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Kenneth J. Willings
Vice President
Health, Safety & Environmental

July 21, 1999

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Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Attn: TSCA 8(e) Coordinator

Re: Notice of Possible Reproductive Effects in an Unaudited Draft Final Report on a Two Generation Drinking Water Study with Phenol in Rats: Supplemental Submission

Dear Sir/Madam:

The BFGoodrich Company (BFG) is submitting a supplement to the information that was submitted on an FYI basis on March 12, 1999. This submission contains the final report of a two generation oral (drinking water) reproduction study of phenol (CAS# 108-95-2) in rats. It does not contain confidential business information.

If you have any questions regarding this submission, please contact Dr. Robert K. Hinderer at (216) 447-5181.

Sincerely,

Kenneth J. Willings
Vice President
Health, Safety, & Environmental

KJW/rh
Enclosure

VIA CERTIFIED MAIL

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TWO-GENERATION ORAL (DRINKING WATER) REPRODUCTIVE TOXICITY STUDY OF PHENOL IN RATS

FINAL REPORT

VOLUME I: Report Narrative, Summary Tables, Figures, Analytical Report, Protocol

IITRI Project No. L08657
Study No. 2

Testing Facility:

IIT Research Institute
10 West 35th Street
Chicago, IL 60616

Sponsor:

Chemical Manufacturers Association (CMA)
1300 Wilson Blvd.
Arlington, VA 22209

Sponsor Representative:

Jon Busch

Study Monitors:

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Ralph Gingell, Ph.D., D.A.B.T. and
John Waechter, Ph.D., D.A.B.T.

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R. HINDERER

June 1999

A 06

TWO-GENERATION ORAL (DRINKING WATER) REPRODUCTIVE TOXICITY STUDY OF PHENOL IN RATS

Study Initiation Date: November 10, 1997
Experimental Initiation Date: November 11, 1997
Experimental Termination Date: August 6, 1998

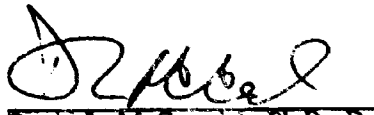
FOREWORD

This report describes a two-generation reproductive toxicity study in rats conducted by IIT Research Institute (IITRI) for the Chemical Manufacturers Association (CMA). The Sponsor Representative for the study was Jon Busch and the Study Monitors were Ralph Gingell, Ph.D., D.A.B.T. and John Waechter, Ph.D., D.A.B.T.

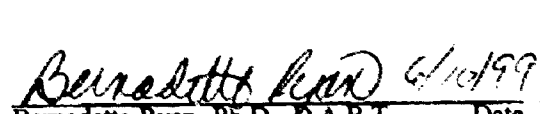
Bernadette Ryan, Ph.D., D.A.B.T., served as Study Director and was responsible for the overall conduct of the study. Raymond Selby, B.S., Laboratory Biologist, was study supervisor and was responsible for collection of data. Scott Garthwaite, B.S., Research Chemist, served as the analytical chemist and was responsible for analysis pertaining to the test water formulations. J. Brooks Harper, D.V.M., IITRI staff veterinarian, was responsible for animal care. Ronald A. Boyne, B.S., was responsible for the quality assurance program. Robert Morrissey, D.V.M., Ph.D., D.A.C.V.P., of Pathology Associates International, Chicago, IL, was the study pathologist.

This report is in three volumes: Volume I contains the report narrative, the summary tables, figures, analytical report, and a copy of the protocol; Volume II contains individual animal data for body weight, clinical observations, water and food consumption, breeding pairs, breeding outcome and litter body weight and survival; Volume III contains immunotoxicity screening/clinical pathology report, individual animal data for estrus cyclicity, sperm evaluations, and organ weights as well as the histopathology report.

This report was prepared by Bernadette Ryan, Study Director, with assistance from Tanya Bryan, B.S., Technical Editor, and Janet Mossman, Secretary.



David L. McCormick, Ph.D., D.A.B.T. Date
Vice President and Director
Life Sciences Operation



Bernadette Ryan, Ph.D., D.A.B.T. Date
Study Director
Life Sciences Operation

A 07

TWO-GENERATION ORAL (DRINKING WATER) REPRODUCTIVE TOXICITY STUDY OF PHENOL IN RATS

GLP COMPLIANCE STATEMENT

This study was conducted in accordance with the U.S. Environmental Protection Agency Good Laboratory Practice Standards (Title 40, *Code of Federal Regulations*, Part 792; TSCA). Analyses and attendant documentation pertaining to the characterization, purity, and stability of the bulk test substance were the responsibility of the Sponsor. The raw data have been reviewed by the Study Director, who certifies that this report accurately reflects and is supported by the study raw data and represents an appropriate interpretation of the data. Minor deviations that occurred during the study are described in the text.

Bernadette Ryan 6/10/99

Bernadette Ryan, Ph.D., D.A.B.T. Date
Study Director
Life Sciences Operation

TWO GENERATION ORAL (DRINKING WATER) REPRODUCTIVE TOXICITY STUDY OF PHENOL IN RATS

SUMMARY

Phenol was administered to 30 male and 30 female Sprague-Dawley rats (Taconic Farms, NY) in the drinking water at concentrations of 200, 1000 and 5000 ppm; the control group was given unadulterated water. Parental (P_1) rats were treated for 10 weeks prior to mating, during a two week mating period, throughout gestation, and through lactation until sacrifice. The F_1 generation was treated following a regimen similar to P_1, while the F_2 generation was not intentionally exposed to the phenol. After mating, approximately 10 P_1 males/group were used for evaluation of standard clinical pathology parameters and immunotoxicity screening using a plaque assay. There was no evidence of immunotoxicity, and a minimal increase in blood urea nitrogen (BUN) was noted in the 5000 ppm group. No other alterations in hematology or clinical chemistry were noted. Significant reductions in water, and to a lesser extent food consumption, were observed in the 5000 ppm group across both generations. The decreased water consumption was believed to be due to flavor aversion. Corollary reductions in body weight/body weight gain were also observed in both generations at 5000 ppm. In addition, some absolute organ weights were significantly reduced in the 5000 ppm group, while some organ-to-body weight ratios were significantly increased. In general, the alterations in organ weights and organ-to-body weight ratios observed across both generations were considered to be secondary effects of the reduced body weight.

Mating performance and fertility in both generations were similar in the treated groups relative to controls. Vaginal cytology/cyclicity and male reproductive functions (epididymal/testicular sperm counts, motility, and morphology) were unaffected by treatment in the P_1 rats, while sporadic, but statistically significant, alterations in testicular sperm counts (number of sperm/gram of testis and sperm production rate) were detected in the F_1 generation. The changes noted in the testicular sperm counts were considered to be associated with artifactual effects caused by reduced testis weight rather than a real change in sperm count or production. No adverse treatment related alterations were observed microscopically in the testes, ovaries, uterus, prostate or any of the other tissues examined in either generation.

SUMMARY (continued)

Litter survival and offspring body weight were reduced in the 5000 ppm group across both generations; for survival, this effect was more pronounced in the F_2 generation. Delays in vaginal opening and preputial separation were noted in the 5000 ppm group and were considered to be secondary to the reduction in F_1 body weight.

Statistically significant reductions in the absolute prostate weight were detected at all concentrations in the F_1 generation, but the decrease in relative prostate to body weight was statistically significant only at the 1000 ppm mid-dose group. Statistically significant reductions in both absolute and relative uterus weights were detected at all concentrations in the F_1 generation, but the magnitude of the decreases in relative weight was not dose-related. Histological examination (Appendix E) of the uterus revealed a lower incidence of uterine dilation in the high dose rats (2/20) than the control group (7/20) which may partially explain the decrease in weight, but no adverse histological changes were observed. It is unclear if the decreased prostate and uterus weights are treatment related. The changes, in the absence of any functional reproductive effect, and in the absence of any adverse histological changes in these reproductive organs, are not considered adverse. Based on a comprehensive examination of all the parameters, the no-observed-adverse-effect level (NOAEL) for reproductive toxicity of phenol in drinking water is 1000 ppm, based on decreased pup survival at the 5000 ppm concentration (which may be related to flavor aversion). The daily intake of phenol in adult rats at 1000 ppm was estimated to be about 70 mg/kg for males, and about 93 mg/kg for females.

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TWO-GENERATION ORAL (DRINKING WATER) REPRODUCTIVE TOXICITY STUDY OF PHENOL IN RATS

I. INTRODUCTION

The purpose of this study was to evaluate the potential of Phenol to alter the parental fertility, including pregnancy and lactation, as well as its ability to alter development of the offspring across two generations of Sprague-Dawley rats.

II. MATERIALS AND METHODS

A. Test Substance: Phenol (lot no. 112796/batch no. 102596) was received on December 27, 1996. Phenol was received in amber glass bottles blanketed with nitrogen to minimize oxidation/degradation of phenol. The test substance was stored in the original containers at room temperature in a ventilated cabinet. Analyses to verify the characterization, purity and stability (relative to laboratory storage conditions) of the bulk test article were the responsibility of the Sponsor. Upon completion of all relevant studies, the residual test substance will be disposed of according to appropriate state and local government requirements.

B. Dosing Formulations: The test substance was administered in the drinking water. Formulations of phenol in drinking water at 0, 200, 1000, and 5000 ppm were prepared weekly by mixing a specified gram quantity of Phenol with City of Chicago tap water in individual 2000 ml volumetric flasks. The phenol was pre-dissolved approximately 1 liter of tap water. The formulations were thoroughly mixed, after which the flasks were brought to volume with tap water (q.s. to the appropriate mark with tap water). The individual 2 liter stock formulations were transferred to the appropriate polyethylene carboy and brought to a total volume of 32 or 42 liters, depending on the anticipated weekly consumption. Each carboy was gently rocked to ensure complete mixing of the dosing formulations. Dosing formulations were dispensed into water bottles and were not stored in the polyethylene carboys. All excess water was dispensed into extra water bottles for use in the event of spillage or as needed for water bottle replacement.

C. Animals, Housing, and Diet: One-hundred and thirty-one (131) male and 131 female Sprague-Dawley rats, 4 weeks of age, were received from Taconic Farms (Germantown, NY) on October 30, 1997. The body weights of a random sample of 15 rats of each sex ranged from 63 g to 99 g (males) and from 54 g to 82 g

(females). Rats were held in quarantine for 12 days and examined daily for mortality and moribundity. During the quarantine period, the rats were examined thoroughly to ensure their health and suitability as test animals. Prior to mating, all rats were single housed in stainless steel wire mesh cages suspended over absorbent paper or cage boards; during mating (and also during gestation and lactation for dams and pups) for both the P_1 and F_1 adult rats, the animals were housed in polycarbonate shoebox cages lined with corncob bedding. Weanlings were single housed in the stainless steel cages. Parental (P_1) animals were identified by ear tag, selected pups by marking the tail with permanent marker (F_1 and F_2 pups) and/or by tattoo (F_1). Each animal received a number unique within the study, and each cage was identified by a cage card with the animal number, study group, generation and test substance.

Temperature and relative humidity in the animal rooms were regulated to avoid extreme fluctuations, and, with a few exceptions, were maintained within the protocol specified range of 18-26°C and 30-70%. The humidity exceeded the low limit during a two week period. These fluctuations had no impact on the conduct of the study. Lights in the animal rooms were on a 12 hour on, 12 hour off cycle.

Rats received Purina Certified Rodent Meal #5002 (PMI Feeds, Inc., St. Louis, MO) and City of Chicago municipal tap water or formulated water *ad libitum*. Both feed and water were periodically analyzed for contaminants and City of Chicago water analytical reports were filed at IITRI. Based on these records, no contaminants were present in the feed or water at levels that would be expected to interfere with the integrity of the data or outcome of the study.

D. Experimental Design: Animals were chosen from the pool of suitable candidates and assigned to one of four groups with each group consisting of 30 animals/sex using an in-house developed computerized randomization procedure constrained by body weight. Groups 2, 3, and 4 (Low, Mid and High dose, respectively) were exposed to 200, 1000 and 5000 ppm, respectively, of Phenol in drinking water. Group 1 animals served as controls, and received unadulterated drinking water (*i.e.*, water without added test substance). Parental (P_1) rats were given phenol in drinking water for 10 weeks prior to mating, during a 2-week mating period, throughout gestation, lactation, and until sacrifice. Rats from the same dose level were mated one male to one female. Daily vaginal smears taken from female rats

during the 2-week mating period were evaluated for sperm presence. The presence of sperm in the smear or a sperm-plug indicated a positive mating and that day was designated as gestation Day 0 for the female rat. After successful mating, female rats were single housed in shoebox cages and males returned to their home cage. The target number of subjects was 23 mated dams per group to produce the F_1 generation.

Dams were allowed a natural parturition. Offspring were sexed and randomly culled (using colored stoppers allowing each pup a 50:50 chance for selection) to 4/sex/litter, where feasible, on postnatal Day 4.

Upon weaning, siblings were initially group housed for 72 hours and then single housed. At weaning (postnatal Day 22), selected F_1 offspring (at least one pup/sex/litter) were exposed to the same concentration of test substance in drinking water as their parents for 11 weeks prior to mating. The F_1 adults were then paired one male and one female with care taken to avoid the mating of siblings; the target size of the groups was 20 mated dams per group. Administration of the test substance to the F_1 rats continued through mating, gestation, lactation, weaning and until sacrifice. F_2 pups were culled to 4 pups/sex/litter, when feasible, on postnatal Day 4. F_2 pups were not intentionally exposed to the test substance; however, during the latter part of the lactation period exposure would occur as the pups learned to drink from the water bottles. All F_2 pups and F_1 dams were sacrificed following weaning (postnatal Day 22). F_1 sires were sacrificed after mating. A list of the mating pairs for the P_1 and F_1 generations is presented in Appendices 61B and 62B. The following table illustrates the study design.

Study Group	Group Number	Treatment Concentration Phenol (ppm)	P_1 Generation Number/sex/group
Control	1	0	30
Low	2	200	30
Mid	3	1000	30
High	4	5000	30

The rats were exposed to the test substance (or control) for 7 days per week, according to the following schedule:

P_1 Generation:
- males - 10 weeks prior to mating during and up to 2-3 weeks of mating and until sacrifice;
- females - 10 weeks prior to mating during and up to 2-3 weeks of mating, during gestation up to the weaning of the F_1 generation (postnatal Day 22) and until sacrifice.

F_1 Generation:
- males - for 11 weeks starting at weaning (postnatal Day 22) during and up to 2 weeks of mating and until sacrifice;
- females - for 11 weeks starting at weaning (postnatal Day 22) during and up to 2 weeks of mating, during gestation up to the weaning of the F_2 generation (postnatal Day 22) and until sacrifice;

F_2 Generation:
- males - no treatment.
- females - no treatment.

When the P_1 males were no longer needed for mating, 10 P_1 males/group were randomly assigned to undergo clinical pathology evaluation and immunotoxicity screening. In addition, 5 extra male rats which were not assigned to study groups were randomly selected as positive controls for the immunotoxicity screening.

The study was stagger-started over two days to facilitate the many procedures and scheduled activities during the study. Thus, exposure of the P_1 generation male and female rats was initiated on November 11, 12, 1997, with 15 animals/sex/group initiated each day.

The schedule for termination of study animal treatment was as follows:

Generation	Sex	Sacrifice	Date
P_1	Males	between end of mating and weaning of F_1 pups	February 23, 1998
	Females not selected for F_1 litter generation	end of mating trial	March 5, 1998
	Females selected for F_1 litter generation	following F_1 weaning (postnatal Day 22)	March 25, 1998
F_1	Culled out Males and Females	postnatal Day 4	February 16, 1998
	Males and Females not selected for F_1 mating	F_1 weaning (postnatal Day 22)	March 12, 1998
	Mated F_1 Males	between the end of mating and weaning (postnatal Day 22)	July 6, 1998

	Mated F_1 Females	after F_2 weaning (postnatal Day 22)	August 4, 1998
F_2	Culled out Males and Females	postnatal Day 4	June 25 1998
	All remaining Males and Females	F_2 weaning (postnatal Day 22)	July 17, 1998

A staggered-start regimen was maintained at all major study milestone events, including termination because of the nature of the study (*i.e.*, variability in the mating times of the various mated pairs). The dates given above indicate the commencement date of each termination.

E. Methods:

1. Moribundity, Mortality, and Clinical Observations: Rats were observed for moribundity and mortality twice daily (once daily on weekends and holidays) during exposure. During gestation dams were observed twice daily beginning on Day 18 for evidence of parturition. Each rat also received a weekly hand-held clinical observation which was recorded by electronic data capture using LABCAT (IPA, Inc., Princeton, NJ, version 4.64).

2. Culling of Litters: Offspring from the litters (F_1 and F_2) were sexed on Day 0 and culled to four males and four females on postnatal Day 4. Where 4/sex/litter was not possible, litters were culled to the closest approximation. Litters with eight pups or less were not culled. Culled pups were euthanized and discarded without necropsy on postnatal Day 4. At weaning, at least two pups/litter (one per sex) from the F_1 generation were selected at random to produce the F_2 generation and were single housed and given phenol in drinking water for eleven weeks prior to mating. Non-selected pups were sacrificed and discarded without necropsy following weaning on postnatal Day 22.

   After 11 weeks of exposure, F_1 adults were paired and mated over a 2-week period. F_2 pups were culled to 4 pups/sex/litter (as closely as possible) on postnatal Day 4. Culled out pups were sacrificed and discarded without necropsy. Remaining pups were sacrificed and discarded without necropsy after weighing on postnatal Day 22. All of these activities were performed following a stagger-start regimen which was begun with the initiation of exposure of the P_1 male and female rats.

3. Body Weight and Offspring Survival: P_1 and F_1 rats were weighed weekly prior to mating. No weights were measured during the two week mating

period. Males were weighed weekly after mating until sacrifice. Dams were weighed on gestation Day 0, 7, 14 and 20. Both dams and offspring were weighed on postnatal Day 0 (observed parturition), 4, 7, 14, and 21. Average pup weight for each litter (male, female and combined) and each dose group was calculated. Body weight gains were calculated for all animals except pups during lactation. Survival was calculated based on the number alive on a given day subtracted from the number alive on the previous day (e.g., alive Day 0 - alive Day 4). Once an entire litter was dead (i.e., no survivors) a zero value was used for survival on all subsequent days.

4. Food Consumption: Food consumption was measured (weighed) for all P_1 and F_1 rats weekly prior to mating. No food consumption measurements were made during cohabitation. Food consumption was measured weekly for males after mating (until sacrifice), and for dams on gestation Day 0, 7, 14 and 20; and on lactation Day 0, 4, 7, 14 and 21 and weekly thereafter until sacrifice.

5. Water Consumption: Water consumption was measured (weighed) for all P_1 and F_1 rats weekly prior to mating. No water consumption measurements were made during cohabitation. Water consumption was measured weekly for males after mating (until sacrifice), and for dams on gestation Day 0, 7, 14, and 20; and on lactation Day 0, 4, 7, 14 and 21 and weekly thereafter until sacrifice.

6. Electronic Data Capture using LABCAT: Body weight data (except pup weight during lactation) were collected and body weight gains were calculated by electronic data capture using LABCAT. Food and water consumption data were collected and calculations were performed by electronic data capture using LABCAT. Technical problems (*e.g.*, broken or spilled water bottle, broken feed jar or saver malfunction, and/or capture of an erroneous weight) are indicated in the individual animal data appendices as "-- data unavailable".

7. Immunotoxicity Screening and Clinical Pathology: A complete description of methods used for the immunotoxicity and clinical pathology is given Appendix C.

8. Vaginal Cytology: Daily vaginal smears were collected and evaluated for the P_1 and selected F_1 females for three weeks prior to mating to ensure and evaluate cyclicity. Vaginal smear evaluations continued through mating and were discontinued when the presence of sperm or a sperm plug was detected. In addition, vaginal smears were collected and evaluated from P_1 and F_1 rats on two to four days prior to, and on the day of necropsy to determine the stage of the estrus cycle at termination.

9. Physical Examination of Offspring: All pups were subjected to a gross external evaluation on the day of birth. In addition, selected P_1 offspring (F_1 generation) were checked for vaginal patency and preputial separation, with female pups checked for patency on postnatal Days 28-45 and males checked for preputial separation on postnatal Days 35-55. Dead or stillborn pups were preserved for possible processing and visceral and/or skeletal examination. Cannibalized pups were documented as such and discarded without necropsy.

10. Postmortem Procedures:

    Necropsy: At least 20 rats/sex/group from the P_1 and F_1 generations were subjected to a gross necropsy. The necropsy included examination of the external surface and pleural, peritoneal and cranial cavities with limited tissue collection (see below). The presence of lesions or abnormal conditions was noted and described for the study record, with special attention given to the reproductive organs.

    Male Reproductive Function Assessment: At termination, the right testis and epididymis were trimmed of excess fat and weighed for at least 20 males/group/generation. Care was taken to maintain the temperature of the epididymis at 37°C in order to assure sperm motility remained unaffected. A pinhead sample of sperm was collected from the right caudal epididymis at the origin of the vas deferens. At least two samples were collected from each animal. Each sample was mixed with test yolk buffer and placed on a microscope stage for video recording of motility. Five fields from the two independently collected samples were recorded for assessment of motility (total and progressive).

Following a preliminary motility evaluation, the cauda epididymis was weighed and then macerated in phosphate-buffered saline (PBS). The epididymis/PBS preparation was used for epididymal sperm count analyses and preparation of slides for sperm morphology evaluation (200 sperm/slide were evaluated for morphology). Male reproductive function was assessed in the control and high dose groups for motility and morphology.

Homogenization resistant sperm were evaluated from the right testis (in some cases, e.g., #219 and 272, the left testis was used because the size or gross morphology of the right testis indicated that it was unsuitable for the processing). The testis of control and high dose rats was processed on the day of collection, while the testis from lower dose groups was frozen at -70°C for possible future processing for evaluation of homogenization resistant sperm. The methodology consisted first of removal of the tunica albuginea and weighing of the parenchyma of the testis. The parenchyma was then minced, the contents transferred to the homogenizing vessel, and the tissue homogenized for approximately 2 minutes in 50 ml of Saline-Merthiolate-Triton (SMT). Sperm counts were determined using the homogenization resistant technique in the control and high dose groups for both generations and in the mid dose group of the F_1 generation. Sperm production rate was calculated and reproductive function was summarized and reported. Data for homogenization is listed as "data unavailable" for those groups of animals not processed (P_1 low and mid dose and F_1 low dose).

Tissue collection: The following tissues were collected from at least 20 control, low, mid and high dose P_1 and F_1 rats:

Vagina*	Prostate* (PRO)
Uterus* (UTE)	Brain (BRN)
Ovaries with oviducts* (OVA)	Liver (LIV)
Cervix*	Kidneys (KID)
Stomach	Adrenals (ADR)
Pituitary	Spleen (SPL)
Testes*	Thymus (THYM)
Epididymides (left total and caudal)*	Seminal vesicles with coagulate glands* (SEM VES).

F_2 generation rats were euthanized and discarded without gross necropsy.

All organs underlined above were weighed at necropsy. Organ weight data listed as "data unavailable" occurred for one animal (number 384; only one adrenal weighed). In addition, any gross lesions observed at necropsy were collected. Collected tissues were sliced into appropriate-sized sections and fixed in 10% neutral buffered formalin. Testes and epididymides were fixed in Bouin's solution.

Histopathology: Tissues marked above with an asterisk (*) for 20 randomly assigned rats in the control and high dose groups from each generation were examined microscopically by a board-certified veterinary pathologist. In addition, the spleen, thymus, liver and kidneys were examined from 10 randomly selected rats in the control and high dose groups from both generations.

F. Statistical Procedures: Body weights, body weight gain, litter weight, litter survival, clinical observations, organ weights, organ-to-body weight ratios, daily food and water consumption, male reproductive function, female cyclicity, developmental landmarks, clinical pathology data, and immunotoxicity data were tabulated and analyzed by analysis of variance (ANOVA) followed, where appropriate, by Dunnett's test using LABCAT (IPA, Princeton, NJ, version 4.64, clinical pathology, version 4.41a) or SYSTAT (SPSS, Inc., Chicago, IL, version 5.0). A $p \leq 0.05$ was considered significant. Recalculation of the exact results as presented in this report may not be possible due to digital storage of numbers in computers or calculators as well as software calculating or rounding procedures.

G. Archives: All original data generated at IITRI and histology related data/specimens and a copy of the final report will be retained in the IITRI Archives (10 West 35th Street, Chicago, IL) for five years after submission of the signed final report. At that time, the Sponsor will be contacted to determine the final disposition of all archival material.

III. RESULTS

A. Test Substance Formulation Analysis (Appendix 1A): Analyses confirmed the stability of the test substance in drinking water under the conditions of use in this study. Analyses of samples of the test water (all three dose levels) prepared during weeks 1, 3, 5, 7, 15, 24 and 33 showed that the mean concentrations in the water

supplied to the animals were within 1.5% of target levels. No test substance was detected in any control drinking water at any time during the study.

Average daily test substance intake for parental males during week 10 of exposure was 0, 14.7, 70.9, and 301.0 mg/kg/day, while P_1 female intake was 0, 20.0, 93.0, and 320.5 mg/kg/day for the control, low, mid and high dose groups, respectively. Average daily intake during week 19 was 0, 13.5, 69.8 and 319.1 mg/kg/day for F_1 males and 0, 20.9, 93.8 and 379.5 mg/kg/day for F_1 females at the same dose levels (control 0 ppm, low 200 ppm, mid 1000 ppm and high 5000 ppm).

B. Mortality/Clinical Observations (Tables 2 through 9; Appendices 1B through 8B):
Three parental male rats died during the study; one control rat died spontaneously prior to the cohabitation, one high dose rat died during cohabitation this death was considered to be related to a bladder infection, and one high dose male rat died during blood collection; this death was accidental in nature.

Shortly after weaning, three high dose female pups (F_1 generation) died; the deaths appeared to be associated with reduced acclimation to the test substance in the drinking water since the animals were not drinking the water. Later, three F_1 dams [one control (125) one low dose (130) and one high dose (188)] died during gestation/lactation; one control died on gestation day 8 (dam number 125), while the others (low dose 130 and high dose 188) died undergoing parturition. The deaths observed in the adult F_1 rats were considered to be spontaneous in nature and, therefore, not related to treatment, while the deaths observed in the 3 high dose weanlings were considered to be the result of flavor aversion to the test substance in the drinking water.

The most prominent clinical signs consisted of discolored or wet inguinal fur and redness around the nose or eyes. These (particularly redness around nose fur and discolored or wet inguinal fur) were observed at slightly higher incidence in the test substance-treated groups than in the control group, particularly in the F_1 weanlings (Table 6). During the course of the study, twitching was observed in one F_1 high dose male rat on one occasion (week 4). Other clinical observations consisted of irritability, alopecia, diarrhea, lacrimation, red nasal discharge, emaciated (thin), vaginal discharge, hyperactive, chromodacryorrhea and discolored paws. These signs were of low or single incidence and sporadically distributed among the groups and were not considered to be treatment-related.

C. Water and Food Consumption, Body Weight, and Body Weight Gains:

1. Parental Generation (P_1) -- Males (Tables 10 through 17; Figures 1 and 2; Appendices 9B through 16B): Daily water consumption was decreased throughout the study in the high dose group (5000 ppm) relative to controls; however, statistical significance was not achieved during the last week of the study. Daily food consumption was slightly reduced in the high dose group (5000 ppm) during weeks 1 and 14 of the study. Corollary changes (*i.e.*, decreases) in body weight were detected in the high dose males throughout the study; these decreases achieved statistical significance beginning in week 4. Mean body weight gain was significantly decreased following the first week of test substance administration in the high dose group. This initial effect on body weight gain resulted in a significant decrease in cumulative body weight gain (total gain) during the 10-week pre-mating period. Other statistically significant differences (increases) observed in the low dose group were considered sporadic events. A similar response pattern (*i.e.*, decreased water consumption and reduced body weight) was observed in the P_1 high dose females, as described in the next section.

2. Parental Generation (P_1) -- Females (Tables 18 through 33; Figures 3 through 7; Appendices 17B through 32B): Daily water consumption was reduced in the P_1 high dose females; this decrease persisted through the periods of gestation and lactation (Figures 3 and 4). Daily food consumption was slightly reduced in the 5000 ppm (high dose) group during the first few weeks of dosing. No difference in daily food consumption was observed in gestating dams; however, during lactation (Figure 5), food consumption was significantly reduced in the high dose group (5000 ppm). Water and food consumption data collected during postnatal days 14-21 reflect the consumption of both the dams and their offspring, since the pups begin drinking water around Day 10 and eating solid food around Day 12. Thus, decreased food and water consumption during this period reflects maternal as well as offspring consumption. Corollary reduction in body weight was observed in the high dose group females throughout the study (Figures 6 and 7). Body weight gain was significantly reduced following one week of treatment; this initial effect in body weight gain resulted in a significant decrease in total body weight gain prior to mating. During gestation, body

weight gain was similar in all groups on gestation days 7 and 14, but by gestation day 20 a significant decrease in body weight gain was observed in the high dose dams. Again, total gain was significantly reduced in the 5000 ppm group during gestation. Body weight gain was unaffected by treatment during the lactation phase of the study. Other statistically significant differences (increases or decreases) noted in, body weight gain (reduced in the mid dose females during week 5) and water consumption (increased in the low dose during week 7) were considered to be sporadic events.

3. Parental Generation (P_1) Summary: In summary, the decrease in water consumption resulted in decreased absolute body weights and decreased body weight gains in the high dose group rats. Body weight gain in the high dose rats did, however, approach control group levels at later time points in the study, even though water consumption remained reduced throughout the study. The overall effect on body weight was considered to be from flavor aversion to the test substance in the drinking water.

4. F_1 Generation -- Pre-weaning (Tables 34 through 36; Figure 8; Appendices 33B and 34B): Offspring body weight was slightly reduced in the 5000 ppm group beginning on postnatal Day 0 (a 5% decrease for male and female combined offspring weight); this decrease persisted through postnatal Day 21 and became more pronounced as time went on (up to 15-20% on postnatal days 4-14 and 30% on postnatal day 21). The effects on postnatal Day 0 offspring body weight were observed in the presence of overt maternal toxicity, as indicated by decreased maternal body weight. The lower maternal body weight contributed to the lower birth weight. As indicated above, the decreases in maternal body weight were considered to be related to a flavor aversion phenomenon. Flavor aversion to the test substance was also considered to be a factor in the increasing magnitude of the response observed in offspring body weight between day 0 and 21, since the offspring begin drinking water between Days 7 and 14 (generally around Day 10). In the high dose group, the weanlings experienced flavor aversion to the test substance and that aversion was reflected in both the pre-weaning maternal/litter food and water consumption, as discussed above, and in the body weights of the weanling pups. Furthermore, as described in detail

below, the decreased water consumption seen in these pups prior to weaning persisted into adulthood and resulted in decreased body weights in the F_1 high dose (5000 ppm) group male and females rats.

5. F_1 Generation -- Males (Tables 37 through 44; Figures 9 and 10; Appendices 35B through 42B): Daily water consumption was decreased from weaning until the end of the study in the high dose (5000 ppm) group relative to controls. Daily food consumption was slightly reduced after weaning and for the duration of the study in the high dose males. Corollary changes (*i.e.*, decreases) in body weight were detected in the high dose group males throughout the study. Mean body weight gain was significantly decreased in the high dose males (5000 ppm) for the first three weeks after weaning. This initial effect on body weight gain resulted in a significant decrease in cumulative body weight gain (total gain) during the 11-week pre-mating period. In addition, a statistically significant decrease in body weight gain was observed in the mid dose males during week 10 and was considered to be sporadic event. After mating, sporadic increases in body weight gain were noted in the treated groups. A similar response pattern (*i.e.*, decreased water consumption and reduced body weight) was observed in the F_1 high dose females as detailed in the following section.

6. F_1 Generation -- Females (Tables 45 through 60; Figures 11 through 14; Appendices 43B through 58B): Daily water consumption was decreased from weaning until the end of the study in the high dose (5000 ppm) group relative to controls. Daily food consumption was slightly reduced after weaning in the high dose females (weeks 2, 4 and 5). Food consumption was unaffected during gestation and lactation. Corollary changes (*i.e.*, decreases) in body weight were detected in the high dose females (5000 ppm) throughout the study, including gestation and lactation (Figures 13 and 14). Mean body weight gain was significantly decreased in the high dose females shortly after weaning (weeks 1 and 3), while total body weight gain was significantly decreased during gestation but was unaffected during lactation. Finally, absolute body weight was increased (significantly so in the 1000 ppm group on days 0 and 7) during gestation in the low and mid dose groups (200 and 1000 ppm, respectively); this change was not considered treatment-related, but

rather normal variability in maternal body weight during gestation. Other sporadic but statistically significant differences were noted in the 200 and 1000 ppm groups (in the low dose group increased water consumption during week 21 and in the mid dose group increased food consumption during week 11).

7. F_2 Generation -- Pre-weaning (Tables 61 through 63; Figure 15; Appendices 59B and 60B): The pre-weaning growth pattern of the F_2 generation was similar to the F_1 generation. F_2 offspring body weight was slightly reduced in the 5000 ppm group beginning on postnatal Day 0 (a 7% decrease for male and female combined offspring weight); this decrease persisted through postnatal Day 21 and became more pronounced as time went on (up to 20-28% on postnatal Days 4-21). Again, maternal body weight and flavor aversion to the test substance in the drinking water were considered as significant factors that contributed to the decreased offspring body weight.

D. Reproductive Toxicity (Tables 64 and 65; Appendices 61B and 62B), Offspring Viability (Tables 66 through 79; Appendices 63B through 70B) and Developmental Landmarks (Table 80; Appendices 71B and 72B): No evidence of reproductive toxicity was observed with respect to fecundity and fertility. The average length of gestation across all groups was approximately 22 to 22.5 days for both generations. The number and percent of animals which mated and percent undergoing successful parturitions (*i.e.*, sperm positive/group and successful parturition/sperm positive) were similar across all groups for both generations (P_1 and F_1). The mating index (sperm positive/group) was 97% in the control, 100% in the low, and 97% in the mid and high dose groups for the P_1 generation. The percentage of P_1 dams undergoing successful parturition was 93% in the control, low, mid and high dose groups. The mating index for the F_1 generation was 100% in the control, mid and high dose groups and 96% in the low dose group. The number of F_1 dams undergoing successful parturition was 84% for the control group, 92% for the low and mid dose groups, and 87% for the high dose group.

The average number of live births/litter and deaths/litter on postnatal Day 0 was similar for all groups and across both generations. However, survival of the high dose (5000 ppm) offspring was adversely affected in both generations. The percent survival was significantly reduced in the F_1 high dose group on postnatal Day 4

(Table 68). After culling (on postnatal Day 4), the percent survival was similar across all groups (F_1 generation). In addition, average survival (percent) from postnatal Day 0-21 was similar across all groups (F_1 generation), while percent survival for the F_2 generation was decreased in the high dose offspring on postnatal Day 4, as well as after culling on postnatal days 7-21 (Table 73). Average survival (percent) throughout the pre-weaning phase of the study was significantly reduced in the high dose group (F_2 generation). Survival was affected in the presence of overt maternal toxicity, as indicated by decreased maternal body weight. Overall, percent survival was comparable between the low and mid test substance-treated and control groups. Average survival across Days 0 to 21 was 99, 99, 100 and 95% and 98, 95, 95 and 77% in the control, low, mid and high dose groups for the F_1 and F_2 generations, respectively.

For both generations, postnatal Day 0 offspring body weights were slightly reduced in the high dose (5000 ppm) groups compared to controls. A greater divergence in growth was noted over postnatal Days 7-21. The divergence in growth pattern was presumably associated with flavor aversion to the test substance, rather than systemic toxicity. For the F_1 generation, the body weight reduction resulting from the flavor aversion had a persistent effect and resulted in delayed vaginal patency and delayed preputial separation in the high dose (5000 ppm) offspring selected to produce the F_2 generation. Visual inspection of the control data (Table 80 and Appendices 71B-72B) indicates that preputial separation occurs after the males are approximately 200 g or more, while females become patent after they reach approximately 100 g or more. The growth rate of the high dose rats was about 2 weeks behind that of the control males (Table 41) and 1 week behind that of the control females (Table 53). Thus, it is not surprising that a 3-day delay in the developmental landmarks was observed. Vaginal patency and preputial separation are correlated with body weight; thus, the delayed development observed in the high dose offspring was most likely related to the decreased water consumption, and corresponding reduced body weight, caused by the aversion to the test substance in the drinking water. Others (Carney, E., *et al.* 1998, Toxicologist 42, Abstract 506) have demonstrated that food restriction results in a delay in vaginal patency and preputial separation, as well as reduced offspring weight.

E. Immunotoxicity Screening and Clinical Pathology in Male Rats (Tables 81 through 83; Appendix C):

1. Immunotoxicity Assay: No significant effects were observed on spleen weight, cellularity (cells/spleen), or antibody-forming cells (per spleen or per 10^6 cells) for any test substance group compared to the vehicle control group. As expected, there was a significant reduction of AFC activity, spleen cellularity and spleen weight in the positive control exposed animals compared to the vehicle control animals.

2. Clinical Pathology: Clinical chemistry and hematology parameters were unaffected by treatment, except for a minimal, but statistically significant, increase in blood urea nitrogen (BUN) in the high dose group following 13 weeks of administration of 5000 ppm phenol in the drinking water. Generally, biologically significant alterations in blood urea nitrogen are associated with increases in creatinine. However, no other alteration in any clinical chemistry parameter was observed; specifically, no corresponding increase in creatinine was detected in the high dose group. Thus, the increase in BUN was deemed to be of minimal to questionable biological significance not only because of the lack of associated change in creatinine, but also because only one high dose BUN value fell outside the control range (the control range values were 11-19 mg/dL, while the high dose values ranged from 14-19, with one value of 22 mg/dL).

F. Absolute and Relative Organ Weights (Tables 84 through 95; Appendices 1D through 12D): For the P_1 generation, no effects on any absolute organ weights were noted in the low (200 ppm) or mid (1000 ppm) group males or females. Differences in relative organ weights (kidney, right cauda) in the low dose males were considered to be sporadic and not related to treatment. Significant decreases in absolute seminal vesicle weights was observed in the P_1 high dose (5000 ppm) male rats and decreases in absolute adrenal, brain, spleen and ovary weights were noted in the P_1 high dose (5000 ppm) female rats. Organ-to-body weight ratios (for the brain, kidneys, liver, testes, epididymides, and right testis parenchyma) were significantly increased in the high dose group (males and/or females), which were ascribed to significantly decreased final body weights. For the P_1 generation, the decreases in absolute organ weights and increases in organ-to-body

weight ratios in the high dose group were considered secondary effects related to decreased body weight and decreased growth. Reductions in absolute organ weights were observed in the high dose (5000 ppm) group of the F_1 generation (males: adrenals, brain, liver, seminal vesicles, spleen, testes, epididymides, and right testis parenchyma; females: spleen). In addition, the absolute adrenal and spleen weights of the mid dose (1000 ppm) F_1 males were slightly decreased. Relative organ-to-body weight ratios were increased in the high (5000 ppm) dose group (males: brain, kidneys, epididymides, testes, right cauda, and right testis parenchyma; females: brain, kidneys and liver). The increased organ-to-body weight ratios were ascribed to the significantly reduced body weight. An increase in F_1 female absolute liver weight was noted in the 1000 ppm group but was not considered treatment-related.

Significant decreases in absolute prostate weight (reduced by approximately 15%) were noted in all three test substance treated groups in the F_1 generation, but not the P_1 generation. Relative prostate weights were significantly reduced only in the mid dose group (1000 ppm). Significant reductions in absolute and relative uterus weights were noted across all three treated groups in the F_1, but not the P_1 generation. There was no dose-related trend in the magnitude of the decrease of relative uterus weights. Although these organ weights were significantly reduced, only a few were below the range observed in the concurrent control. In the control group (F_1 generation), absolute prostate weights ranged from 0.572 to 1.323g. Most of the weights for the treated animals fell within this range, however a few were slightly below; specifically, lower weights were noted in 4, 3 and 2 animals in the low, mid and high dose groups, respectively (Appendix 7D).

In the control group (F_1 generation), the absolute uterus weight ranged from 0.403 to 1.467g. Again, most of the weights for the treated animals fell within this range, however a few were slightly below; specifically, lower weights were noted in 2 low, 3 mid and 4 high dose rats (Appendix 9D). Histological examination (Appendix E) of the uterus revealed a lower incidence of uterine dilatation (F_1 generation) in the high dose group (2/20) than in the control group (7/20), which may partially explain the decreases in weight. The stage of the estrus cycle can alter uterine weight at necropsy; vaginal cytology of rats with uterine dilatation indicated that the stage of the estrus cycle prior to necropsy was either proestrus

or estrus, since the smears consisted of nucleated epithelial or cornified epithelial cells. However, based on vaginal cytology data collected prior to necropsy, the number of F_1 rats in proestrus/estrus was similar across all groups with the exception of the high dose group which had the lowest number in estrus: 16/24 controls, 15/24 low, 13/25 mid and 9/22 high. The stage of estrus at necropsy does not appear to account for the reduction in uterine weight.

G. Vaginal Cytology and Sperm Morphology (Tables 96 and 97; Appendices 13D to 18D): During the 21 day evaluation period, the mean frequency of estrus (3.8 to 4.7 days) was similar across all groups for both generations and was unaffected by treatment with the test substance. Testicular sperm count and production rate was unaffected in the P_1 generation. While statistically significant increases in testicular sperm count and production rate were noted in the high dose group of the F_1 generation compared to controls, these increases were presumed to be associated with the reduced absolute testis weight, which was secondary to reduced body weight and therefore artifactual in nature. However, in an effort to fully characterize any potential adverse effect on the testis, the testicular count was extended to the mid dose group. No difference in testicular count was noted in the mid dose group compared to controls; therefore, the observed change in the high dose group was ascribed to lower testis weight rather than a true alteration in sperm count or production. Overall, sperm count, motility (% motile and % progressively motile) and sperm morphology across both generations were unaffected by treatment with the test substance.

H. Pathology (Table 98; Appendix E):

1. Gross Necropsy: No treatment-related necropsy findings were recorded. Some of the more common incidental necropsy findings included variations in organ size (small or enlarged), mass on median lobe of liver (generally due to a hepatodiaphragmatic herniation in an animal of this age), white calculus in lumen of urinary bladder (generally due to agonal contraction of seminal vesicle), pigmentation of the organ (red, red focus, mottled), dilatation of the uterus and ovarian cyst.

2. Histopathology: Microscopic examination of the reproductive organs including accessory sex organs failed to indicate any adverse treatment-related lesions. No treatment-related lesions were detected in any of the other organs

examined (kidneys, spleen, liver, and thymus) in the P_1 or F_1 rats. Although organ weight changes were noted in the prostate and uterus, no adverse histological changes were observed in these organs. Coincidentally, histological examination (Appendix E) of the uterus (F_1 generation) revealed a lower incidence of uterine dilatation in the high dose (2/20) than in the control group (7/20 controls) which may partially explain the decrease in uterus weight; vaginal cytology of rats with uterine dilatation indicated that the stage of the estrus cycle prior to necropsy was either proestrus or estrus since the smears consisted of nucleated epithelial or cornified epithelial cells. Based on vaginal cytology data collected prior to necropsy, the number of F_1 rats in proestrus/estrus was similar across all groups (16/24 controls, 15/24 low, 13/25 mid and 9/22 high); however, it was lowest in the high dose group.

IV. DISCUSSION AND CONCLUSIONS

Phenol was administered to 30 male and 30 female Sprague-Dawley rats (Taconic Farms, NY) in the drinking water at concentrations of 200, 1000 and 5000 ppm; the control group was given unadulterated water. Parental (P_1) rats were treated for 10 weeks prior to mating, during a two week mating period, throughout gestation and through lactation until sacrifice. The F_1 generation was treated following a regimen similar to P_1, while the F_2 generation was not intentionally exposed to the phenol. After mating, approximately 10 P_1 males/group were used for evaluation of standard clinical pathology parameters and immunotoxicity screening using a plaque assay. There was no evidence of immunotoxicity, and a minimal increase in blood urea nitrogen (BUN) was noted in the 5000 ppm group. No other alterations in hematology or clinical chemistry were noted. Significant reductions in water consumption, and to a lesser extent in food consumption, were observed in the 5000 ppm group in both generations. The decreased water consumption was believed to be due to the animals' aversion to the flavor of phenol in the drinking water. Corollary reductions in body weight/body weight gain were also observed in both generations at 5000 ppm. In addition, some absolute organ weights were significantly reduced in the 5000 ppm group, while some relative organ-to-body weight ratios were significantly increased. In general, the alterations in absolute and relative organ weights observed across both generations were considered to be secondary effects of the reduced body weights.

Mating performance and fertility in both generations were similar in all treated groups, relative to controls. Vaginal cytology/cyclicity and male reproductive functions [epididymal/testicular sperm counts, motility, and morphology] were unaffected by treatment in the P_1 rats, while sporadic, but statistically significant, increases in testicular sperm counts [numbers of sperm/gram testis and sperm production rate] were detected in the F_1 generation. These changes were considered to be artifactual effects caused by reduced body weight and hence decreases in absolute but not relative testis weight, rather than an alteration in sperm production. No adverse treatment-related alterations were observed microscopically in the testes, ovaries, uterus, prostate or any of the other tissues examined in either generation.

Litter survival and offspring body weights were reduced in the 5000 ppm group across both generations; for survival, this effect was more pronounced in the F_2 generation, again believed to be due to the animals' aversion to the flavor of the phenol-containing drinking water and subsequent decrease body weight. Delays in vaginal opening and preputial separation in the 5000 ppm group were considered to be secondary to the reduction in the pup body weights. Others have reported that food restriction results in reduced offspring weight, as well as delays in vaginal patency and preputial separation [Carney E et al., Toxicologist 42, abstract 506 1998].

Statistically significant reductions in the absolute prostate weight were detected at all concentrations in the F_1 generation, but the decrease in relative prostate to body weight was statistically significant only at the 1000 ppm mid-dose. Statistically significant reductions in both absolute and relative uterus weights were detected at all concentrations in the F_1 generation, but the magnitude of the decrease in relative weight was not dose-related. Histological examination [Appendix E] of the uterus revealed a lower incidence of uterine dilation to the high dose rats [2/20] than the control group [7/20] which may partially explain the decrease in weight, but no adverse histological changes were observed. It is unlikely that the decreased prostate and uterus weights represent an adverse effect of phenol treatment because: 1) the lack of a dose-response relationship; 2) there is an absence of any functional reproductive effects [other than associated with decreased body weight at the top dose due to the decrease in water consumption]; 3) there is an absence of any adverse histological changes in these reproductive organs and 4) only a few animals had organ weights outside the range of the concurrent control values.

Based on a comprehensive examination of all the parameters, the no-observed-adverse-effect level [NOAEL] of phenol in drinking water is 1000 ppm, based on decreased pup survival at the 5000 ppm concentration [which may be related to flavor aversion]. The daily intake of phenol in adult rats at 1000 ppm was estimated to be about 70 mg/kg for males, and about 93 mg/kg for females.

V. QUALITY ASSURANCE STATEMENT

Study Title: Two-Generation Oral (Drinking Water) Reproductive Toxicity Study of Phenol in Rats

Project Number: L08657

Study Number: 2

Study Director: Bernadette Ryan, Ph.D., D.A.B.T.

This study has been inspected and the report audited by the IITRI Quality Assurance Unit in accordance with U.S. Environmental Protection Agency (EPA; TSCA) Good Laboratory Practice (GLP) Standards, CFR Title 40 Section 792.35. The report describes the methods and procedures used in the study and the reported results accurately reflect the raw data of the study.

The following are the inspection dates, and the dates inspection findings were reported:

	Findings Reported to:	
Date of Inspection	Study Director	Management
October 20, 1997	October 21, 1997	October 21, 1997
October 21, 1997	October 21, 1997	October 21, 1997
November 10, 1997	November 10, 1997	November 10, 1997
November 11, 1997	November 11, 1997	November 11, 1997
November 14, 1997	November 14, 1997	December 3, 1997
November 20, 1997	November 20, 1997	November 20, 1997
December 30, 1997	December 30, 1997	December 30, 1997
January 20, 1998	January 20, 1998	January 20, 1998
January 22, 1998	January 22, 1998	January 22, 1998
January 23, 1998	January 23, 1998	January 23, 1998
February 5, 1998	February 5, 1998	February 5, 1998
February 10, 1998	February 10, 1998	February 10, 1998
February 11, 1998	February 11, 1998	February 11, 1998
February 13, 1998	February 13, 1998	February 13, 1998
February 16, 1998	February 16, 1998	February 16, 1998
February 19, 1998	February 19, 1998	February 19, 1998
February 20, 1998	February 20, 1998	February 20, 1998
February 23, 1998	February 23, 1998	February 23, 1998
February 24, 1998	February 24, 1998	March 11, 1998
March 6, 1998	March 6, 1998	March 6, 1998
March 25, 1998	March 25, 1998	March 25, 1998
April 10, 1998	April 10, 1998	April 10, 1998
May 13, 1998	May 13, 1998	May 13, 1998
June 2, 1998	June 2, 1998	June 2, 1998
June 3-4, 1998	June 4, 1998	June 4, 1998
June 5, 1998	June 5, 1998	June 5, 1998

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V. QUALITY ASSURANCE STATEMENT (Cont.)

	Findings Reported to:	
Date of Inspection	Study Director	Management
June 15-16, 1998	June 16, 1998	June 16, 1998
June 17, 1998	June 17, 1998	June 17, 1998
June 19, 1998	June 19, 1998	June 19, 1998
June 25, 26, and 29, 1998	June 29, 1998	June 29, 1998
June 26, 1998	June 26, 1998	June 26, 1998
June 30, 1998	June 30, 1998	June 30, 1998
July 7, 1998	July 7, 1998	February 9, 1999
July 17, 1998	May 13, 1999	May 13, 1999
July 27, 1998	May 13, 1999	May 13, 1999
August 4, 1998	August 4, 1998	September 8, 1998
September 17, 1998	September 17, 1998	May 13, 1999
November 23-25, 30 and December 1-4, 1998	December 4, 1998	May 13, 1999
December 13, 1998 to January 20, 1999	December 14, 1998 to January 20, 1999	May 13, 1999
January 27-28, 1999	January 28, 1999	May 13, 1999
January 30, 1999	February 1, 1999	May 13, 1999
January 30, February 1, 1999	February 1, 1999	May 13, 1999
January 26-27, 1999, February 2-3, 1999	February 3, 1999	May 13, 1999
February 4, 1999	February 15, 1999	May 13, 1999
February 8, 9, 12, 15, 1999	February 15, 1999	May 13, 1999
May 11-14, 1999	May 14, 1999	May 19, 1999
May 19, 1999	May 19, 1999	June 7, 1999
June 7, 1999	June 7, 1999	June 9, 1999

R. A. Boyne 6-10-99

Ronald A. Boyne, B.S. Date
Manager, Quality Assurance

VI. TABLES