groups. Inflammation of the stomach mucosa (glandular or forestomach) was also observed microscopically in a few 3000 ppm female rats. Other lesions that were observed microscopically were not considered to be compound-related.

In conclusion, exposures to n-butyl acetate vapors resulted in acute, transient signs of reduced activity levels during exposure to 1500 and 3000 ppm. Decreased body weight and feed consumption were noted for the 1500 and 3000 ppm groups, but there was no systemic or organ-specific toxicity. Signs of upper respiratory tract irritation were seen in the nasal passages of 1500 and 3000 ppm animals. The no-observed-effect level (NOEL) for this study is considered to be 500 ppm.

STUDY TITLE

n-BUTYL ACETATE

**A THIRTEEN-WEEK SUBCHRONIC INHALATION
TOXICITY STUDY IN THE RAT**

HAEL NO. 94-0305 KAN 900710
CAS NO. 000123-86-4

FINAL REPORT

AUTHORS

Lisa G. Bernard, B.S.
Raymond M. David, Ph.D., D.A.B.T.

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PERFORMING LABORATORY

Toxicological Sciences Laboratory
Health and Environment Laboratories
Eastman Kodak Company
Rochester, New York 14652-6272
USA

LABORATORY PROJECT ID

94030517

STUDY SPONSOR

Oxo Process Panel
Chemical Manufacturers Association
1300 Wilson Boulevard
Arlington, VA 22209

CMA REFERENCE NUMBER

OXO-17.0-BA-KODAK

STUDY COMPLETION DATE

October 7, 1996

Feed and Water

Certified Rodent Diet (Agway® Prolab® RMH 3200, ground chow) was available *ad libitum* except during exposure. Feed containers were cleaned weekly for all animals and were refilled at least once a week. No known contaminants which would interfere with the outcome of this study were present in the feed. Analyses of feed are maintained on file within the testing laboratory.

Water was available *ad libitum*, except during exposure, through an automatic watering system. The source of the water was the Monroe County (NY) Water Authority. There have been no contaminants identified in previous water analyses that would be expected to interfere with the conduct of the study. Semiannual analyses of water are maintained on file within the testing laboratory.

Identification

Upon arrival, all rats were identified by uniquely-numbered metal ear tags. Ear tags which were lost during the study were replaced. During randomization, study-specific animal numbers were assigned to each animal. Cage cards, color-coded for each group, contained the study-specific animal numbers and the ear tag number.

Randomization

The test animals were selected from the stock population based on body weight and were randomly assigned to groups using computer-generated lists from the Automated Animal Toxicology System. The body weights of individual animals in the selected population did not exceed 20% of the mean for each sex. Following randomization, the body weights of all groups were compared by analysis of variance to insure that there were no statistically significant differences prior to initiation of exposure.

Treatment Groups

Animals were distributed into groups as follows:

Group	Exposure Concentrations	Number of Animals	Animal Numbers	
			Males	Females
1	Control / 0 ppm	15 Males & 15 Females	601 - 615	661 - 675
2	Low / 500 ppm	15 Males & 15 Females	616 - 630	676 - 690
3	Mid / 1500 ppm	15 Males & 15 Females	631 - 645	691 - 705
4	High / 3000 ppm	15 Males & 15 Females	646 - 660	706 - 720

Disposition of Groups

Exposure began on Monday, September 12, 1994 (Day 0). Exposures were conducted 6 hours/day, 5 days per week (Monday to Friday) for 13 consecutive weeks. The surviving animals were exposed for an additional one (males) or two days (females) of the 14th week.

On Day 30, five male and five female rats from each group were anesthetized with Metofane™ and blood was collected for clinical pathology; these animals were then euthanatized and the carcasses were discarded. On the day following their last exposure, the remaining animals were anesthetized with Metofane™ and blood was collected for clinical pathology [Days 93 (males) and 94 (female)]. These animals were then euthanatized and necropsied.

Group	Exposure Concentrations	Animals Bled on Day 30 for Clinical Pathology	Animals Necropsied at Study Termination
1	Control / 0 ppm	Male: 611 - 615 Female: 671 - 675	Male: 601 - 610 Female: 661 - 670
2	Low / 500 ppm	Male: 626 - 630 Female: 686 - 690	Male: 616 - 625 Female: 676 - 685
3	Mid / 1500 ppm	Male: 641 - 645 Female: 701 - 705	Male: 631 - 640 Female: 691 - 700
4	High / 3000 ppm	Male: 656 - 660 Female: 716 - 720	Male: 646 - 655 Female: 706 - 715

Body Weight Determinations

Body weights were measured, prior to exposure, on Days 0, 7, and weekly thereafter. Animals were fasted the day prior to necropsy. Fasted body weights were measured after exsanguination, but prior to necropsy.

Feed Consumption Determinations

Feed consumption was measured, prior to exposure, on Days 7, 14, and weekly thereafter.

Clinical Observations

Rats visible through chamber windows were observed for clinical signs during exposure. Tapping sounds were made on the outside of the chamber with a key or other metal object to assess the animals' activity level. If the majority of animals in the group demonstrated similar signs, the observations were recorded for the entire group. Before and after exposure, each rat was removed from its cage and examined. Cageside observations were conducted once a day on weekends. Observations included, but were not limited to, examination of the hair, skin, eyes and mucous membranes, motor activity, feces, urine, respiratory system, circulatory system, autonomic nervous system, central nervous system, and behavior patterns.

Ophthalmic Examinations

All rats were examined by the staff veterinarian for retinal and corneal lesions prior to the start of the study using a direct ophthalmoscope. During the last week of exposure, animals from the control and high-concentration groups were re-examined. Since no changes were detected in the eyes of the high-concentration animals, the animals from the low- and mid-concentration groups were not re-examined.

Blood Collection

Animals were fasted beginning after their last exposure. The following day, animals were anesthetized with Metofane™, and blood was collected from the posterior vena cava. The blood was placed into vacutainer tubes and allowed to clot for analyses of serum. Other tubes containing an anticoagulant were used for analyses of whole blood samples. Blood smears were also prepared for blood cell counts. Following blood collection, the animals were humanely killed by exsanguination under anesthesia. Animals were bled and euthanized in random order based on a computer-generated list.

Hematology

Whole blood was analyzed for the following parameters using an Ortho Diagnostics Systems ELT-8/ds hematology analyzer.

Hemoglobin Concentration
Red Blood Cell Count
White Blood Cell Count

Hematocrit
Red Blood Cell Indices

Prothrombin time was measured using a BBL Fibrosystems analyzer. Slides with blood smears were stained and examined for cellular morphology and differential white blood cell count.

Clinical Chemistry

Serum was analyzed for the following parameters using a Roche Analytical Instruments Cobas Bio serum analyzer.

Aspartate Aminotransferase	Alanine Aminotransferase
Sorbitol Dehydrogenase	Gamma Glutamyltranspeptidase
Alkaline Phosphatase	Urea Nitrogen
Creatinine	Glucose
Total Protein	Calcium
Total Bilirubin	Phosphorus

Albumin concentration and isozyme profile were determined using a Helena Laboratories Titan Gel Electrophoresis System. The albumin/globulin ratio was calculated from total protein and albumin concentrations. Serum sodium and potassium concentrations were determined using a Corning Flame 480 Photometer, and serum chloride concentration was measured using a Corning Chloride Analyzer 925.

Necropsy

Animals were necropsied in a random pattern using a computer-generated list. Following euthanasia, the following organs were excised and placed into neutral buffered formalin. Gross lesions were recorded.

Nasal Passages	Adrenal Glands	Mesenteric Lymph Nodes
Trachea	Pituitary Gland	Sternum (with Bone Marrow)
Larynx	Thymus	Femur
Lungs	Pancreas	Right Testis*
Heart	Urinary Bladder	Right Epididymis*
Aorta	Thyroid Gland	Male Accessory Sex Glands
Esophagus	Parathyroid Glands	Quadriceps Femoris Muscle
Stomach	Spleen	Skin
Duodenum	Ovaries	Mammary Gland
Jejunum	Vagina	Eyes
Ileum	Uterus	Zymbal Gland
Cecum	Fallopian Tubes	Lachrimal Gland
Colon	Liver	Salivary Glands
Rectum	Kidneys	Gross Lesions

* The left testis and left epididymis were placed on dry ice and stored at - 25 °C.

Organ Weights

Wet weights of the liver, kidneys, testes or ovaries, spleen, adrenal glands, lungs, and brain were recorded for all animals at necropsy. Paired organs were weighed together except for the testes which were weighed individually.

Histopathology

All tissues listed below were embedded in paraffin, sectioned at 5 μm , and stained with hematoxylin and eosin (H&E). The nasal passages were decalcified prior to being embedded and sectioned. The lungs were sectioned along a plane allowing visual examination of the major bronchi and bronchioles. All tissues were examined microscopically from the control and high-concentration groups. In addition, the lungs, nasal passages, thymus (males only), stomach (females only), and gross lesions were examined from the mid-and low-concentration groups.

Nasal Passages	Heart	Mesenteric Lymph Nodes
Trachea	Aorta	Sternum (with Bone Marrow)
Larynx	Adrenal Glands	Right Testis
Lungs	Pituitary Gland	Right Epididymis
Esophagus	Thymus	Male Accessory Sex Glands
Stomach	Pancreas	Ovaries
Duodenum	Urinary Bladder	Vagina
Jejunum	Thyroid Gland	Uterus
Ileum	Parathyroid Glands	Fallopian Tubes
Cecum	Spleen	Salivary Glands
Colon	Liver	Gross Lesions
Rectum	Kidneys	

Assessment of Sperm Morphology and Development

The left testis and left epididymis of each male rat were placed into individual bags and frozen at - 25 °C. The right testis was preserved in 10% buffered formalin. Both frozen and preserved samples of testes and epididymis were submitted to Research Triangle Institute, Research Triangle Park, NC for sectioning and evaluation of sperm morphology and development.

Statistical Procedures

Mean values were calculated for analytical concentration, chamber temperature, chamber relative humidity, body weight, feed consumption, serum chemistry, hematology, and organ weights. Body weight, feed consumption, serum chemistry, hematology, and organ weight data were evaluated using the following statistical tests: Bartlett's test ($p \leq 0.01$), one-way analysis of variance (ANOVA) ($p \leq 0.05$), and Duncan's multiple range test ($p \leq 0.05$) to indicate statistical significance. A probability of $p \leq 0.05$ (two-tailed) was used to determine significance. If the Bartlett's test indicated unequal variances, the data were evaluated using a Kruskal-Wallis H-test and Mann-Whitney U-test.

Data Storage

The final report, tissues, data sheets, all nonperishable raw data, and an aliquot of the test substance are stored in the archives of the Health and Environment Laboratories, Eastman Kodak Company.

Project Participants

Study Director	Raymond M. David, Ph.D., D.A.B.T.
Toxicologist	Lisa G. Bernard, B.S.
Study Technicians	Reade A. Moulton Alison M. Warthling, A.A.S James F. Murphy, B.S.
Necropsy Pathologist/Staff Veterinarian	Milan S. Vlaovic, D.V.M., Ph.D.
Histopathologist	Robert M. Kovatch, D.V.M., D.A.C.V.P., Pathology Associates, Inc.
Analytical Chemist	Kathy Staudenmayer, B.S.
Statistician	Merrilee Ritter, M.S.

Study Dates

Initiation Date:	September 2, 1994
Experiment Start:	September 12, 1994
Experiment Completion:	August 16, 1996

SOP and Protocol Deviations

The Day 9 During Exposure Clinical Signs raw data sheet for the control group was misplaced after the data were entered into the computer. This deviation did not affect the outcome of the study.

Body weights of male rats were 271 ± 7 g at initiation of exposure which is outside the weight specifications of 200 ± 50 listed in the protocol. This deviation did not affect the outcome of the study.

There were no SOP deviations and no other protocol deviations during the study.

RESULTS

Exposure Conditions

Although the males and females of the same exposure groups were exposed together in a single chamber, the final exposures were staggered by one day for necropsy scheduling purposes. This difference in the number of exposure-days resulted in a slight difference in the mean chamber concentrations between sexes. The overall time-weighted average analytical concentrations of 548.4, 1487.5, and 3009.6 ppm for the male rats and 547.9, 1487.6, and 3008.8 ppm for the female rats were within 10% of the target concentrations of 550, 1500, and 3000 ppm. Daily time-weighted average concentrations were also within 10% of the target concentrations. The target analytical concentration for the 500 ppm group was increased to 550 ppm after consultation with the Sponsor because the test of chamber atmosphere homogeneity showed that the variation in actual exposure concentration at various locations in the chamber was as much as 28% lower than the analytical concentration determined at the reference point and was a mean of 13% lower than the reference point. Since the analytical concentration for the chamber is taken at the reference point, if a target concentration of 500 ppm were used, some animals might be exposed to substantially less than 500 ppm. Therefore, the target analytical concentration was increased to 550 ppm so that the actual exposure to the animals would be closer to 500 ppm. At the conclusion of exposures, the chamber atmosphere homogeneity was re-evaluated. Actual exposure concentrations at various locations in the chamber were 1 to 13% lower than the 550 ppm measured at the reference point indicating that the actual exposure condition of animals was probably not more than 3% lower than 500 ppm.

Nominal concentrations were generally 13-70% higher than the analytical concentrations. The daily mean temperatures and relative humidity inside the chamber during exposure were 21.1 - 24.7°C and 36.7 - 68.7%, respectively. Mean and standard deviation time-weighted average analytical concentrations and nominal exposure concentrations are presented in the summary tables. Individual readings during each exposure are provided in Appendix A.

Mortality

No spontaneous mortality occurred during the study.

Clinical Observations

Clinical signs observed during exposure are summarized on pages 36 - 38 followed by summaries of clinical examinations prior to and following exposure. Each clinical sign observed during the 6-hour exposure period is listed for each group, as is each clinical sign observed before or after exposure. Individual animal data are presented in Appendix B.

Animals exposed to 3000 ppm had reduced activity levels of generally minor severity during exposure. Reduced activity is defined as less movement, decreased alertness, and slower

response to tapping on the chamber wall compared with activity levels exhibited by control animals. Sialorrhoea was observed in three animals for no more than one or two exposure days. Red discoloration of the chin hair were observed for several female rats for no more than one or two exposure days. Animals exposed to 1500 ppm appeared normal for the first 5 hours of Day 0 and the first hour or two of Days 1 and 2, then exhibited reduced activity of generally minimal severity for the remainder of the daily exposure periods. Reduced activity of minimal severity was generally seen throughout daily exposures thereafter. Control and 500 ppm animals appeared normal during exposure.

After exposure, animals in all groups had porphyrin nasal discharges and dried porphyrin stains around the nose. There was no apparent difference among groups in the severity or incidence of these clinical conditions. Dried porphyrin stains were occasionally observed in the morning prior to exposure. Animals from all groups exhibited discolored-red facial hair, usually the chin hair. The incidence of this clinical condition was slightly higher in the 3000 ppm group than in other groups. Red discoloration of the facial hair was occasionally observed in the morning prior to exposure. All other observations were considered to be incidental to treatment.

Body Weights

Body weights were measured weekly and are presented graphically and as mean and standard deviation on pages 50 -54 (male) and 55 - 59 (female). Individual animal data are presented in Appendix C.

Mean body weights for the 3000 ppm groups were significantly ($p \leq 0.05$) lower than the control group beginning on Day 7 for male rats and on Day 14 for female rats continuing through the remainder of the study. Overall weight gains for the 3000 ppm group were 62 and 78% of weight gains for the control group (males and females, respectively). Mean weight gains for the 3000 ppm male group were significantly ($p \leq 0.05$) lower than for the control group during Weeks 1, 2, and 5 - 7; while mean weight gains for the 3000 ppm female group were significantly ($p \leq 0.05$) lower than for the control group during Weeks 2, 4, and 6.

Mean body weights for the 1500 ppm groups were significantly ($p \leq 0.05$) lower than the control group beginning on Day 42 for male rats and on Day 14 for female rats continuing through the remainder of the study. Overall weight gains were 77 and 70% of the control group (males and females, respectively). Mean weight gains for the 1500 ppm male group were significantly ($p \leq 0.05$) lower than for the control group during Week 11; while mean weight gains for the 1500 ppm female group were significantly ($p \leq 0.05$) lower than for the control group during Week 2.

Mean body weights and weight gains for the 500 ppm group were comparable to the control group throughout the study, and no statistically significant differences were noted. Overall weight gains were 90 and 107% of the control group (males and females, respectively).

Feed Consumption

Feed consumption was measured weekly and is presented graphically and as mean and standard deviation on pages 60 - 62 (male) and 63 - 65 (female). Individual animal data are presented in Appendix C.

Mean feed consumption for the 3000 ppm groups were significantly lower ($p \leq 0.05$) than for the control group throughout the study for male rats and at all intervals except Days 84 and 91 for female rats. Mean weekly feed consumption values for the 3000 ppm groups were 14-25% lower than the control group for male rats and were 6-16% lower than the control group for female rats. Mean feed consumption values for the 1500 ppm groups were significantly lower ($p \leq 0.05$) than for the control group on Days 7, 35, 42, 49, 56, 63, 70, 77, and 84 for male rats and at all intervals except Day 91 for female rats. Mean weekly feed consumption values for the 1500 ppm groups were 4-17% lower than the control group for male rats and were 10-15% lower than the control group for female rats. Mean feed consumption values for the 500 ppm groups were significantly lower ($p \leq 0.05$) than for the control group on Days 35, 42, 63, and 70, for male rats and on Days 7 and 14 for female rats. Mean weekly feed consumption values for the 500 ppm groups were 3-12% lower than the control group for male rats and were from 2% higher to 7% lower than the control group for female rats.

Ophthalmologic Examination

No treatment-related ophthalmologic changes were observed. The data are reported in the summary of clinical signs. Individual animal data are presented in Appendix B.

Hematology

Blood was analyzed for hematologic parameters after 30 and 90 days on test. Means and standard deviations are presented on pages 66 - 69. Individual animal data are presented in Appendix D.

No significant differences in hematologic parameters were seen after 30 days on test. Significantly higher ($p \leq 0.05$) mean erythrocyte counts, hemoglobin concentration, and hematocrit values were observed for the 3000 ppm male and female rats after 90 days on test compared with the control groups. The mean eosinophil percentage for male 3000 ppm rats was also significantly higher ($p \leq 0.05$) than for the control group. None of the differences were biologically significant, however.

Evaluation of blood cell morphology did not suggest any compound-related effects. After 30 days on test, spherocytosis and poikilocytosis were seen in blood smears of animals from most groups. Increased polychromasia was observed in one male control rat (# 613), while decreased polychromasia was seen in two female 3000 ppm rats (# 719 and 720). Howell-Jolly bodies in the blood and anisocytosis were also noted for Rat # 720. After 90 days on

test, poikilocytosis was seen in animals from all groups. Anisocytosis was noted in animals from the control, 500, and 1500 ppm groups. Microcytosis was seen in one male 1500 ppm rat (# 632) and in one male 500 ppm rat (#624) and spherocytosis was seen in two male 1500 ppm rats (# 631 and 638).

Clinical Chemistry

Serum was analyzed for clinical chemistry parameters after 30 and 90 days on test. Means and standard deviations are presented on pages 74 - 77. Individual animal data are presented in Appendix D.

After 30 days on test, mean sodium concentrations for the male and female 3000 ppm groups were significantly lower ($p \leq 0.05$) than for the control group. The differences were slight (~ 1 Meq/L), however. The mean chloride concentration for the 1500 ppm male group was significantly lower ($p \leq 0.05$) compared with the control group, however, the difference was small (< 4 Meq/L). No other differences in serum chemistries were seen among groups.

After 90 days on test, mean albumin and total protein concentrations for the 3000 ppm female group were significantly lower ($p \leq 0.05$) than for the control group. Mean sorbitol dehydrogenase activity for the 1500 ppm male group was significantly higher than for the control group. These changes were not considered to be toxicologically meaningful, and no other differences in serum chemistry were observed among groups.

Organ Weights

Mean and standard deviations of selected organ weights and organ-to-body weight ratios are presented on pages 78 - 79. Individual animal data are listed in Appendix E.

Mean terminal body weights measured after exsanguination were significantly lower ($p \leq 0.05$) for the 1500 and 3000 ppm male and female groups compared with the control group. Mean absolute weights of the liver, kidneys, and spleen reflect this reduced body weight. Mean absolute liver and spleen weights for the 1500 and 3000 ppm male and female groups were significantly lower ($p \leq 0.05$) than for the control groups. Mean absolute kidney weights for the 1500 female and 3000 ppm male and female groups were also significantly lower ($p \leq 0.05$) than for the control groups. However, relative organ weights (to body weight) were not significantly different except for the mean spleen-to-body weight ratio for the 3000 ppm male group which was significantly lower than for the control group. Reduced body weight was also reflected in the significantly lower ($p \leq 0.05$) mean absolute brain weight for the 3000 ppm male group and significantly higher ($p \leq 0.05$) mean brain-to-body weight for the 1500 ppm female and 3000 ppm male groups compared with their respective control groups. In addition, mean testes-to-body weights for the 1500 and 3000 ppm male groups and the mean relative lung (to body weight) weight for the 3000 ppm male group were significantly higher ($p \leq 0.05$) than for the control group. Mean adrenal

gland-to-body weight ratios for the 1500 ppm female and 3000 ppm male and female groups were significantly higher ($p \leq 0.05$) than for the respective control groups.

Gross Pathology

No exposure-related changes were detected on necropsy examination of male rats. Hemorrhage involving the glandular stomach (minimal severity) was observed in two 3000 ppm female rats. White discoloration in the non-glandular stomach was also observed for these animals. These findings may be related to exposure to the test substance. No changes were seen in female rats from the 1500 and 500 ppm groups. The gross pathology report is presented on pages 80 - 86.

Histopathology

Exposure-related changes were observed in the nasal passages and stomach of 1500 and 3000 ppm rats. All male and female 3000 ppm rats and 4/10 male and 6/10 female 1500 ppm rats had necrosis of the olfactory epithelium. The severity of the olfactory lesion was mild to moderate for the 3000 ppm group and minimal to mild for the 1500 ppm group. No lesions were observed in the nasal passages of the 500 ppm group. A few (3/10) 3000 ppm female rats had inflammation of the stomach mucosa (glandular or forestomach). The severity was minimal to mild. Lesions of this type in the stomach may be associated with swallowing of mucous containing the test substance, but due to the location of the lesion are more likely caused by stress. No effects were seen in the low- and mid-concentration groups. An occasional 3000 ppm male rat had atrophy of the thymus, but this was not considered to be a direct compound-related effect. Instead, the histopathologist attributed this lesion to stress. The histopathology report is presented on pages 87 -99.

Assessment of Sperm Morphology and Development

No exposure-related effect on epididymidal or testicular sperm count was observed. Effects on testicular staging or spermatogenic were not evaluated due to the unacceptable condition of tissue. The report is presented in Appendix G.

DISCUSSION

Exposure to 1500 and 3000 ppm of n-butyl acetate vapor resulted in decreased feed consumption and lower body weight, but no other overt signs of systemic toxicity. Reduced body weight for the 3000 ppm groups affected the weights of several organs. The absolute weight of the liver and kidneys decreased in proportion with body weight in that there were no differences in organ-to-body weight ratios. Lower absolute spleen weight also reflects lower body weight; however, the spleen-to-body weight ratio for 3000 ppm male rats was also significantly lower, suggesting that the caloric intake was sufficiently reduced to affect the spleen-to-body weight ratio. Decreases in liver and kidney weight as well as decreases in absolute and relative spleen weight are consistent with studies reported by Oishi *et al.* (1979) and Feron *et al.* (1973) in which the absolute weights of these organs decrease as body weight decreases from lower caloric intake. Absolute spleen weights have also been reported to be decreased by stress (Azoulay-Dupuis *et al.*, 1987) accompanied by decreased relative organ weight. Therefore, the differences in the weights of the liver, kidneys, and spleen were not considered to be indicative of direct test substance-related systemic toxicity.

In the case of the adrenal glands, lungs, and testes, the weights of these organs did not change in proportion to body weight. Instead, the absolute weights of these organs were generally comparable among groups but the organ-to-body weight ratios were higher because the body weight was lower. One exception is brain weight for the 3000 ppm groups. Absolute brain weight was reduced, but brain-to-body weight was increased for the 3000 ppm groups. However, these differences may also have been the result of reduced caloric intake. Similar changes in the weights of the brain and lungs were reported by Feron *et al.* (1973) in a study of the effect of reduced caloric intake over a thirteen-week period. Neurohistologic examination of the brain and other tissues of the central and peripheral nervous systems and neurotoxicity evaluations conducted as part of a companion study in which animals were exposed concurrently to the same concentrations did not indicate any evidence of neurotoxicity or histopathologic lesions in the nervous tissues (Eastman Kodak Company Report TX-95-27). Changes in adrenal gland weight have also been associated with decreased body weight, but usually for only short periods of time such as 28 days (Oishi *et al.*, 1979; Feron *et al.*, 1973). Longer periods of food restriction may cause chronic stress which is associated with increased relative adrenal gland weight (Ribelin, 1984). In addition, there were no histopathologic changes seen in the adrenal glands or lungs. Thus, the differences in relative adrenal gland, brain, and especially lung weights do not suggest any direct test substance-related organ toxicity.

Serum chemistry and hematology values at termination also did not indicate any specific organ toxicity. After 90 days, only total protein and albumin for the female 3000 ppm group were different than for the control group. Changes in SDH activity for the male 1500 ppm group were not considered to be toxicologically important because the effect was seen only for this mid-concentration group. In addition, there were no indications of cumulative effects based on a comparison of serum chemistry and hematology values from Day 30 and those

from termination. After 30 days, only sodium and chloride values for the 3000 and 1500 ppm groups were different from the control group, and these were comparable after 90 days.

No pulmonary toxicity was noted in the study. Higher lung-to-body weight ratios were not correlated to histopathology, but were considered to reflect reduced caloric intake. There was evidence of test substance-related respiratory tract irritation. Histopathologic findings in the nasal passages of male and female rats, and the stomach of female rats are consistent with irritation by n-butyl acetate, or, as may be the case for the stomach, stress induced by irritation. Bisesi (1994) indicated that many low molecular weight straight-chain alkyl acetate esters are irritating to the upper respiratory tract, and necrosis of the olfactory epithelium resulting from irritation has been described for other respiratory tract irritants (Buckley *et al.*, 1984).

In conclusion, n-butyl acetate vapor resulted in acute, transient signs of reduced activity levels during exposure to 1500 and 3000 ppm. Decreased body weight and feed consumption were noted for the 1500 and 3000 ppm groups, but there was no systemic or organ-specific toxicity. Signs of upper respiratory tract irritation were seen in the nasal passages of 1500 and 3000 ppm animals, but there was no evidence of pulmonary toxicity. The no-observed-effect level (NOEL) for this study is considered to be 500 ppm.

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n-BUTYL ACETATE

**A THIRTEEN-WEEK SUBCHRONIC INHALATION
TOXICITY STUDY IN THE RAT**

**HAEL NO. 94-0305 KAN 900710
CAS NO. 000123-86-4**

SIGNATURE PAGE



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Sept. 16, 1996
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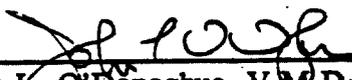
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SUMMARY OF EXPOSURE CONDITIONS - MALE RATS

EXPERIMENT # 94030517

TARGET CONCENTRATION (PPM)		0	500	1500	3000
NUMBER OF EXPOSURES		67	67	67	67
ANALYZED CONCENTRATION (PPM)	Mean	0.0	548.4	1487.5	3009.6
	SD	0.0	15.5	45.0	65.2
	n	67	67	67	67
Extremes of Daily Values	Low	0.0	514.3	1378.5	2793.9
	High	0.0	593.4	1603.2	3151.0
NOMINAL CONCENTRATION (PPM)	Mean	0.0	752.1	2522.2	3390.9
	SD	0.0	27.2	129.9	179.2
	n	67	67	67	67
Extremes of Daily Values	Low	0.0	625.1	2206.4	3026.9
	High	0.0	794.4	2850.0	3809.6
TEMPERATURE (°C)	Mean	22.1	21.9	22.7	23.0
	SD	0.4	0.4	0.5	0.8
	n	804	804	804	804
RELATIVE HUMIDITY (%)	Mean	53.4	52.1	46.9	50.1
	SD	7.8	7.9	7.0	7.0
	n	804	804	804	804
AIRFLOW (Lpm)	Mean	854.5	862.2	852.2	882.1
	SD	12.2	11.9	3.4	36.8
	n	67	67	67	67

SUMMARY OF EXPOSURE CONDITIONS - FEMALE RATS

EXPERIMENT # 94030517

TARGET CONCENTRATION (PPM)		0	500	1500	3000
NUMBER OF EXPOSURES		68	68	68	68
ANALYZED CONCENTRATION (PPM)	Mean	0.0	547.9	1487.6	3008.8
	SD	0.0	16.0	44.7	65.0
	n	68	68	68	68
Extremes of Daily Values	Low	0.0	514.3	1378.5	2793.9
	High	0.0	593.4	1603.2	3151.0
NOMINAL CONCENTRATION (PPM)	Mean	0.0	751.2	2522.2	3391.5
	SD	0.0	28.0	129.0	177.9
	n	68	68	68	68
Extremes of Daily Values	Low	0.0	625.1	2206.4	3026.9
	High	0.0	794.4	2850.0	3809.6
TEMPERATURE (°C)	Mean	22.1	21.9	22.7	22.9
	SD	0.4	0.4	0.5	0.8
	n	816	816	816	816
RELATIVE HUMIDITY (%)	Mean	53.5	52.1	46.9	50.3
	SD	7.7	7.9	7.0	7.1
	n	816	816	816	816
AIRFLOW (Lpm)	Mean	854.2	862.3	852.2	881.8
	SD	12.3	11.8	3.4	36.5
	n	68	68	68	68

**Summary of During Exposure Clinical Signs - Male Rats
 n-Butyl Acetate 13-Week Inhalation Study**

		Day of Onset	Last Day of Observation	Number of Rats Displaying Sign	Mean of Daily Maximum Severity	Frequency (Days)
0 ppm	Normal	0	92	15	-	67
500 ppm	Normal	0	92	15	-	67
1500 ppm	Normal	0	31	15	-	7
	Reduced Activity	0	92	15		67
			Week 1		1.17	
			Week 2		1.00	
			Week 3		1.00	
			Week 4		1.00	
			Week 5		1.00	
			Week 6		1.00	
			Week 7		1.00	
			Week 8		1.00	
			Week 9		1.00	
			Week 10		1.00	
			Week 11		1.00	
			Week 12		1.00	
			Week 13		1.00	
			Week 14		1.00	

Severities: 1 = Minimal, 2 = Minor, 3 = Moderate, 4 = Severe

**Summary of During Exposure Clinical Signs - Male Rats
 n-Butyl Acetate 13-Week Inhalation Study**

		Day of Onset	Last Day of Observation	Number of Rats Displaying Sign	Mean of Daily Maximum Severity	Frequency (Days)
3000 ppm						
	Reduced Activity	0	92	15		67
	Week 1				2.17	
	Week 2				2.00	
	Week 3				2.00	
	Week 4				2.00	
	Week 5				2.00	
	Week 6				2.00	
	Week 7				2.00	
	Week 8				2.00	
	Week 9				2.00	
	Week 10				2.00	
	Week 11				2.00	
	Week 12				2.00	
	Week 13				2.00	
	Week 14				2.00	
	Sialorrhea	51	53	1	2.00	3
	Sialorrhea - Red Discoloration	8	92	1	2.00	2
	Porphyrin Nasal Discharge	8	8	1	2.00	1

Severities: 1 = Minimal, 2 = Minor, 3 = Moderate, 4 = Severe

**Summary of During Exposure Clinical Signs - Female Rats
 n-Butyl Acetate 13-Week Inhalation Study**

		Day of Onset	Last Day of Observation	Number of Rats Displaying Sign	Mean of Daily Maximum Severity	Frequency (Days)
0 ppm						
	Normal	0	93	15	-	68
500 ppm						
	Normal	0	93	15	-	68
1500 ppm						
	Normal	0	31	15	-	7
	Reduced Activity	0	93	15		68
	Week 1				1.17	
	Week 2				1.00	
	Week 3				1.00	
	Week 4				1.00	
	Week 5				1.00	
	Week 6				1.00	
	Week 7				1.00	
	Week 8				1.00	
	Week 9				1.00	
	Week 10				1.00	
	Week 11				1.00	
	Week 12				1.00	
	Week 13				1.00	
	Week 14				1.00	
3000 ppm						
	Reduced Activity	0	93	15		68
	Week 1				2.17	
	Week 2				2.00	
	Week 3				2.00	
	Week 4				2.00	
	Week 5				2.00	
	Week 6				2.00	
	Week 7				2.00	
	Week 8				2.00	
	Week 9				2.00	
	Week 10				2.00	
	Week 11				2.00	
	Week 12				2.00	
	Week 13				2.00	
	Week 14				2.00	
	Sialorrhea	9	9	1	1.00	1

Severities: 1 = Minimal, 2 = Minor, 3 = Moderate, 4 = Severe

GROUPED SUMMARY OF CLINICAL SIGNS - MALE RATS

EXPERIMENT # 94030517

OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED

GROUP 1 - 0 PPM				

* NORMAL	6			602,604,608,611-612,615
OPHTHALMOLOGICAL EXAMINATION, NORMAL	10	85.	0.	601-610
INDUCED DEATH,METOFANE,EXSANGUINATION	15	72.	31.	601-615
EYES				
DRIED PORPHYRIN DISCHARGE	1	2.	0.	605
NOSE				
DRIED PORPHYRIN DISCHARGE	6	43.	37.	601,605-607,610,613
CAGE OBS. -URINE				
DISCOLORATION,RED	1	22.	0.	614
CAGE OBS. -FECES				
DIARRHEA	3	31.	4.	603,605-606
HAIR OF ARM				
DISCOLORATION,RED	1	59.	0.	609
HAIR OF FACE				
DISCOLORATION,RED	1	79.	0.	603
HAIR OF NECK				
DISCOLORATION,RED	2	80.	1.	603,610
GROUP 2 - 500 PPM				

* NORMAL	7			623,625-630
INDUCED DEATH,METOFANE,EXSANGUINATION	15	72.	31.	616-630
NOSE				
DRIED PORPHYRIN DISCHARGE	5	9.	7.	616,619-622
LEFT EYE				
DRIED PORPHYRIN DISCHARGE	1	87.	0.	619
CAGE OBS. -FECES				
DIARRHEA	1	48.	0.	618
HAIR OF NECK				
DISCOLORATION,RED	1	74.	0.	624
HAIR OF BACK				
DISCOLORATION,RED	1	74.	0.	624
SKIN OF NECK				
CRUST/SCALE ON SKIN	1	77.	0.	617
HAIR OF FACE				
DISCOLORATION,RED	1	77.	0.	619

KEY: *-INDICATES ANIMALS SHOWING CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - MALE RATS

EXPERIMENT # 94030517

OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED

GROUP 3 - 1500 PPM				

* NORMAL	6			631,634,637,641-642,644
INDUCED DEATH,METOFANE,EXSANGUINATION	15	72.	31.	631-645
NOSE				
DRIED PORPHYRIN DISCHARGE	6	23.	35.	632-633,639-640,643,645
TOOTH				
MALOCCLUSION	2	80.	16.	639-640
EYES				
PORPHYRIN TEARS	1	68.	0.	640
DRIED PORPHYRIN DISCHARGE	2	82.	13.	639-640
LEFT EYE				
PORPHYRIN TEARS	1	82.	0.	640
DRIED PORPHYRIN DISCHARGE	1	83.	0.	640
CAGE OBS. -FECES				
DIARRHEA	1	17.	0.	638
SKIN OF ARM				
ALOPECIA	1	38.	0.	635
HAIR				
UNKEMPT HAIRCOAT	1	71.	0.	640
HAIR OF FACE				
DISCOLORATION,RED	1	81.	0.	639
HAIR OF SCROTUM				
DISCOLORATION,BROWN	1	36.	0.	636

KEY: *-INDICATES ANIMALS SHOWING CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - MALE RATS

EXPERIMENT # 94030517

OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED

GROUP 4 - 3000 PPM				

* NORMAL	7			647,652,654-655,657,659-660
OPHTHALMOLOGICAL EXAMINATION, NORMAL	10	85.	0.	646-655
INDUCED DEATH,METOFANE,EXSANGUINATION	15	72.	31.	646-660
NOSE				
DRIED PORPHYRIN DISCHARGE	5	20.	21.	646,649-651,656
CAGE OBS. -FECES				
DECREASED VOLUME	3	1.	0.	653,656,658
DIARRHEA	1	30.	0.	648
HAIR OF NECK				
DISCOLORATION,RED	1	67.	0.	648
HAIR OF BACK				
DISCOLORATION,RED	1	67.	0.	648
HAIR OF FACE				
DISCOLORATION,RED	1	79.	0.	651

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - MALE RATS

EXPERIMENT # 94030517

OBSERVATION PERIOD - P.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED

GROUP 1 - 0 PPM				

* NORMAL	8			604,606-608,611-612,614-615
EYES				
PORPHYRIN TEARS	1	0.	0.	605
NOSE				
PORPHYRIN NASAL DISCHARGE	4	17.	13.	602,605,609,613
DRIED PORPHYRIN DISCHARGE	1	52.	0.	601
HAIR OF NECK				
DISCOLORATION,RED	2	80.	1.	603,610
HAIR OF ARM				
DISCOLORATION,RED	1	79.	0.	609
HAIR OF FACE				
DISCOLORATION,RED	1	80.	0.	603
GROUP 2 - 500 PPM				

* NORMAL	5			617,620,625-626,630
EYES				
PORPHYRIN TEARS	3	2.	1.	616,621-622
LEFT EYE				
DRIED PORPHYRIN DISCHARGE	1	87.	0.	619
PORPHYRIN TEARS	1	91.	0.	619
RIGHT EYE				
PORPHYRIN TEARS	1	92.	0.	616
NOSE				
PORPHYRIN NASAL DISCHARGE	6	10.	8.	616,618-619,622,624,629
DRIED PORPHYRIN DISCHARGE	7	23.	29.	616,618-619,621-622,624,629
TOOTH				
MALOCCLUSION	1	86.	0.	619
HAIR OF FACE				
DISCOLORATION,RED	5	34.	23.	616,623-624,627-628
HAIR OF INGUINAL REGION				
UNKEMPT HAIRCOAT	1	21.	0.	628
DISCOLORATION,BROWN	1	21.	0.	628
HAIR OF BACK				
DISCOLORATION,RED	1	80.	0.	618

KEY: *-INDICATES ANIMALS SHOWING CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - MALE RATS

EXPERIMENT # 94030517

OBSERVATION PERIOD - P.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED
GROUP 3 - 1500 PPM				
* NORMAL	7			631,636,638,641-644
NOSE				
PORPHYRIN NASAL DISCHARGE	5	32.	7.	632,637,639-640,645
DRIED PORPHYRIN DISCHARGE	3	74.	15.	634,639-640
TOOTH				
MALOCCLUSION	1	70.	0.	640
EYES				
DRIED PORPHYRIN DISCHARGE	2	81.	14.	639-640
LEFT EYE				
PORPHYRIN TEARS	1	78.	0.	640
DRIED PORPHYRIN DISCHARGE	1	81.	0.	640
SKIN OF ARM				
ALOPECIA	1	38.	0.	635
HAIR				
UNKEMPT HAIRCOAT	1	70.	0.	640
HAIR OF FACE				
DISCOLORATION,RED	7	47.	21.	632-635,637,640,645
GROUP 4 - 3000 PPM				
* NORMAL	6			653-654,657-660
NOSE				
DRIED PORPHYRIN DISCHARGE	5	45.	29.	647,649-652
PORPHYRIN NASAL DISCHARGE	3	32.	4.	647,652,655
DISCOLORATION,RED	1	72.	0.	649
MOUTH				
SIALORRHEA	1	53.	0.	649
HAIR OF FACE				
DISCOLORATION,RED	7	40.	28.	646-647,649,651-652,655-656
UNKEMPT HAIRCOAT	3	50.	10.	649-651
HAIR OF NECK				
DISCOLORATION,RED	1	70.	0.	648

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - FEMALE RATS

EXPERIMENT # 94030517

OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED

GROUP 1 - 0 PPM				

* NORMAL	5			662,666,672-673,675
OPHTHALMOLOGICAL EXAMINATION, NORMAL	10	85.	0.	661-670
INDUCED DEATH,METOFANE,EXSANGUINATION	15	73.	31.	661-675
NOSE				
DRIED PORPHYRIN DISCHARGE	5	12.	20.	667-669,671,674
PORPHYRIN NASAL DISCHARGE	1	85.	0.	669
EYES				
DRIED PORPHYRIN DISCHARGE	1	70.	0.	669
PORPHYRIN TEARS	1	85.	0.	669
RIGHT EYE				
DRIED PORPHYRIN DISCHARGE	1	58.	0.	665
LEFT EYE				
DRIED PORPHYRIN DISCHARGE	1	72.	0.	665
TOOTH				
MALOCCLUSION	1	85.	0.	669
CAGE OBS. -FECES				
DIARRHEA	1	39.	0.	661
DECREASED VOLUME	1	86.	0.	669
SKIN OF ARM				
ALOPECIA	1	16.	0.	663
SKIN OF FLANK				
ALOPECIA	1	91.	0.	663
HAIR OF ABDOMEN				
DISCOLORATION,RED	1	58.	0.	667
HAIR OF ARM				
DISCOLORATION,RED	1	78.	0.	667
HAIR OF NECK				
DISCOLORATION,RED	1	59.	0.	661
HAIR OF BACK				
DISCOLORATION,RED	2	69.	14.	661,668
HAIR OF FACE				
DISCOLORATION,RED	4	46.	18.	664,667-668,670

KEY: *-INDICATES ANIMALS SHOWING CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - FEMALE RATS

EXPERIMENT # 94030517

OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED

GROUP 2 - 500 PPM				

* NORMAL	8			677-679,682-683,688-690
DEHYDRATION	1	14.	0.	687
INDUCED DEATH,METOFANE,EXSANGUINATION	15	73.	31.	676-690
NOSE				
DRIED PORPHYRIN DISCHARGE	2	38.	50.	681,685
CAGE OBS. -FECES				
DECREASED VOLUME	1	14.	0.	687
DIARRHEA	1	36.	0.	684
SKIN OF ABDOMEN				
ALOPECIA	1	21.	0.	686
SKIN OF ARM				
ALOPECIA	1	28.	0.	687
HAIR OF ARM				
DISCOLORATION,RED	2	68.	16.	676,684
HAIR OF ABDOMEN				
DISCOLORATION,RED	1	56.	0.	676
HAIR OF FACE				
DISCOLORATION,RED	1	71.	0.	676
HAIR OF NECK				
DISCOLORATION,RED	1	82.	0.	680

GROUP 3 - 1500 PPM				

* NORMAL	8			692,694,697-698,700-702,705
INDUCED DEATH,METOFANE,EXSANGUINATION	15	73.	31.	691-705
NOSE				
DRIED PORPHYRIN DISCHARGE	5	24.	27.	691,695,699,703-704
HAIR OF FACE				
DISCOLORATION,RED	3	77.	17.	693,695-696
HAIR OF NECK				
DISCOLORATION,RED	2	74.	9.	693,696

KEY: *-INDICATES ANIMALS SHOWING CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - FEMALE RATS

EXPERIMENT # 94030517

OBSERVATION PERIOD - A.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED

GROUP 4 - 3000 PPM				

* NORMAL	4			706,709,719-720
EAR TAG LOST	1	2.	0.	720
EAR TAG REPLACED	1	2.	0.	720
OPHTHALMOLOGICAL EXAMINATION, NORMAL	10	85.	0.	706-715
INDUCED DEATH,METOFANE,EXSANGUINATION	15	73.	31.	706-720
LEFT EYE				
PORPHYRIN TEARS	1	54.	0.	711
DRIED PORPHYRIN DISCHARGE	1	55.	0.	711
NOSE				
DRIED PORPHYRIN DISCHARGE	6	30.	22.	707-708,710,712,715,717
CRUST/SCALE ON SKIN	1	57.	0.	715
ENLARGED,NOS	2	62.	2.	707,715
FECES				
DIARRHEA	1	41.	0.	715
CAGE OBS. -FECES				
SMALL	1	1.	0.	707
DECREASED VOLUME	2	60.	47.	714,717
SKIN OF FACE				
CRUST/SCALE ON SKIN	1	1.	0.	718
HAIR OF FACE				
DISCOLORATION,RED	5	43.	30.	707-708,713,715-716
HAIR OF NECK				
DISCOLORATION,RED	1	71.	0.	713
HAIR OF ARM				
DISCOLORATION,RED	2	72.	1.	710,713

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - FEMALE RATS

EXPERIMENT # 94030517

OBSERVATION PERIOD - P.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED

GROUP 1 - 0 PPM				

* NORMAL	5			662,671-673,675
NOSE				
PORPHYRIN NASAL DISCHARGE	2	5.	4.	668,670
DRIED PORPHYRIN DISCHARGE	6	34.	20.	664-665,668-670,674
DISCOLORATION,RED	1	85.	0.	669
EYES				
DRIED PORPHYRIN DISCHARGE	2	82.	15.	665,669
PORPHYRIN TEARS	1	85.	0.	669
RIGHT EYE				
DRIED PORPHYRIN DISCHARGE	1	72.	0.	669
LEFT EYE				
DRIED PORPHYRIN DISCHARGE	2	77.	5.	665,669
PALATE				
WOUND	1	85.	0.	669
SKIN OF FLANK				
ALOPECIA	1	91.	0.	663
SKIN OF ARM				
ALOPECIA	1	16.	0.	663
HAIR OF FACE				
DISCOLORATION,RED	5	47.	25.	665-668,670
HAIR OF ABDOMEN				
DISCOLORATION,RED	2	61.	4.	666-667
HAIR OF NECK				
DISCOLORATION,RED	2	70.	15.	661,667
HAIR OF BACK				
DISCOLORATION,RED	2	69.	14.	661,668
HAIR OF ARM				
DISCOLORATION,RED	1	79.	0.	667

KEY: *-INDICATES ANIMALS SHOWING CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - FEMALE RATS

EXPERIMENT # 94030517

OBSERVATION PERIOD - P.H.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED

GROUP 2 - 500 PPM				

* NORMAL	6			677,679,682,688-690
NOSE				
DRIED PORPHYRIN DISCHARGE	2	9.	2.	678,685
PORPHYRIN NASAL DISCHARGE	3	26.	19.	676,678,684
SKIN OF ABDOMEN				
ALOPECIA	1	21.	0.	686
SKIN OF ARM				
ALOPECIA	1	28.	0.	687
HAIR OF FACE				
DISCOLORATION,RED	8	27.	21.	676,680-681,683-687
HAIR OF ARM				
DISCOLORATION,RED	2	69.	18.	676,684
HAIR OF ABDOMEN				
DISCOLORATION,RED	1	56.	0.	676
HAIR OF NECK				
DISCOLORATION,RED	2	83.	3.	680,683
HAIR OF BACK				
DISCOLORATION,RED	1	85.	0.	683

GROUP 3 - 1500 PPM				

* NORMAL	4			691,702-703,705
HAIR OF FACE				
DISCOLORATION,RED	9	38.	21.	692-700
NOSE				
DRIED PORPHYRIN DISCHARGE	9	51.	28.	693-699,701,704
PORPHYRIN NASAL DISCHARGE	1	39.	0.	695
HAIR OF NECK				
DISCOLORATION,RED	2	81.	6.	696,699

KEY: *-INDICATES ANIMALS SHOWING CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL

GROUPED SUMMARY OF CLINICAL SIGNS - FEMALE RATS

EXPERIMENT # 94030517

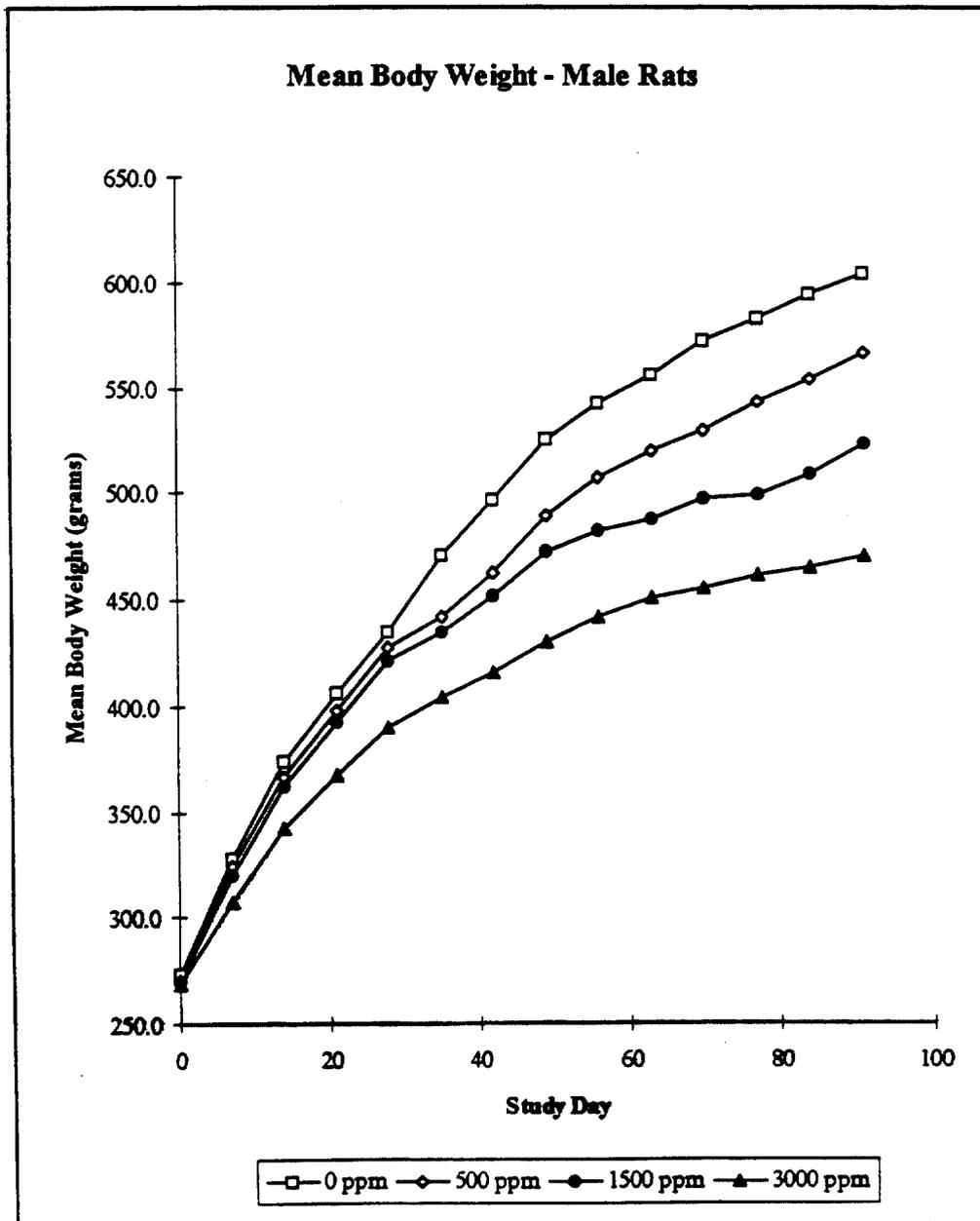
OBSERVATION PERIOD - P.M.

CLINICAL SIGN	NO. OF ANIMALS	MEAN ONSET DAY	ONSET S.D. #DAYS	ANIMALS AFFECTED

GROUP 4 - 3000 PPM				

* NORMAL	3			706,717,719
EYES				
PORPHYRIN TEARS	1	2.	0.	720
LEFT EYE				
PORPHYRIN TEARS	1	53.	0.	711
NOSE				
PORPHYRIN NASAL DISCHARGE	2	20.	23.	707,715
DRIED PORPHYRIN DISCHARGE	10	30.	23.	707-712,714-716,720
DISCOLORATION,RED	2	63.	10.	707,715
WOUND	1	56.	0.	715
CRUST/SCALE ON SKIN	1	58.	0.	715
ENLARGED,NOS	2	63.	4.	707,715
SKIN OF FOOT AND TOE				
DISCOLORATION,RED	1	72.	0.	707
SKIN OF FACE				
CRUST/SCALE ON SKIN	1	2.	0.	718
HAIR OF ARM				
DISCOLORATION,RED	3	77.	9.	709-710,713
HAIR OF NECK				
DISCOLORATION,RED	1	72.	0.	713
HAIR OF ABDOMEN				
DISCOLORATION,RED	1	92.	0.	713
HAIR OF FACE				
DISCOLORATION,RED	10	15.	15.	707-713,715-716,720
UNKEMPT HAIRCOAT	3	35.	6.	710,715-716

KEY: *-INDICATES ANIMALS SHOWING ONLY CLINICAL EXAM NORMAL, MORIBUNDITY/MORTALITY CHECK NORMAL, CAGESIDE OBSERVATION NORMAL, OR CHAMBER OBSERVATION NORMAL



MEAN BODY WEIGHTS - MALE RATS (GRAMS)

EXPERIMENT # 94030517

	0 PPM	500 PPM	1500 PPM	3000 PPM
WEEK # 1				
DAY 0	273.7 5.0 15	270.2 7.8 15	269.7 8.9 15	268.5 7.4 15
DAY 7	328.4 11.5 15	324.1 10.3 15	319.7 15.0 15	307.8 * 13.7 15
WEEK # 2				
DAY 14	374.0 16.3 15	366.4 16.8 15	362.0 26.2 15	342.2 * 18.2 15
WEEK # 3				
DAY 21	405.8 21.2 15	397.7 21.5 15	392.9 33.2 15	367.1 * 23.9 15
WEEK # 4				
DAY 28	434.6 24.7 15	428.0 27.5 15	421.3 41.4 15	389.7 * 25.7 15
WEEK # 5				
DAY 35	470.3 29.1 10	442.3 33.5 10	435.2 55.2 10	403.9 * 28.7 10
WEEK # 6				
DAY 42	496.4 33.1 10	462.6 34.4 10	451.6 * 60.1 10	416.2 * 30.4 10
WEEK # 7				
DAY 49	525.0 32.5 10	489.1 40.6 10	472.3 * 64.7 10	430.3 * 32.0 10
WEEK # 8				
DAY 56	542.4 34.3 10	507.8 42.9 10	482.6 * 68.2 10	441.6 * 34.8 10
WEEK # 9				
DAY 63	556.2 35.8 10	519.6 44.5 10	487.8 * 69.0 10	450.8 * 33.9 10
WEEK # 10				
DAY 70	572.2 40.0 10	529.4 49.8 10	497.1 * 77.5 10	455.4 * 36.7 10

KEY: DATA REPORTED AS MEAN, STANDARD DEVIATION, AND NUMBER PER GROUP
 * - STATISTICALLY DIFFERENT FROM CONTROL (P ≤ 0.05)

MEAN BODY WEIGHTS - MALE RATS (GRAMS)

EXPERIMENT # 94030517

	0 PPM	500 PPM	1500 PPM	3000 PPM
WEEK # 11				
DAY 77	582.7 38.5 10	543.2 54.1 10	499.7 * 76.7 10	462.1 * 38.6 10
WEEK # 12				
DAY 84	594.0 43.9 10	553.8 56.4 10	509.3 * 75.9 10	465.1 * 38.7 10
WEEK # 13				
DAY 91	604.2 47.5 10	566.4 56.8 10	523.4 * 82.8 10	470.4 * 41.8 10

KEY: DATA REPORTED AS MEAN, STANDARD DEVIATION, AND NUMBER PER GROUP
* - STATISTICALLY DIFFERENT FROM CONTROL ($P \leq 0.05$)

MEAN BODY WEIGHT CHANGE (GRAMS) - MALE RATS

EXPERIMENT # 94030517

	0 PPM	750 PPM	1500 PPM	3000 PPM
WEEK # 1				
DAYS 0-7	54.6 8.4 15	53.9 7.0 15	50.0 11.6 15	39.4 * 9.3 15
WEEK # 2				
DAYS 7-14	45.7 6.7 15	42.3 8.2 15	42.4 14.7 15	34.4 * 7.0 15
WEEK # 3				
DAYS 14-21	31.8 8.5 15	31.2 10.0 15	30.8 10.0 15	24.9 7.6 15
WEEK # 4				
DAYS 21-28	28.8 5.9 15	30.3 7.9 15	28.4 9.1 15	22.6 5.0 15
WEEK # 5				
DAYS 28-35	28.6 8.6 10	21.6 8.8 10	22.9 11.1 10	15.0 * 5.3 10
WEEK # 6				
DAYS 35-42	26.1 11.2 10	20.3 5.7 10	16.3 11.4 10	12.3 * 6.8 10
WEEK # 7				
DAYS 42-49	28.6 5.6 10	26.5 10.5 10	20.8 7.0 10	14.1 * 5.7 10
WEEK # 8				
DAYS 49-56	17.4 9.5 10	18.7 7.0 10	10.2 8.0 10	11.4 4.6 10
WEEK # 9				
DAYS 56-63	13.8 8.8 10	11.8 4.7 10	5.2 9.2 10	9.1 5.9 10
WEEK # 10				
DAYS 63-70	15.9 7.1 10	9.7 8.3 10	9.2 19.7 10	4.7 8.3 10

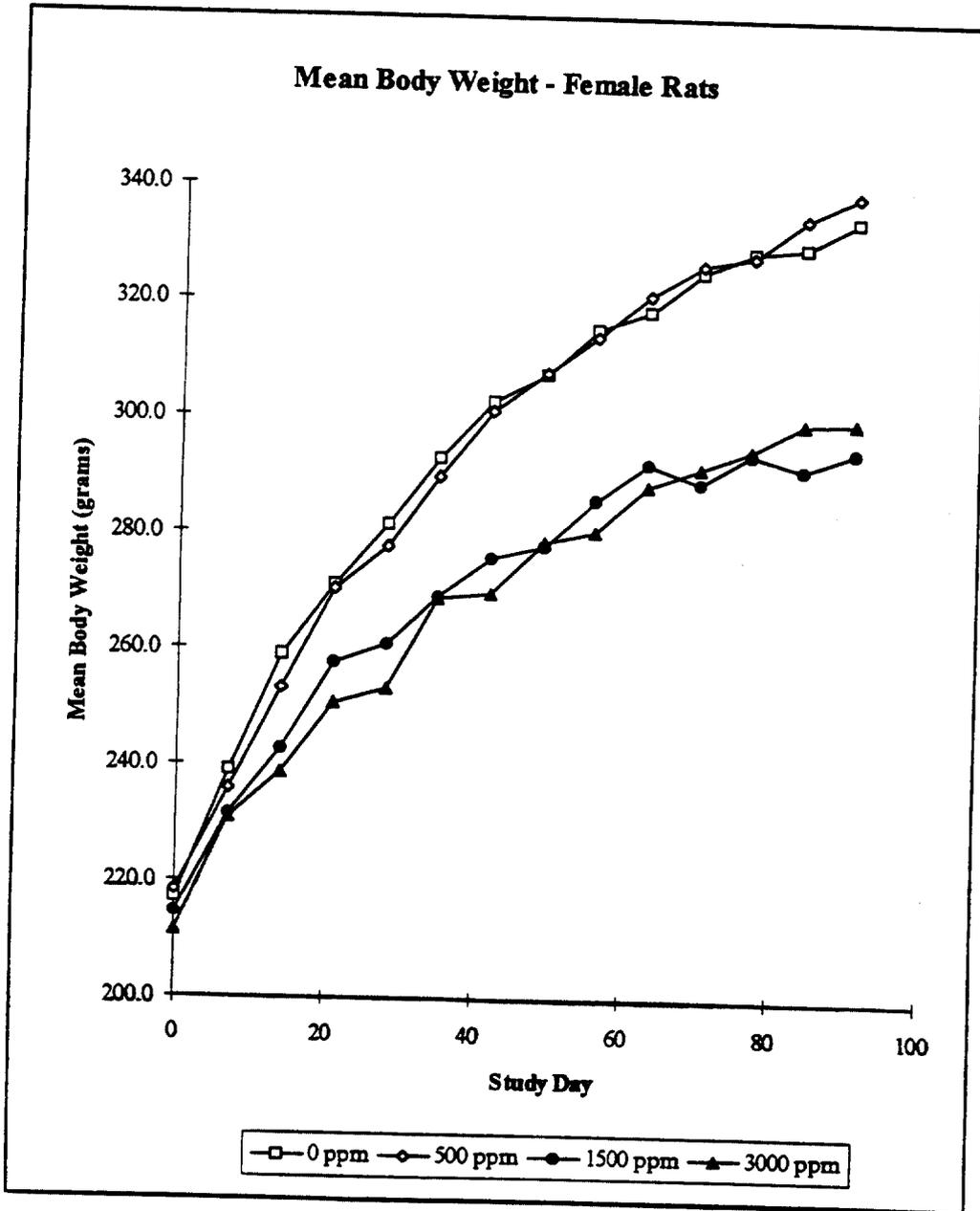
KEY: DATA REPORTED AS MEAN, STANDARD DEVIATION, AND NUMBER PER GROUP
 * - STATISTICALLY DIFFERENT FROM CONTROL (P ≤ 0.05)

MEAN BODY WEIGHT CHANGE (GRAMS) - MALE RATS

EXPERIMENT # 94030517

	0 PPM	750 PPM	1500 PPM	3000 PPM
WEEK # 11				
DAYS 70-77	10.5 5.8 10	13.8 7.8 10	2.6 * 6.5 10	6.6 3.3 10
WEEK # 12				
DAYS 77-84	11.3 7.5 10	10.7 10.9 10	9.7 7.3 10	2.9 4.7 10
WEEK # 13				
DAYS 84-91	10.2 6.8 10	12.6 12.4 10	14.0 8.5 10	5.3 5.4 10
TOTAL				
DAYS 0-91	329.4 43.7 10	296.4 55.3 10	254.6 * 80.5 10	202.9 * 35.0 10

KEY: DATA REPORTED AS MEAN, STANDARD DEVIATION, AND NUMBER PER GROUP
 * - STATISTICALLY DIFFERENT FROM CONTROL (P ≤ 0.05)



MEAN BODY WEIGHTS - FEMALE RATS (GRAMS)

EXPERIMENT # 94030517

	0 PPM	500 PPM	1500 PPM	3000 PPM
WEEK # 1				
DAY 0	217.0 9.2 15	218.4 8.2 15	214.5 8.0 15	211.5 6.1 15
DAY 7	239.3 12.8 15	235.9 10.5 15	231.6 10.0 15	230.9 9.8 15
WEEK # 2				
DAY 14	259.1 13.9 15	253.4 13.8 15	243.1 * 9.5 15	238.9 * 14.0 15
WEEK # 3				
DAY 21	271.2 13.7 15	270.4 11.8 15	257.7 * 9.4 15	250.8 * 13.1 15
WEEK # 4				
DAY 28	281.5 18.0 15	277.8 12.7 15	261.0 * 11.1 15	253.4 * 15.4 15
WEEK # 5				
DAY 35	293.0 14.7 10	289.7 13.6 10	269.1 * 10.5 10	268.8 * 19.6 10
WEEK # 6				
DAY 42	302.7 17.3 10	301.0 18.2 10	275.8 * 10.5 10	269.7 * 20.0 10
WEEK # 7				
DAY 49	307.5 17.6 10	307.8 18.0 10	278.2 * 6.3 10	278.7 * 20.0 10
WEEK # 8				
DAY 56	315.4 14.9 10	314.2 16.4 10	286.1 * 8.5 10	280.5 * 20.1 10
WEEK # 9				
DAY 63	318.5 17.9 10	321.5 20.7 10	292.3 * 11.4 10	288.4 * 25.2 10
WEEK # 10				
DAY 70	325.5 19.0 10	326.8 36.2 10	289.2 * 12.9 10	291.8 * 33.1 10

KEY: DATA REPORTED AS MEAN, STANDARD DEVIATION, AND NUMBER PER GROUP
 * - STATISTICALLY DIFFERENT FROM CONTROL (P ≤ 0.05)

MEAN BODY WEIGHTS - FEMALE RATS (GRAMS)

EXPERIMENT # 94030517

	0 PPM	500 PPM	1500 PPM	3000 PPM
WEEK # 11				
DAY 77	328.8 19.0 10	328.4 25.6 10	294.2 * 12.3 10	294.8 * 28.9 10
WEEK # 12				
DAY 84	330.0 15.6 10	334.8 27.0 10	291.6 * 8.6 10	299.4 * 29.6 10
WEEK # 13				
DAY 91	334.5 23.9 10	338.9 26.6 10	294.7 * 11.5 10	299.8 * 35.1 10

KEY: DATA REPORTED AS MEAN, STANDARD DEVIATION, AND NUMBER PER GROUP
 * - STATISTICALLY DIFFERENT FROM CONTROL (P ≤ 0.05)

MEAN BODY WEIGHT CHANGE (GRAMS) - FEMALE RATS

EXPERIMENT # 94030517

	0 PPM	750 PPM	1500 PPM	3000 PPM
WEEK # 1				
DAYS 0-7	22.4 13.5 15	17.5 10.2 15	17.1 8.4 15	19.3 8.3 15
WEEK # 2				
DAYS 7-14	19.8 9.5 15	17.5 18.3 15	11.4 * 6.9 15	8.1 * 10.2 15
WEEK # 3				
DAYS 14-21	12.1 8.0 15	17.0 14.1 15	14.7 7.3 15	11.8 9.9 15
WEEK # 4				
DAYS 21-28	10.3 9.4 15	7.4 7.9 15	3.3 7.6 15	2.6 * 8.1 15
WEEK # 5				
DAYS 28-35	8.6 8.0 10	9.3 11.1 10	10.9 9.7 10	18.4 5.6 10
WEEK # 6				
DAYS 35-42	9.7 6.9 10	11.2 9.1 10	6.8 8.6 10	0.9 * 5.3 10
WEEK # 7				
DAYS 42-49	4.9 8.0 10	6.8 9.5 10	2.4 9.8 10	9.1 7.7 10
WEEK # 8				
DAYS 49-56	7.9 6.9 10	6.5 7.4 10	7.9 6.4 10	1.7 10.7 10
WEEK # 9				
DAYS 56-63	3.1 8.8 10	7.3 7.3 10	6.2 7.7 10	8.0 12.0 10
WEEK # 10				
DAYS 63-70	7.0 10.9 10	5.3 17.9 10	-3.1 8.1 10	3.3 12.6 10

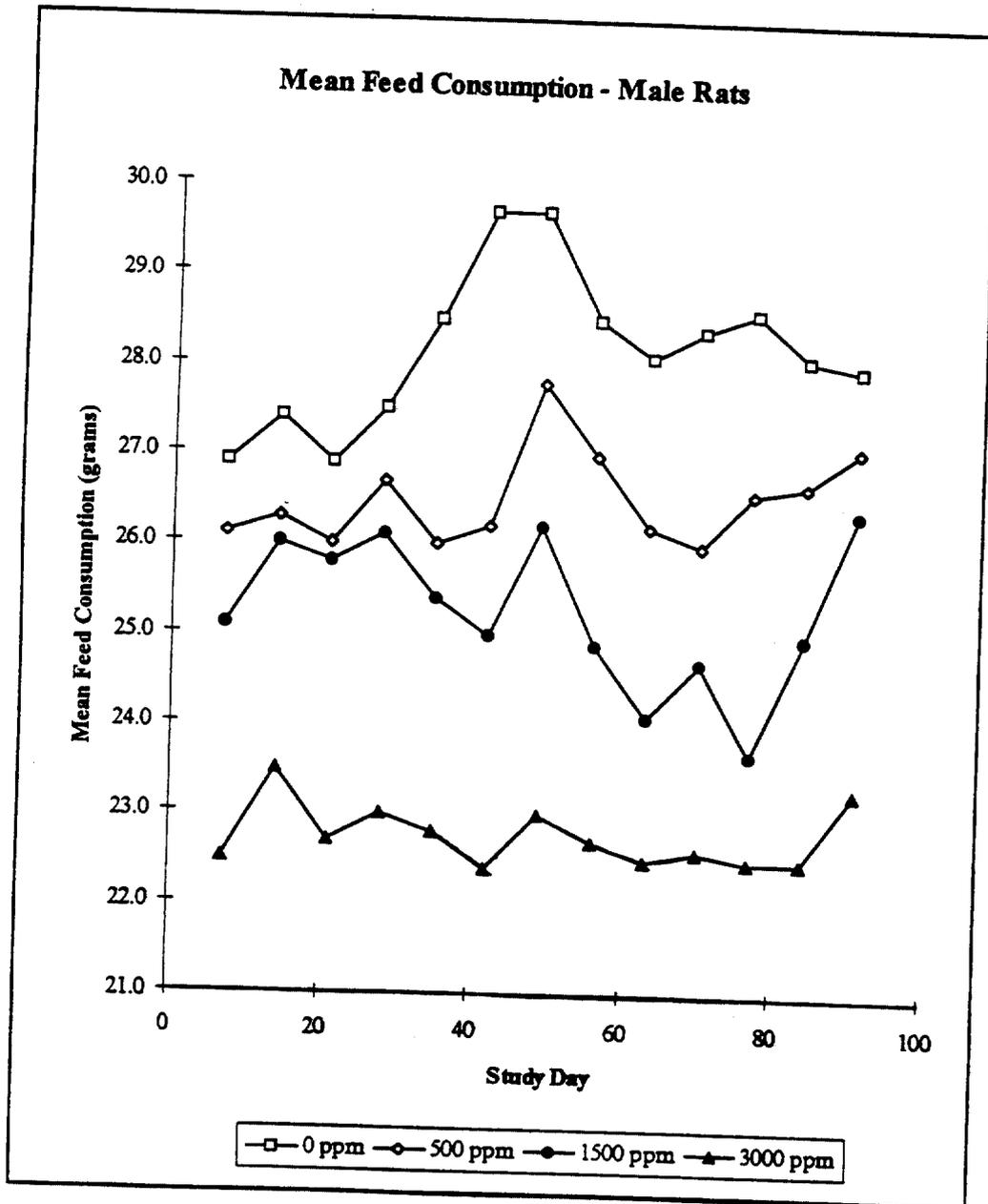
KEY: DATA REPORTED AS MEAN, STANDARD DEVIATION, AND NUMBER PER GROUP
 * - STATISTICALLY DIFFERENT FROM CONTROL (P ≤ 0.05)

MEAN BODY WEIGHT CHANGE (GRAMS) - FEMALE RATS

EXPERIMENT # 94030517

	0 PPM	750 PPM	1500 PPM	3000 PPM
WEEK # 11				
DAYS 70-77	3.3 7.1 10	1.5 18.5 10	5.0 10.7 10	3.0 9.7 10
WEEK # 12				
DAYS 77-84	1.2 9.8 10	6.4 9.4 10	-2.6 11.2 10	4.6 5.4 10
WEEK # 13				
DAYS 84-91	4.5 11.3 10	4.1 7.0 10	3.0 9.8 10	0.4 10.0 10
TOTAL				
DAYS 0-91	114.1 19.4 10	121.9 27.5 10	79.8 * 12.3 10	89.5 * 33.3 10

KEY: DATA REPORTED AS MEAN, STANDARD DEVIATION, AND NUMBER PER GROUP
 * - STATISTICALLY DIFFERENT FROM CONTROL (P ≤ 0.05)



MEAN FEED CONSUMPTION - MALE RATS (GRAMS/ANIMAL/DAY)

EXPERIMENT # 94030517

	0 PPM	500 PPM	1500 PPM	3000 PPM
WEEK # 1				
DAY 7	26.9 2.4 15	26.1 1.7 15	25.1 * 2.2 15	22.5 * 2.0 15
WEEK # 2				
DAY 14	27.4 1.8 15	26.3 1.9 15	26.0 3.2 15	23.5 * 1.8 15
WEEK # 3				
DAY 21	26.9 1.8 15	26.0 2.4 15	25.8 3.4 15	22.7 * 1.9 15
WEEK # 4				
DAY 28	27.5 2.0 15	26.7 2.4 15	26.1 3.3 15	23.0 * 1.6 15
WEEK # 5				
DAY 35	28.5 2.5 10	26.0 * 2.6 10	25.4 * 3.9 10	22.8 * 1.5 10
WEEK # 6				
DAY 42	29.7 2.2 10	26.2 * 2.3 10	25.0 * 3.7 10	22.4 * 1.8 10
WEEK # 7				
DAY 49	29.7 1.8 10	27.8 2.5 10	26.2 * 3.4 10	23.0 * 1.5 10
WEEK # 8				
DAY 56	28.5 1.9 10	27.0 2.1 10	24.9 * 3.1 10	22.7 * 1.8 10
WEEK # 9				
DAY 63	28.1 2.1 10	26.2 * 2.0 10	24.1 * 2.2 10	22.5 * 1.3 10
WEEK # 10				
DAY 70	28.4 1.9 10	26.0 * 2.3 10	24.7 * 3.4 10	22.6 * 1.8 10

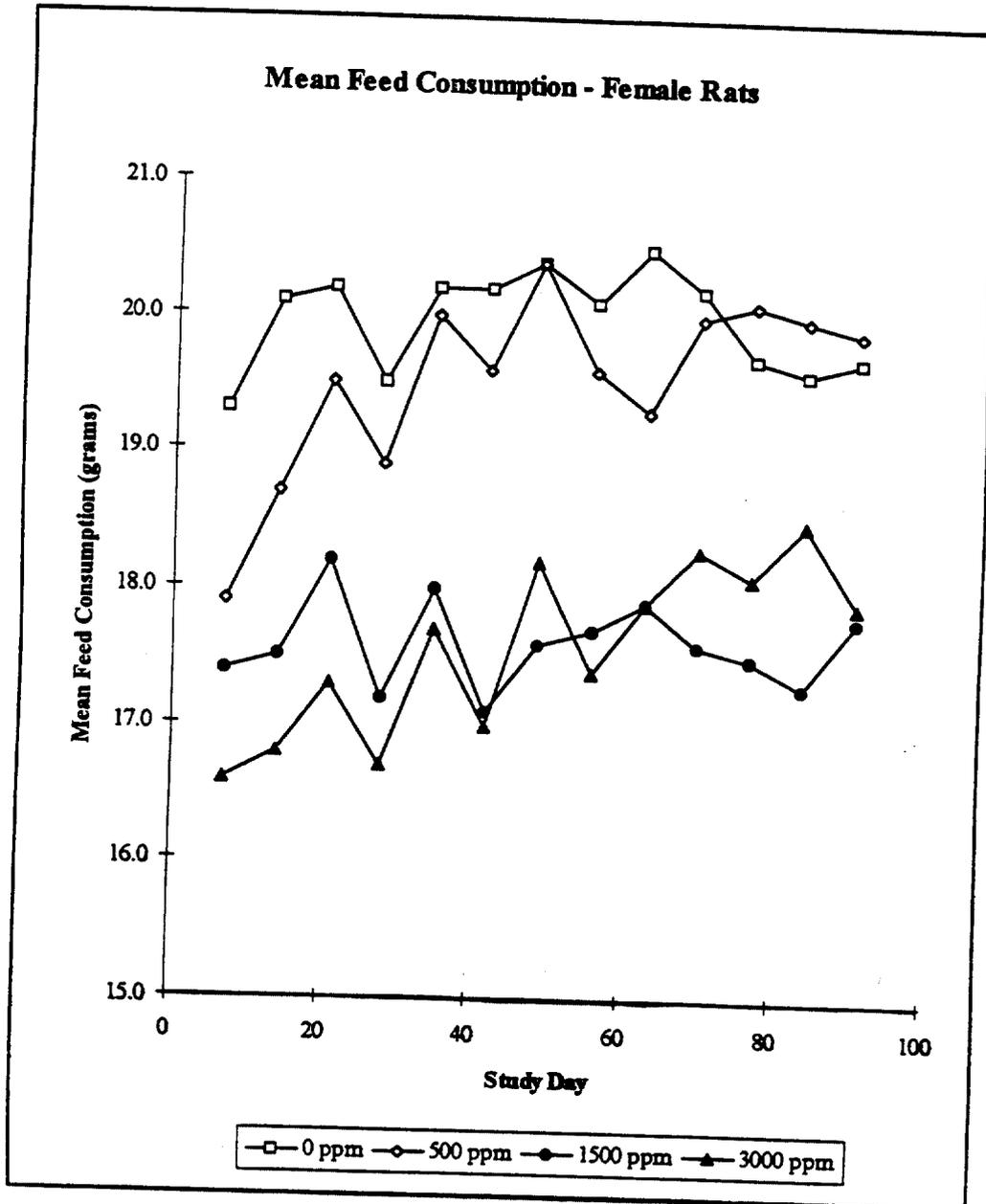
KEY: DATA REPORTED AS MEAN, STANDARD DEVIATION, AND NUMBER PER GROUP
 * - STATISTICALLY DIFFERENT FROM CONTROL (P ≤ 0.05)

MEAN FEED CONSUMPTION - MALE RATS (GRAMS/ANIMAL/DAY)

EXPERIMENT # 94030517

	0 PPM	500 PPM	1500 PPM	3000 PPM
WEEK # 11				
DAY 77	28.6 2.0 10	26.6 2.2 10	23.7 * 3.8 10	22.5 * 1.9 10
WEEK # 12				
DAY 84	28.1 2.0 10	26.7 2.3 10	25.0 * 3.0 10	22.5 * 1.3 10
WEEK # 13				
DAY 91	28.0 2.4 10	27.1 2.5 10	26.4 3.1 10	23.3 * 1.9 10

KEY: DATA REPORTED AS MEAN, STANDARD DEVIATION, AND NUMBER PER GROUP
* - STATISTICALLY DIFFERENT FROM CONTROL ($P \leq 0.05$)



MEAN FEED CONSUMPTION - FEMALE RATS (GRAMS/ANIMAL/DAY)

EXPERIMENT # 94030517

	0 PPM	500 PPM	1500 PPM	3000 PPM
WEEK # 1				
DAY 7	19.3 1.7 15	17.9 * 1.1 15	17.4 * 1.1 15	16.6 * 1.2 15
WEEK # 2				
DAY 14	20.1 1.3 15	18.7 * 1.9 15	17.5 * 0.9 15	16.8 * 1.2 15
WEEK # 3				
DAY 21	20.2 1.3 15	19.5 1.3 15	18.2 * 1.0 15	17.3 * 1.4 15
WEEK # 4				
DAY 28	19.5 2.1 15	18.9 1.4 15	17.2 * 1.0 15	16.7 * 1.5 15
WEEK # 5				
DAY 35	20.2 1.0 10	20.0 1.8 10	18.0 * 0.9 10	17.7 * 1.2 10
WEEK # 6				
DAY 42	20.2 1.4 10	19.6 2.2 10	17.1 * 1.3 10	17.0 * 1.0 10
WEEK # 7				
DAY 49	20.4 1.3 10	20.4 1.3 10	17.6 * 1.4 10	18.2 * 2.2 10
WEEK # 8				
DAY 56	20.1 1.6 10	19.6 1.1 10	17.7 * 1.2 10	17.4 * 1.1 10
WEEK # 9				
DAY 63	20.5 1.8 10	19.3 2.0 10	17.9 * 2.0 10	17.9 * 1.8 10
WEEK # 10				
DAY 70	20.2 1.4 10	20.0 1.6 10	17.6 * 1.9 10	18.3 * 2.6 10

KEY: DATA REPORTED AS MEAN, STANDARD DEVIATION, AND NUMBER PER GROUP
 * - STATISTICALLY DIFFERENT FROM CONTROL (P ≤ 0.05)

MEAN FEED CONSUMPTION - FEMALE RATS (GRAMS/ANIMAL/DAY)

EXPERIMENT # 94030517

	0 PPM	500 PPM	1500 PPM	3000 PPM
WEEK # 11				
DAY 77	19.7 1.8 10	20.1 1.9 10	17.5 * 1.7 10	18.1 * 1.7 10
WEEK # 12				
DAY 84	19.6 1.6 10	20.0 2.3 10	17.3 * 1.0 10	18.5 2.1 10
WEEK # 13				
DAY 91	19.7 3.2 10	19.9 1.8 10	17.8 1.2 10	17.9 2.5 10

KEY: DATA REPORTED AS MEAN, STANDARD DEVIATION, AND NUMBER PER GROUP
 * - STATISTICALLY DIFFERENT FROM CONTROL ($P \leq 0.05$)

SUMMARY HEMATOLOGY DETERMINATION - MALE RATS

EXPERIMENT # 94030517

ANALYTICAL MATERIAL: BLOOD

SAMPLE DAY # 30

	0 PPM	500 PPM	1500 PPM	3000 PPM
WBC/MM3 X3	9.1 2.4 5	9.6 2.8 5	8.9 3.4 5	10.7 2.5 5
RBC/MM3 X6	7.3 0.5 5	7.1 0.2 5	7.3 0.2 5	7.5 0.2 5
HB CONC , G/DL	14.3 1.0 5	14.0 0.3 5	14.5 0.2 5	14.9 0.3 5
HCT , %	42.4 2.4 5	40.8 1.2 5	43.0 1.2 5	43.6 1.5 5
MCV , U3	58.0 1.7 5	57.8 2.4 5	58.8 2.2 5	58.6 3.5 5
MCH , UUG	19.6 0.1 5	19.9 0.9 5	19.8 0.5 5	19.9 0.8 5
MCHC , %	33.7 0.6 5	34.5 1.5 5	33.8 1.0 5	34.1 0.6 5
POLYS , %	8.8 2.7 5	8.8 4.2 5	8.0 6.2 5	11.4 3.2 5
BANDS , %	0.0 0.0 5	0.0 0.0 5	0.0 0.0 5	0.0 0.0 5
LYMPHOCYTES,%	86.6 5.6 5	85.6 3.6 5	87.0 6.4 5	84.2 4.4 5
MONOCYTES,%	3.2 3.1 5	4.6 2.1 5	4.4 2.6 5	2.8 1.9 5
EOSINOPHIL,%	1.2 0.8 5	0.8 0.8 5	0.2 0.4 5	1.0 1.4 5
BASOPHIL,%	0.0 0.0 5	0.0 0.0 5	0.0 0.0 5	0.0 0.0 5
LYMPHOCYTES ATYPICAL, %	0.2 0.4 5	0.2 0.4 5	0.4 0.5 5	0.6 0.5 5
NUCLEATED RBC/100WBC	0.0 0.0 5	0.0 0.0 5	0.0 0.0 5	0.0 0.0 5
PROTHROMBIN TIME,SEC	17.6 0.5 5	17.5 1.0 5	19.0 0.8 4	18.3 0.8 4

KEY: DATA REPORTED AS MEAN, STANDARD DEVIATION, AND NUMBER PER GROUP

SUMMARY HEMATOLOGY DETERMINATION - FEMALE RATS

EXPERIMENT # 94030517	ANALYTICAL MATERIAL: BLOOD				SAMPLE DAY # 30
	0 PPM	500 PPM	1500 PPM	3000 PPM	
WBC/MM3 X3	5.8 1.7 5	5.5 1.9 5	6.0 1.9 5	9.2 1.3 3	
RBC/MM3 X6	7.0 0.3 5	7.1 0.2 5	7.2 0.3 5	7.4 0.3 3	
HB CONC , G/DL	14.2 0.6 5	13.8 0.4 5	14.1 0.5 5	14.3 0.8 3	
HCT , %	42.3 2.6 5	42.1 1.4 5	42.6 1.0 5	43.0 1.0 3	
MCV , U3	60.2 1.3 5	59.4 1.1 5	59.6 1.8 5	58.0 1.7 3	
MCH , UUG	20.1 0.5 5	19.4 0.4 5	19.7 0.7 5	19.2 0.6 3	
MCHC , %	33.6 1.0 5	32.7 0.8 5	33.0 0.7 5	33.2 1.2 3	
POLYS , %	13.4 5.3 5	14.6 2.1 5	11.8 1.9 5	11.0 3.0 5	
BANDS , %	0.0 0.0 5	0.0 0.0 5	0.0 0.0 5	0.0 0.0 5	
LYMPHOCYTES,%	81.2 4.3 5	79.4 1.5 5	85.0 2.9 5	85.6 3.4 5	
MONOCYTES,%	3.4 1.8 5	4.2 1.3 5	2.8 1.9 5	2.2 1.8 5	
EOSINOPHIL,%	1.6 1.5 5	1.2 0.8 5	0.2 0.4 5	0.8 0.8 5	
BASOPHIL,%	0.0 0.0 5	0.0 0.0 5	0.0 0.0 5	0.0 0.0 5	
LYMPHOCYTES ATYPICAL, %	0.4 0.5 5	0.6 0.9 5	0.2 0.4 5	0.4 0.5 5	
NUCLEATED RBC/100WBC	0.2 0.4 5	0.0 0.0 5	0.0 0.0 5	0.0 0.0 5	
PROTHROMBIN TIME,SEC	18.9 1.2 5	18.6 1.1 4	18.0 0.6 5	19.2 0.3 3	

KEY: DATA REPORTED AS MEAN, STANDARD DEVIATION, AND NUMBER PER GROUP