NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 206

# CARCINOGENESIS BIOASSAY OF 1,2-DIBROMO-3-CHLOROPROPANE (CAS NO. 96-12-8) IN F344 RATS AND B6C3F$_1$ MICE (INHALATION STUDY)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NTP Technical Report

on the

# CARCINOGENESIS BIOASSAY

of

# 1,2-DIBROMO-3-CHLOROPROPANE

(CAS NO. 96-12-8)

IN F344 RATS AND B6C3F$_1$ MICE

(INHALATION STUDY)


National Toxicology Program
Research Triangle Park
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March 1982

NTP-81-21
NIH Publication No. 82-1762

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

## NOTE TO THE READER

This is one in a series of experiments designed to determine whether selected chemicals produce cancer in animals. Chemicals selected for testing in the NTP carcinogenesis bioassay program are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical is a potential hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

This study was initiated by the National Cancer Institute's Carcinogenesis Testing Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program.

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Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to communicate any mistakes to the Deputy Director, NTP (P.O. Box 12233, Research Triangle Park, NC 27709), so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP.

TABLE OF CONTENTS



TABLES

FIGURES

## ABSTRACT

A carcinogenesis bioassay of technical grade 1,2-dibromo-3-chloropropane (DBCP), which contained trace amounts of epichlorohydrin and 1,2-dibromoethane, was conducted by exposing groups of 50 F344 rats and B6C3F1 mice of each sex by inhalation to concentrations of 0.6 or 3.0 ppm DBCP for 6 hours per day, 5 days per week, for 76 to 103 weeks. Untreated chamber controls consisted of 50 rats and 50 mice of each sex. Surviving high-dose rats were killed at week 84. Surviving high-dose female mice and low- and high-dose male mice were killed at week 76. Low-dose rats and female mice were killed at week 104.

Accelerated mortality occurred in the high-dose groups of both species. Early deaths of high-dose rats and mice were associated with respiratory tract tumors. Interference with breathing and metastasis to the brain were major contributing factors in these deaths. Among male mice, accelerated mortality occurred in low-dose and control groups as well as in the high-dose group. Urogenital infection appeared to be associated with these deaths.

Carcinomas, squamous-cell carcinomas, and adenocarcinomas of the nasal cavity and squamous-cell papillomas of the tongue each occurred in high-dose male rats at incidences significantly higher than those in the corresponding controls. Adenocarcinomas, adenomas, adenomatous polyps, and squamous-cell papillomas of the nasal cavity and adenomatous polyps of the nasal turbinates occurred in low-dose male rats with significantly increased incidences relative to controls.

Carcinomas and adenocarcinomas of the nasal cavity, squamous-cell papillomas of the tongue, squamous-cell papillomas and carcinomas (combined) of the pharynx, and adenomas of the adrenal cortex each occurred in high-dose female rats at incidences significantly higher than those in the corresponding controls. Also, adenomas and squamous-cell papillomas of the nasal cavity, adenomas of the adrenal cortex, and fibroadenomas of the mammary gland were increased significantly in low-dose female rats when compared with controls.

Adenocarcinomas of the nasal cavity in high-dose female mice, papillary carcinomas in low-dose female mice, and carcinomas, squamous cell carcinomas of the nasal cavity, and alveolar/bronchiolar adenomas or carcinomas of the lung in high-dose male and female mice occurred at incidences significantly higher than those in the corresponding controls.

Exposure to DBCP vapor was also associated with toxic tubular nephropathy in rats and mice of either sex and with proliferative changes in the nasal mucosa, lung, and forestomach in mice.

Under the conditions of this bioassay, DBCP was carcinogenic for male and female F344 rats, inducing increased incidences of nasal cavity tumors and tumors of the tongue in both sexes, and cortical adenomas in the adrenal glands of females. DBCP was carcinogenic in male and female B6C3F1 mice, inducing increased incidences of nasal cavity tumors and lung tumors.

## CONTRIBUTORS

This bioassay of 1,2-dibromo-3-chloropropane was conducted from August 1976 to August 1978 by Hazleton Laboratories America, Inc., Vienna, Virginia, initially under direct contract to NCI and subsequently under a subcontract to Tracor Jitco, Inc., Rockville, Maryland, prime contractor for the NTP Carcinogenesis Testing Program.

The persons responsible for selecting the protocols used in this bioassay were Drs. O. G. Fitzhugh (1,2), C. Wessel (1,3), N. Page (4,5), and C. Cueto (1,6), and representatives of Shell Oil Company, Dow Chemical Company, and The Ethyl Corporation participated in the dose selection. The principal investigators were Drs. M. B. Powers (7,4), R. W. Voelker (8), and W. B. Coate (8). Ms. K. J. Petrovics (8) was responsible for data management, and Mr. R. Hardy (8) was the supervisor of animal care. Histopathologic examinations were performed by Dr. B. Ulland (8). The pathology report and selected slides were evaluated by the NCI Pathology Working Group as described by Ward et al. (1978). The diagnoses represent a consensus of contracting pathologists and the NCI Pathology Working Group, with final approval by the NCI Pathology Working Group.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (9). Statistical analyses were performed by Dr. J. R. Joiner (1) and Ms. S. Vatsan (1), using methods selected for the bioassay program by Dr. J. J. Gart (10).

Chemicals used in this bioassay were analyzed at Midwest Research Institute (11), and concentrations of the test chemical in the exposure chambers were monitored at Hazleton Laboratories under the direction of Dr. W. B. Coate (8).

This report was prepared at Tracor Jitco in collaboration with Hazleton Laboratories and reviewed by NCI/NTP. Those responsible for the report at Tracor Jitco (1) were Dr. L. A. Campbell, Acting Director of the Bioassay Program; Dr. S. S. Olin, Associate Director; Dr. M. A. Stedham, pathologist; Dr. D. J. Beach, reports manager; Dr. A. C. Jacobs, bioscience writer; and Dr. W. D. Theriault and Ms. M. W. Glasser, technical editors.

The following scientists at NCI/NTP (4) were responsible for evaluating the bioassay, interpreting the results, and reporting the findings: Dr. J. Fielding Douglas, Dr. Richard A. Griesemer, Dr. Charles K. Grieshaber, Dr. Larry Hart, Dr. Joseph Haseman, Dr. James E. Huff, Dr. William Kluwe, Dr. Mary R. Kornreich, Dr. Ernest E. McConnell, Dr. John A. Moore, Dr. Michael Shelby, Dr. Sherman F. Stinson, Dr. Raymond Tennant, and Dr. Jerrold M. Ward.

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## SUMMARY OF PEER REVIEW COMMENTS

On June 27, 1980, this report underwent peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting began at 9 a.m. in Room 1331, Switzer Building, 330 C Street, S.W., Washington, D.C.

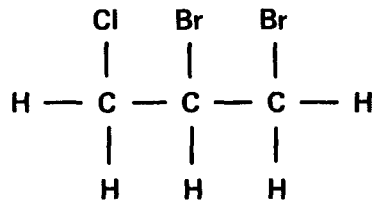
Dr. Harper, a principal reviewer for the report on the inhalation bioassay of 1,2-dibromo-3-chloropropane (DBCP), agreed with the conclusion that, under the conditions of the bioassay, DBCP was carcinogenic for rats and mice. DBCP induced tumors of the nasal cavity and tongue in male and female rats and induced squamous-cell papillomas or carcinomas in the pharynx and cortical adenomas in the adrenal glands of female rats. DBCP induced alveolar/bronchiolar adenomas or carcinomas and tumors of the nasal cavity in male and female mice.

The second principal reviewer, Dr. Shore, also agreed with this conclusion. He commented on the testicular degeneration (in this study, 1/50 control; 8/50 low dose; 4/48 high dose) and atrophy in exposed rats and the possible relation of this toxicity to aspermia reported in humans. He noted that without the early mortality in the high-dose groups the positive results would probably have been enhanced further.

Dr. Shore observed that the technical grade of DBCP used in the study contained two probable carcinogens as contaminants: epichlorohydrin and 1,2-dibromoethane. Some minor co-carcinogenic effect of these contaminants could not be ruled out. [The DBCP used in this study was 96% pure].

Dr. Harper moved that the report on the inhalation bioassay of dibromochloropropane be accepted with modifications. Dr. Shore seconded the motion and the report was approved unanimously by the Peer Review Panel.

# I. INTRODUCTION



## 1, 2-DIBROMO-3-CHLOROPROPANE

(Dibromochloropropane, Nemagon, Fumazone)

Percentage Composition: C 15.2%, H 2.1%, Br 67.6%, Cl 15.0%

Molecular Formula: $C_3H_5Br_2Cl$

Molecular Weight: 236.4

CAS No. 96-12-8

1,2-Dibromo-3-chloropropane (DBCP), a contaminant (0.05%) of the flame retardant tris(2,3-dibromopropyl)phosphate (Blum and Ames, 1977), has been used primarily as a soil fumigant to control nematodes (Kirk-Othmer, 1964). Unlike other halogenated nematocides, DBCP can be applied to soil without damaging growing perennials (Kirk-Othmer, 1964). Since it is slightly soluble in water at the concentrations used (30 ppm), DBCP can be either injected directly into the soil or added to irrigation water (Kirk-Othmer, 1964). By 1972, an estimated 12.3 million pounds were being used annually (NIOSH, 1977; Federal Register, 1977a); in 1977, a total of 832,000 pounds were used in California, mostly on grapes and tomatoes (IARC, 1979a).

Formulations of DBCP were registered as fumigant nematocides for numerous vegetable, fruit, nut, and ornamental crops in 1964. Tolerances, ranging from 5 to 125 ppm, were set for residues of inorganic bromide but not for organic bromide residues (Code of Federal Regulations, 1977). Residues of DBCP have been found in carrots (1.5 ppm) and radishes (0.2 ppm) grown in soil fumigated with the nematocide (Newsome, et al., 1977).

Altered testicular function has been found in employees in several plants producing or formulating DBCP (Federal Register, 1977a; Whorton et al., 1979; Biava et al., 1978; and Marshall et al., 1978). Low sperm counts (less than

1,000,000/ml compared with a normal value of 40,000,000/ml) were first found in workers exposed to DBCP in 1977 (Whorton, 1977). Some workers had sperm counts of zero. Later that year, the United States Environmental Protection Agency suspended registration of pesticide products containing DBCP for use on 19 fruits and vegetables (Federal Register, 1977b), but use of DBCP on soybeans, citrus fruits, grapes, and nuts was retained. The air standard established for the workplace by OSHA is 10 ppb in air as an 8-hour time-weighted-average value (Federal Register, 1977c). Although California banned the application of DBCP in 1977, the nematocide was still used in Arizona, Florida, Hawaii, Texas, and South Carolina. Two years after the California ban, residues of DBCP (at concentrations averaging 5 ppb) were found in wells in the San Joaquin Valley (Richards, 1979). By October 1979, DBCP could be used only on pineapple crops (EPA, 1979); in March 1981, EPA announced that manufacturers had agreed to stop making and using the compound, except for Hawaiian pineapples.

Kodama and Dunlap (1956) reported that the toxicity of DBCP by inhalation was dependent on the duration of exposure as well as on the concentration and found that the inhalation $LC_{50}$'s for rats were 369, 232, 154, or 103 ppm, respectively, at 1, 2, 4, or 8 hours (Table 1). Reported effects include: gross lesions in the lungs, intestinal mucosa, kidneys, and testes; growth retardation; severe atrophy and degeneration of the testes; decreased sperm count and motility, and prolonged estrus cycle (Torkelson et al., 1961; Kodama and Dunlap, 1956; Reznik and Sprinchan, 1975; and Rakhmatullaev, 1971) in short-term studies of rats, guinea pigs, and rabbits exposed to DBCP by inhalation or gavage.

As reported in an abstract, Lipscomb et al. (1977) described the covalent binding of radioactivity to nucleic acids following intraperitoneal administration of $^{14}C$-DBCP to rats. However, the relative impurity of the labelled material (89% radiochemically pure; Weisberger, 1980) used in this study precludes an assessment of the ability of pure DBCP to interact with genetic macromolecules.

Two metabolites, 5-(2,3-dihydroxypropyl)cysteine and 1,3-(bis-cysteinyl) propan-2-ol, have been identified in rat urine following intraperitoneal injection of DBCP (Jones et al., 1979), suggesting the conjugation of

Table 1. Effects of Exposing Animals by the Inhalation or Gavage Routes to 1,2-Dibromo-3-chloropropane

| Route of Administration | Species | Number/Sex | Concentration and Duration | Effects | Reference |
|---|---|---|---|---|---|
| Inhalation | Rats (Long-Evans) | 15M | | $LC_{50}$ (calculated)= 369 ppm/1hr | Kodama and Dunlop, 1956 |
| " | " | 15M | | $LC_{50}$ (calculated)= 232 ppm/2hr | Kodama and Dunlop, 1956 |
| " | " | 15M | | $LC_{50}$ (calculated)= 154 ppm/4hr | Kodama and Dunlop, 1956 |
| " | " | 15M | | $LC_{50}$ (calculated)= 103 ppm/8hr | Kodama and Dunlop, 1956 |
| " | " | 15M | 20 or 50 ppm x 50 over 10 wk | Growth retardation | Kodama and Dunlop, 1956 |
| " | " | 20M, 20F | 12 ppm x 50 over 70-92 d | Mortality for 40% of males and 50% of females; severe atrophy and degeneration of testes | Torkelson et al., 1961 |
| " | " | 15M | 0, 5, 10, 20 or 40 ppm x 50 over 70 d | Gross lesions in lungs, intestinal mucosa, kidneys, and testes at 10 ppm or greater | Torkelson et al., 1961 |
| " | Guinea pigs | 10M, 10F | 12 ppm, 50 x over 70-92 d | Severe atrophy and degeneration of testes | Torkelson et al., 1961 |
| " | Rabbits | 3M, 3F | 12 ppm, 50 x over 70-92 d | Severe atrophy and degeneration of testes | Torkelson et al., 1961 |
| Gavage | Rats (albino) | 7M | 5, 0.5, 0.05, or 0.005 mg/kg daily/8 mos. | Decreased motility time of spermatozoa at 5 mg/kg | Rakhmatullaev, 1971 |
| " | Rats | 95M, 95F | 100 mg/kg (single dose) | Decreased sperm count and prolonged estrus cycle | Reznik and Sprinchan, 1975 |
| " | " | 95M, 95F | 10 mg/kg daily/4-5 mos. | Decreased sperm count and prolonged estrus cycle | Reznik and Sprinchan, 1975 |

electrophilic metabolites with endogenous glutathione. The same urinary metabolites were observed after administration of epichlorohydrin and epibromohydrin, two proposed epoxide intermediates of DBCP metabolism.

The direct mutagenic activity of technical grade DBCP in bacterial systems (Rosenkranz, 1975) can be attributed to contamination with epichlorohydrin (Biles et al., 1978), a direct acting bacterial mutagen. Several investigators, however, have reported the mutagenic effects of DBCP in Salmonella typhimurium following metabolic activation with rat liver S9 (TA 1535, Biles et al., 1978; TA 1530, Rosenkranz, 1975; TA 100, Blum and Ames, 1977). Because epichlorohydrin is used as a stabilizer in DBCP, investigators must specify the purity of DBCP samples studied.

The genetic effects of DBCP in mammalian germ cells have been reported for rats, mice, and humans. Lee and Suzuki (1979) detected unscheduled DNA synthesis in the premeiotic germ cells (but not spermatozoa) of mice given a maximum tolerated dose (100 mg/kg) intraperitoneally. DBCP was also reported to induce dominant lethal mutations in rats (highest dose, 50 mg/kg) but not in mice at a high dose of 150 mg/kg (Teramoto et al., 1980). The dominant lethal effects in rats were observed in postmeiotic cells, particularly spermatids.

In a study of 18 chemical workers exposed to DBCP (Kapp et al., 1979), 16 showed a significantly higher frequency of sperm with 2 fluorescent YF bodies than was observed among 15 control workers. (The report does not state whether the workers were exposed to other chemicals.) Two YF bodies in the sperm indicate but do not prove the presence of two Y chromosomes instead of the normal one. Kapp et al. (1979) propose that exposure to certain chemicals interferes with the meiotic process and leads to germ cells with abnormal chromosome numbers, such as those with two Y chromosomes.

The available data indicate that DBCP can be metabolized by rat liver S9 to form a bacterial mutagen. DBCP or its metabolites are apparently distributed to the testes and can induce genetic damage as reflected by dominant lethal mutations and unscheduled DNA synthesis in premeiotic germ cells of rodents and perhaps by an increase in Y-chromosomal nondisjunction in humans.

DBCP was given by gavage on days 6 to 15 of gestation to Wistar rats. No teratogenic effects were observed from doses of 0, 12.5, 25, or 50 mg/kg;

yet DBCP was fetotoxic and caused a significant decrement in maternal weight gain at the two highest doses (Ruddick and Newsome, 1979).

The mechanism of DBCP toxicity in F344 rats is currently being investigated by the NTP, with emphasis on gonadal toxicity and carcinogenicity, and on developing improved methodologies for monitoring exposed populations for deleterious effects.

In other carcinogenesis studies on the related chemical 1,2-dibromoethane (NCI, 1978b; NTP, 1982), results showed that this chemical was carcinogenic by two routes. Administered by gavage to Osborne-Mendel rats, 1,2-dibromoethane produced squamous-cell carcinomas of the forestomach (in males and females), hepatocellular carcinomas (in females), and hemangiosarcomas (in males). Administration of 1,2-dibromoethane by the same route to B6C3F1 mice produced squamous-cell carcinomas of the forestomach and alveolar/bronchiolar adenomas in both sexes. When administered to F344 rats by inhalation, 1,2-dibromoethane produced a variety of nasal cavity tumors in males and females, hemangiosarcomas of the circulatory system and mesotheliomas in the tunica vaginalis in males, and mammary gland fibroadenomas in females. Administered by inhalation to B6C3F1 mice, 1,2-dibromoethane produced alveolar/bronchiolar carcinomas and adenomas in males and females and hemangiosarcomas of the circulatory system, subcutaneous fibrosarcomas, tumors of the nasal cavity, and mammary gland adenocarcinomas in females.

1,2-Dibromo-3-chloropropane (technical grade) was carcinogenic by gavage to Osborne-Mendel rats and B6C3F1 mice, causing squamous-cell carcinomas of the forestomach in both sexes of both species and adenocarcinomas of the mammary gland in female rats (Olson et al., 1973; Powers et al., 1975; NCI, 1978a).

1,2-Dibromo-3-chloropropane (technical grade) was retested by the Bioassay Program, this time using the inhalation route. Since workers are exposed to airborne DBCP, it was considered important to determine effects by this route.

## II. MATERIALS AND METHODS

### A. Chemical

Technical grade 1,2-dibromo-3-chloropropane (dark brown liquid) -- CAS No. 96-12-8 -- was obtained from Shell Chemical Company, San Ramon, California, as a single batch (Lot No. 7). The DBCP used in the gavage study was also obtained from Shell Chemical Company but from a different batch (NCI, 1978). Purity and identity analyses were performed at Midwest Research Institute, Kansas City, Missouri (Appendix E).

Results of elemental analyses agreed with the theoretical values, and the infrared spectrum was consistent with the reference spectrum (Sadtler Standard Spectra). The major peaks of the nuclear magnetic resonance spectrum also were consistent with the reference spectrum (Sadtler Standard Spectra); impurity peaks were observed in the ranges of 0.90-3.73 ppm and 4.58-6.54 ppm (Appendix E).

The results of vapor-phase chromatography in one system indicated the presence of seven impurities with areas 2.2%, 1.0%, 0.4%, 0.4%, 0.3%, 0.1%, and 0.06% of the major peak; results of vapor-phase chromatography in a second system indicated the presence of four impurities with areas 0.6%, 0.3%, 0.07%, and 0.05% of the major peak. The results generally agreed with the purity and analysis reported by Shell: DBCP, 96%; allyl chloride, 0.7%; epichlorohydrin, 0.8%; and heavy ends (residue), 2.5% (written communication from Shell to Hazleton Laboratories, 1976).

In additional tests at Midwest Research Institute, the residual chemical remaining in the generation flask after 4 weeks was analyzed and compared with a sample that had the same lot number and had been stored at Hazleton Laboratories (Appendix F). Vapor-phase chromatography/mass spectrometry with one system detected 20 impurities in the residue sample. Four of these were too weak for investigators to obtain good spectra. Mass spectra were reported for the other impurities. The two largest impurities could not be identified. A tentative assignment of some of the clusters in the fragmentation pattern indicated that they were also bromochloropropanes. The impurities that were identified, and their area percent in the sample stored

at Hazleton and in the residue from the generation flask used in DBCP inhalation studies, are presented in Table 2.

B. Generation of DBCP Air Mixtures

Metered, filtered, dried air, regulated at 10 psi, was bubbled through liquid DBCP in a 1,000-ml glass globe flask that contained at least 500 ml of the test chemical and that was wrapped with black tape to reduce light exposure. It was then forced into the inhalation chambers through 8 feet of 1/4 inch (inside diameter) Teflon® tubing attached to the make-up air input duct. Each chamber had a separate flask and generation system. Each flask was located in a Plexiglas® box and equipped with an air line attached to its chamber exhaust duct and thus was under negative pressure with respect to the chamber room.

Before animal exposures began, a Royco Model 230 Photometer was used to assess the presence of aerosol during DBCP vapor generation. No aerosol was detected. Actual concentrations of DBCP in each inhalation chamber were determined 4 times per day by analyzing samples obtained from a closed-loop system sample line with a gas syringe. The gas samples were discharged into 15-ml test tubes containing 1.0 ml isopropanol. Aliquots of the mixed isopropanol solutions were injected directly into a Varian 600-D gas chromatograph equipped with an electron capture detector. Standards of 1,2-dibromo-3-chloropropane were prepared daily and used for calibration of the gas chromatograph.

The inhalation chambers were continuously monitored using an HNU Systems Model P1201 analyzer (HNU Systems Inc., Newton Upper Falls, Mass.) to detect fluctuations from the target concentrations occurring within the day.

The measured chamber concentrations were usually within 10% of the desired target concentrations. The mean of 102 weekly mean vapor concentrations for the low-concentration chamber was $0.592 \pm 0.08$ ppm (range 0.40-1.05 ppm) compared with a target concentration of 0.6 ppm. For the high-concentration chamber, the mean of 84 weekly mean chamber concentrations was $2.87 \pm 0.42$ ppm (range 1.57-3.83 ppm) compared with target concentration of 3.0 ppm (Appendix G).

Table 2. Impurities Identified in a Stored Sample of DBCP and in the Residue from the DBCP Generation Flask

| Impurity | Area Percent | |
|---|---|---|
| | Stored Sample | Residue |
| System 1(a) | | |
| Epichlorohydrin | 0.7 | 0.04 |
| Dibromoethane | <0.7 (unresolved shoulder) | 0.004 |
| 1-Chloro-3-bromopropane | <0.4 | 0.1 |
| 2-Bromo-1,2-dichloropropane | No discrete peak in either sample (Probably an unresolved shoulder) | |
| 2-3-Dibromo-1-propanol | No discrete peak in either sample with flame ionization detection | |
| System 2(a) | | |
| 3-(or 1- or 2-)Chloropropene | 0.7 | 0.02 |
| 1,2-Dichlorpropane | Not detected (<0.01) | Not detected (<0.01) |
| Epichlorohydrin | 0.6 | Not detected (<0.01) |
| 1,2-Dibromoethane | 0.07 | Not detected (<0.01) |
| 1,1,1-Trichloro-3-bromopropane | 0.2 | 0.3 |

(a) Conditions for System 1 and System 2 are described in Appendix F.

## C. Animals

Four- to five-week-old F344 rats and 3- to 4-week-old B6C3F1 mice were obtained from the NCI Frederick Cancer Research Center, Frederick, Maryland, marked for individual identification, and then assigned to dosed or control groups according to a published table of random permutations. All animals were housed and observed in their chambers for 1 week before the start of the bioassay. The control groups were shared with an inhalation study of 1,2-dibromoethane that started 2 weeks earlier.

## D. Animal Maintenance

Male rats were housed three per cage, female rats were housed four per cage, and mice were housed four per cage in stainless steel wire mesh cages that were suspended in three tiers on aluminum racks inside the inhalation chambers. Rats were on the top two tiers and mice on the bottom tier. Waste collection pans were placed beneath the two top tiers to catch urine, feces, and dropped food.

Animal cages (Hoeltge, Cincinnati, Ohio) were changed once per month initially and later twice per month (at the same time that the animals were weighed). Soiled cages were sanitized in an industrial cage washer at 99°C using Acclaim® (Economics Laboratories). Water bottles were sanitized weekly in a bottle washer. The inhalation chambers and waste pans were flushed daily with tap water after the animals had been removed from the chambers. The chambers were washed with Zep® Formula 7961 (Zep Manufacturing Company) initially once per month and later twice per month while the animals were being weighed. The chamber room floor was hosed down with tap water and dried with a squeegee daily.

The food (Wayne® Lab Blox, Allied Mills, Inc., Chicago, Ill.) was placed in the chambers 1 hour after the end of the DBCP exposure period each weekday and was removed the following morning before the start of the exposure period. Used feed was incinerated. Food was available ad libitum on weekends. Water was available from water bottles equipped with stainless steel sipper tubes. Water bottles were changed once per week. The animals lived in the inhalation chambers continuously, except when being weighed or

observed. Animals in the control groups lived in identical inhalation chambers in the same room and were exposed to charcoal- and HEPA-filtered, conditioned air. The temperature was maintained at $22.2^{\circ}\pm1^{\circ}C$ and the humidity at 50%. Fluorescent light was provided 12 hours per day.

Airflow into the cubical glass and stainless steel inhalation chambers ($6\ m^3$) was maintained at 1,000 liters per minute and was monitored by flow calibrated Magnehelic® or Photohelic® pressure gauges. Entering air was drawn through HEPA filters (Cambridge®) and charcoal beds immediately before being mixed with DBCP vapor. Exhaust air was filtered through two 6-inch charcoal beds before entering a dilution system and exiting the building via a stack. The chambers were maintained under negative pressure relative to the chamber rooms by individual positive-displacement exhaust pumps (Roots).

## E. Subchronic Studies

Subchronic inhalation studies were conducted using F344 rats and B6C3F1 mice to determine the concentrations of DBCP vapor to be used in the chronic studies. Groups of 5 male rats, 5 female rats, 8 to 10 male mice, and 10 or 12 female mice were exposed to DBCP in air at concentrations of 1, 5, or 25 ppm for 6 hours per day, 5 days per week for 13 weeks. Animals were observed twice daily for mortality and for signs of toxicity or abnormal behavior. Individual animal weights were recorded weekly. After 13 weeks, all surviving animals were killed by intraperitoneal injections of sodium pentabarbital (Diabutal®, Diamond Laboratories, Inc., Des Moines, Iowa) and necropsied. Representative tissues were examined microscopically as described in the section on chronic studies. The concentrations administered, survival, and mean body weights of the exposed and control groups are shown in Tables 3 and 4.

RATS: One male exposed to 25 ppm was killed when moribund. Of the five female rats exposed to 25 ppm, two died and two were killed when moribund. Male and female rats exposed to 25 ppm lost weight, had blood stains around the nasal area and mouth throughout the 13 weeks, and had severe hair loss (33% to 95% of body surface area).

Table 3. Exposure Concentrations, Survival, and Mean Body Weights of Rats Exposed by Inhalation to 1,2-Dibromo-3-chloropropane for 90 Days

| Concentration(a) (ppm) | Survival(b) | Mean Body Weights (grams) Initial | Final | Gain | Weight Change(c) Relative to Controls (%) |
|---|---|---|---|---|---|
| Male | | | | | |
| 0 | 5/5 | 153.2 | 343.8 | 190.6 | |
| 1 | 5/5 | 139.8 | 254.4 | 114.6 | -40 |
| 5 | 5/5 | 101.6 | 279.6 | 178.0 | -7 |
| 25 | 4/5 | 137.2 | 136.8 | -.4 | -100 |
| Female | | | | | |
| 0 | 5/5 | 115.0 | 172.8 | 57.8 | |
| 1 | 5/5 | 118.6 | 173.4 | 54.8 | -5 |
| 5 | 5/5 | 105.8 | 170.6 | 64.8 | +12 |
| 25 | 1/5 | 115.4 | 107.2 | -8.2 | -114 |

(a) Exposure was 6 hours per day, 5 days per week.
(b) Number surviving/number per group.
(c) Weight change relative to controls =

$$\frac{\text{Weight Gain (Dosed Group)} - \text{Weight Gain (Control Group)}}{\text{Weight Gain (Control Group)}} \times 100$$

Table 4. Exposure Concentrations, Survival, and Mean Body Weights of Mice Exposed by Inhalation to 1,2-Dibromo-3-chloropropane for 90 Days

| Concentration(a) (ppm) | Survival(b) | Mean Body Weights (grams) Initial | Final | Gain | Weight Change(c) Relative to Controls (%) |
|---|---|---|---|---|---|
| Male | | | | | |
| 0 | 10/10 | 17.4 | 31.7 | 14.3 | |
| 1 | 9/9 | 25.5 | 32.3 | 6.8 | -52 |
| 5 | 8/8 | 16.9 | 29.6 | 12.7 | -11 |
| 25 | 6/10 | 21.7 | 26.2 | 4.5 | -69 |
| Female | | | | | |
| 0 | 10/10 | 16.6 | 24.7 | 8.1 | |
| 1 | 10/10 | 22.1 | 24.1 | 2.0 | -75 |
| 5 | 11/12 | 17.3 | 24.2 | 6.9 | -15 |
| 25 | 10/10 | 18.2 | 24.8 | 6.6 | -19 |

(a) Exposure was 6 hours per day, 5 days per week.
(b) Number surviving/number per group.
(c) Weight change relative to controls =

$$\frac{\text{Weight Gain (Dosed Group)} - \text{Weight Gain (Control Group)}}{\text{Weight Gain (Control Group)}} \times 100$$

The compound-related effects in rats receiving 25 ppm were meningoencephalitis (4/5 females and 1/5 males), vacuolation or necrosis of the adrenal (3/5 males and 3/5 females), focal necrosis of the liver accompanied by hepatic regeneration (5/5 males and 5/5 females), tubular nephrosis of the kidney accompanied by megalocytosis (5/5 males and 5/5 females), necrosis of the trachea and bronchial epithelium and/or squamous metaplasia of the mucosa accompanied by regeneration and hyperplasia of the bronchial epithelium (3/5 males and 4/5 females), atrophy of testes with hypospermatogenesis (3/5 males), hypocellularity of bone marrow (5/5 males and 5/5 females), and thymic atrophy with lymphoid depletion (4/5 males and 3/5 females). Hydropic changes of hepatocytes were found in male rats exposed to 1 or 5 ppm and nephrosis was found in both male and female rats exposed to 1 or 5 ppm. Additional subsequent pathologic examinations revealed inflammatory, necrotizing, and proliferative lesions in the epithelium of the nasal cavity of high-dose animals. The severity of these lesions was dose related.

The concentrations selected for the chronic studies with rats were 0.6 and 3.0 ppm.

MICE: Four of the 10 male mice exposed to 25 ppm and 1/12 female mice exposed to 5 ppm died. A compound-related depression in weight gain occurred in all exposed mice. Hydropic changes of hepatocytes and nephrosis were found in male mice exposed to 25 ppm and necrosis of the bronchiolar epithelium was found in both male and female mice exposed to 25 ppm. Regeneration and hyperplasia of the bronchiolar epithelium and megalocytic epithelial cells were found in all 20 of the mice exposed to 5 ppm. Additional subsequent pathologic examinations revealed lesions in the epithelium of the nasal cavity of mice exposed to 25 ppm. Inflammatory, necrotizing, and proliferative lesions were among the types found. The severity of these lesions was dose related.

The exposure levels selected for the chronic studies with mice were 0.6 and 3.0 ppm.

## F. Chronic Studies

The test groups, doses administered, and durations of the chronic studies are shown in Table 5.

## G. Clinical Examinations and Pathology

Animals were observed twice daily. Examinations of animals for clinical signs and the presence of palpable masses were recorded weekly. Animals were initially weighed monthly and then twice monthly beginning at week 80.

Moribund animals and those that survived to the end of the study were killed and necropsied following anesthetization by intraperitoneal injections of sodium pentobarbital (Diabutal®, Diamond Laboratories, Inc., Des Moines, Iowa).

Gross and microscopic examinations were performed on all major tissues, organs, and gross lesions. The following tissues and organs were taken from killed animals and, where feasible, from animals found dead unless precluded in whole or part by autolysis or cannibalization: brain, pituitary, lymph nodes (cervical and mesenteric), spleen, thyroid, parathyroid, salivary glands, lung, trachea, heart, diaphragm, stomach, duodenum, jejunum or ileum, large intestine, pancreas, adrenal, kidney, liver, skin, ovary or testis, urinary bladder, prostate or uterus, and femur. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, routinely stained with hematoxylin and eosin, and examined histopathologically. An occasional section was subjected to special staining techniques for more definitive diagnosis.

Since the nasal cavity was a major target tissue, special processing was conducted. The nasal cavity and sinuses were fixed whole in neutral buffered 10% formalin and/or in Bouin's solution and were decalcified using Perenyi's method. Step cuts were made from the nostril to the cranial vault to ensure adequate tissue sampling and visualization of the extent of tumor.

The number of animals from which particular organs or tissues were examined microscopically varies and does not necessarily represent the number of animals that were placed on study in each group.

Table 5. Experimental Design of Chronic Inhalation Studies with 1,2-Dibromo-3-Chloropropane in Rats and Mice

| Test Group | Initial No. of Animals | Concentration(a) (ppm) | Time on Study: Exposed (weeks) | Time on Study: Observed (weeks) |
|---|---|---|---|---|
| Male Rats | | | | |
| Untreated Control (b) | 50 | 0 | 0 | 105-107 |
| Low-Dose | 50 | 0.6 | 103 | 1 |
| High-Dose | 50 | 3.0 | 84 | 0-1 |
| Female Rats | | | | |
| Untreated Control (b) | 50 | 0 | 0 | 105-107 |
| Low-Dose | 50 | 0.6 | 103 | 1 |
| High-Dose | 50 | 3.0 | 84 | 0-1 |
| Male Mice | | | | |
| Untreated Control (b) | 50 | 0 | 0 | 80 |
| Low-Dose | 50 | 0.6 | 76 | 0-1 |
| High-Dose | 50 | 3.0 | 76 | 0-1 |
| Female Mice | | | | |
| Untreated Control (b) | 50 | 0 | 0 | 105-107 |
| Low-Dose | 50 | 0.6 | 103 | 1 |
| High-Dose | 50 | 3.0 | 76 | 0-1 |

(a) Rats and mice were exposed to DBCP vapor 6 hours per day, 5 days per week.

(b) Untreated control groups were shared with an inhalation study of 1,2-dibromoethane that started 2 weeks previously (NTP, 1982).

## H. Data Recording and Statistical Analyses

Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. One-tailed P values are reported for all tests except the departure from linearity test, which is reported only when its two-tailed P value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been presented as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site is examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) before histologic sampling or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The statistical analyses of tumor incidence are intended to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of dosed animals at each dose level. When results for two dosed groups are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni test for inequality (Miller, 1966) requires that the P value for any comparison be less than or

equal to 0.025. When this correction was used, it is discussed in the narrative section. It is not presented in the tables where the Fisher exact P values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. Under the assumption of a linear trend, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

Life table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which an animal died naturally or was killed was entered as the time point of tumor observation. The methods of Cox and of Tarone were used for the statistical tests of the groups. The statistical tests were one-tailed.

The approximate 95% confidence interval for the relative risk of each dosed group compared with its control was calculated from the exact interval on the odds ratio (Gart, 1971). The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that, in approximately 95% of a large number of identical experiments, the true ratio of the risk in a dosed group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result has occurred (P less than 0.025 one-tailed test when the control incidence is not zero, P less than 0.050 when the control incidence is zero). When the lower limit is less than unity but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

## III. RESULTS - RATS

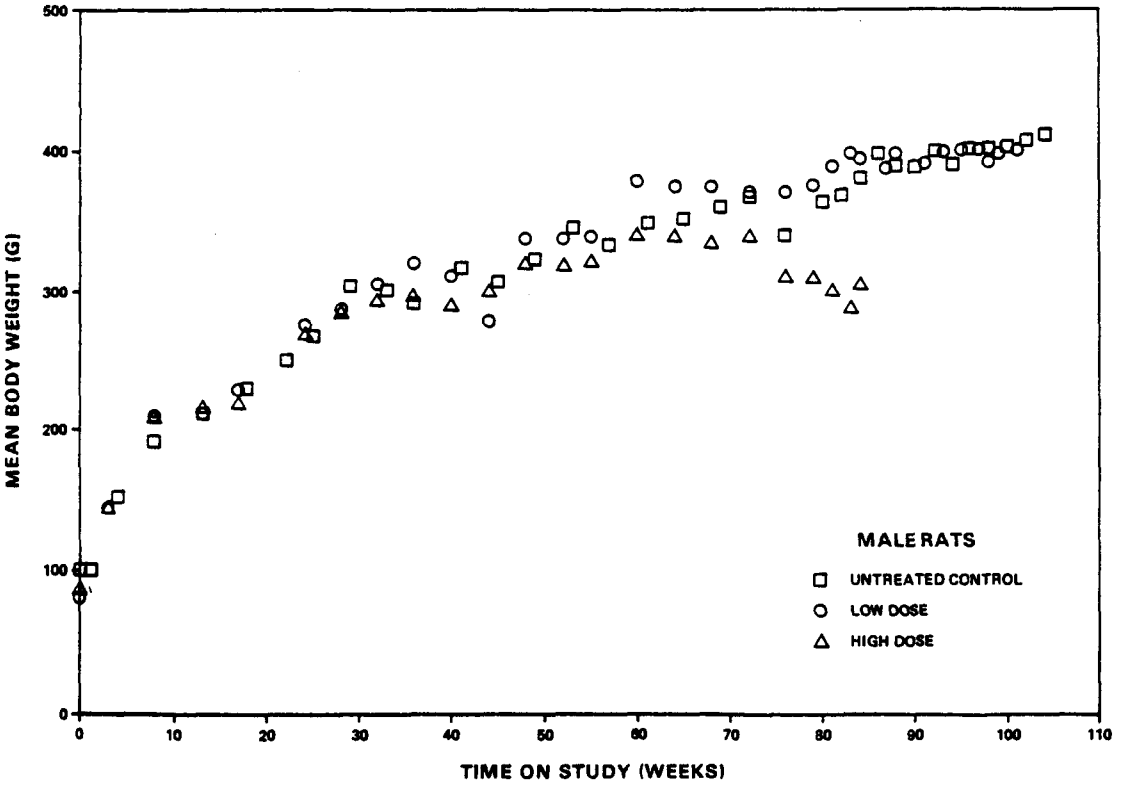
### A. Body Weights and Clinical Signs (Rats)

Mean body weight gains of male and female rats exposed to DBCP were comparable with those of corresponding controls for the first 65 weeks of the chronic study (Figure 1); thereafter, the mean body weight gain of the high-dose males was depressed as much as 22%, and the mean body weight gain of the high-dose females was depressed as much as 12%. The decrease in mean body weight gain was first observed when mortality in the high-dose groups began to increase. Beginning at week 46, increasing numbers of animals were detected with respiratory involvement characterized by wheezing or sneezing and bloody appearing crust on the nose and eyes; palpable masses were also noted on the face or nasal areas.

### B. Survival (Rats)

Estimates of the probabilities of survival for male and female rats administered DBCP by inhalation, together with those of the matched controls, are shown by the Kaplan and Meier curves in Figure 2. The results of the Tarone test for a positive dose-related trend in mortality indicate significant differences ($P<0.001$) in both sexes due to shortened survival in high-dose groups. The results of the Cox test comparing the survival of the high-dose group in each sex with that of the low-dose group and control group were also significant ($P<0.001$); however, survival in the untreated control group and the low-dose group was comparable in either sex.

In male rats, 41/50 (82%) of the control group and 42/50 (84%) of the low-dose group lived to the end of the study at 104-107 weeks. The surviving members of the high-dose group were killed at 84 weeks, at which time 5/49 (10%) of the animals were alive. In female rats, 42/50 (84%) of the control group and 40/50 (80%) of the low-dose group were alive at the end of the study at 104 weeks. Surviving members of the high-dose group were killed and necropsied at 84 weeks, at which time 6/50 (12%) of the animals were alive.



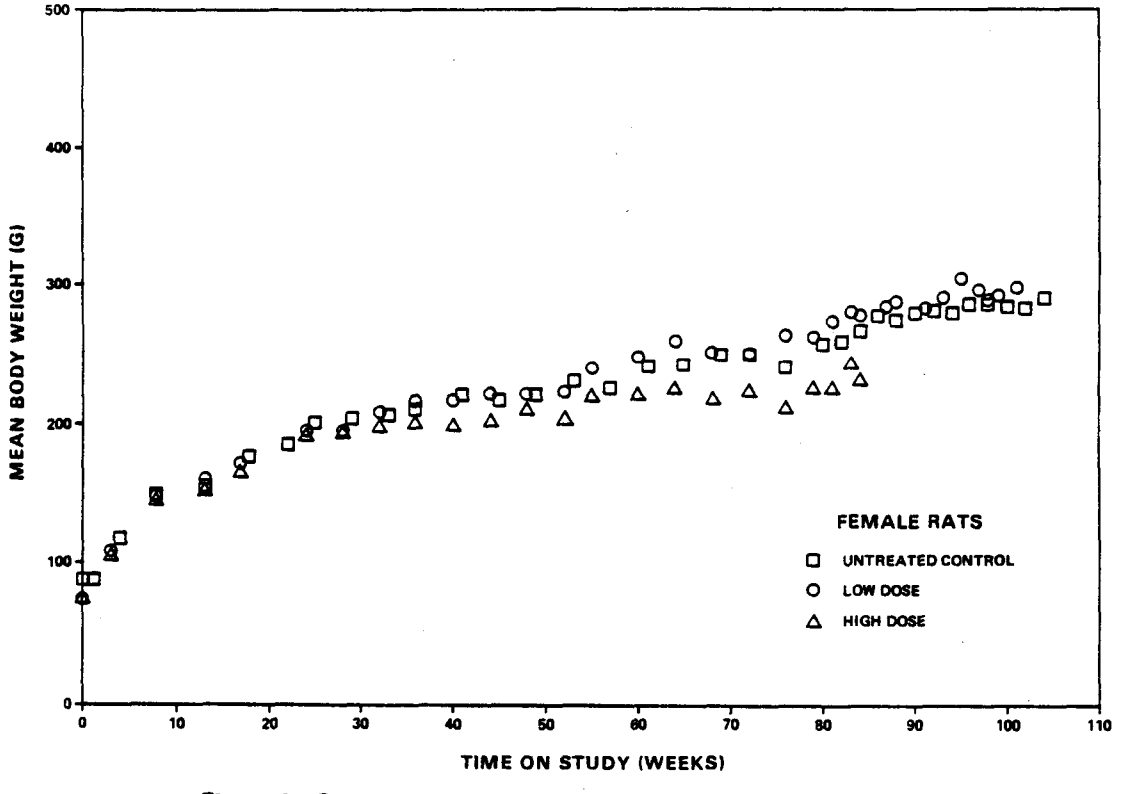




**Figure 1. Growth Curves for Rats Exposed to Air Containing DBCP**

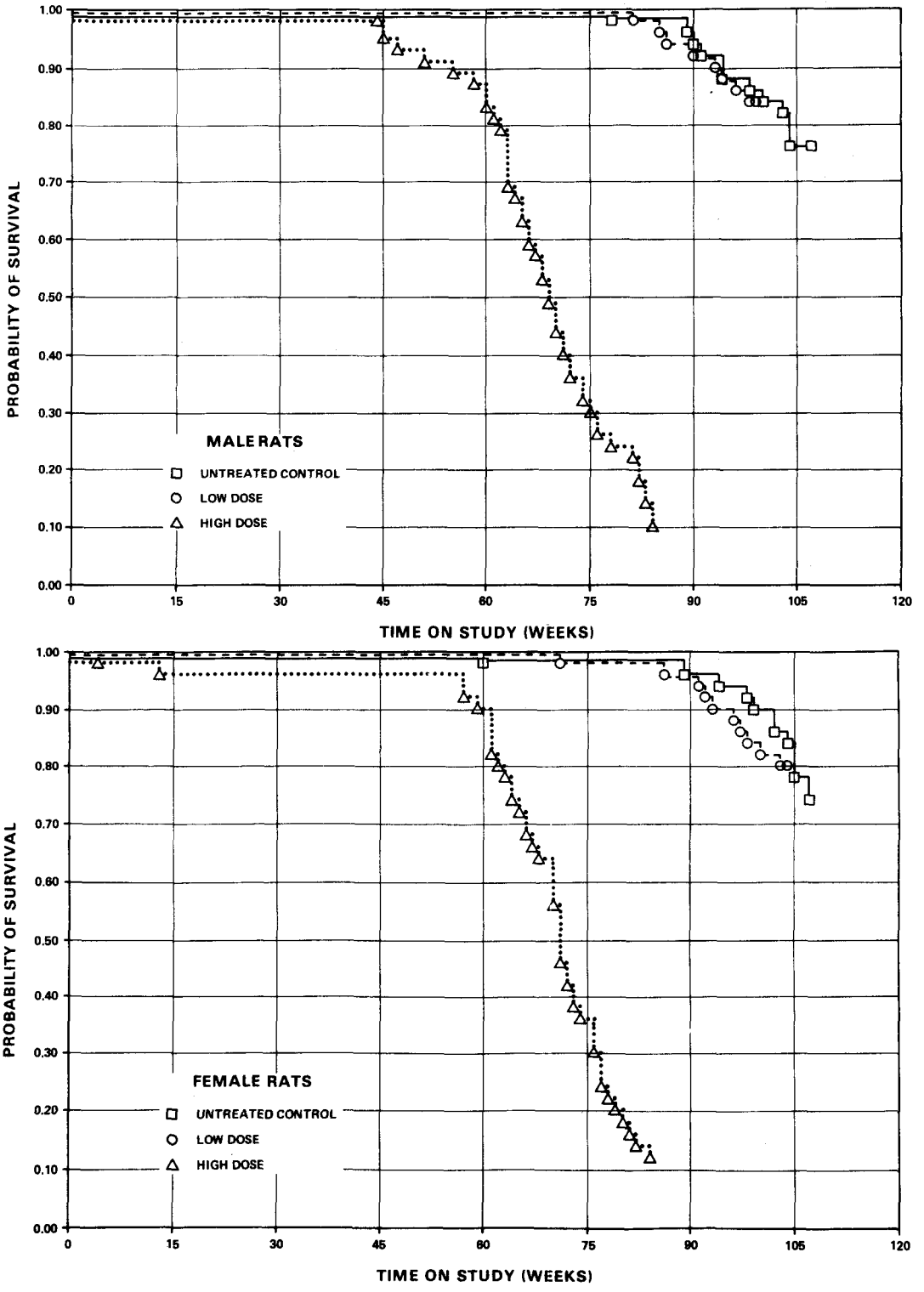



**Figure 2. Survival Curves for Rats Exposed to Air Containing DBCP**

## C. Pathology (Rats)

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2.

The neoplasms of the nasal cavity, tongue, pharynx, larynx, and kidney were considered to be related to DBCP administration. The spectrum of nasal neoplasms consisted of adenomatous polyps, adenomas, squamous-cell papillomas, adenocarcinomas, squamous-cell carcinomas, and carcinomas. The incidence of each type is given in Table 6. Nasal tumors were multiple in many animals. In the high-dose groups, 39/50 (78%) males and 42/50 (84%) females had some type of nasal cavity tumor.

The carcinomas were composed of sheets of proliferating, deeply basophilic, large, pleomorphic, undifferentiated, epithelial cells that were often in mitosis and that had infiltrated underlying tissues and bones of the major nasal structures and had spread by extension to the anterior cerebrum in many rats (16 high-dose males, 18 high-dose females, and 2 low-dose females). The squamous-cell carcinomas also were invasive, forming fronds or finger-like structures and nests of anaplastic cells in underlying tissues, masses of keratin, and often metastases to the cerebrum (six high-dose males, three high-dose females, and one low-dose female).

The adenocarcinomas varied from poorly differentiated growths in high-dose animals to well-differentiated tumors in low-dose animals. The poorly differentiated adenocarcinomas could be distinguished from carcinomas only by the presence, in areas, of glands and/or ducts. These neoplasms commonly metastasized to the cerebrum (six high-dose males, one low-dose male, four low-dose females, and one low-dose female). The well-differentiated tumors seen in low-dose animals were not highly invasive and did not metastasize. They were characterized by the presence of proliferating eosinophilic epithelial cells forming numerous well-formed glands and ducts. These neoplasms were usually attached by a broad base to the nasal mucosa. Mitotic figures (some bizarre) were not uncommon, and cells grew in sheets between the glands and ducts, apparently losing their relationship to the basement membrane.

Table 6. Summary of Incidences of Male and Female Rats with Selected Tumors after Exposure to DBCP by Inhalation (a)

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | Untreated Control (0 ppm) | Low Dose (0.6 ppm) | High Dose (3.0 ppm) | Untreated Control (0 ppm) | Low Dose (0.6 ppm) | High Dose (3.0 ppm) |
| Animals examined | 50 | 50 | 49 | 50 | 50 | 50 |
| NASAL CAVITY | | | | | | |
| Adenomatous Polyp | 0 | 13 | 1 | 0 | 5 | 5 |
| Adenoma, NOS | 0 | 9 | 1 | 0 | 6 | 5 |
| Squamous-cell Papilloma | 0 | 7 | 3 | 0 | 10 | 3 |
| Squamous-cell Carcinoma | 0 | 2 | 11 | 1 | 2 | 6 |
| Carcinoma, NOS | 0 | 2 | 22 | 0 | 0 | 23 |
| Adenocarcinoma, NOS | 0 | 8 | 6 | 0 | 2 | 6 |
| Animals with nasal cavity tumors | 0 | 32 | 39 | 1 | 21 | 32 |
| TONGUE | | | | | | |
| Squamous-cell Papilloma | 0 | 1 | 8 | 0 | 3 | 6 |
| Squamous-cell Carcinoma | 0 | 0 | 3 | 0 | 1 | 3 |
| Animals with Tongue Tumors | 0 | 1 | 11 | 0 | 4 | 9 |
| LARYNX | | | | | | |
| Squamous-cell Carcinoma | 0 | 1 | 0 | 0 | 0 | 0 |
| Squamous-cell Papilloma | 0 | 0 | 0 | 0 | 0 | 1 |
| Animals with Larynx Tumors | 0 | 1 | 0 | 0 | 0 | 1 |
| PHARYNX | | | | | | |
| Squamous-cell Papilloma | 0 | 2 | 1 | 0 | 0 | 5 |
| Squamous-cell Carcinoma | 0 | 1 | 0 | 0 | 0 | 2 |
| Animals with Pharynx Tumors | 0 | 3 | 1 | 0 | 0 | 6 |

(a) The incidence of tumors expressed in this table is greater than the incidence of animals with tumors, since more than one type of tumor was detected in some of the animals.

The adenomas and adenomatous polyps were somewhat similar to the well-differentiated adenocarcinomas in morphology; however, they were usually small growths. The cells maintained the relationship to the basement membrane and did not grow in sheets; mitoses were infrequent.

The squamous-cell papillomas typically were composed of an acanthotic epithelium resting on fibrous stalks that projected into the lumen from the surface attachment.

A small number of unusual kidney neoplasms were observed in exposed male rats. Tubular-cell adenomas were found in two low-dose males and tubular-cell adenocarcinoma was observed in one low-dose and one high-dose male. Since these represent unusual neoplasms in this strain of rat, they may be related to exposure. Four high-dose females and one low-dose female had mammary adenocarcinoma, as did one control female. In the high-dose females, the first neoplasm was observed at week 61, and this group was killed at week 84. The increased incidence and early onset of these tumors suggest a relation to exposure.

An increase in the incidence of benign mammary neoplasms in exposed female rats, of mesotheliomas of the tunica vaginalis in exposed male rats, and of adrenal cortical adenomas in exposed female rats was observed. Since these are relatively common neoplasms in this strain of rat, the increase in incidence in exposed groups is considered an equivocal effect.

Toxic changes related to DBCP exposure included toxic tubular nephropathy in the kidneys of high-dose male and female rats which was characterized by cytomegalic nuclei in tubule cells, especially in those of the pars recta. A few exposed animals had focal hyperplasia of renal tubular cells characterized by the presence of pale, very large cells. This unusual change may be related to exposure, since the morphology of these cells was similar to that observed in the tubular-cell adenomas and adenocarcinomas. Inflammation, hyperplasia, and hyperkeratosis of the nasal mucosa and adjacent structures were present in rats exposed to DBCP. In the stomach, an increase in the incidence of hyperkeratosis, acanthosis, and chronic inflammation was observed in the high-dose animals.

The results of histopathologic examination indicated that DBCP was carcinogenic in male and female F344 rats, causing epithelial neoplasms of the nasal cavity and other upper respiratory and upper alimentary tract tissues. The principal toxic change consisted of tubular nephropathy.

## D. Statistical Analyses of Results (Rats)

Tables 7 and 8 contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals in one group and with an incidence of at least 5% in one or more groups.

The incidence of animals with tumors of the nasal cavity, nasal turbinate, or nasal septum was significantly higher than that of the controls ($P<0.001$ in each dose-group of either sex). The Cochran-Armitage test indicates a significant positive dose-related trend ($P<0.001$) in each sex. Significant differences were observed in the times that these tumors were seen in either sex. The times to observation of such tumors are shown by the Kaplan-Meier curves in Figures 3 and 4; and there is a significantly shorter time to such observation in the high-dose groups than in the control groups ($P<0.001$) in either sex. Specific tumors in the nasal cavity are analyzed in the following paragraphs.

Carcinomas of the nasal cavity (not otherwise specified) were significantly dose related ($P < 0.001$) in both sexes. The incidence of nasal cavity carcinomas in the high-dose groups of each sex was statistically significant ($P < 0.001$) when compared with controls. A significant dose-related trend ($P < 0.001$) and a significantly higher incidence ($P < 0.001$) in the high-dose group were also observed for squamous-cell carcinomas in the nasal cavity of male rats.

The incidence of adenomas (not otherwise specified) in the nasal cavity of females was higher in each of the dosed groups ($P=0.013$ and $P=0.028$, respectively) than in the controls. A departure from linear trend ($P=0.036$) was due to the higher incidence in the low-dose group than in the high-dose group.

The incidences of animals with adenocarcinomas in the nasal cavity were significantly higher in each of the dosed groups of males ($P=0.003$ and

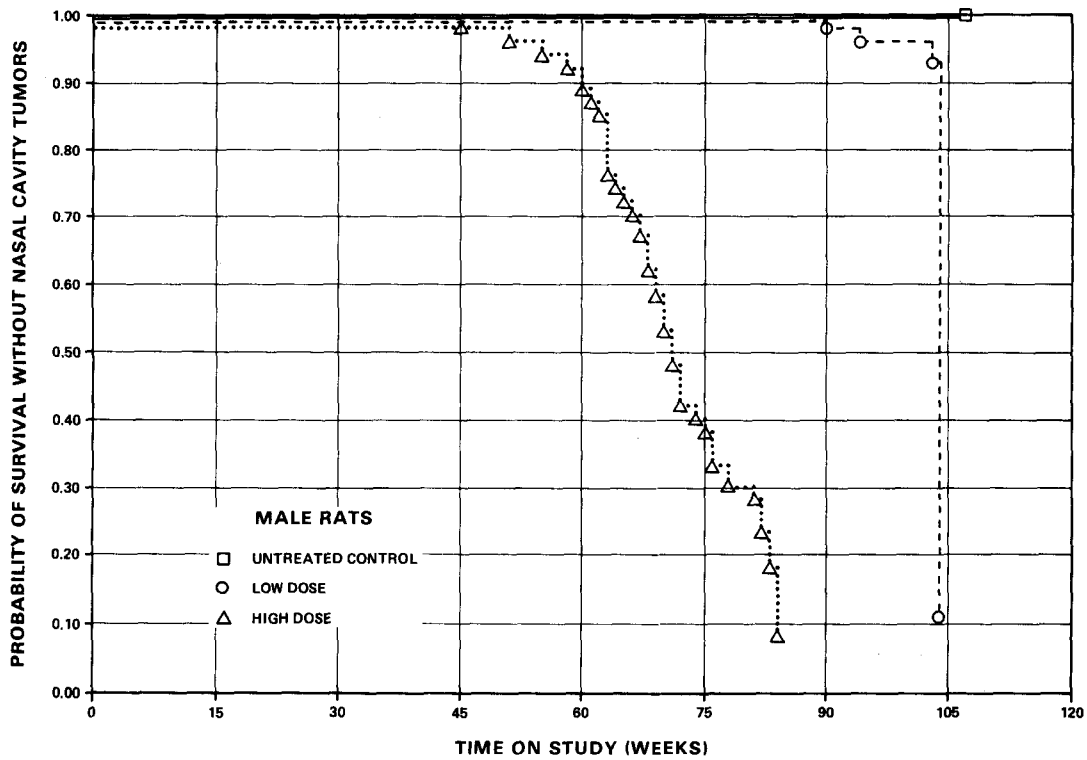



**Figure 3. Life Table for Male Rats Exposed to Air Containing DBCP: Nasal Cavity Tumors**

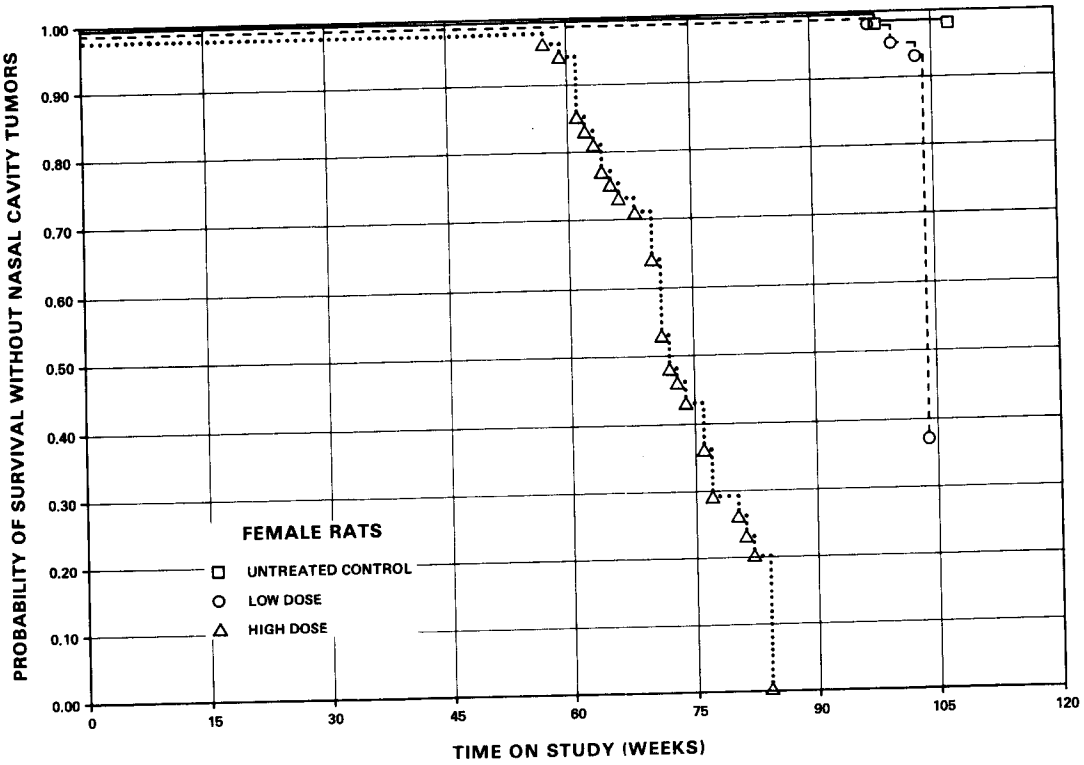



**Figure 4. Life Table for Female Rats Exposed to Air Containing DBCP: Nasal Cavity Tumors**

P=0.012, respectively) and in the high-dose group of females (P=0.013) than in the control group.

The incidences of animals with squamous-cell papillomas of the nasal cavity were significantly higher in the low-dose groups (P=0.006 in males and P=0.001 in females) than in the controls.

In male rats, incidences of adenomas and adenomatous polyps of the nasal cavity were significantly higher (P=0.001 and $P<0.001$, respectively) in the low-dose group than in the control group.

The incidence of adenomatous polyps in the nasal turbinate of male rats was significantly higher (P=0.003) in the low-dose group than in the control group. This tumor was not found in the high-dose group.

In female rats, the Fisher exact test indicated a higher incidence of adenomatous polyps of the nasal cavity (P=0.028) in each of the dosed groups and of adenomatous polyps in the nasal turbinate (P=0.028) of the low-dose group.

The incidence of female rats with fibroadenomas of the mammary glands was significantly higher (P=0.016) in the low-dose group than in the control group, and the Cochran-Armitage test indicated a departure (P=0.005) from linear trend because of the higher incidence in the low-dose group (13/50, 26%) than in the high-dose group (4/50, 8%). The shortened survival in the high-dose group may have curtailed the development of this tumor. The historical incidence in female F344 rats for this type of lesion in all laboratories in the Bioassay Program is 345/2,094 (16%), and at this laboratory is 39/200 (19.5%) as compared with the 4/50 (8%) observed in the control group. The use of 345/2,094 as an estimate of the binomial parameter (Fears et al., 1977) for the incidence of this tumor type in females would result in a probability of 0.058 for observing 13 or more incidences in 50 animals of the low-dose group; therefore, the statistical evidence for the dose association of this tumor with the chemical is not conclusive. When the occurrences of all mammary gland tumors are analyzed together, the results are similar.

Significantly higher incidences of high-dose rats and significant dose-related trends ($P < 0.001$, males; P=0.011, females) for squamous-cell papillomas of the tongue (P=0.003, males; P=0.013, females) were observed in both sexes.

The combined incidence of squamous-cell papillomas and carcinomas in the pharynx was dose related ($P < 0.001$) in females and was statistically significant (P=0.013) in the high-dose female group. The Cochran-Armitage test indicated a dose-related trend (P=0.001) in the incidence of female rats with squamous-cell papillomas of the pharynx. The incidence in the high-dose group was higher than that in the controls (P=0.028). Squamous-cell carcinomas alone were not significant.

A significant dose-related trend was observed in the incidence of males with mesotheliomas of the tunica vaginalis (P=0.004). The Fisher exact test indicated an increased incidence in the high-dose group (P=0.027).

The results of the Fisher exact test indicated significantly higher incidences of animals with adenomas of the adrenal cortex in the low- and high-dose groups of female rats (P=0.006 and P=0.025, respectively).

The results of the Cochran-Armitage test indicated significant positive dose-related trends in the incidences of animals with trichoepitheliomas in the skin of males (P=0.037), of squamous-cell carcinomas of the tongue in males and females (P=0.010 in males and P=0.040 in females), and of squamous-cell carcinomas of the nasal cavity in females (P=0.016), but Fisher exact tests are not significant in these instances.

In male rats, the incidence of interstitial-cell tumors of the testis had a negative trend ($P < 0.001$) with a significantly lower incidence ($P < 0.001$) found in the high-dose group than in the control group. These results may be due to early mortality observed among high-dose group animals. The historical control incidence accumulated from all laboratories for this type of tumor in male F344 rats is 1,607/2,130 (75%). The historical control incidence at this laboratory is 162/200 (81%).

Significant trends in the negative direction were observed in the incidence of either leukemia or lymphomas in males and in the incidence of monocytic leukemia and of endometrial stromal polyps of the uterus in females.

A significant negative trend and a significantly lower incidence of chromophobe adenomas of the pituitary were observed in the high-dose groups of either sex. The historical incidence for this lesion in the bioassay program is 161/2,130 (8%) in male F344 rats and 389/2,094 (19%) in females as compared with 10/45 (22%) in males and 20/50 (40%) in females of control

groups in this experiment. The historical incidence of chromophobe adenomas of the pituitary at this laboratory is 16/200 (8%) for males and 70/200 (35%) for females. The historical incidence of pituitary adenomas, NOS, at this laboratory is 0/200 for males and 1/200 for females. The higher incidences in the control groups (compared with the historical incidences) are responsible for the negative trend.

In summary, statistical analysis indicates that there was a dose-related increase in the incidence of nasal cavity tumors and in the incidence of tumors of the tongue in male and female rats. The combined incidence of squamous-cell papillomas and carcinomas of the pharynx and the incidence of cortical adenomas of the adrenal in female rats were also associated with the administration of DBCP by inhalation. The incidence of trichoepitheliomas of the skin and of mesotheliomas of the tunica vaginalis in males may also have been related to the administration of DBCP by this route.

Table 7. Analyses of the Incidence of Primary Tumors In Male Rats Exposed to DBCP by Inhalation (a)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Skin: Trichoepithelioma (b) | 0/50 (0) | 1/50 (2) | 3/49 (6) |
| P Values (c,d) | P=0.037 | N.S. | N.S. |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 0.054 | 0.614 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | — | 104 | 84 |
| Subcutaneous Tissue: Fibroma (b) | 3/50 (6) | 0/50 (0) | 0/49 (0) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | 0.000 | 0.000 |
| Lower Limit | | 0.000 | 0.000 |
| Upper Limit | | 1.663 | 1.696 |
| Weeks to First Observed Tumor | 105 | — | -- |
| Nasal Cavity: Carcinoma, NOS (b) | 0/50 (0) | 2/50 (4) | 22/49 (45) |
| P Values (c,d) | P<0.001 | N.S. | P<0.001 |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 0.296 | 7.313 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | — | 94 | 45 |
| Nasal Cavity: Squamous-cell Papilloma (b) | 0/50 (0) | 7/50 (14) | 3/49 (6) |
| P Values (c,d) | N.S. | P=0.006 | N.S. |
| Departure from Linear Trend (f) | P<0.006 | | |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 1.941 | 0.614 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 104 | 74 |

Table 7. Analyses of the Incidence of Primary Tumors In Male Rats Exposed to DBCP by Inhalation (a)

(Continued)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Nasal Cavity: Squamous-cell Carcinoma (b) | 0/50 (0) | 2/50 (4) | 11/49 (22) |
| P Values (c,d) | P<0.001 | N.S. | P<0.001 |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 0.296 | 3.389 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 104 | 62 |
| Nasal Cavity: Adenoma, NOS (b) | 0/50 (0) | 9/50 (18) | 1/49 (2) |
| P Values (c,d) | P<0.001 | P=0.001 | N.S. |
| Departure from Linear Trend (f) | P<0.001 | | |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 2.629 | 0.055 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 104 | 69 |
| Nasal Cavity: Adenocarcinoma, NOS (b) | 0/50 (0) | 8/50 (16) | 6/49 (12) |
| P Values (c,d) | N.S. | P=0.003 | P=0.012 |
| Departure from Linear Trend (f) | P=0.011 | | |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 2.284 | 1.633 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 90 | 51 |
| Nasal Cavity: Adenomatous Polyp, NOS (b) | 0/50 (0) | 13/50 (26) | 1/49 (2) |
| P Values (c,d) | N.S. | P<0.001 | N.S. |
| Departure from Linear Trend (f) | P<0.001 | | |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 4.014 | 0.055 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 103 | 69 |

Table 7. Analyses of the Incidence of Primary Tumors In Male Rats Exposed to DBCP by Inhalation (a)
(Continued)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Nasal Turbinate: Squamous-cell Papilloma (b) | 0/50 (0) | 3/50 (6) | 0/49 (0) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Departure from Linear Trend (f) | P=0.020 | | |
| Relative Risk (Control) (e) | | Infinite | — |
| Lower Limit | | 0.601 | — |
| Upper Limit | | Infinite | — |
| Weeks to First Observed Tumor | — | 104 | — |
| Nasal Turbinate: Adenomatous Polyp (b) | 0/50 (0) | 8/50 (16) | 0/49 (0) |
| P Values (c,d) | N.S. | P=0.003 | N.S. |
| Departure from Linear Trend (f) | P=0.001 | | |
| Relative Risk (Control) (e) | | Infinite | — |
| Lower Limit | | 2.284 | — |
| Upper Limit | | Infinite | — |
| Weeks to First Observed Tumor | — | 104 | — |
| Nasal Turbinate, Nasal Cavity, Nasal Septum: Carcinoma, NOS, Squamous Cell Papilloma, Squamous Cell Carcinoma, Adenoma, NOS, Adenocarcinoma, NOS, Squamous Cell Papilloma, Adenomatous Polyp, NOS, and Carcinosarcoma (b) | 0/50 (0) | 40/50 (80) | 39/49(80) |
| P Values (c,d) | P<0.001 | P<0.001 | P<0.001 |
| Departure from Linear Trend (f) | P<0.001 | | |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 13.771 | 687 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | — | 90 | 45 |
| Hematopoietic System: Monocytic Leukemia (b) | 6/50 (12) | 8/50 (16) | 0/49 (0) |
| P Values (c,d) | P=0.006 (N) | N.S. | P=0.014 (N) |
| Relative Risk (Control) (e) | | 1.333 | 0.000 |
| Lower Limit | | 0.438 | 0.000 |
| Upper Limit | | 4.331 | 0.637 |
| Weeks to First Observed Tumor | 89 | 103 | — |

Table 7. Analyses of the Incidence of Primary Tumors In Male Rats Exposed to DBCP by Inhalation (a)

(Continued)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Hematopoietic System: Leukemia or Lymphoma (b) | 6/50 (12) | 10/50 (20) | 0/49 (0) |
| P Values (c,d) | P=0.005 (N) | N.S. | P=0.014 (N) |
| Relative Risk (Control) (e) | | 1.667 | 0.000 |
| Lower Limit | | 0.597 | 0.000 |
| Upper Limit | | 5.164 | 0.637 |
| Weeks to First Observed Tumor | 89 | 81 | -- |
| Tongue: Squamous-cell Papilloma (b) | 0/50 (0) | 1/50 (2) | 8/49 (16) |
| P Values (c,d) | P<0.001 | N.S. | P=0.003 |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 0.054 | 2.331 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 81 | 58 |
| Tongue: Squamous-cell Carcinoma (b) | 0/50 (0) | 0/50 (0) | 3/49 (6) |
| P Values (c,d) | P=0.010 | N.S. | N.S. |
| Relative Risk (Control) (e) | | -- | Infinite |
| Lower Limit | | -- | 0.614 |
| Upper Limit | | -- | Infinite |
| Weeks to First Observed Tumor | -- | -- | 64 |
| Tongue: Squamous-cell Papilloma or Carcinoma (b) | 0/50 (0) | 1/50 (2) | 11/49 (22) |
| P Values (c,d) | P<0.001 | N.S. | P<0.001 |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 0.054 | 3.389 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 81 | 58 |

Table 7. Analyses of the Incidence of Primary Tumors In Male Rats Exposed to DBCP by Inhalation (a)

(Continued)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Kidney: Tubular-cell Adenoma (b) | 0/50 (0) | 3/50 (6) | 1/49 (2) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 0.601 | 0.055 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 104 | 84 |
| Kidney: Tubular-cell Adenoma or Adenocarcinoma (b) | 0/50 (0) | 4/50 (8) | 2/49 (4) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Departure from Linear Trend (f) | P=0.046 | | |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 0.927 | 0.302 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 104 | 84 |
| Pituitary: Chromophobe Adenoma (b) | 10/45 (22) | 7/48 (15) | 0/44 (0) |
| P Values (c,d) | P=0.001 (N) | N.S. | P=0.001 (N) |
| Relative Risk (Control) (e) | | 0.656 | 0.000 |
| Lower Limit | | 0.232 | 0.000 |
| Upper Limit | | 1.742 | 0.342 |
| Weeks to First Observed Tumor | 104 | 86 | -- |
| Adrenal: Cortical Adenoma (b) | 1/49 (2) | 6/49 (12) | 3/48 (6) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Departure from Linear Trend (f) | P=0.045 | | |
| Relative Risk (Control) (e) | | 6.000 | 3.063 |
| Lower Limit | | 0.769 | 0.257 |
| Upper Limit | | 269.767 | 157.336 |
| Weeks to First Observed Tumor | 103 | 86 | 76 |

Table 7. Analyses of the Incidence of Primary Tumors In Male Rats Exposed to DBCP by Inhalation (a)

(Continued)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Adrenal: Pheochromocytoma (b) | 4/49 (8) | 1/49 (2) | 2/48 (4) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | 0.250 | 0.510 |
| Lower Limit | | 0.005 | 0.048 |
| Upper Limit | | 2.409 | 3.381 |
| Weeks to First Observed Tumor | 91 | 104 | 82 |
| Thyroid: C-cell Carcinoma (b) | 3/48 (6) | 0/49 (0) | 0/49 (0) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | 0.000 | 0.000 |
| Lower Limit | | 0.000 | 0.000 |
| Upper Limit | | 1.628 | 1.628 |
| Weeks to First Observed Tumor | 104 | -- | -- |
| Thyroid: C-cell Carcinoma or Adenoma (b) | 3/48 (6) | 1/49 (2) | 0/49 (0) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | 0.327 | 0.000 |
| Lower Limit | | 0.006 | 0.000 |
| Upper Limit | | 3.898 | 1.628 |
| Weeks to First Observed Tumor | 104 | 86 | -- |
| Testis: Interstitial-cell Tumor (b) | 35/50 (70) | 48/50 (96) | 11/48 (23) |
| P Values (c,d) | P<0.001(N) | P<0.001 | P<0.001(N) |
| Departure from Linear Trend (f) | P<0.001 | | |
| Relative Risk (Control) (e) | | 1.371 | 0.327 |
| Lower Limit | | 1.133 | 0.183 |
| Upper Limit | | 1.496 | 0.564 |
| Weeks to First Observed Tumor | 94 | 81 | 62 |

Table 7. Analyses of the Incidence of Primary Tumors In Male Rats Exposed to DBCP by Inhalation (a)

(Continued)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Epididymis: Mesothelioma, Invasive (b) | 1/50 (2) | 1/50 (2) | 3/49 (6) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | 1.000 | 3.061 |
| Lower Limit | | 0.013 | 0.256 |
| Upper Limit | | 76.970 | 157.341 |
| Weeks to First Observed Tumor | 105 | 85 | 47 |
| Epididymis: Mesothelioma, Invasive or NOS (b) | 3/50 (6) | 1/50 (2) | 3/49 (6) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | 0.333 | 1.020 |
| Lower Limit | | 0.006 | 0.143 |
| Upper Limit | | 3.983 | 7.273 |
| Weeks to First Observed Tumor | 105 | 85 | 47 |
| Scrotum: Mesothelioma, Invasive (b) | 1/50 (2) | 1/50 (2) | 3/49 (6) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | 1.000 | 3.061 |
| Lower Limit | | 0.013 | 0.256 |
| Upper Limit | | 76.970 | 157.341 |
| Weeks to First Observed Tumor | 105 | 85 | 47 |
| Tunica Vaginalis: Mesothelioma, NOS (b) | 0/50 (0) | 1/50 (2) | 5/49 (10) |
| P Values (c,d) | P=0.004 | N.S. | P=0.027 |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 0.054 | 1.287 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 104 | 47 |

Table 7. Analyses of the Incidence of Primary Tumors In Male Rats Exposed to DBCP by Inhalation (a)

(Continued)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Tunica Vaginalis: Mesothelioma, NOS or Malignant (b) | 1/50 (2) | 2/50 (4) | 5/49 (10) |
| P Values (c,d) | P=0.036 | N.S. | N.S. |
| Relative Risk (Control) (e) | | 2.000 | 5.102 |
| Lower Limit | | 0.108 | 0.601 |
| Upper Limit | | 115.621 | 236.025 |
| Weeks to First Observed Tumor | 105 | 85 | 47 |

(a) Dosed groups were exposed to 0.6 or 3 ppm by inhalation.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
(e) The 95 percent confidence interval of the relative risk between each dosed group and the control group.
(f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

Table 8. Analyses of the Incidence of Primary Tumors In Female Rats Exposed to DBCP by Inhalation (a)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Nasal Cavity: Carcinoma, NOS (b) | 0/50 (0) | 0/50 (0) | 23/50 (46) |
| P Values (c,d) | P<0.001 | N.S. | P<0.001 |
| Relative Risk (Control) (e) | | -- | Infinite |
| Lower Limit | | -- | 7.515 |
| Upper Limit | | -- | Infinite |
| Weeks to First Observed Tumor | -- | -- | 61 |
| Nasal Cavity: Squamous-cell Papilloma (b) | 0/50 (0) | 10/50 (20) | 3/50 (6) |
| P Values (c,d) | N.S. | P=0.001 | N.S. |
| Departure from Linear Trend (f) | P<0.001 | | |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 2.974 | 0.601 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 97 | 77 |
| Nasal Cavity: Squamous-cell Carcinoma (b) | 1/50 (2) | 2/50 (4) | 6/50 (12) |
| P Values (c,d) | P=0.016 | N.S. | N.S. |
| Relative Risk (Control) (e) | | 2.000 | 6.000 |
| Lower Limit | | 0.108 | 0.768 |
| Upper Limit | | 115.621 | 269.891 |
| Weeks to First Observed Tumor | 98 | 104 | 57 |
| Nasal Cavity: Adenoma, NOS (b) | 0/50 (0) | 6/50 (12) | 5/50 (10) |
| P Values (c,d) | N.S. | P=0.013 | P=0.028 |
| Departure from Linear Trend (f) | P=0.036 | | |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 1.600 | 1.261 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 104 | 63 |

Table 8. Analyses of the Incidence of Primary Tumors In Female Rats Exposed to DBCP by Inhalation (a)
(Continued)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Nasal Cavity: Adenocarcinoma, NOS (b) | 0/50 (0) | 2/50 (4) | 6/50 (12) |
| P Values (c,d) | P=0.005 | N.S. | P=0.013 |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 0.296 | 1.600 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | — | 103 | 57 |
| Nasal Cavity: Adenomatous Polyp, NOS (b) | 0/50 (0) | 5/50 (10) | 5/50 (10) |
| P Values (c,d) | N.S. | P=0.028 | P=0.028 |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 1.261 | 1.261 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | — | 104 | 68 |
| Nasal Turbinate: Adenomatous Polyp, NOS (b) | 0/50 (0) | 5/50 (10) | 1/50 (2) |
| P Values (c,d) | N.S. | P=0.028 | N.S. |
| Departure from Linear Trend (f) | P=0.008 | | |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 1.261 | 0.054 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | — | 100 | 84 |
| Nasal Cavity, Nasal Turbinate, Carcinoma, NOS, Squamous Cell Papilloma, Squamous Cell Carcinoma, Adenoma, NOS, Adenocarcinoma, NOS, and Adenomatous Polyp, NOS (b) | 1/50 (2) | 27/50 (54) | 42/50(84) |
| P Values (c,d) | P<0.001 | P<0.001 | P<0.001 |
| Departure from Linear Trend (e) | P<0.001 | | |
| Relative Risk (Control) (f) | | 27.000 | 42.000 |
| Lower Limit | | 4.826 | 8.141 |
| Upper Limit | | 1058.510 | 1490.272 |
| Weeks to First Observed Tumor | — | 97 | 57 |

Table 8. Analyses of the Incidence of Primary Tumors In Female Rats Exposed to DBCP by Inhalation (a)

(Continued)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Hematopoietic System: Monocytic Leukemia (b) | 6/50 (12) | 7/50 (14) | 0/50 (0) |
| P Values (c,d) | P=0.007 (N) | N.S. | P=0.013 (N) |
| Relative Risk (Control) (f) | | 1.167 | 0.000 |
| Lower Limit | | 0.361 | 0.000 |
| Upper Limit | | 3.911 | 0.625 |
| Weeks to First Observed Tumor | 89 | 104 | -- |
| Hematopoietic System: All Leukemias (b) | 6/50 (12) | 7/50 (14) | 1/50 (2) |
| P Values (c,d) | P=0.022 (N) | N.S. | N.S. |
| Relative Risk (Control) (e) | | 1.167 | 0.167 |
| Lower Limit | | 0.361 | 0.004 |
| Upper Limit | | 3.911 | 1.302 |
| Weeks to First Observed Tumor | 89 | 104 | 13 |
| Hematopoietic System: Leukemia or Lymphoma (b) | 6/50 (12) | 7/50 (14) | 2/50 (4) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | 1.167 | 0.333 |
| Lower Limit | | 0.361 | 0.034 |
| Upper Limit | | 3.911 | 1.758 |
| Weeks to First Observed Tumor | 89 | 104 | 13 |
| Tongue: Squamous-cell Papilloma (b) | 0/50 (0) | 3/50 (6) | 6/50 (12) |
| P Values (c,d) | P=0.011 | N.S. | P=0.013 |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 0.601 | 1.600 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 104 | 61 |

Table 8. Analyses of the Incidence of Primary Tumors In Female Rats Exposed to DBCP by Inhalation (a)

(Continued)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Tongue: Squamous-cell Carcinoma (b) | 0/50 (0) | 1/50 (2) | 3/50 (6) |
| P Values (c,d) | P=0.040 | N.S. | N.S. |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 0.054 | 0.601 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 93 | 70 |
| Tongue: Squamous-cell Papilloma or Carcinoma (b) | 0/50 (0) | 4/50 (8) | 9/50 (18) |
| P Values (c,d) | P=0.002 | N.S. | P=0.001 |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 0.927 | 2.629 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 93 | 61 |
| Liver: Neoplastic Nodule (b) | 2/50 (4) | 3/50 (6) | 0/48 (0) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | 1.500 | 0.000 |
| Lower Limit | | 0.180 | 0.000 |
| Upper Limit | | 17.329 | 3.518 |
| Weeks to First Observed Tumor | 105 | 97 | -- |
| Liver: Neoplastic Nodule or Hepatocellular Carcinoma (b) | 2/50 (4) | 4/50 (8) | 0/48 (0) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | 2.000 | 0.000 |
| Lower Limit | | 0.301 | 0.000 |
| Upper Limit | | 21.316 | 3.518 |
| Weeks to First Observed Tumor | 105 | 97 | -- |

Table 8. Analyses of the Incidence of Primary Tumors In Female Rats Exposed to DBCP by Inhalation (a)

(Continued)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Pharynx: Squamous-cell Papilloma (b) | 0/50 (0) | 0/50 (0) | 5/50 (10) |
| P Values (c,d) | P=0.001 | N.S. | P=0.028 |
| Relative Risk (Control) (e) | | -- | Infinite |
| Lower Limit | | -- | 1.261 |
| Upper Limit | | -- | Infinite |
| Weeks to First Observed Tumor | -- | -- | 68 |
| Pharynx: Squamous-cell Papilloma or Carcinoma (b) | 0/50 (0) | 0/50 (0) | 6/50 (12) |
| P Values (c,d) | P<0.001 | N.S. | P=0.013 |
| Relative Risk (Control) (e) | | -- | Infinite |
| Lower Limit | | -- | 1.600 |
| Upper Limit | | -- | Infinite |
| Weeks to First Observed Tumor | -- | -- | 68 |
| Pituitary: Chromophobe Adenoma (b) | 20/50 (40) | 20/47 (43) | 2/46 (4) |
| P Values (c,d) | P<0.001 (N) | N.S. | P<0.001 (N) |
| Relative Risk (Control) (e) | | 1.064 | 0.109 |
| Lower Limit | | 0.629 | 0.013 |
| Upper Limit | | 1.791 | 0.411 |
| Weeks to First Observed Tumor | 94 | 91 | 84 |
| Adrenal: Cortical Adenoma (b) | 0/50 (0) | 7/50 (14) | 5/48 (10) |
| P Values (c,d) | N.S. | P=0.006 | P=0.025 |
| Departure from Linear Trend (f) | P=0.017 | | |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 1.941 | 1.314 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 104 | 71 |

Table 8. Analyses of the Incidence of Primary Tumors In Female Rats Exposed to DBCP by Inhalation (a)

(Continued)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Adrenal: Pheochromocytoma (b) | 3/50 (6) | 0/50 (0) | 0/48 (0) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | 0.000 | 0.000 |
| Lower Limit | | 0.000 | 0.000 |
| Upper Limit | | 1.663 | 1.730 |
| Weeks to First Observed Tumor | 104 | -- | -- |
| Thyroid: C-cell Carcinoma (b) | 1/49 (2) | 4/47 (9) | 1/48 (2) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | 4.170 | 1.021 |
| Lower Limit | | 0.433 | 0.013 |
| Upper Limit | | 200.705 | 78.494 |
| Weeks to First Observed Tumor | 105 | 97 | 84 |
| Mammary Gland: Adenocarcinoma, NOS (b) | 1/50 (2) | 1/50 (2) | 4/50 (8) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | 1.000 | 4.000 |
| Lower Limit | | 0.013 | 0.415 |
| Upper Limit | | 76.970 | 192.805 |
| Weeks to First Observed Tumor | 107 | 104 | 61 |
| Mammary Gland: Fibroadenoma (b) | 4/50 (8) | 13/50 (26) | 4/50 (8) |
| P Values (c,d) | N.S. | P=0.016 | N.S. |
| Departure from Linear Trend (f) | P=0.005 | | |
| Relative Risk (Control) (e) | | 3.250 | 1.000 |
| Lower Limit | | 1.091 | 0.197 |
| Upper Limit | | 12.780 | 5.083 |
| Weeks to First Observed Tumor | 105 | 96 | 74 |

Table 8. Analyses of the Incidence of Primary Tumors In Female Rats Exposed to DBCP by Inhalation (a)

(Continued)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Mammary Gland: Adenoma, NOS, or Carcinoma, NOS, or Adenocarcinoma, NOS, or Papillary Cystadenoma, NOS, or Fibroadenoma (b) | 5/50(10) | 14/50(28) | 9/50(18) |
| P Values (c,d) | N.S. | P=0.020 | N.S. |
| Departure from Linear Trend (f) | P=0.022 | | |
| Relative Risk (Control) (e) | | 2.800 | 1.800 |
| Lower Limit | | 1.041 | 1.586 |
| Upper Limit | | 9.186 | 6.377 |
| Weeks to First Observed Tumor | 105 | 96 | 61 |
| Uterus: Endometrial Stromal Polyp (b) | 6/50 (12) | 4/49 (8) | 0/46 (0) |
| P Values (c,d) | P=0.012 (N) | N.S. | P=0.017 (N) |
| Relative Risk (Control) (e) | | 0.680 | 0.000 |
| Lower Limit | | 0.150 | 0.000 |
| Upper Limit | | 2.686 | 0.678 |
| Weeks to First Observed Tumor | 102 | 104 | -- |

(a) Dosed groups were exposed to 0.6 or 3 ppm by inhalation.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
(e) The 95 percent confidence interval of the relative risk between each dosed group and the control group.
(f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

# IV. RESULTS - MICE

## A. Body Weights and Clinical Signs (Mice)

Mean body weights of the mice exposed to DBCP were comparable with those of corresponding controls for the first 60 weeks of the chronic study; thereafter, mean body weight gain of the high-dose male mice was depressed 17%-28% (Figure 5). Mean body weight gain was depressed 25% in the female mice still alive at week 76.

## B. Survival (Mice)

Estimates of the probabilities of survival for male and female mice administered DBCP by inhalation at the concentrations used in this bioassay, together with those of the matched controls, are shown by the Kaplan and Meier curves in Figure 6. The Tarone test for positive dose-related trend in mortality indicated a significant difference in female mice ($P < 0.001$). The results of the Cox test comparing the survival of the high-dose group with that of the low-dose group and the control group were also significant in females ($P < 0.001$) due to early mortality in the high-dose group; however, the survival among the three groups of male mice is comparable. The survival of the control group and the low-dose group of female mice is also comparable.

In male mice, 13/50 (26%) of the control group, 15/50 (30%) of the low-dose group, and 7/50 (14%) of the high-dose group were alive at the end of the study at 76 weeks. Only 35% of male mice lived to 70 weeks or longer. In females, 40/50 (80%) of the control group and 37/50 (74%) of the low-dose group lived until all animals in these groups were killed at 104 weeks. Over 75% of female mice lived to or beyond 70 weeks.

Between week 51 and week 74, 43/50 of the high-dose females died.

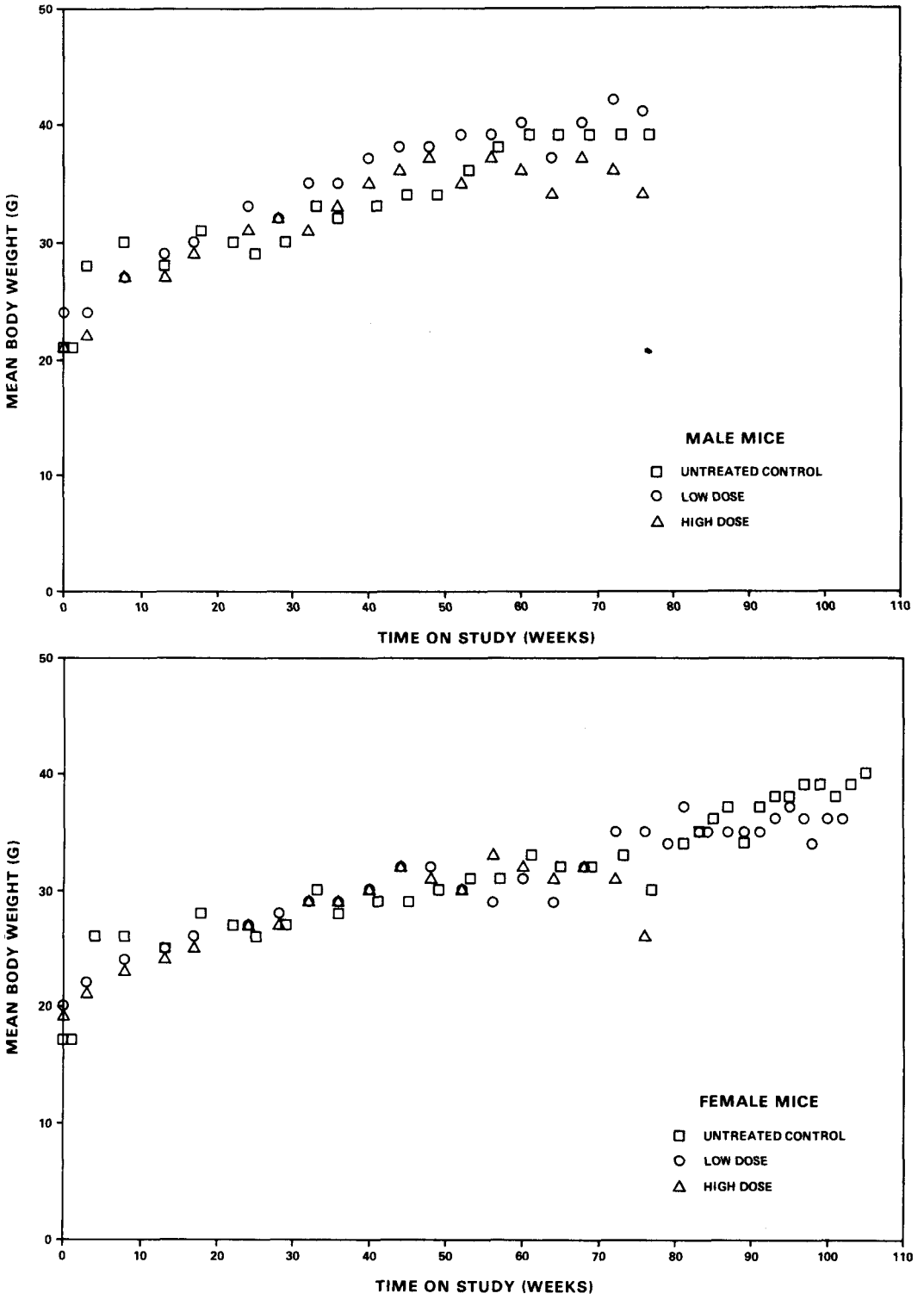



**Figure 5. Growth Curves for Mice Exposed to Air Containing DBCP**

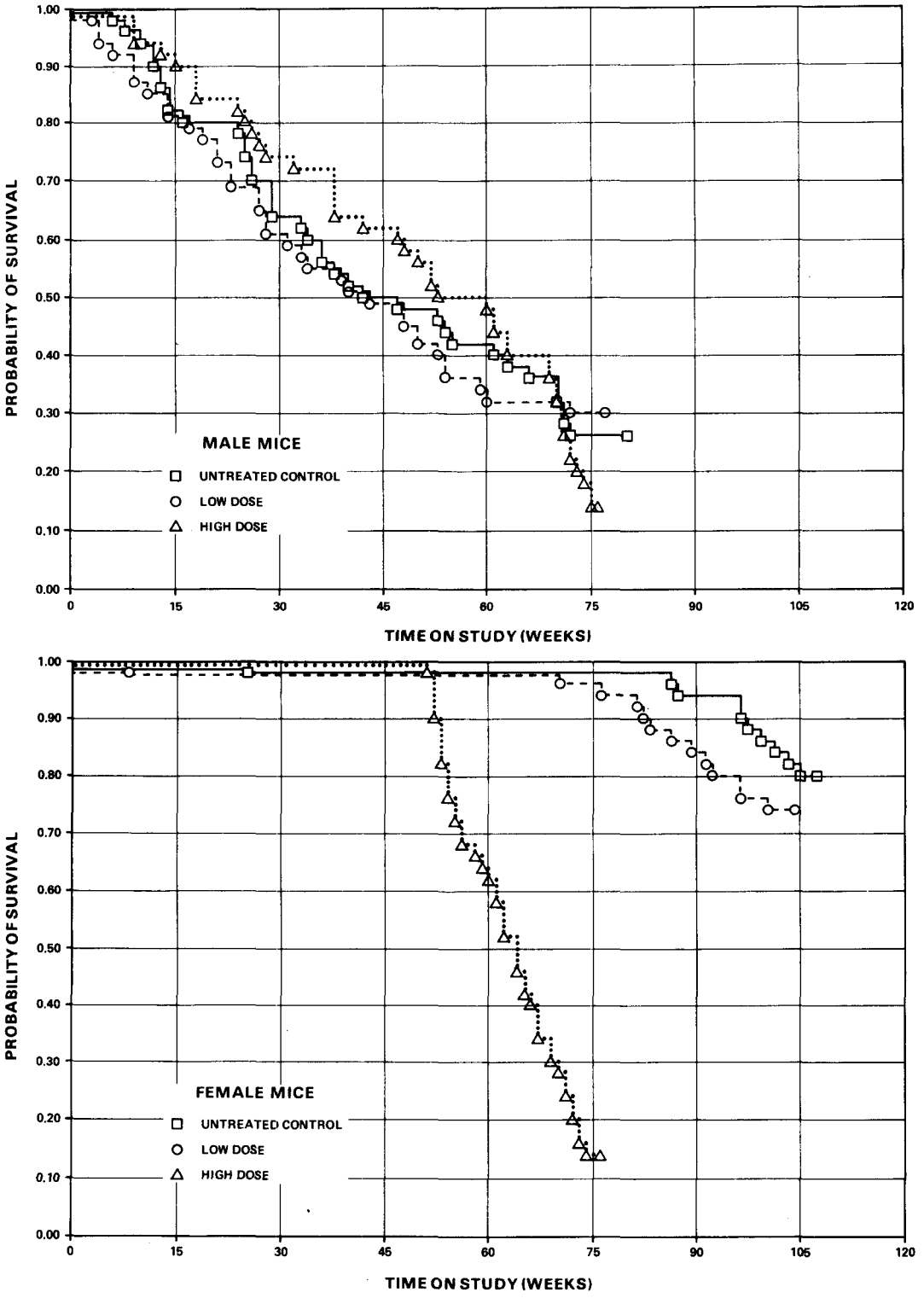



**Figure 6. Survival Curves for Mice Exposed to Air Containing DBCP**

## C. Pathology (Mice)

Histopathologic findings on neoplasms in mice are summarized in Appendix B, Tables B1 and B2; findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2.

A variety of tumors were seen in control and exposed mice. Those of the nasal cavity and lungs were related to DBCP exposure. In the nasal cavity, the most commonly occurring tumors were carcinomas, squamous-cell carcinomas and adenocarcinomas, and a small number of mesenchymal tumors (sarcoma, fibrosarcoma, carcinosarcoma, hemangiosarcoma). The carcinomas and squamous-cell carcinomas were highly invasive, involving most of the nasal structure, infiltrating underlying tissue and bone, and occasionally metastasizing to the cerebrum (4 high-dose males, 17 high-dose females). Nasal tumors metastasized to the lung in 2 low-dose females and in 3 high-dose females. Of the high-dose groups, 21/48 (44%) of the male mice and 38/50 (76%) of the female mice had some type of nasal cavity tumor. Alveolar/bronchiolar adenomas and carcinomas and unusual papillary carcinomas and squamous cell carcinomas were observed in the lung, particularly in female mice. The pulmonary carcinomas were invasive, often having intrapulmonic metastases or multicentric foci, while the adenomas were solitary, well-circumscribed, and well-differentiated. The incidences of neoplasms observed in the nasal cavity and lung are summarized in Table 9.

Nonneoplastic lesions related to exposure to DBCP included inflammation and hyperplasia of the nasal mucosa and related structures, multifocal hyperplasia in the lungs, hyperkeratosis and acanthosis in the forestomach, and minimal toxic tubular nephropathy in the kidneys characterized by cytomegaly of occasional tubular epithelial cells.

Various spontaneous lesions were observed in all groups and appeared to be without relationship to experimental regimen. In the males, an ascending, often fulminating, urogenital infection was frequently noted. The prepuce, penis, urinary bladder, accessory sex organs, and kidneys were the usual sites of involvement. The lesions may have been contributing causes to early mortality.

Table 9. Summary of Incidences of Male and Female Mice with Lung and Nasal Cavity Tumors after Exposure to DBCP by Inhalation (a)

| | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | Untreated Control (0 ppm) | Low Dose (0.6 ppm) | High Dose (3.0 ppm) | Untreated Control (0 ppm) | Low Dose (0.6 ppm) | High Dose (3.0 ppm) |
| Animals examined | 45 | 42 | 48 | 50 | 50 | 50 |
| NASAL CAVITY | | | | | | |
| Adenomatous polyp | 0 | 1 | 5 | 0 | 3 | 0 |
| Squamous-cell papilloma | 0 | 0 | 1 | 0 | 2 | 0 |
| Squamous-cell carcinoma | 0 | 0 | 6 | 0 | 1 | 6 |
| Carcinoma, NOS | 0 | 0 | 7 | 0 | 3 | 17 |
| Adenocarcinoma, NOS | 0 | 0 | 2 | 0 | 2 | 6 |
| Neoplasm, NOS, malignant | 0 | 0 | 1 | 0 | 0 | 1 |
| Carcinosarcoma | 0 | 0 | 0 | 0 | 0 | 3 |
| Fibrosarcoma | 0 | 0 | 0 | 0 | 0 | 3 |
| Sarcoma, NOS | 0 | 0 | 0 | 0 | 0 | 1 |
| Keranthoacanthoma | 0 | 0 | 0 | 0 | 0 | 1 |
| Hemangiosarcoma | 0 | 0 | 3 | 0 | 0 | 0 |
| Animals with Nasal Cavity Tumors | 0 | 1 | 21 | 0 | 11 | 38 |
| Animals examined | 41 | 40 | 45 | 50 | 50 | 50 |
| LUNG | | | | | | |
| Alveolar/bronchiolar adenoma | 0 | 1 | 6 | 3 | 3 | 10 |
| carcinoma | 0 | 2 | 1 | 1 | 2 | 4 |
| Squamous-cell carcinoma | 0 | 0 | 0 | 0 | 0 | 1 |
| Squamous-cell carcinoma (bronchus) | 0 | 0 | 1 | 0 | 0 | 1 |
| Papillary adenoma (bronchus/bronchiole) | 0 | 0 | 0 | 0 | 0 | 1 |
| Papillary carcinoma (bronchus/bronchiole) | 0 | 0 | 3 | 0 | 7 | 6 |
| Animals with Lung Tumors | 0 | 3 | 11 | 4 | 12 | 18 |

(a) The incidence of tumors expressed in this table is greater than the incidence of animals with tumors since more than one type of tumor was detected in some of the animals.

## D. Statistical Analyses of Results (Mice)

Tables 10 and 11 contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals in one group and with an incidence of at least 5% in one or more groups.

The incidence of animals with some type of nasal cavity or nasal turbinate tumor was significantly higher ($P < 0.001$) in each of the dosed groups of females and in the high-dose group of males than in their respective control groups. A significant dose-related trend ($P < 0.001$) was also indicated in both sexes. The analysis of the time to observed tumors indicates a significantly shorter time to tumor in the high-dose group than in the controls of either sex. The times of observation of these tumors are shown by the Kaplan-Meier curves in Figures 7 and 8.

There are significant, positive, dose-related trends and significantly higher incidences of animals with carcinomas of the nasal cavity in the high-dose groups than in the control groups ($P < 0.001$ for the trend in both sexes, $P=0.008$ in males, and $P < 0.001$ in females for the Fisher exact test). The occurrence of dose-related trends and the incidences of squamous-cell carcinomas of the nasal cavity were significantly higher in the high-dose groups than in the control groups ($P < 0.001$ for the trend in males and $P=0.002$ for the trend in females; $P=0.016$ in the high-dose group of males and $P=0.013$ in the high-dose group of females). The results of the Cochran-Armitage test indicate dose-related linear trends in the combined incidence of squamous-cell carcinomas and papillomas ($P=0.011$) and in the incidence of adenocarcinomas, ($P=0.005$) in the nasal cavity of female mice. The incidences in the high-dose female mice group are significantly higher ($P=0.013$) than those of the control group in these two instances.

Respiratory tract tumors occurred at statistically significant incidences in dosed mice of both sexes. For the combined incidence of papillary carcinomas, squamous-cell carcinomas, alveolar/bronchiolar carcinomas, and alveolar/bronchiolar adenomas of the lung, bronchus, or bronchiole, significant positive dose-related trends ($P < 0.001$ in males and $P=0.001$ in females) and significantly increased incidences in the high-dose male group ($P < 0.001$), the low-dose female group ($P=0.027$) and the high-dose female

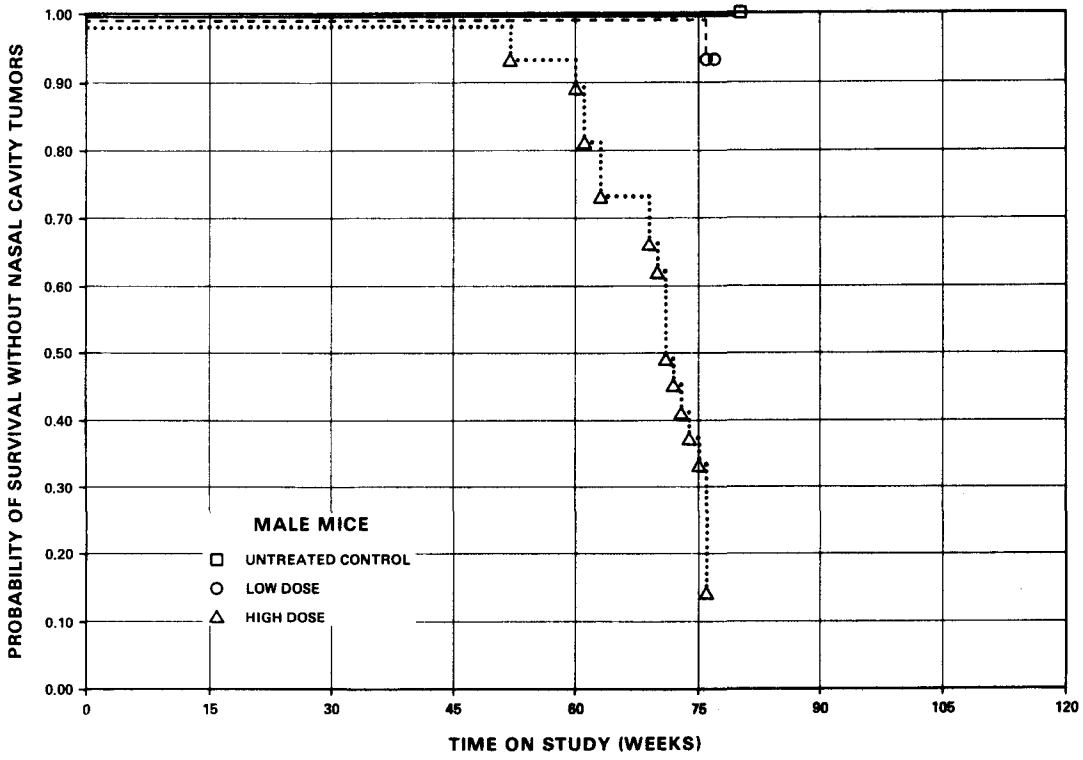



**Figure 7. Life Table for Male Mice Exposed to Air Containing DBCP: Nasal Cavity Tumors**

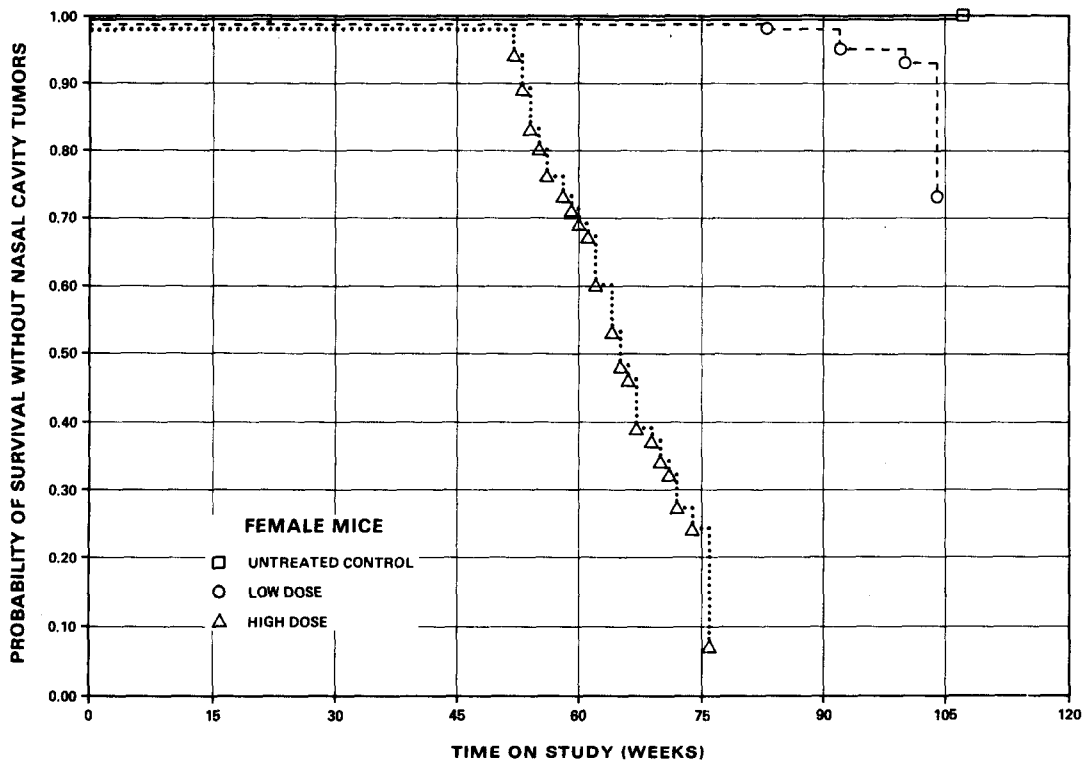



**Figure 8. Life Table for Female Mice Exposed to Air Containing DBCP: Nasal Cavity Tumors**

group ($P < 0.001$) were observed. Among male mice, alveolar/bronchiolar adenomas alone were significantly increased with a positive dose-related trend (P=0.003) and a significant incidence in the high-dose group (P= 0.017). None of the other tumor types was significant by itself in male mice. Among female mice, papillary carcinomas of the lung or bronchiole were significant in the low-dose group, and alveolar/bronchiolar adenomas exhibited a positive dose-related trend (P=0.005) and a significant incidence in the high-dose group (P=0.029). None of the other tumor types was significant by itself in female mice.

There are significant trends, in relation to increasing dose, in the incidences of fibrosarcomas (P=0.011) and of carcinosarcomas of the nasal cavity (P=0.011) in females, in the incidences of hemangiosarcomas of the circulatory system (P=0.015) and of squamous-cell papillomas or carcinomas of the stomach (P=0.016), and in the incidence of adenomatous polyps of the nasal cavity (P=0.007) in males. Comparing the dosed groups with the control group does not indicate statistical significance.

A negative trend (P=0.012) with significantly lower incidence (P=0.015) of lymphomas was observed in the high-dose female group. Such results may have been influenced by differences in the survival of mice of the various groups.

The Fisher exact test indicates a significantly lower incidence (P=0.021) of adenomas in the pituitary in the low-dose female group than in the control group, but the control group incidence of 8/48 (17%) is much higher than the historical incidence across all laboratories of 43/2,767 (1.6%) for this lesion in female B6C3F1 mice. The Cochran-Armitage test indicates a departure from linear trend (P=0.027) due to a sharp decrease in the incidence in each of the dosed groups.

In summary, the statistical analysis indicates that there is a dose-related increase in the incidence of nasal cavity tumors and respiratory tract tumors in male and female mice. The incidences of hemangiosarcomas of the circulatory system and the combined incidence of squamous-cell papillomas and carcinomas in the stomach of males may also be related to the administration of DBCP.

Table 10. Analyses of the Incidence of Primary Tumors In Male Mice Exposed to DBCP by Inhalation (a)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Nasal Cavity: Carcinoma, NOS (b) | 0/45 (0) | 0/42 (0) | 7/48 (15) |
| P Values (c) | P< 0.001 | N.S. | P=0.008 |
| Relative Risk (Control) (d) | | — | Infinite |
| Lower Limit | | — | 1.826 |
| Upper Limit | | — | Infinite |
| Weeks to First Observed Tumor | — | — | 61 |
| Nasal Cavity: Squamous-cell Carcinoma (b) | 0/45 (0) | 0/42 (0) | 6/48 (13) |
| P Values (c) | P=0.001 | N.S. | P=0.016 |
| Relative Risk (Control) (d) | | — | Infinite |
| Lower Limit | | — | 1.505 |
| Upper Limit | | — | Infinite |
| Weeks to First Observed Tumor | — | — | 60 |
| Nasal Cavity: Adenomatous Polyp, NOS (b) | 0/45 (0) | 1/42 (2) | 5/48 (10) |
| P Values (c) | P=0.007 | N.S. | P=0.033 |
| Relative Risk (Control) (d) | | Infinite | Infinite |
| Lower Limit | | 0.058 | 1.186 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | — | 76 | 70 |
| Nasal Cavity: Carcinoma, NOS, Squamous Cell Carcinoma, Squamous Cell Papilloma, Adenocarcinoma, NOS, and Adenomatous Polyp, NOS, Neoplasm, NOS, Malignant (b) | 0/45 (0) | 1/42 (2) | 19/48(40) |
| P Values (c) | P< 0.001 | N.S. | P<0.001 |
| Departure From Linear Trend (e) | P=0.007 | | |
| Relative Risk (Control) (d) | | Infinite | Infinite |
| Lower Limit | | 0.058 | 5.749 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | — | 76 | 60 |

Table 10. Analyses of the Incidence of Primary Tumors In Male Mice Exposed to DBCP by Inhalation (a)
Continued

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Lung: Alveolar/Bronchiolar Adenoma (b) | 0/41 (0) | 1/40 (3) | 6/45 (13) |
| P Values (c) | P=0.003 | N.S. | P=0.017 |
| Relative Risk (Control) (d) | | Infinite | Infinite |
| Lower Limit | | 0.055 | 1.468 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 59 | 63 |
| Lung: Alveolar/Bronchiolar Carcinoma (b) | 0/41 (0) | 2/40 (5) | 1/45 (2) |
| P Values (c) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (d) | | Infinite | Infinite |
| Lower Limit | | 0.305 | 0.049 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 77 | 76 |
| Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b) | 0/41 (0) | 3/40 (8) | 7/45 (16) |
| P Values (c) | P=0.007 | N.S. | P=0.008 |
| Relative Risk (Control) (d) | | Infinite | Infinite |
| Lower Limit | | 0.621 | 1.781 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 59 | 63 |
| Lung/Bronchus/Bronchiole: Papillary Carcinoma, Squamous-Cell Carcinoma, Alveolar/Bronchiolar Adenoma or Carcinoma (b) | 0/41 (0) | 3/40 (8) | 11/45 (24) |
| P Values (c) | P<0.001 | N.S. | P<0.001 |
| Relative Risk (Control) (d) | | Infinite | Infinite |
| Lower Limit | | 0.621 | 3.047 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 59 | 60 |

Table 10. Analyses of the Incidence of Primary Tumors In Male Mice Exposed to DBCP by Inhalation (a)
Continued

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Circulatory System: Hemangiosarcoma (b) | 0/45 (0) | 0/42 (0) | 3/48 (6) |
| P Values (c) | P=0.015 | N.S. | N.S. |
| Relative Risk (Control) (d) | | — | Infinite |
| Lower Limit | | — | 0.566 |
| Upper Limit | | — | Infinite |
| Weeks to First Observed Tumor | — | — | 63 |
| Liver: Hepatocellular Carcinoma (b) | 3/41 (7) | 2/42 (5) | 3/46 (7) |
| P Values (c) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (d) | | 0.651 | 0.891 |
| Lower Limit | | 0.057 | 0.126 |
| Upper Limit | | 5.388 | 6.321 |
| Weeks to First Observed Tumor | 72 | 59 | 69 |
| Stomach: Squamous-cell Papilloma (b) | 0/37 (0) | 0/41 (0) | 2/44 (5) |
| P Values (c) | P=0.045 | N.S. | N.S. |
| Relative Risk (Control) (d) | | — | Infinite |
| Lower Limit | | — | 0.251 |
| Upper Limit | | — | Infinite |
| Weeks to First Observed Tumor | — | — | 71 |
| Stomach: Squamous-cell Papilloma or Carcinoma (b) | 0/37 (0) | 0/41 (0) | 3/44 (7) |
| P Values (c) | P=0.016 | N.S. | N.S. |
| Relative Risk (Control) (d) | | — | Infinite |
| Lower Limit | | — | 0.511 |
| Upper Limit | | — | Infinite |
| Weeks to First Observed Tumor | — | — | 60 |

Table 10. Analyses of the Incidence of Primary Tumors In Male Mice Exposed to DBCP by Inhalation (a)

(Continued)

(a) Dosed groups were exposed to 0.6 or 3 ppm by inhalation.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
(d) The 95 percent confidence interval of the relative risk between each dosed group and the control group.
(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

Table 11. Analyses of the Incidence of Primary Tumors In Female Mice Exposed to DBCP by Inhalation (a)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Nasal Cavity: Carcinoma, NOS (b) | 0/50 (0) | 4/50 (8) | 17/50 (34) |
| P Values (c,d) | P<0.001 | N.S. | P<0.001 |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 0.927 | 5.408 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 83 | 52 |
| Nasal Cavity: Squamous-cell Carcinoma (b) | 0/50 (0) | 1/50 (2) | 6/50 (12) |
| P Values (c,d) | P=0.002 | N.S. | P=0.013 |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 0.054 | 1.600 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 100 | 53 |
| Nasal Cavity: Squamous-cell Carcinoma or Papilloma (b) | 0/50 (0) | 3/50 (6) | 6/50 (12) |
| P Values (c,d) | P=0.011 | N.S. | P=0.013 |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 0.601 | 1.600 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 100 | 53 |
| Nasal Cavity: Adenocarcinoma, NOS (b) | 0/50 (0) | 2/50 (4) | 6/50 (12) |
| P Values (c,d) | P=0.005 | N.S. | P=0.013 |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 0.296 | 1.600 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 92 | 53 |

Table 11. Analyses of the Incidence of Primary Tumors In Female Mice Exposed to DBCP by Inhalation (a)

(Continued)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Nasal Cavity: Adenomatous Polyp, NOS (b) | 0/50 (0) | 3/50 (6) | 0/50 (0) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Departure from Linear Trend (f) | P=0.019 | | |
| Relative Risk (Control) (e) | | Infinite | -- |
| Lower Limit | | 0.601 | -- |
| Upper Limit | | Infinite | -- |
| Weeks to First Observed Tumor | -- | 104 | -- |
| Nasal Cavity: Fibrosarcoma (b) | 0/50 (0) | 0/50 (0) | 3/50 (6) |
| P Values (c,d) | P=0.011 | N.S. | N.S. |
| Relative Risk (Control) (e) | | -- | Infinite |
| Lower Limit | | -- | 0.601 |
| Upper Limit | | -- | Infinite |
| Weeks to First Observed Tumor | -- | -- | 70 |
| Nasal Cavity: Carcinosarcoma (b) | 0/50 (0) | 0/50 (0) | 3/50 (6) |
| P Values (c,d) | P=0.011 | N.S. | N.S. |
| Relative Risk (Control) (e) | | -- | Infinite |
| Lower Limit | | -- | 0.601 |
| Upper Limit | | -- | Infinite |
| Weeks to First Observed Tumor | -- | -- | 62 |
| Nasal Cavity; Nasal Turbinate Carcinoma, NOS, Squamous-cell Carcinoma, Squamous-cell Papilloma, Adenocarcinoma, NOS, Adenomatous Polyp, NOS, Carcinosarcoma, Sarcoma, NOS, Keratoacanthoma, Fibrosarcoma, Neoplasm, NOS, Malignant, (b) | 0/50 (0) | 11/50(22) | 38/50(76) |
| P Values (c,d) | P<0.001 | P<0.001 | P<0.001 |
| Departure from Linear Trend (f) | | | |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 3.320 | 12.980 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 83 | 52 |

Table 11. Analyses of the Incidence of Primary Tumors In Female Mice Exposed to DBCP by Inhalation (a)

(Continued)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Lung/Bronchiole: Papillary Carcinoma (b) | 0/49 (0) | 7/49 (14) | 4/47 (9) |
| P Values (c,d) | N.S. | P=0.006 | N.S. |
| Departure from Linear Trend (f) | P=0.011 | | |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 1.943 | 0.967 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 104 | 64 |
| Lung: Alveolar/Bronchiolar Adenoma (b) | 3/49 (6) | 3/49 (6) | 10/47 (21) |
| P Values (c,d) | P=0.005 | N.S. | P=0.029 |
| Relative Risk (Control) (e) | | 1.000 | 3.475 |
| Lower Limit | | 0.140 | 0.965 |
| Upper Limit | | 7.126 | 18.545 |
| Weeks to First Observed Tumor | 105 | 104 | 53 |
| Lung: Alveolar/Bronchiolar Carcinoma (b) | 1/49 (2) | 2/49 (4) | 4/47 (9) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | 2.000 | 4.170 |
| Lower Limit | | 0.108 | 0.433 |
| Upper Limit | | 115.581 | 200.705 |
| Weeks to First Observed Tumor | 105 | 104 | 53 |
| Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b) | 4/49 (8) | 5/49 (10) | 13/47 (28) |
| P Values (c,d) | P=0.002 | N.S. | P=0.012 |
| Relative Risk (Control) (e) | | 1.250 | 3.388 |
| Lower Limit | | 0.286 | 1.141 |
| Upper Limit | | 5.947 | 13.260 |
| Weeks to First Observed Tumor | 105 | 104 | 53 |

Table 11. Analyses of the Incidence of Primary Tumors In Female Mice Exposed to DBCP by Inhalation (a)

(Continued)

| Torpography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Lung/Bronchus/Bronchiole: Papillary Carcinoma, Squamous-Cell Carcinoma, Papillary Adenoma Alveolar/Bronchiolar Adenoma or Carcinoma (b) | 4/49 (8) | 12/48 (24) | 18/47 (38) |
| P Values (c), (d) | P=0.001 | P=0.027 | P<0.001 |
| Relative Risk (Control) (e) | | 3.000 | 4.691 |
| Lower Limit | | 0.988 | 1.700 |
| Upper Limit | | 11.919 | 17.531 |
| Weeks to First Observed Tumor | 105 | 104 | 53 |
| Hematopoietic System: Malignant Lymphoma, Undifferentiated Type (b) | 3/50 (6) | 0/50 (0) | 0/50 (0) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | 0.000 | 0.000 |
| Lower Limit | | 0.000 | 0.000 |
| Upper Limit | | 1.663 | 1.663 |
| Weeks to First Observed Tumor | 87 | -- | -- |
| Hematopoietic System: Malignant Lymphoma, Lymphocytic Type (b) | 2/50 (4) | 3/50 (6) | 0/50 (0) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | 1.500 | 0.000 |
| Lower Limit | | [illegible] | 0.000 |
| Upper Limit | | 17.379 | 3.381 |
| Weeks to First Observed Tumor | 105 | 104 | -- |
| Hematopoietic System: All Lymphomas (b) | 8/50 (16) | 5/50 (10) | 1/50 (2) |
| P Values (c,d) | P=0.012 (N) | N.S. | P=0.015 (N) |
| Relative Risk (Control) (e) | | 0.625 | 0.125 |
| Lower Limit | | 0.172 | 0.003 |
| Upper Limit | | 2.011 | 0.880 |
| Weeks to First Observed Tumor | 87 | 76 | 73 |

Table 11. Analyses of the Incidence of Primary Tumors In Female Mice Exposed to DBCP by Inhalation (a)

(Continued)

| Topography: Morphology | Control | Low Dose | High Dose |
|---|---|---|---|
| Liver: Hepatocellular Carcinoma (b) | 2/50 (4) | 4/48 (8) | 2/47 (4) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | 2.083 | 1.064 |
| Lower Limit | | 0.314 | 0.080 |
| Upper Limit | | 22.174 | 14.150 |
| Weeks to First Observed Tumor | 105 | 104 | 64 |
| Liver: Hepatocellular Carcinoma or Adenoma (b) | 2/50 (4) | 5/48 (10) | 2/47 (4) |
| P Values (c,d) | N.S. | N.S. | N.S. |
| Relative Risk (Control) (e) | | 2.604 | 1.064 |
| Lower Limit | | 0.451 | 0.080 |
| Upper Limit | | 26.304 | 14.150 |
| Weeks to First Observed Tumor | 105 | 104 | 64 |
| Pituitary: Adenoma, NOS (b) | 8/48 (17) | 1/44 (2) | 1/28 (4) |
| P Values (c,d) | N.S. | P=0.021 (N) | N.S. |
| Departure from Linear Trend (f) | P=0.027 | | |
| Relative Risk (Control) (e) | | 0.136 | 0.214 |
| Lower Limit | | 0.003 | 0.005 |
| Upper Limit | | 0.955 | 1.463 |
| Weeks to First Observed Tumor | 105 | 104 | 62 |
| Harderian Gland: Adenoma, NOS (b) | 0/50 (0) | 5/50 (10) | 1/50 (2) |
| P Values (c,d) | N.S. | P=0.028 | N.S. |
| Departure from Linear Trend (f) | P=0.008 | | |
| Relative Risk (Control) (e) | | Infinite | Infinite |
| Lower Limit | | 1.261 | 0.054 |
| Upper Limit | | Infinite | Infinite |
| Weeks to First Observed Tumor | -- | 104 | 62 |

Table 11. Analyses of the Incidence of Primary Tumors In Female Mice Exposed to DBCP by Inhalation (a)
(Continued)

(a) Dosed groups received doses of 0.6 or 3 ppm by inhalation.
(b) Number of tumor-bearing animals/number of animals examined at site (percent).
(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
(e) The 95 percent confidence interval of the relative risk between each dosed group and the control group.
(f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

## V. DISCUSSION

Accelerated mortality occurred in all high-dose groups of both species. Early deaths of high-dose rats and mice were associated with respiratory tract tumors. Interference with breathing and metastasis to the brain were major contributing factors to deaths. Among male mice, accelerated mortality occurred in low-dose and control groups as well as in the high-dose group. Urogenital infection appeared to be associated with these deaths.

This study provides strong evidence for an association between tumors of the upper respiratory tract in rats and inhalation exposure to DBCP. Tumors found at significantly increased incidences in high-dose male rats include carcinomas, squamous-cell carcinomas, and adenocarcinomas of the nasal cavity and squamous-cell papillomas of the tongue. Among low-dose male rats, adenocarcinomas, adenomas, adenomatous polyps, and squamous-cell papillomas of the nasal cavity and adenomatous polyps of the nasal turbinates were statistically significant. The degree of malignancy of nasal cavity tumors in male rats was dose related in several instances, with benign tumors significantly increased in low-dose groups while corresponding malignant tumors were significantly increased in high-dose groups.

Evidence for carcinogenicity of inhaled DBCP in male rats was supported by increases in tumor incidence in female rats. Among high-dose female rats, carcinomas and adenocarcinomas of the nasal cavity, squamous-cell papillomas of the tongue, squamous-cell papillomas and carcinomas (combined) of the pharynx, and adenomas of the adrenal cortex were statistically significant. Adenomas and squamous-cell papillomas of the nasal cavity, adenomas of the adrenal cortex, and fibroadenomas of the mammary gland were increased significantly for low-dose female rats.

In both low-dose and high-dose groups of male and female rats, the combined incidences of nasal tumors were significant at the $P<0.001$ level. The nasal tumors were similar to those induced by 1,2-dibromoethane (NTP, 1982).

Despite the accelerated mortality in high-dose groups, carcinomas and squamous-cell carcinomas of the nasal cavity occurred at significantly dose-related incidences in both sexes. No nasal cavity tumors occurred in

control male rats. Except for a single squamous-cell carcinoma, no nasal cavity tumors occurred in female rats.

Certain tumors occurred in dosed rats at incidences which were increased relative to controls, but were either not statistically significant or only marginally significant; in male rats, these included trichoepitheliomas, mesotheliomas of the scrotum and tunica vaginalis, and tumors of the esophagus, larynx, trachea, and kidney and in female rats these included mammary adenomas and carcinomas. These tumors may have occurred at higher incidences if the survival time had not been shortened in high-dose animals. The hyperplastic and dysplastic lesions in some of these tissues support the conclusion that these tumors were compound related. In addition, several of these tumors, (esophagus, trachea, larynx) occur rarely in rats.

In mice this study provides strong evidence for an association between inhalation exposure and tumors of both the upper and lower respiratory tract. Nasal tumors found at increased incidences in dosed mice include carcinomas of the nasal cavity, squamous-cell carcinomas, adenocarcinomas, adenomatous polyps, fibrosarcomas, and carcinosarcomas. The combined incidence of nasal cavity tumors was statistically significant at the $P < 0.001$ level for low-dose and high-dose female mice and for high-dose male mice. The incidences of carcinomas alone and squamous-cell carcinomas alone were significant in the high-dose groups and were significantly dose related in each sex. For nasal tumors in high-dose mice, the time to observed tumor was significantly shorter than that in the controls of either sex.

Lung tumors found at increased incidences in dosed mice include adenomas, carcinomas, squamous-cell carcinomas, and papillary carcinomas. The combined incidence of these tumors was significantly dose related ($P<0.001$) and statistically significant in the high-dose group ($P < 0.001$) in each sex.

Administration of DBCP was also associated with toxic and proliferative lesions in the kidney, nasal mucosa, forestomach, and spleen in rats and mice, and in the larynx, trachea, and lungs of mice. Several of these lesions were seen in the subchronic study as well.

In other bioassays that employed feed, gavage, or skin application as the route of administration, DBCP was associated with increased incidences of squamous-cell carcinomas or papillomas of the forestomach in Osborne-Mendel

rats, Charles River albino rats, B6C3F1 mice, HAM/ICR Swiss Albino mice, and ICR/Ha Swiss mice (females); adenocarcinomas of the mammary gland in Osborne-Mendel rats (females); renal tubular tumors in Charles River albino rats; lung papillomas in ICR/Ha Swiss mice (females); and lung tumors in Charles River rats (Table 12).

In a chronic skin application study and in initiation-promotion experiments reported by Van Duuren et al. (1979), groups of 30 female ICR/Ha Swiss mice given 11.7 or 35 mg DBCP in 0.2 ml acetone three times per week for 62 weeks had increased incidences of lung papillomas and squamous-cell carcinomas or papillomas of the forestomach. In these experiments, no skin tumors were induced. However, after skin initiation with DBCP and promotion with phorbol myristate acetate, animals had a significant increase in skin tumors.

In a chronic feeding study conducted for Dow Chemical Company in the same laboratory as the present study, groups of 60 Charles River albino rats and 50 HAM/ICR Swiss albino mice were fed diets containing DBCP for 104 or 78 weeks, respectively. DBCP in the diet was associated with statistically significant increased incidences of squamous-cell carcinomas and papillomas of the forestomach in the rats and mice of either sex and of liver and renal tubular tumors in rats (Federal Register, 1979). Forestomach tumors were also found in the NCI gavage study (NCI, 1978a).

In a previous NCI study conducted by the same laboratory, DBCP administered by gavage was found to be carcinogenic for Osborne-Mendel rats and B6C3F1 mice, inducing squamous-cell carcinomas of the forestomach in rats and mice of either sex and adenocarcinomas of the mammary gland in female rats (NCI, 1978a).

From the results of these animal bioassays, it appears that DBCP causes tumors at the direct site of exposure in the stomach and nasal cavity but not on the skin. In addition, DBCP or its metabolites cause toxic lesions and tumors at distant sites.

Testicular degeneration and atrophy were seen in acute (Torkelson et al., 1961) and chronic (NCI, 1978a) bioassays in rats, but they were not seen in mice or in this chronic bioassay. Reduced spermatogenesis and infertility have been reported in male workers exposed to DBCP (Wharton et al., 1977; Biava et al., 1978; and Marshall et al., 1978). Potashnik et al. (1979) reported a close correlation between exposure time and sperm density for 23 male DBCP production line employees. Exposure greater than 100 hours was

Table 12. Comparison of Target Organs Affected in Chronic Bioassays of DBCP

| Route | Species | Sex | Dose or Dose Equivalent | Duration (weeks) | Site and Type of Leison Observed | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Tongue and/or Pharynx | Nasal Cavity | Fore-Stomach | Mammary Gland | Kidney | Lung | Liver | Adrenal Cortex |
| Gavage (NCI, 1978) | Rat (Osborne-Mendel) | M | 29 or 15 mg/kg 5 x per week | 64-78 | - | - | N(a) | - | T(b) | | | |
| | | F | 29 or 15 mg/kg 5 x per week | 64-78 | - | - | N | N | T | | | |
| Gavage (NCI, 1978) | Mouse B6C3F1 | M | 219 or 114 mg/kg 5 x per week | 47-60 | - | - | N | - | T | | | |
| | | F | 209 or 110 mg/kg 5 x per week | | - | - | N | - | T | | | |
| Feed (Fed. Reg. 1979) | Rat (Charles River Albino) | M | 0.3, 1.0 or 3.0 mg/kg | 104 | - | - | N | - | N | - | N | |
| | | F | 0.3, 1.0 or 3.0 mg/kg | 104 | - | - | N | - | N | - | N | |
| Feed (Fed. Reg. 1979) | Mouse (HAM/ICR) | M | 0.3, 1.0 or 3.0 mg/kg | 78 | - | - | N | | | | | |
| | | F | 0.3, 1.0 or 3.0 mg/kg | 78 | - | - | N | | | | | |
| Inhalation (Current Study) | Rat (F344) | M | 0.6 or 3.0 ppm 6 hours per day | 84 or 103 | N | N | - | - | T(c) | - | - | |
| | | F | 0.6 or 3.0 ppm 6 hours per day | 84 or 103 | N | N | - | - | T | - | - | N |
| Inhalation (Current Study) | Mouse (B6C3F1) | M | 0.6 or 3.0 ppm 6 hours per day | 76 | - | N | T | - | T | N | | |
| | | F | 0.6 or 3.0 ppm 6 hours per day | 76 or 103 | - | N | T | - | T | N | | |
| Skin (Van Duuren, 1979) | Mouse (Ha:ICR) | F | 11.7 or 35 mg in 0.2 ml acetone 3 x per week | 62 | - | - | N | - | - | N | | |

(a) N = neoplastic lesion
(b) T = toxic lesion
(c) Unusual kidney neoplasms observed in four dosed male rats.

associated with azoospermia and elevated follicle-stimulating hormone. Legator (1979) has compiled a chronology of DBCP toxicity studies from 1961 to 1978.

The contaminants of the technical grade DBCP used in the present study included several mutagens, such as epichlorohydrin (IARC, 1976), 1,2-dibromoethane (IARC, 1977: NTP, 1982), and 2,3-dibromo-1-propanol (Blum and Ames, 1977). The third chemical is a metabolite of tris(2,3-dibromopropyl)phosphate (IARC, 1979b, Reznik et al., 1981), the carcinogen found in the urine of some adults and children wearing sleepwear treated with this flame retardant (Blum and Ames, 1977). Epichlorohydrin (Laskin et al., 1980) at 100 ppm and 1,2-dibromoethane (NTP, 1982) at 40 or 10 ppm induced nasal tumors when inhaled. These concentrations are considerably higher than the concentrations of the respective chemicals to which rats or mice in the current study were exposed. These rats and mice may have been exposed to a maximum level of 0.021 ppm epichlorohydrin. In the epichlorohydrin study, only 1 of 100 Sprague-Dawley rats exposed to 30 ppm developed nasal carcinomas. It is not likely that the nasal tumors in the DBCP inhalation study were caused by exposure to these contaminants, but a co-carcinogenic effect cannot be ruled out.

From these DBCP bioassay data, separate reports have been published on the carcinogenic effect of oral intubation (Olson et al., 1973; Powers et al., 1975; IARC, 1979a; NCI, 1978a) on the morphology of nasal tumors induced by inhalation exposure in rats (Reznik et al., 1980a) and in mice (Reznik et al., 1980c), and on the inhalation-induced lung tumors in mice (Reznik et al., 1980b).

# VI. CONCLUSIONS

Under the conditions of this bioassay, DBCP was carcinogenic for male and female F344 rats, inducing increased incidences of nasal cavity tumors and tumors of the tongue in both sexes, and cortical adenomas in the adrenal gland of females. DBCP was carcinogenic in male and female B6C3F1 mice, inducing increased incidences of nasal cavity tumors and lung tumors.

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# APPENDIX A

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS EXPOSED TO AIR CONTAINING DBCP

## TABLE A1.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS EXPOSED TO AIR CONTAINING DBCP

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 49 |
| ANIMALS NECROPSIED | 50 | 50 | 49 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 50 | 49 |
| INTEGUMENTARY SYSTEM | | | |
| *MULTIPLE ORGANS | (50) | (50) | (49) |
| FIBROUS HISTIOCYTOMA | | 1 (2%) | |
| *SKIN | (50) | (50) | (49) |
| SQUAMOUS CELL CARCINOMA | | 1 (2%) | |
| BASAL-CELL CARCINOMA | | | 2 (4%) |
| TRICHOEPITHELIOMA | | 1 (2%) | 3 (6%) |
| KERATOACANTHOMA | | 1 (2%) | |
| *SUBCUT TISSUE | (50) | (50) | (49) |
| SARCOMA, NOS | | 1 (2%) | |
| FIBROMA | 3 (6%) | | |
| FIBROSARCOMA | 1 (2%) | | |
| LIPOMA | 1 (2%) | | |
| RESPIRATORY SYSTEM | | | |
| *NASAL CAVITY | (50) | (50) | (49) |
| CARCINOMA,NOS | | 2 (4%) | 22 (45%) |
| SQUAMOUS CELL PAPILLOMA | | 7 (14%) | 3 (6%) |
| SQUAMOUS CELL CARCINOMA | | 2 (4%) | 10 (20%) |
| SQUAMOUS CELL CARCINOMA, INVASIV | | | 1 (2%) |
| ADENOMA, NOS | | 9 (18%) | 1 (2%) |
| ADENOCARCINOMA, NOS | | 8 (16%) | 6 (12%) |
| ADENOMATOUS POLYP, NOS | | 13 (26%) | 1 (2%) |
| CARCINOSARCOMA | | | 1 (2%) |
| *NASAL SEPTUM | (50) | (50) | (49) |
| SQUAMOUS CELL CARCINOMA | | | 1 (2%) |
| *NASAL TURBINATE | (50) | (50) | (49) |
| SQUAMOUS CELL PAPILLOMA | | 3 (6%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ADENOMATOUS POLYP, NOS | | 8 (16%) | |
| *LARYNX | (50) | (50) | (49) |
| SQUAMOUS CELL CARCINOMA | | 1 (2%) | |
| #TRACHEA | (50) | (50) | (49) |
| SQUAMOUS CELL CARCINOMA | | 1 (2%) | |
| #LUNG | (50) | (50) | (49) |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | 1 (2%) | 2 (4%) | |
| PHEOCHROMOCYTOMA, METASTATIC | 1 (2%) | | |
| SARCOMA, NOS, METASTATIC | | 1 (2%) | |
| OSTEOSARCOMA, METASTATIC | | 1 (2%) | |
| **HEMATOPOIETIC SYSTEM** | | | |
| *MULTIPLE SITES | (50) | (50) | (49) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | 1 (2%) | |
| *MULTIPLE ORGANS | (50) | (50) | (49) |
| MONOCYTIC LEUKEMIA | 6 (12%) | 7 (14%) | |
| #BONE MARROW | (50) | (49) | (49) |
| PHEOCHROMOCYTOMA, METASTATIC | 1 (2%) | | |
| #SPLEEN | (50) | (50) | (49) |
| PHEOCHROMOCYTOMA, METASTATIC | 1 (2%) | | |
| #CERVICAL LYMPH NODE | (50) | (50) | (49) |
| CARCINOMA, NOS, METASTATIC | | | 1 (2%) |
| PHEOCHROMOCYTOMA, METASTATIC | 1 (2%) | | |
| #LIVER | (50) | (50) | (47) |
| MONOCYTIC LEUKEMIA | | 1 (2%) | |
| #THYMUS | (29) | (36) | (19) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | 1 (3%) | |
| **CIRCULATORY SYSTEM** | | | |
| NONE | | | |
| **DIGESTIVE SYSTEM** | | | |
| *TONGUE | (50) | (50) | (49) |
| SQUAMOUS CELL PAPILLOMA | | 1 (2%) | 8 (16%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| SQUAMOUS CELL CARCINOMA | | | 3 (6%) |
| #LIVER | (50) | (50) | (47) |
| HEPATOCELLULAR CARCINOMA | | 1 (2%) | 1 (2%) |
| *PHARYNX | (50) | (50) | (49) |
| SQUAMOUS CELL PAPILLOMA | | 2 (4%) | 1 (2%) |
| SQUAMOUS CELL CARCINOMA | | 1 (2%) | |
| #STOMACH | (50) | (49) | (49) |
| SQUAMOUS CELL PAPILLOMA | | 1 (2%) | |
| #JEJUNUM | (50) | (50) | (48) |
| ADENOCARCINOMA, NOS | 1 (2%) | | 1 (2%) |
| URINARY SYSTEM | | | |
| #KIDNEY | (50) | (50) | (49) |
| TUBULAR-CELL ADENOMA | | 3 (6%) | 1 (2%) |
| TUBULAR-CELL ADENOCARCINOMA | | 1 (2%) | 1 (2%) |
| OSTEOSARCOMA, METASTATIC | | 1 (2%) | |
| #URINARY BLADDER | (48) | (49) | (44) |
| MESOTHELIOMA, INVASIVE | | 1 (2%) | |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (45) | (48) | (44) |
| CARCINOMA,NOS | 1 (2%) | | |
| CHROMOPHOBE ADENOMA | 10 (22%) | 7 (15%) | |
| #ADRENAL | (49) | (49) | (48) |
| CORTICAL ADENOMA | 1 (2%) | 6 (12%) | 3 (6%) |
| PHEOCHROMOCYTOMA | 4 (8%) | 1 (2%) | 2 (4%) |
| PHEOCHROMOCYTOMA, MALIGNANT | 1 (2%) | | |
| #THYROID | (48) | (49) | (49) |
| FOLLICULAR-CELL CARCINOMA | | 1 (2%) | |
| C-CELL ADENOMA | | 1 (2%) | |
| C-CELL CARCINOMA | 3 (6%) | | |
| #PANCREATIC ISLETS | (49) | (50) | (49) |
| ISLET-CELL CARCINOMA | 1 (2%) | 1 (2%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| REPRODUCTIVE SYSTEM | | | |
| *PREPUTIAL GLAND | (50) | (50) | (49) |
| CARCINOMA,NOS | 1 (2%) | 1 (2%) | 1 (2%) |
| SQUAMOUS CELL CARCINOMA | 1 (2%) | | |
| #TESTIS | (50) | (50) | (48) |
| INTERSTITIAL-CELL TUMOR | 35 (70%) | 48 (96%) | 11 (23%) |
| *EPIDIDYMIS | (50) | (50) | (49) |
| MESOTHELIOMA, NOS | 2 (4%) | | |
| MESOTHELIOMA, INVASIVE | 1 (2%) | 1 (2%) | 3 (6%) |
| *SCROTUM | (50) | (50) | (49) |
| MESOTHELIOMA, INVASIVE | 1 (2%) | 1 (2%) | 3 (6%) |
| NERVOUS SYSTEM | | | |
| #CEREBRUM | (50) | (50) | (49) |
| CARCINOMA, NOS, METASTATIC | 1 (2%) | | 16 (33%) |
| SQUAMOUS CELL CARCINOMA, METASTA | | | 6 (12%) |
| ADENOCARCINOMA, NOS, METASTATIC | | 1 (2%) | 6 (12%) |
| CARCINOSARCOMA, METASTATIC | | | 1 (2%) |
| GRANULAR-CELL TUMOR, NOS | | | 1 (2%) |
| SPECIAL SENSE ORGANS | | | |
| NONE | | | |
| MUSCULOSKELETAL SYSTEM | | | |
| *STERNUM | (50) | (50) | (49) |
| LIPOMA | 1 (2%) | 1 (2%) | |
| *RIB | (50) | (50) | (49) |
| OSTEOSARCOMA | | 1 (2%) | |
| *MUSCLE OF PERINEUM | (50) | (50) | (49) |
| MESOTHELIOMA, INVASIVE | 1 (2%) | | |
| BODY CAVITIES | | | |
| *PERITONEUM | (50) | (50) | (49) |
| MESOTHELIOMA, INVASIVE | 1 (2%) | 1 (2%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| *MESENTERY | (50) | (50) | (49) |
| MESOTHELIOMA, INVASIVE | | 1 (2%) | |
| *TUNICA VAGINALIS | (50) | (50) | (49) |
| MESOTHELIOMA, NOS | | 1 (2%) | 5 (10%) |
| MESOTHELIOMA, MALIGNANT | 1 (2%) | 1 (2%) | |
| ALL OTHER SYSTEMS | | | |
| NONE | | | |
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 49 |
| NATURAL DEATH@ | 5 | 4 | 21 |
| MORIBUND SACRIFICE | 7 | 4 | 23 |
| SCHEDULED SACRIFICE | 19 | | |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 19 | 42 | 5 |
| ANIMAL MISSING | | | |
| @ INCLUDES AUTOLYZED ANIMALS | | | |
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 45 | 50 | 45 |
| TOTAL PRIMARY TUMORS | 75 | 151 | 89 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 40 | 50 | 22 |
| TOTAL BENIGN TUMORS | 55 | 114 | 34 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 18 | 27 | 41 |
| TOTAL MALIGNANT TUMORS | 18 | 36 | 49 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | 3 | 4 | 32 |
| TOTAL SECONDARY TUMORS | 9 | 9 | 37 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | 2 | 1 | 6 |
| TOTAL UNCERTAIN TUMORS | 2 | 1 | 6 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | | |
| TOTAL UNCERTAIN TUMORS | | | |
| * PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS | | | |
| # SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN | | | |

## TABLE A2.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS EXPOSED TO AIR CONTAINING DBCP

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 51 |
| ANIMALS NECROPSIED | 50 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 50 | 50 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (50) | (50) | (50) |
| SQUAMOUS CELL CARCINOMA | | 1 (2%) | 1 (2%) |
| BASAL-CELL CARCINOMA | | | 1 (2%) |
| *SUBCUT TISSUE | (50) | (50) | (50) |
| FIBROSARCOMA | | 1 (2%) | |
| LIPOMA | | 1 (2%) | |
| RESPIRATORY SYSTEM | | | |
| *NASAL CAVITY | (50) | (50) | (50) |
| CARCINOMA,NOS | | | 23 (46%) |
| SQUAMOUS CELL PAPILLOMA | | 10 (20%) | 3 (6%) |
| SQUAMOUS CELL CARCINOMA | 1 (2%) | 2 (4%) | 6 (12%) |
| SQUAMOUS CELL CARCINOMA, INVASIV | | | 1 (2%) |
| ADENOMA, NOS | | 6 (12%) | 5 (10%) |
| ADENOCARCINOMA, NOS | | 2 (4%) | 6 (12%) |
| ADENOMATOUS POLYP, NOS | | 5 (10%) | 5 (10%) |
| CARCINOSARCOMA | | 1 (2%) | |
| *NASAL TURBINATE | (50) | (50) | (50) |
| SQUAMOUS CELL PAPILLOMA | | 1 (2%) | 2 (4%) |
| ADENOMA, NOS | | 1 (2%) | 1 (2%) |
| ADENOMATOUS POLYP, NOS | | 5 (10%) | 1 (2%) |
| *LARYNX | (50) | (50) | (50) |
| SQUAMOUS CELL PAPILLOMA | | | 1 (2%) |
| #LUNG | (50) | (50) | (49) |
| ADENOCARCINOMA, NOS, METASTATIC | | | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (50) | (50) | (50) |
| MALIG.LYMPHOMA, UNDIFFER-TYPE | | | 1 (2%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| MYELOMONOCYTIC LEUKEMIA | | | 1 (2%) |
| MONOCYTIC LEUKEMIA | 6 (12%) | 6 (12%) | |
| #CERVICAL LYMPH NODE | (50) | (50) | (48) |
| CARCINOMA, NOS, METASTATIC | | | 1 (2%) |
| #LIVER | (50) | (50) | (48) |
| MONOCYTIC LEUKEMIA | | 1 (2%) | |
| **CIRCULATORY SYSTEM** | | | |
| NONE | | | |
| **DIGESTIVE SYSTEM** | | | |
| *TONGUE | (50) | (50) | (50) |
| SQUAMOUS CELL PAPILLOMA | | 3 (6%) | 6 (12%) |
| SQUAMOUS CELL CARCINOMA | | 1 (2%) | 3 (6%) |
| #LIVER | (50) | (50) | (48) |
| NEOPLASTIC NODULE | 2 (4%) | 3 (6%) | |
| HEPATOCELLULAR CARCINOMA | | 1 (2%) | |
| *PHARYNX | (50) | (50) | (50) |
| SQUAMOUS CELL PAPILLOMA | | | 5 (10%) |
| SQUAMOUS CELL CARCINOMA | | | 2 (4%) |
| SQUAMOUS CELL CARCINOMA, INVASIV | 1 (2%) | | |
| #ESOPHAGUS | (48) | (41) | (49) |
| SQUAMOUS CELL PAPILLOMA | | | 2 (4%) |
| **URINARY SYSTEM** | | | |
| NONE | | | |
| **ENDOCRINE SYSTEM** | | | |
| #PITUITARY | (50) | (47) | (46) |
| CARCINOMA,NOS | 1 (2%) | 2 (4%) | 1 (2%) |
| ADENOMA, NOS | 1 (2%) | | |
| CHROMOPHOBE ADENOMA | 20 (40%) | 20 (43%) | 2 (4%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #ADRENAL | (50) | (50) | (48) |
| CORTICAL ADENOMA | | 7 (14%) | 5 (10%) |
| PHEOCHROMOCYTOMA | 3 (6%) | | |
| #THYROID | (49) | (47) | (48) |
| C-CELL CARCINOMA | 1 (2%) | 4 (9%) | 1 (2%) |
| #PANCREATIC ISLETS | (50) | (50) | (48) |
| ISLET-CELL CARCINOMA | | 1 (2%) | |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (50) | (50) | (50) |
| CARCINOMA,NOS | | | 1 (2%) |
| ADENOMA, NOS | | | 1 (2%) |
| ADENOCARCINOMA, NOS | 1 (2%) | 1 (2%) | 4 (8%) |
| PAPILLARY CYSTADENOMA, NOS | | | 1 (2%) |
| FIBROADENOMA | 4 (8%) | 13 (26%) | 4 (8%) |
| *PREPUTIAL GLAND | (50) | (50) | (50) |
| KERATOACANTHOMA | | 1 (2%) | |
| #UTERUS | (50) | (49) | (46) |
| ENDOMETRIAL STROMAL POLYP | 6 (12%) | 4 (8%) | |
| NERVOUS SYSTEM | | | |
| #CEREBRUM | (50) | (50) | (49) |
| CARCINOMA, NOS, INVASIVE | 1 (2%) | 2 (4%) | 1 (2%) |
| CARCINOMA, NOS, METASTATIC | | | 17 (35%) |
| SQUAMOUS CELL CARCINOMA, METASTA | | 1 (2%) | 3 (6%) |
| ADENOCARCINOMA, NOS, METASTATIC | | 1 (2%) | 4 (8%) |
| C-CELL CARCINOMA, METASTATIC | | 1 (2%) | |
| ASTROCYTOMA | | | 1 (2%) |
| *OLFACTORY NERVE | (50) | (50) | (50) |
| SQUAMOUS CELL CARCINOMA, INVASIV | 1 (2%) | | |
| SPECIAL SENSE ORGANS | | | |
| *NASOLACRIMAL DUCT | (50) | (50) | (50) |
| SQUAMOUS CELL CARCINOMA | | 1 (2%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

**TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)**

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| *ZYMBAL'S GLAND | (50) | (50) | (50) |
| SQUAMOUS CELL CARCINOMA | 1 (2%) | 1 (2%) | |
| MUSCULOSKELETAL SYSTEM | | | |
| *MUSCLE OF NECK | (50) | (50) | (50) |
| SQUAMOUS CELL CARCINOMA, INVASIV | 1 (2%) | | |
| BODY CAVITIES | | | |
| *ABDOMINAL CAVITY | (50) | (50) | (50) |
| LIPOMA | | 1 (2%) | |
| ALL OTHER SYSTEMS | | | |
| NONE | | | |
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 51 |
| NATURAL DEATH@ | 7 | 7 | 24 |
| MORIBUND SACRIFICE | 5 | 3 | 20 |
| SCHEDULED SACRIFICE | 18 | | |
| ACCIDENTALLY KILLED | | | 1 |
| TERMINAL SACRIFICE | 20 | 40 | 6 |
| ANIMAL MISSING | | | |

@ INCLUDES AUTOLYZED ANIMALS

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

**TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)**

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 33 | 44 | 46 |
| TOTAL PRIMARY TUMORS | 47 | 107 | 96 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 27 | 41 | 25 |
| TOTAL BENIGN TUMORS | 34 | 78 | 44 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 9 | 21 | 41 |
| TOTAL MALIGNANT TUMORS | 11 | 26 | 52 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | 2 | 5 | 26 |
| TOTAL SECONDARY TUMORS | 4 | 5 | 28 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | 2 | 3 | |
| TOTAL UNCERTAIN TUMORS | 2 | 3 | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | | |
| TOTAL UNCERTAIN TUMORS | | | |

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

# APPENDIX B

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE EXPOSED TO AIR CONTAINING DBCP

## TABLE B1.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE EXPOSED TO AIR CONTAINING DBCP

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS MISSING | | 1 | |
| ANIMALS NECROPSIED | 45 | 42 | 48 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 44 | 42 | 46 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (45) | (42) | (48) |
| SQUAMOUS CELL PAPILLOMA | | | 1 (2%) |
| FIBROMA | | 1 (2%) | |
| *SUBCUT TISSUE | (45) | (42) | (48) |
| FIBROSARCOMA | | | 1 (2%) |
| NEUROFIBROSARCOMA | | 1 (2%) | |
| RESPIRATORY SYSTEM | | | |
| *NASAL CAVITY | (45) | (42) | (48) |
| NEOPLASM, NOS, MALIGNANT | | | 1 (2%) |
| CARCINOMA,NOS | | | 7 (15%) |
| SQUAMOUS CELL PAPILLOMA | | | 1 (2%) |
| SQUAMOUS CELL CARCINOMA | | | 6 (13%) |
| ADENOCARCINOMA, NOS | | | 2 (4%) |
| ADENOMATOUS POLYP, NOS | | 1 (2%) | 5 (10%) |
| #TRACHEA | (38) | (40) | (41) |
| SQUAMOUS CELL PAPILLOMA | | | 1 (2%) |
| #LUNG/BRONCHUS | (41) | (40) | (45) |
| PAPILLARY CARCINOMA | | | 1 (2%) |
| SQUAMOUS CELL CARCINOMA | | | 1 (2%) |
| #LUNG/BRONCHIOLE | (41) | (40) | (45) |
| PAPILLARY CARCINOMA | | | 2 (4%) |
| #LUNG | (41) | (40) | (45) |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | 1 (3%) | 6 (13%) |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | 2 (5%) | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | |
| NONE | | | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| CIRCULATORY SYSTEM | | | |
| #CEREBRUM | (38) | (41) | (46) |
| HEMANGIOSARCOMA, METASTATIC | | | 1 (2%) |
| *NASAL CAVITY | (45) | (42) | (48) |
| HEMANGIOSARCOMA | | | 3 (6%) |
| DIGESTIVE SYSTEM | | | |
| #LIVER | (41) | (42) | (46) |
| HEPATOCELLULAR CARCINOMA | 3 (7%) | 2 (5%) | 3 (7%) |
| #STOMACH | (37) | (41) | (44) |
| SQUAMOUS CELL PAPILLOMA | | | 2 (5%) |
| SQUAMOUS CELL CARCINOMA | | | 1 (2%) |
| URINARY SYSTEM | | | |
| NONE | | | |
| ENDOCRINE SYSTEM | | | |
| NONE | | | |
| REPRODUCTIVE SYSTEM | | | |
| NONE | | | |
| NERVOUS SYSTEM | | | |
| #CEREBRUM | (38) | (41) | (46) |
| CARCINOMA, NOS, METASTATIC | | | 3 (7%) |
| SQUAMOUS CELL CARCINOMA, METASTA | | | 1 (2%) |
| SPECIAL SENSE ORGANS | | | |
| *HARDERIAN GLAND | (45) | (42) | (48) |
| ADENOMA, NOS | | | 1 (2%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| MUSCULOSKELETAL SYSTEM | | | |
| NONE | | | |
| BODY CAVITIES | | | |
| NONE | | | |
| ALL OTHER SYSTEMS | | | |
| NONE | | | |
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| NATURAL DEATH@ | 34 | 33 | 39 |
| MORIBUND SACRIFICE | 3 | 1 | 4 |
| SCHEDULED SACRIFICE | | | |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 13 | 15 | 7 |
| ANIMAL MISSING | | 1 | |

@ INCLUDES AUTOLYZED ANIMALS

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

**TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)**

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 3 | 7 | 23 |
| TOTAL PRIMARY TUMORS | 3 | 8 | 46 |
| TOTAL ANIMALS WITH BENIGN TUMORS | | 3 | 15 |
| TOTAL BENIGN TUMORS | | 3 | 17 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 3 | 5 | 21 |
| TOTAL MALIGNANT TUMORS | 3 | 5 | 29 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | | | 5 |
| TOTAL SECONDARY TUMORS | | | 5 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | | | |
| TOTAL UNCERTAIN TUMORS | | | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | | |
| TOTAL UNCERTAIN TUMORS | | | |

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

## TABLE B2.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE EXPOSED TO AIR CONTAINING DBCP

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS NECROPSIED | 50 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 49 | 47 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (50) | (50) | (50) |
| CARCINOMA, NOS, INVASIVE | | | 1 (2%) |
| SQUAMOUS CELL CARCINOMA | | | 1 (2%) |
| SQUAMOUS CELL CARCINOMA, INVASIV | | | 1 (2%) |
| FIBROSARCOMA | | 1 (2%) | |
| RESPIRATORY SYSTEM | | | |
| *NASAL CAVITY | (50) | (50) | (50) |
| NEOPLASM, NOS, MALIGNANT | | | 1 (2%) |
| CARCINOMA,NOS | | 3 (6%) | 17 (34%) |
| SQUAMOUS CELL PAPILLOMA | | 2 (4%) | |
| SQUAMOUS CELL CARCINOMA | | 1 (2%) | 6 (12%) |
| ADENOCARCINOMA, NOS | | 2 (4%) | 6 (12%) |
| ADENOMATOUS POLYP, NOS | | 3 (6%) | |
| KERATOACANTHOMA | | | 1 (2%) |
| SARCOMA, NOS | | | 1 (2%) |
| FIBROSARCOMA | | | 3 (6%) |
| CARCINOSARCOMA | | | 3 (6%) |
| *NASAL TURBINATE | (50) | (50) | (50) |
| ADENOMATOUS POLYP, NOS | | 1 (2%) | |
| *LARYNX | (50) | (50) | (50) |
| CARCINOMA-IN-SITU, NOS | | 1 (2%) | |
| #TRACHEA | (49) | (47) | (45) |
| CARCINOMA-IN-SITU, NOS | | | 1 (2%) |
| #LUNG/BRONCHUS | (49) | (49) | (47) |
| PAPILLARY CARCINOMA | | | 2 (4%) |
| SQUAMOUS CELL CARCINOMA | | | 1 (2%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #LUNG/BRONCHIOLE | (49) | (49) | (47) |
| PAPILLARY CARCINOMA | | 7 (14%) | 4 (9%) |
| SQUAMOUS CELL CARCINOMA, METASTA | | | 1 (2%) |
| PAPILLARY ADENOMA | | | 1 (2%) |
| #LUNG | (49) | (49) | (47) |
| CARCINOMA, NOS, METASTATIC | | 2 (4%) | 1 (2%) |
| SQUAMOUS CELL CARCINOMA | | | 1 (2%) |
| SQUAMOUS CELL CARCINOMA, METASTA | | 1 (2%) | 2 (4%) |
| ADENOCARCINOMA, NOS, METASTATIC | | 1 (2%) | 2 (4%) |
| ALVEOLAR/BRONCHIOLAR ADENOMA | 3 (6%) | 3 (6%) | 10 (21%) |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | 1 (2%) | 2 (4%) | 4 (9%) |
| CARCINOSARCOMA, METASTATIC | | | 1 (2%) |
| OSTEOSARCOMA, METASTATIC | 1 (2%) | | |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (50) | (50) | (50) |
| MALIGNANT LYMPHOMA, NOS | 1 (2%) | 1 (2%) | |
| MALIG.LYMPHOMA, UNDIFFER-TYPE | 3 (6%) | | |
| MALIG.LYMPHOMA, LYMPHOCYTIC TYPE | 2 (4%) | 3 (6%) | |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | 1 (2%) | 1 (2%) | 1 (2%) |
| MALIGNANT LYMPHOMA, MIXED TYPE | 1 (2%) | | |
| #PULMONARY LYMPH NODE | (49) | (46) | (39) |
| SQUAMOUS CELL CARCINOMA, METASTA | | | 1 (3%) |
| #LUMBAR LYMPH NODE | (49) | (46) | (39) |
| SQUAMOUS CELL CARCINOMA, METASTA | | | 1 (3%) |
| CIRCULATORY SYSTEM | | | |
| NONE | | | |
| DIGESTIVE SYSTEM | | | |
| #LIVER | (50) | (48) | (47) |
| HEPATOCELLULAR ADENOMA | | 1 (2%) | |
| HEPATOCELLULAR CARCINOMA | 2 (4%) | 4 (8%) | 2 (4%) |
| *PHARYNX | (50) | (50) | (50) |
| SQUAMOUS CELL CARCINOMA | | | 1 (2%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

**TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)**

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #STOMACH | (50) | (48) | (46) |
| SQUAMOUS CELL PAPILLOMA | | 1 (2%) | 1 (2%) |
| SQUAMOUS CELL CARCINOMA | | | 2 (4%) |
| #SMALL INTESTINE | (47) | (47) | (44) |
| FIBROSARCOMA | | | 1 (2%) |
| URINARY SYSTEM | | | |
| #KIDNEY | (50) | (49) | (46) |
| OSTEOSARCOMA, METASTATIC | 1 (2%) | | |
| #URINARY BLADDER | (48) | (47) | (40) |
| SQUAMOUS CELL CARCINOMA, METASTA | | | 1 (3%) |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (48) | (44) | (28) |
| ADENOMA, NOS | 8 (17%) | 1 (2%) | 1 (4%) |
| #THYROID | (45) | (46) | (41) |
| FOLLICULAR-CELL ADENOMA | 1 (2%) | 1 (2%) | |
| #PANCREATIC ISLETS | (48) | (48) | (43) |
| ISLET-CELL ADENOMA | | 1 (2%) | |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (50) | (50) | (50) |
| ADENOCARCINOMA, NOS | 2 (4%) | 2 (4%) | 2 (4%) |
| *VAGINA | (50) | (50) | (50) |
| SQUAMOUS CELL CARCINOMA | | | 1 (2%) |
| LEIOMYOSARCOMA | 1 (2%) | | |
| #UTERUS | (50) | (49) | (45) |
| ENDOMETRIAL STROMAL POLYP | | 2 (4%) | |
| #CERVIX UTERI | (50) | (49) | (45) |
| SARCOMA, NOS | | 1 (2%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

**TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)**

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| NERVOUS SYSTEM | | | |
| #CEREBRUM | (50) | (49) | (46) |
| CARCINOMA, NOS, METASTATIC | | | 9 (20%) |
| SQUAMOUS CELL CARCINOMA, METASTA | | | 2 (4%) |
| ADENOCARCINOMA, NOS, METASTATIC | | | 3 (7%) |
| CARCINOSARCOMA, METASTATIC | | | 2 (4%) |
| #CEREBELLUM | (50) | (49) | (46) |
| SQUAMOUS CELL CARCINOMA, METASTA | | | 1 (2%) |
| MENINGIOMA | | | 1 (2%) |
| SPECIAL SENSE ORGANS | | | |
| *EYELID | (50) | (50) | (50) |
| SQUAMOUS CELL CARCINOMA, INVASIV | | | 1 (2%) |
| CARCINOSARCOMA, INVASIVE | | | 1 (2%) |
| *HARDERIAN GLAND | (50) | (50) | (50) |
| CARCINOMA,NOS | | | 1 (2%) |
| ADENOMA, NOS | | 5 (10%) | 1 (2%) |
| MUSCULOSKELETAL SYSTEM | | | |
| NONE | | | |
| BODY CAVITIES | | | |
| NONE | | | |
| ALL OTHER SYSTEMS | | | |
| NONE | | | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

**TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)**

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| NATURAL DEATH@ | 7 | 11 | 36 |
| MORIBUND SACRIFICE | 3 | 2 | 7 |
| SCHEDULED SACRIFICE | 21 | | |
| ACCIDENTALLY KILLED | | | |
| TERMINAL SACRIFICE | 19 | 37 | 7 |
| ANIMAL MISSING | | | |
| @ INCLUDES AUTOLYZED ANIMALS | | | |
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 22 | 31 | 45 |
| TOTAL PRIMARY TUMORS | 26 | 50 | 78 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 12 | 16 | 15 |
| TOTAL BENIGN TUMORS | 12 | 21 | 16 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 13 | 23 | 43 |
| TOTAL MALIGNANT TUMORS | 14 | 29 | 62 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | 1 | 4 | 20 |
| TOTAL SECONDARY TUMORS | 2 | 4 | 31 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | | | |
| TOTAL UNCERTAIN TUMORS | | | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | | |
| TOTAL UNCERTAIN TUMORS | | | |

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

# APPENDIX C

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS EXPOSED TO AIR CONTAINING DBCP

## TABLE C1.

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS EXPOSED TO AIR CONTAINING DBCP

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 49 |
| ANIMALS NECROPSIED | 50 | 50 | 49 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 50 | 49 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (50) | (50) | (49) |
| EPIDERMAL INCLUSION CYST | 1 (2%) | | |
| INFLAMMATION, CHRONIC | 1 (2%) | | |
| NECROSIS, FOCAL | | | 1 (2%) |
| NECROSIS, FAT | 1 (2%) | | |
| RESPIRATORY SYSTEM | | | |
| *NASAL CAVITY | (50) | (50) | (49) |
| CONGESTION, NOS | 1 (2%) | | |
| INFLAMMATION, ACUTE | | 1 (2%) | 4 (8%) |
| ABSCESS, NOS | | 1 (2%) | 3 (6%) |
| INFLAMMATION, CHRONIC | 2 (4%) | | 1 (2%) |
| NECROSIS, NOS | | 1 (2%) | |
| HYPERPLASIA, FOCAL | | 31 (62%) | 1 (2%) |
| HYPERPLASIA, DIFFUSE | | 1 (2%) | |
| HYPERPLASIA, PAPILLARY | | | 1 (2%) |
| HYPERKERATOSIS | | 2 (4%) | 2 (4%) |
| ACANTHOSIS | | | 3 (6%) |
| ANGIECTASIS | | 1 (2%) | |
| METAPLASIA, SQUAMOUS | | 2 (4%) | |
| *NASAL SEPTUM | (50) | (50) | (49) |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| FIBROUS OSTEODYSTROPHY | | | 1 (2%) |
| HYPERKERATOSIS | | | 1 (2%) |
| ACANTHOSIS | | | 1 (2%) |
| *LARYNX | (50) | (50) | (49) |
| HYPERKERATOSIS | | | 2 (4%) |
| ACANTHOSIS | | | 1 (2%) |
| METAPLASIA, SQUAMOUS | | 1 (2%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #TRACHEA | (50) | (50) | (49) |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| METAPLASIA, SQUAMOUS | | 1 (2%) | 1 (2%) |
| #LUNG/BRONCHUS | (50) | (50) | (49) |
| HYPERPLASIA, PAPILLARY | | 1 (2%) | |
| #LUNG/BRONCHIOLE | (50) | (50) | (49) |
| HYPERPLASIA, PAPILLARY | | | 1 (2%) |
| #LUNG | (50) | (50) | (49) |
| HEMORRHAGE | | 1 (2%) | |
| INFLAMMATION, ACUTE | | 3 (6%) | 4 (8%) |
| ABSCESS, NOS | | | 1 (2%) |
| PNEUMONIA, CHRONIC MURINE | 5 (10%) | 3 (6%) | 1 (2%) |
| NECROSIS, NOS | | 3 (6%) | |
| HYPERPLASIA, ALVEOLAR EPITHELIUM | 2 (4%) | 1 (2%) | 3 (6%) |
| HEMATOPOIETIC SYSTEM | | | |
| *RETICULOENDOTHELIAL | (50) | (50) | (49) |
| HYPERPLASIA, NOS | 1 (2%) | | |
| #BONE MARROW | (50) | (49) | (49) |
| HYPOPLASIA, NOS | 1 (2%) | | |
| #SPLEEN | (50) | (50) | (49) |
| HEMORRHAGE | | 1 (2%) | |
| PIGMENTATION, NOS | 4 (8%) | 1 (2%) | 13 (27%) |
| HEMATOPOIESIS | 2 (4%) | 8 (16%) | |
| #SPLENIC FOLLICLES | (50) | (50) | (49) |
| ATROPHY, NOS | | | 8 (16%) |
| #CERVICAL LYMPH NODE | (50) | (50) | (49) |
| HEMORRHAGE | 2 (4%) | 1 (2%) | |
| ABSCESS, NOS | | | 1 (2%) |
| PIGMENTATION, NOS | 1 (2%) | 1 (2%) | |
| HYPERPLASIA, LYMPHOID | 1 (2%) | 2 (4%) | 4 (8%) |
| #BRONCHIAL LYMPH NODE | (50) | (50) | (49) |
| HYPERPLASIA, LYMPHOID | | 1 (2%) | |
| #MESENTERIC L. NODE | (50) | (50) | (49) |
| HYPERPLASIA, LYMPHOID | | 1 (2%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #RENAL LYMPH NODE | (50) | (50) | (49) |
| PIGMENTATION, NOS | | | 1 (2%) |
| #LIVER | (50) | (50) | (47) |
| LEUKOCYTOSIS, NOS | | | 1 (2%) |
| #HEPATIC SINUSOID | (50) | (50) | (47) |
| LEUKOCYTOSIS, NOS | | 1 (2%) | |
| #THYMUS | (29) | (36) | (19) |
| HEMORRHAGE | 1 (3%) | | |
| CIRCULATORY SYSTEM | | | |
| #LUMBAR LYMPH NODE | (50) | (50) | (49) |
| LYMPHANGIECTASIS | | 1 (2%) | |
| #MESENTERIC L. NODE | (50) | (50) | (49) |
| LYMPHANGIECTASIS | | 1 (2%) | |
| #HEART | (50) | (50) | (49) |
| INFLAMMATION, CHRONIC | 1 (2%) | | |
| #MYOCARDIUM | (50) | (50) | (49) |
| INFLAMMATION, NOS | | | 1 (2%) |
| INFLAMMATION, CHRONIC | 32 (64%) | 39 (78%) | 26 (53%) |
| FIBROSIS | 2 (4%) | 2 (4%) | 4 (8%) |
| DEGENERATION, NOS | | | 2 (4%) |
| CALCIFICATION, NOS | | | 1 (2%) |
| #PANCREAS | (49) | (50) | (49) |
| PERIARTERITIS | | 1 (2%) | 1 (2%) |
| *MESENTERY | (50) | (50) | (49) |
| PERIARTERITIS | | | 1 (2%) |
| #TESTIS | (50) | (50) | (48) |
| PERIARTERITIS | 1 (2%) | | |
| *EPIDIDYMIS | (50) | (50) | (49) |
| PERIARTERITIS | 1 (2%) | | |
| #ADRENAL | (49) | (49) | (48) |
| THROMBOSIS, NOS | | 1 (2%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| DIGESTIVE SYSTEM | | | |
| *PALATE | (50) | (50) | (49) |
| ABSCESS, NOS | | 1 (2%) | |
| *HARD PALATE | (50) | (50) | (49) |
| ABSCESS, NOS | | 1 (2%) | |
| FIBROUS OSTEODYSTROPHY | 1 (2%) | | |
| *LIP | (50) | (50) | (49) |
| ABSCESS, NOS | 1 (2%) | | |
| INFLAMMATION, CHRONIC | 1 (2%) | | |
| *TONGUE | (50) | (50) | (49) |
| HYPERKERATOSIS | | | 2 (4%) |
| ACANTHOSIS | | | 1 (2%) |
| #SALIVARY GLAND | (49) | (50) | (49) |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| #LIVER | (50) | (50) | (47) |
| HERNIA, NOS | 2 (4%) | 4 (8%) | 1 (2%) |
| CHOLANGIOFIBROSIS | 5 (10%) | 10 (20%) | |
| HEPATITIS, TOXIC | 2 (4%) | 1 (2%) | |
| NECROSIS, NOS | | 1 (2%) | 1 (2%) |
| NECROSIS, FOCAL | 1 (2%) | | |
| INFARCT, NOS | 1 (2%) | | |
| METAMORPHOSIS FATTY | 1 (2%) | 10 (20%) | |
| FOCAL CELLULAR CHANGE | 8 (16%) | 7 (14%) | 1 (2%) |
| ANGIECTASIS | | | 1 (2%) |
| #LIVER/CENTRILOBULAR | (50) | (50) | (47) |
| NECROSIS, NOS | 1 (2%) | | |
| #BILE DUCT | (50) | (50) | (47) |
| CYST, NOS | | 1 (2%) | |
| INFLAMMATION, CHRONIC | | 3 (6%) | |
| HYPERPLASIA, NOS | 7 (14%) | 11 (22%) | 1 (2%) |
| #PANCREAS | (49) | (50) | (49) |
| INFLAMMATION, CHRONIC FOCAL | | 1 (2%) | |
| PIGMENTATION, NOS | | 1 (2%) | |
| ATROPHY, FOCAL | 8 (16%) | 3 (6%) | 2 (4%) |
| *PHARYNX | (50) | (50) | (49) |
| HYPERKERATOSIS | | | 1 (2%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

**TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)**

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ACANTHOSIS | | | 1 (2%) |
| #ESOPHAGUS | (48) | (47) | (49) |
| HYPERKERATOSIS | 1 (2%) | 4 (9%) | 18 (37%) |
| #STOMACH | (50) | (49) | (49) |
| EDEMA, NOS | | | 1 (2%) |
| ULCER, NOS | 1 (2%) | | |
| INFLAMMATION, CHRONIC | 1 (2%) | 2 (4%) | 5 (10%) |
| NECROSIS, NOS | | | 3 (6%) |
| NECROSIS, FOCAL | | | 2 (4%) |
| CALCIFICATION, NOS | | 1 (2%) | |
| HYPERKERATOSIS | | 1 (2%) | 9 (18%) |
| ACANTHOSIS | 1 (2%) | 1 (2%) | 6 (12%) |
| #LARGE INTESTINE | (49) | (49) | (43) |
| PARASITISM | 5 (10%) | 8 (16%) | 1 (2%) |
| URINARY SYSTEM | | | |
| #KIDNEY | (50) | (50) | (49) |
| ABSCESS, NOS | | 1 (2%) | |
| INFLAMMATION, CHRONIC | 43 (86%) | 48 (96%) | 21 (43%) |
| NEPHROPATHY, TOXIC | | 2 (4%) | 49 (100%) |
| PIGMENTATION, NOS | 1 (2%) | 2 (4%) | |
| HYPERPLASIA, TUBULAR CELL | | 6 (12%) | 1 (2%) |
| #URINARY BLADDER | (48) | (49) | (44) |
| INFLAMMATION, CHRONIC | | 1 (2%) | |
| HYPERPLASIA, PAPILLARY | | 1 (2%) | |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (45) | (48) | (44) |
| CYST, NOS | | 1 (2%) | |
| HEMORRHAGE | 1 (2%) | 3 (6%) | |
| HEMORRHAGIC CYST | | 1 (2%) | |
| HYPERPLASIA, FOCAL | 5 (11%) | 4 (8%) | |
| #ADRENAL | (49) | (49) | (48) |
| METAMORPHOSIS FATTY | | 1 (2%) | |
| ANGIECTASIS | | 1 (2%) | |
| #ADRENAL CORTEX | (49) | (49) | (48) |
| DEGENERATION, NOS | | 9 (18%) | 3 (6%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| METAMORPHOSIS FATTY | 5 (10%) | | |
| HYPERPLASIA, NOS | | | 1 (2%) |
| HYPERPLASIA, FOCAL | 1 (2%) | | 1 (2%) |
| #ADRENAL MEDULLA | (49) | (49) | (48) |
| HYPERPLASIA, NOS | 2 (4%) | 1 (2%) | |
| HYPERPLASIA, FOCAL | 2 (4%) | | |
| #THYROID | (48) | (49) | (49) |
| FOLLICULAR CYST, NOS | 3 (6%) | | |
| HYPERPLASIA, C-CELL | | 2 (4%) | 1 (2%) |
| #PANCREATIC ISLETS | (49) | (50) | (49) |
| HYPERPLASIA, NOS | 1 (2%) | 1 (2%) | |
| HYPERPLASIA, FOCAL | | 2 (4%) | |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (50) | (50) | (49) |
| GALACTOCELE | 1 (2%) | | 1 (2%) |
| CYSTIC DUCTS | 1 (2%) | | |
| HYPERPLASIA, CYSTIC | | 1 (2%) | |
| *PREPUCE | (50) | (50) | (49) |
| NECROSIS, FOCAL | | | 1 (2%) |
| *PREPUTIAL GLAND | (50) | (50) | (49) |
| CYSTIC DUCTS | | | 1 (2%) |
| #PROSTATE | (48) | (50) | (46) |
| ABSCESS, NOS | 4 (8%) | 17 (34%) | 8 (17%) |
| INFLAMMATION, CHRONIC | 11 (23%) | 12 (24%) | 9 (20%) |
| INFLAMMATION, CHRONIC FOCAL | 2 (4%) | | |
| *SEMINAL VESICLE | (50) | (50) | (49) |
| NECROSIS, FAT | | | 1 (2%) |
| #TESTIS | (50) | (50) | (48) |
| DEGENERATION, NOS | 1 (2%) | 8 (16%) | 4 (8%) |
| NECROSIS, NOS | 1 (2%) | | |
| INFARCT, NOS | 1 (2%) | | |
| ATROPHY, NOS | 1 (2%) | | |
| HYPERPLASIA, INTERSTITIAL CELL | 41 (82%) | 18 (36%) | 6 (13%) |
| *EPIDIDYMIS | (50) | (50) | (49) |
| STEATITIS | | 1 (2%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| GRANULOMA, SPERMATIC | 1 (2%) | | 2 (4%) |
| NECROSIS, FAT | | 2 (4%) | 1 (2%) |
| HYPERPLASIA, PAPILLARY | | | 1 (2%) |
| *SCROTUM | (50) | (50) | (49) |
| STEATITIS | | | 1 (2%) |
| **NERVOUS SYSTEM** | | | |
| #CEREBRUM | (50) | (50) | (49) |
| HEMORRHAGE | 1 (2%) | 1 (2%) | 1 (2%) |
| INFLAMMATION, FOCAL | | 1 (2%) | |
| NECROSIS, NOS | | 2 (4%) | 7 (14%) |
| **SPECIAL SENSE ORGANS** | | | |
| *EYE | (50) | (50) | (49) |
| HEMORRHAGE | | | 1 (2%) |
| PUS | | | 1 (2%) |
| SYNECHIA, ANTERIOR | 1 (2%) | | |
| SYNECHIA, POSTERIOR | 1 (2%) | | |
| CATARACT | 1 (2%) | | |
| PHTHISIS BULBI | | | 1 (2%) |
| *EYE/CORNEA | (50) | (50) | (49) |
| ULCER, NOS | | | 1 (2%) |
| INFLAMMATION, CHRONIC | 1 (2%) | | 3 (6%) |
| *EYE/RETINA | (50) | (50) | (49) |
| DEGENERATION, NOS | 1 (2%) | | |
| *EYE/CONJUNCTIVA | (50) | (50) | (49) |
| INFLAMMATION, CHRONIC | 1 (2%) | | |
| **MUSCULOSKELETAL SYSTEM** | | | |
| *ORBICULARIS OCULI MU | (50) | (50) | (49) |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| *MUSCLE OF NECK | (50) | (50) | (49) |
| INFLAMMATION, CHRONIC | | 1 (2%) | |
| DEGENERATION, NOS | | 1 (2%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| *ABDOMINAL MUSCLE | (50) | (50) | (49) |
| HEMORRHAGE | | | 1 (2%) |
| BODY CAVITIES | | | |
| *PLEURA | (50) | (50) | (49) |
| INFLAMMATION, CHRONIC | 1 (2%) | | |
| *EPICARDIUM | (50) | (50) | (49) |
| INFLAMMATION, ACUTE | | 1 (2%) | |
| *MESENTERY | (50) | (50) | (49) |
| NECROSIS, FAT | | 1 (2%) | |
| ALL OTHER SYSTEMS | | | |
| CHEEK | | | |
| ABSCESS, NOS | | 1 | 1 |
| INFLAMMATION, CHRONIC | 1 | | |
| SPECIAL MORPHOLOGY SUMMARY | | | |
| NONE | | | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C2.

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS EXPOSED TO AIR CONTAINING DBCP

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 51 |
| ANIMALS NECROPSIED | 50 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 50 | 50 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (50) | (50) | (50) |
| EPIDERMAL INCLUSION CYST | | | 2 (4%) |
| ABSCESS, NOS | 1 (2%) | | |
| RESPIRATORY SYSTEM | | | |
| *NASAL CAVITY | (50) | (50) | (50) |
| HEMORRHAGE | | | 1 (2%) |
| INFLAMMATION, ACUTE | 2 (4%) | | 7 (14%) |
| ABSCESS, NOS | 1 (2%) | 5 (10%) | 12 (24%) |
| INFLAMMATION, CHRONIC | | | 6 (12%) |
| NECROSIS, NOS | | | 1 (2%) |
| FIBROUS OSTEODYSTROPHY | | | 1 (2%) |
| HYPERPLASIA, NOS | | | 2 (4%) |
| HYPERPLASIA, FOCAL | | 24 (48%) | 23 (46%) |
| HYPERKERATOSIS | | 1 (2%) | 11 (22%) |
| ACANTHOSIS | | 2 (4%) | 2 (4%) |
| ANGIECTASIS | | | 2 (4%) |
| METAPLASIA, SQUAMOUS | | 1 (2%) | 15 (30%) |
| *NASAL TURBINATE | (50) | (50) | (50) |
| HYPERPLASIA, FOCAL | 1 (2%) | 2 (4%) | |
| HYPERKERATOSIS | | | 1 (2%) |
| *LARYNX | (50) | (50) | (50) |
| INFLAMMATION, SUPPURATIVE | 1 (2%) | | |
| HYPERKERATOSIS | | | 3 (6%) |
| METAPLASIA, SQUAMOUS | | | 1 (2%) |
| #TRACHEA | (50) | (50) | (50) |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| #LUNG/BRONCHIOLE | (50) | (50) | (49) |
| HYPERPLASIA, PAPILLARY | | 1 (2%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #LUNG | (50) | (50) | (49) |
| CONGESTION, NOS | | | 1 (2%) |
| HEMORRHAGE | | 1 (2%) | |
| PNEUMONIA, ASPIRATION | 1 (2%) | | |
| INFLAMMATION, ACUTE | | | 1 (2%) |
| ABSCESS, NOS | | 1 (2%) | |
| PNEUMONIA, CHRONIC MURINE | 2 (4%) | 2 (4%) | 5 (10%) |
| HYPERPLASIA, ALVEOLAR EPITHELIUM | 3 (6%) | 1 (2%) | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | |
| #BONE MARROW | (48) | (49) | (48) |
| HEMORRHAGE | | | 1 (2%) |
| #SPLEEN | (50) | (50) | (48) |
| CONGESTION, NOS | | 1 (2%) | |
| HEMORRHAGE | | 4 (8%) | 1 (2%) |
| FIBROSIS, FOCAL | | 1 (2%) | |
| PIGMENTATION, NOS | 10 (20%) | 28 (56%) | 34 (71%) |
| ATROPHY, NOS | 1 (2%) | | |
| HYPERPLASIA, STROMAL | | 1 (2%) | |
| HYPERPLASIA, LYMPHOID | | 1 (2%) | |
| HEMATOPOIESIS | 22 (44%) | 25 (50%) | 14 (29%) |
| #SPLENIC FOLLICLES | (50) | (50) | (48) |
| ATROPHY, NOS | | 1 (2%) | 4 (8%) |
| #SPLENIC RED PULP | (50) | (50) | (48) |
| HYPERPLASIA, NOS | | 1 (2%) | |
| #CERVICAL LYMPH NODE | (50) | (50) | (48) |
| HEMORRHAGE | | | 1 (2%) |
| PIGMENTATION, NOS | | 1 (2%) | 1 (2%) |
| HYPERPLASIA, LYMPHOID | | 2 (4%) | 7 (15%) |
| #BRONCHIAL LYMPH NODE | (50) | (50) | (48) |
| HEMORRHAGE | | | 1 (2%) |
| PIGMENTATION, NOS | | 1 (2%) | |
| #MESENTERIC L. NODE | (50) | (50) | (48) |
| ERYTHROPHAGOCYTOSIS | | 1 (2%) | |
| HYPERPLASIA, LYMPHOID | | 1 (2%) | 1 (2%) |
| #RENAL LYMPH NODE | (50) | (50) | (48) |
| HEMORRHAGE | | | 1 (2%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| PIGMENTATION, NOS | | | 1 (2%) |
| #THYMUS | (38) | (27) | (20) |
| CYST, NOS | 2 (5%) | 2 (7%) | 1 (5%) |
| #THYMIC MEDULLA | (38) | (27) | (20) |
| HYPERPLASIA, NOS | 1 (3%) | | |
| **CIRCULATORY SYSTEM** | | | |
| #MESENTERIC L. NODE | (50) | (50) | (48) |
| LYMPHANGIECTASIS | | | 1 (2%) |
| #LUNG | (50) | (50) | (49) |
| THROMBOSIS, NOS | 1 (2%) | | |
| #HEART/ATRIUM | (50) | (50) | (50) |
| THROMBOSIS, NOS | | 1 (2%) | |
| #MYOCARDIUM | (50) | (50) | (50) |
| HEMORRHAGE | | | 1 (2%) |
| INFLAMMATION, CHRONIC | 36 (72%) | 24 (48%) | 19 (38%) |
| FIBROSIS | 1 (2%) | | |
| DEGENERATION, NOS | | 5 (10%) | 3 (6%) |
| #ENDOCARDIUM | (50) | (50) | (50) |
| FIBROSIS | 3 (6%) | | |
| *MESENTERIC ARTERY | (50) | (50) | (50) |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| #PANCREAS | (50) | (50) | (48) |
| PERIARTERITIS | 1 (2%) | | |
| #ADRENAL | (50) | (50) | (48) |
| THROMBOSIS, NOS | | | 1 (2%) |
| **DIGESTIVE SYSTEM** | | | |
| *TONGUE | (50) | (50) | (50) |
| HYPERKERATOSIS | | 1 (2%) | 4 (8%) |
| ACANTHOSIS | | | 3 (6%) |
| #LIVER | (50) | (50) | (48) |
| HERNIA, NOS | 2 (4%) | 8 (16%) | 5 (10%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| CONGESTION, NOS | | 1 (2%) | |
| CHOLANGIOFIBROSIS | 4 (8%) | | |
| HEPATITIS, TOXIC | 6 (12%) | 2 (4%) | |
| NECROSIS, NOS | 2 (4%) | | 2 (4%) |
| NECROSIS, FOCAL | | 6 (12%) | 2 (4%) |
| METAMORPHOSIS FATTY | 2 (4%) | 5 (10%) | 5 (10%) |
| FOCAL CELLULAR CHANGE | 39 (78%) | 28 (56%) | 10 (21%) |
| #BILE DUCT | (50) | (50) | (48) |
| INFLAMMATION, CHRONIC | 1 (2%) | 1 (2%) | |
| HYPERPLASIA, NOS | 5 (10%) | 4 (8%) | 1 (2%) |
| HYPERPLASIA, FOCAL | | 1 (2%) | |
| #PANCREAS | (50) | (50) | (48) |
| ECTOPIA | | | 1 (2%) |
| ATROPHY, NOS | 1 (2%) | 1 (2%) | |
| ATROPHY, FOCAL | 3 (6%) | 4 (8%) | 1 (2%) |
| *PHARYNX | (50) | (50) | (50) |
| ABSCESS, NOS | 2 (4%) | | 1 (2%) |
| HYPERKERATOSIS | | 1 (2%) | 4 (8%) |
| ACANTHOSIS | | | 1 (2%) |
| #ESOPHAGUS | (48) | (41) | (49) |
| INFLAMMATION, CHRONIC | 1 (2%) | | |
| HYPERKERATOSIS | 4 (8%) | 2 (5%) | 22 (45%) |
| #STOMACH | (50) | (50) | (48) |
| CYST, NOS | | 1 (2%) | |
| HEMORRHAGE | 1 (2%) | | 2 (4%) |
| INFLAMMATION, ACUTE | 1 (2%) | | |
| ABSCESS, NOS | 1 (2%) | | |
| INFLAMMATION, CHRONIC | 1 (2%) | 2 (4%) | 7 (15%) |
| NECROSIS, NOS | 1 (2%) | | 4 (8%) |
| NECROSIS, FOCAL | 2 (4%) | 2 (4%) | 2 (4%) |
| HYPERKERATOSIS | | 2 (4%) | 15 (31%) |
| ACANTHOSIS | | 3 (6%) | 12 (25%) |
| #LARGE INTESTINE | (49) | (50) | (47) |
| PARASITISM | 8 (16%) | 8 (16%) | 2 (4%) |
| HYPERPLASIA, NOS | | 1 (2%) | |
| URINARY SYSTEM | | | |
| #KIDNEY | (50) | (50) | (49) |
| MINERALIZATION | | 1 (2%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| HYDRONEPHROSIS | 1 (2%) | | |
| CONGESTION, NOS | | 1 (2%) | |
| INFLAMMATION, CHRONIC | 39 (78%) | 43 (86%) | 15 (31%) |
| NEPHROPATHY, TOXIC | | | 46 (94%) |
| INFARCT, NOS | | | 1 (2%) |
| PIGMENTATION, NOS | | 2 (4%) | 1 (2%) |
| HYPERPLASIA, TUBULAR CELL | | | 3 (6%) |
| #KIDNEY/CORTEX | (50) | (50) | (49) |
| CYST, NOS | | | 1 (2%) |
| #URINARY BLADDER | (50) | (47) | (41) |
| INFLAMMATION, CHRONIC | | 1 (2%) | |
| HYPERPLASIA, EPITHELIAL | | | 1 (2%) |
| **ENDOCRINE SYSTEM** | | | |
| #PITUITARY | (50) | (47) | (46) |
| CYST, NOS | 9 (18%) | 8 (17%) | |
| HEMORRHAGE | | 2 (4%) | |
| HEMORRHAGIC CYST | 2 (4%) | 1 (2%) | |
| HYPERPLASIA, FOCAL | 7 (14%) | | |
| ANGIECTASIS | 1 (2%) | | |
| #ADRENAL | (50) | (50) | (48) |
| CONGESTION, NOS | | 1 (2%) | |
| METAMORPHOSIS FATTY | 1 (2%) | 3 (6%) | 6 (13%) |
| HYPERPLASIA, FOCAL | | 3 (6%) | |
| ANGIECTASIS | 2 (4%) | 9 (18%) | 11 (23%) |
| #ADRENAL CORTEX | (50) | (50) | (48) |
| HEMORRHAGE | 1 (2%) | | |
| DEGENERATION, NOS | 4 (8%) | 19 (38%) | 13 (27%) |
| HYPERPLASIA, NOS | 2 (4%) | | |
| HYPERPLASIA, FOCAL | | 4 (8%) | 2 (4%) |
| #THYROID | (49) | (47) | (48) |
| FOLLICULAR CYST, NOS | | | 1 (2%) |
| HYPERPLASIA, C-CELL | | 1 (2%) | |
| #PARATHYROID | (19) | (14) | (27) |
| HYPERPLASIA, NOS | 1 (5%) | | |
| **REPRODUCTIVE SYSTEM** | | | |
| *MAMMARY GLAND | (50) | (50) | (50) |
| GALACTOCELE | 1 (2%) | 4 (8%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| CYSTIC DUCTS | 7 (14%) | 8 (16%) | 3 (6%) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| HYPERPLASIA, DIFFUSE | | 1 (2%) | |
| HYPERPLASIA, CYSTIC | 4 (8%) | 16 (32%) | |
| *PREPUTIAL GLAND | (50) | (50) | (50) |
| CYSTIC DUCTS | | 2 (4%) | 5 (10%) |
| #UTERUS | (50) | (49) | (46) |
| HYDROMETRA | 3 (6%) | 1 (2%) | 3 (7%) |
| HEMORRHAGE | 1 (2%) | | |
| PYOMETRA | | | 1 (2%) |
| GRANULOMA, NOS | | | 1 (2%) |
| FIBROSIS, FOCAL | | | 1 (2%) |
| #UTERUS/ENDOMETRIUM | (50) | (49) | (46) |
| HYPERPLASIA, PAPILLARY | | 2 (4%) | |
| HYPERPLASIA, CYSTIC | | 3 (6%) | 2 (4%) |
| #OVARY | (50) | (49) | (47) |
| CYST, NOS | | 2 (4%) | |
| FOLLICULAR CYST, NOS | | 1 (2%) | |
| PAROVARIAN CYST | | | 1 (2%) |
| **NERVOUS SYSTEM** | | | |
| #CEREBRUM | (50) | (50) | (49) |
| HEMORRHAGE | | | 3 (6%) |
| ABSCESS, NOS | | | 2 (4%) |
| NECROSIS, NOS | | | 8 (16%) |
| #CEREBELLUM | (50) | (50) | (49) |
| HEMORRHAGE | 1 (2%) | | 1 (2%) |
| **SPECIAL SENSE ORGANS** | | | |
| *EYE | (50) | (50) | (50) |
| INFLAMMATION, ACUTE | 2 (4%) | | |
| CATARACT | 1 (2%) | 1 (2%) | |
| NECROSIS, NOS | 1 (2%) | | |
| PHTHISIS BULBI | 1 (2%) | | |
| *EYE/RETINA | (50) | (50) | (50) |
| HEMORRHAGE | | 1 (2%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| DEGENERATION, NOS | 1 (2%) | 1 (2%) | |
| *EYE/CONJUNCTIVA | (50) | (50) | (50) |
| INFLAMMATION, CHRONIC | | 1 (2%) | |
| *NASOLACRIMAL DUCT | (50) | (50) | (50) |
| INFLAMMATION, SUPPURATIVE | 1 (2%) | | |
| INFLAMMATION, ACUTE | 1 (2%) | | |
| *ZYMBAL'S GLAND | (50) | (50) | (50) |
| CYSTIC DUCTS | | | 1 (2%) |
| HYPERKERATOSIS | | | 1 (2%) |
| MUSCULOSKELETAL SYSTEM | | | |
| *MAXILLA | (50) | (50) | (50) |
| INFLAMMATION, CHRONIC | 1 (2%) | | |
| BODY CAVITIES | | | |
| *ABDOMINAL CAVITY | (50) | (50) | (50) |
| STEATITIS | 1 (2%) | | |
| NECROSIS, FAT | 8 (16%) | 2 (4%) | 1 (2%) |
| ALL OTHER SYSTEMS | | | |
| CHEEK | | | |
| ABSCESS, NOS | | | 2 |
| INFLAMMATION, CHRONIC | | | 1 |
| SPECIAL MORPHOLOGY SUMMARY | | | |
| ACCIDENTAL DEATH | | | 1 |
| AUTO/NECROPSY/HISTO PERF | 1 | 1 | 1 |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

# APPENDIX D

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE EXPOSED TO AIR CONTAINING DBCP

## TABLE D1.

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE EXPOSED TO AIR CONTAINING DBCP

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS MISSING | | 1 | |
| ANIMALS NECROPSIED | 45 | 42 | 48 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 44 | 42 | 46 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (45) | (42) | (48) |
| EPIDERMAL INCLUSION CYST | | | 2 (4%) |
| CYSTIC DUCTS | | 1 (2%) | |
| ULCER, FOCAL | 1 (2%) | | |
| INFLAMMATION, SUPPURATIVE | 1 (2%) | 1 (2%) | 1 (2%) |
| ABSCESS, NOS | | | 4 (8%) |
| INFLAMMATION, CHRONIC | | 1 (2%) | 3 (6%) |
| INFLAMMATION, FOCAL GRANULOMATOU | 1 (2%) | | |
| NECROSIS, NOS | | | 1 (2%) |
| NECROSIS, FOCAL | | 1 (2%) | |
| NECROSIS, DIFFUSE | | 1 (2%) | |
| HYPERPLASIA, FOCAL | | | 1 (2%) |
| RESPIRATORY SYSTEM | | | |
| *NASAL CAVITY | (45) | (42) | (48) |
| HEMORRHAGE | | 1 (2%) | 4 (8%) |
| INFLAMMATION, SEROUS | | | 5 (10%) |
| INFLAMMATION, SUPPURATIVE | | | 21 (44%) |
| ABSCESS, NOS | | | 2 (4%) |
| NECROSIS, FOCAL | | | 2 (4%) |
| HYPERPLASIA, FOCAL | | 2 (5%) | 12 (25%) |
| HYPERPLASIA, PAPILLARY | | 1 (2%) | |
| HYPERKERATOSIS | | | 1 (2%) |
| METAPLASIA, SQUAMOUS | | | 2 (4%) |
| *MAXILLARY SINUS | (45) | (42) | (48) |
| HYPERPLASIA, FOCAL | | | 1 (2%) |
| *LARYNX | (45) | (42) | (48) |
| HYPERPLASIA, NOS | | 1 (2%) | |
| HYPERPLASIA, FOCAL | | | 5 (10%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #TRACHEA | (38) | (40) | (41) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| HYPERPLASIA, NOS | | | 2 (5%) |
| HYPERPLASIA, EPITHELIAL | | | 1 (2%) |
| HYPERPLASIA, FOCAL | | | 4 (10%) |
| #LUNG/BRONCHUS | (41) | (40) | (45) |
| FOREIGN BODY, NOS | | 1 (3%) | |
| HYPERPLASIA, FOCAL | | | 14 (31%) |
| HYPERPLASIA, PAPILLARY | | | 2 (4%) |
| #LUNG/BRONCHIOLE | (41) | (40) | (45) |
| ABSCESS, NOS | | | 1 (2%) |
| HYPERPLASIA, NOS | | 1 (3%) | 4 (9%) |
| HYPERPLASIA, FOCAL | | 7 (18%) | 29 (64%) |
| HYPERPLASIA, PAPILLARY | | 1 (3%) | 3 (7%) |
| #LUNG | (41) | (40) | (45) |
| CONGESTION, NOS | 14 (34%) | 1 (3%) | 1 (2%) |
| ABSCESS, NOS | | 1 (3%) | |
| GRANULOMA, NOS | | | 1 (2%) |
| HYPERPLASIA, ALVEOLAR EPITHELIUM | | 2 (5%) | 7 (16%) |
| HEMATOPOIETIC SYSTEM | | | |
| #BONE MARROW | (35) | (37) | (42) |
| HYPERPLASIA, NOS | | 5 (14%) | 4 (10%) |
| #SPLEEN | (37) | (42) | (45) |
| ATROPHY, NOS | 1 (3%) | | 16 (36%) |
| HEMATOPOIESIS | 9 (24%) | 12 (29%) | 13 (29%) |
| MYELOPOIESIS | 1 (3%) | | |
| GRANULOPOIESIS | | 4 (10%) | |
| #SPLENIC CAPSULE | (37) | (42) | (45) |
| INFLAMMATION, CHRONIC | | 1 (2%) | |
| #SPLENIC FOLLICLES | (37) | (42) | (45) |
| NECROSIS, NOS | | 7 (17%) | |
| #CERVICAL LYMPH NODE | (32) | (36) | (37) |
| PIGMENTATION, NOS | | | 1 (3%) |
| HYPERPLASIA, LYMPHOID | | | 2 (5%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #ABDOMINAL LYMPH NODE | (32) | (36) | (37) |
| HYPERPLASIA, LYMPHOID | | 1 (3%) | |
| #PANCREATIC L.NODE | (32) | (36) | (37) |
| NECROSIS, NOS | | 1 (3%) | |
| HYPERPLASIA, LYMPHOID | | 1 (3%) | |
| #MESENTERIC L. NODE | (32) | (36) | (37) |
| HYPERPLASIA, LYMPHOID | 1 (3%) | | |
| #RENAL LYMPH NODE | (32) | (36) | (37) |
| HYPERPLASIA, LYMPHOID | | 1 (3%) | |
| #INGUINAL LYMPH NODE | (32) | (36) | (37) |
| NECROSIS, NOS | | 1 (3%) | |
| HYPERPLASIA, LYMPHOID | | 2 (6%) | |
| #LUNG | (41) | (40) | (45) |
| LEUKOCYTOSIS, NOS | | 1 (3%) | 4 (9%) |
| HYPERPLASIA, LYMPHOID | | | 1 (2%) |
| #LIVER | (41) | (42) | (46) |
| LEUKOCYTOSIS, NOS | | 1 (2%) | |
| GRANULOPOIESIS | | 1 (2%) | |
| #KIDNEY | (40) | (42) | (46) |
| HYPERPLASIA, LYMPHOID | | 2 (5%) | |
| #URINARY BLADDER | (41) | (42) | (41) |
| HYPERPLASIA, LYMPHOID | | 1 (2%) | |
| CIRCULATORY SYSTEM | | | |
| *SKELETAL MUSCLE | (45) | (42) | (48) |
| THROMBOSIS, NOS | 1 (2%) | | |
| #LUNG | (41) | (40) | (45) |
| THROMBOSIS, NOS | | 1 (3%) | |
| #HEART | (41) | (41) | (45) |
| THROMBOSIS, NOS | | 1 (2%) | |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| NECROSIS, NOS | | | 1 (2%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #MYOCARDIUM | (41) | (41) | (45) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| ABSCESS, NOS | | 1 (2%) | |
| INFLAMMATION, CHRONIC | | 2 (5%) | 2 (4%) |
| CALCIFICATION, NOS | | | 1 (2%) |
| #LIVER | (41) | (42) | (46) |
| THROMBOSIS, NOS | | 1 (2%) | |
| #KIDNEY | (40) | (42) | (46) |
| THROMBOSIS, NOS | | 1 (2%) | |
| #URINARY BLADDER | (41) | (42) | (41) |
| PERIARTERITIS | 1 (2%) | | |
| DIGESTIVE SYSTEM | | | |
| *LIP | (45) | (42) | (48) |
| ULCER, FOCAL | 1 (2%) | | |
| INFLAMMATION, SUPPURATIVE | 1 (2%) | | |
| ABSCESS, NOS | 1 (2%) | | |
| *ROOT OF TOOTH | (45) | (42) | (48) |
| ABSCESS, NOS | 1 (2%) | | |
| #SALIVARY GLAND | (36) | (40) | (43) |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| FIBROSIS | | 1 (3%) | |
| DEGENERATION, NOS | | | 1 (2%) |
| #PAROTID GLAND | (36) | (40) | (43) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| NECROSIS, NOS | | | 1 (2%) |
| #LIVER | (41) | (42) | (46) |
| INFLAMMATION, SUPPURATIVE | 1 (2%) | | |
| ABSCESS, NOS | | 1 (2%) | |
| NECROSIS, NOS | | 2 (5%) | |
| NECROSIS, FOCAL | 2 (5%) | 1 (2%) | 1 (2%) |
| FOCAL CELLULAR CHANGE | | 1 (2%) | |
| #LIVER/CENTRILOBULAR | (41) | (42) | (46) |
| NECROSIS, FOCAL | 1 (2%) | | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #PANCREAS | (35) | (42) | (46) |
| EDEMA, INTERSTITIAL | 1 (3%) | | |
| INFLAMMATION, CHRONIC | | 1 (2%) | |
| NECROSIS, FOCAL | 1 (3%) | | |
| ATROPHY, NOS | | | 1 (2%) |
| *PHARYNX | (45) | (42) | (48) |
| ACANTHOSIS | | | 1 (2%) |
| #ESOPHAGUS | (37) | (36) | (40) |
| HYPERPLASIA, FOCAL | | 1 (3%) | 1 (3%) |
| #STOMACH | (37) | (41) | (44) |
| HEMORRHAGE | | | 3 (7%) |
| INFLAMMATION, CHRONIC | | | 2 (5%) |
| NECROSIS, FOCAL | | 1 (2%) | |
| HYPERKERATOSIS | | 10 (24%) | 17 (39%) |
| ACANTHOSIS | | 6 (15%) | 11 (25%) |
| #LARGE INTESTINE | (39) | (40) | (46) |
| INFLAMMATION, CHRONIC | | 1 (3%) | |
| URINARY SYSTEM | | | |
| #KIDNEY | (40) | (42) | (46) |
| HYDRONEPHROSIS | | 2 (5%) | 2 (4%) |
| HEMORRHAGE | | 3 (7%) | |
| INFLAMMATION, SUPPURATIVE | | 9 (21%) | 7 (15%) |
| PYELONEPHRITIS SUPPURATIVE | 8 (20%) | | 3 (7%) |
| ABSCESS, NOS | | 7 (17%) | 1 (2%) |
| INFLAMMATION, CHRONIC | 1 (3%) | 3 (7%) | 6 (13%) |
| PYELONEPHRITIS, CHRONIC | 3 (8%) | | |
| FIBROSIS | | 5 (12%) | 2 (4%) |
| NEPHROPATHY, TOXIC | | 1 (2%) | 9 (20%) |
| NECROSIS, NOS | | 4 (10%) | 2 (4%) |
| NECROSIS, FOCAL | | 1 (2%) | 2 (4%) |
| NECROSIS, DIFFUSE | | 1 (2%) | 1 (2%) |
| NECROSIS, MEDULLARY | | 1 (2%) | 1 (2%) |
| INFARCT, NOS | | | 2 (4%) |
| CALCIFICATION, NOS | | 4 (10%) | |
| ATROPHY, NOS | | 2 (5%) | |
| #KIDNEY/CORTEX | (40) | (42) | (46) |
| CYST, NOS | | 2 (5%) | 1 (2%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #RENAL PAPILLA | (40) | (42) | (46) |
| HYPERPLASIA, PAPILLARY | | | 1 (2%) |
| #PERIRENAL TISSUE | (40) | (42) | (46) |
| INFLAMMATION, CHRONIC | | 1 (2%) | |
| #KIDNEY/PELVIS | (40) | (42) | (46) |
| INFLAMMATION, NOS | | | 1 (2%) |
| INFLAMMATION, SUPPURATIVE | | 4 (10%) | 6 (13%) |
| NECROSIS, NOS | 2 (5%) | | |
| *URETER | (45) | (42) | (48) |
| ABSCESS, NOS | | | 1 (2%) |
| #URINARY BLADDER | (41) | (42) | (41) |
| DISTENTION | 10 (24%) | | |
| CONGESTION, NOS | | 1 (2%) | |
| EDEMA, NOS | | 1 (2%) | |
| INFLAMMATION, SUPPURATIVE | 1 (2%) | 5 (12%) | 2 (5%) |
| INFLAMMATION, HEMORRHAGIC | 1 (2%) | 1 (2%) | |
| INFLAMMATION, CHRONIC | 6 (15%) | 1 (2%) | 9 (22%) |
| INFLAMMATION, CHRONIC SUPPURATIV | 3 (7%) | | |
| FIBROSIS | | 3 (7%) | |
| NECROSIS, NOS | | 2 (5%) | 3 (7%) |
| NECROSIS, FOCAL | | | 1 (2%) |
| NECROSIS, DIFFUSE | | 4 (10%) | 2 (5%) |
| HYPERPLASIA, EPITHELIAL | | 3 (7%) | 5 (12%) |
| HYPERPLASIA, DIFFUSE | | 1 (2%) | 1 (2%) |
| HYPERPLASIA, PAPILLARY | | | 1 (2%) |
| *URETHRA | (45) | (42) | (48) |
| ABSCESS, NOS | | | 1 (2%) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| ENDOCRINE SYSTEM | | | |
| #ADRENAL | (34) | (40) | (44) |
| ANGIECTASIS | | | 1 (2%) |
| #ADRENAL MEDULLA | (34) | (40) | (44) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| #PERIADRENAL TISSUE | (34) | (40) | (44) |
| INFLAMMATION, SUPPURATIVE | | 2 (5%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #THYROID | (31) | (34) | (36) |
| FOLLICULAR CYST, NOS | | 1 (3%) | 1 (3%) |
| REPRODUCTIVE SYSTEM | | | |
| *PENIS | (45) | (42) | (48) |
| HEMORRHAGE | 1 (2%) | | 1 (2%) |
| ULCER, NOS | 4 (9%) | | |
| INFLAMMATION, SUPPURATIVE | 5 (11%) | 2 (5%) | 1 (2%) |
| NECROSIS, NOS | 1 (2%) | 1 (2%) | |
| *PREPUCE | (45) | (42) | (48) |
| HEMORRHAGE | | 2 (5%) | |
| ULCER, NOS | 8 (18%) | | |
| INFLAMMATION, SUPPURATIVE | 10 (22%) | 7 (17%) | 3 (6%) |
| ABSCESS, NOS | 1 (2%) | | 1 (2%) |
| INFLAMMATION, CHRONIC | 1 (2%) | 4 (10%) | 3 (6%) |
| NECROSIS, NOS | | 7 (17%) | 3 (6%) |
| NECROSIS, FOCAL | | 2 (5%) | 2 (4%) |
| HYPERKERATOSIS | | | 2 (4%) |
| ACANTHOSIS | | 1 (2%) | 3 (6%) |
| *PREPUTIAL GLAND | (45) | (42) | (48) |
| CYST, NOS | 3 (7%) | | |
| CYSTIC DUCTS | | 1 (2%) | 4 (8%) |
| INFLAMMATION, SUPPURATIVE | 1 (2%) | | |
| ABSCESS, NOS | 1 (2%) | 1 (2%) | |
| INFLAMMATION, CHRONIC | 2 (4%) | 2 (5%) | |
| HYPERKERATOSIS | | | 3 (6%) |
| #PROSTATE | (41) | (40) | (43) |
| INFLAMMATION, SUPPURATIVE | 6 (15%) | 10 (25%) | 9 (21%) |
| ABSCESS, NOS | | 1 (3%) | 2 (5%) |
| INFLAMMATION, CHRONIC | 2 (5%) | 2 (5%) | 4 (9%) |
| *SEMINAL VESICLE | (45) | (42) | (48) |
| DISTENTION | 1 (2%) | | |
| CYST, NOS | | | 2 (4%) |
| INFLAMMATION, SUPPURATIVE | 2 (4%) | 1 (2%) | 2 (4%) |
| ABSCESS, NOS | | | 1 (2%) |
| HYPERPLASIA, NOS | | | 1 (2%) |
| #TESTIS | (42) | (41) | (45) |
| INFLAMMATION, SUPPURATIVE | | 2 (5%) | 1 (2%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| DEGENERATION, NOS | | | 2 (4%) |
| NECROSIS, NOS | | 2 (5%) | |
| *EPIDIDYMIS | (45) | (42) | (48) |
| INFLAMMATION, SUPPURATIVE | 1 (2%) | 3 (7%) | 1 (2%) |
| INFLAMMATION, CHRONIC | 1 (2%) | | |
| **NERVOUS SYSTEM** | | | |
| #CEREBRUM | (38) | (41) | (46) |
| HEMORRHAGE | | | 1 (2%) |
| ABSCESS, NOS | | 2 (5%) | |
| INFLAMMATION ACUTE PUSTULAR | | 1 (2%) | |
| #BRAIN | (38) | (41) | (46) |
| CALCIFICATION, FOCAL | 9 (24%) | | |
| #CEREBELLUM | (38) | (41) | (46) |
| ABSCESS, NOS | | 1 (2%) | |
| **SPECIAL SENSE ORGANS** | | | |
| *EYE | (45) | (42) | (48) |
| HEMORRHAGE | | | 1 (2%) |
| **MUSCULOSKELETAL SYSTEM** | | | |
| *MANDIBLE | (45) | (42) | (48) |
| INFLAMMATION, SUPPURATIVE | 1 (2%) | | |
| *SKELETAL MUSCLE | (45) | (42) | (48) |
| INFLAMMATION, SUPPURATIVE | 1 (2%) | | |
| **BODY CAVITIES** | | | |
| *ABDOMINAL CAVITY | (45) | (42) | (48) |
| NECROSIS, FAT | | 1 (2%) | |
| *PERITONEUM | (45) | (42) | (48) |
| INFLAMMATION, SUPPURATIVE | | 1 (2%) | |
| *TUNICA VAGINALIS | (45) | (42) | (48) |
| INFLAMMATION, CHRONIC | 1 (2%) | | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ALL OTHER SYSTEMS | | | |
| CHIN | | | |
| INFLAMMATION, PYOGRANULOMATOUS | 1 | | |
| SPECIAL MORPHOLOGY SUMMARY | | | |
| NO LESION REPORTED | 6 | 2 | |
| ANIMAL MISSING/NO NECROPSY | | 1 | |
| AUTO/NECROPSY/HISTO PERF | 3 | 3 | 1 |
| AUTO/NECROPSY/NO HISTO | 1 | | 2 |
| AUTOLYSIS/NO NECROPSY | 5 | 7 | 2 |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D2.

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE EXPOSED TO AIR CONTAINING DBCP

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS NECROPSIED | 50 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 49 | 47 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (50) | (50) | (50) |
| INFLAMMATION, SUPPURATIVE | | 1 (2%) | |
| INFLAMMATION, CHRONIC | | 1 (2%) | |
| NECROSIS, FOCAL | | 1 (2%) | |
| ACANTHOSIS | | 1 (2%) | |
| RESPIRATORY SYSTEM | | | |
| *NASAL CAVITY | (50) | (50) | (50) |
| HEMORRHAGE | | 1 (2%) | |
| INFLAMMATION, SEROUS | | 4 (8%) | 4 (8%) |
| INFLAMMATION, SUPPURATIVE | | 5 (10%) | 13 (26%) |
| FIBROUS OSTEODYSTROPHY | | 1 (2%) | |
| HYPERPLASIA, FOCAL | | 17 (34%) | 3 (6%) |
| HYPERPLASIA, PAPILLARY | | 1 (2%) | |
| HYPERKERATOSIS | | | 1 (2%) |
| ANGIECTASIS | | 1 (2%) | |
| METAPLASIA, SQUAMOUS | | | 1 (2%) |
| *NASAL TURBINATE | (50) | (50) | (50) |
| HYPERPLASIA, FOCAL | | | 1 (2%) |
| HYPERKERATOSIS | | | 1 (2%) |
| *LARYNX | (50) | (50) | (50) |
| NECROSIS, FOCAL | | | 1 (2%) |
| HYPERPLASIA, NOS | | 1 (2%) | 3 (6%) |
| HYPERPLASIA, FOCAL | | 3 (6%) | 2 (4%) |
| #TRACHEA | (49) | (47) | (45) |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| #LUNG/BRONCHUS | (49) | (49) | (47) |
| CONGESTION, NOS | 1 (2%) | | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| HYPERPLASIA, FOCAL | | 1 (2%) | 2 (4%) |
| HYPERPLASIA, PAPILLARY | | | 2 (4%) |
| METAPLASIA, SQUAMOUS | | | 1 (2%) |
| #LUNG/BRONCHIOLE | (49) | (49) | (47) |
| HYPERPLASIA, NOS | | 5 (10%) | 11 (23%) |
| HYPERPLASIA, FOCAL | | 2 (4%) | 13 (28%) |
| #LUNG | (49) | (49) | (47) |
| CONGESTION, NOS | | 1 (2%) | 1 (2%) |
| HEMORRHAGE | 1 (2%) | | |
| INFLAMMATION, SUPPURATIVE | | | 3 (6%) |
| ABSCESS, NOS | | | 2 (4%) |
| PNEUMONIA, CHRONIC MURINE | | 2 (4%) | 2 (4%) |
| NECROSIS, NOS | | | 1 (2%) |
| HYPERPLASIA, ALVEOLAR EPITHELIUM | | 5 (10%) | 11 (23%) |
| HEMATOPOIETIC SYSTEM | | | |
| #BONE MARROW | (47) | (48) | (46) |
| FIBROUS OSTEODYSTROPHY | 28 (60%) | | |
| HYPERPLASIA, NOS | | | 2 (4%) |
| #SPLEEN | (50) | (49) | (43) |
| ATROPHY, NOS | | 3 (6%) | 19 (44%) |
| ANGIECTASIS | 1 (2%) | | |
| HYPERPLASIA, LYMPHOID | 7 (14%) | 10 (20%) | |
| HEMATOPOIESIS | | 1 (2%) | 5 (12%) |
| #LYMPH NODE | (49) | (46) | (39) |
| HYPERPLASIA, LYMPHOID | | 1 (2%) | |
| #CERVICAL LYMPH NODE | (49) | (46) | (39) |
| HYPERPLASIA, LYMPHOID | 2 (4%) | | 1 (3%) |
| #BRONCHIAL LYMPH NODE | (49) | (46) | (39) |
| HYPERPLASIA, NOS | | | 1 (3%) |
| HYPERPLASIA, LYMPHOID | 2 (4%) | 2 (4%) | |
| #MESENTERIC L. NODE | (49) | (46) | (39) |
| ANGIECTASIS | | | 1 (3%) |
| HYPERPLASIA, LYMPHOID | 3 (6%) | 4 (9%) | |
| #LUNG | (49) | (49) | (47) |
| LEUKOCYTOSIS, NOS | | | 1 (2%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| HYPERPLASIA, LYMPHOID | | 3 (6%) | 1 (2%) |
| #LIVER | (50) | (48) | (47) |
| HYPERPLASIA, LYMPHOID | | 1 (2%) | |
| #KIDNEY | (50) | (49) | (46) |
| HYPERPLASIA, LYMPHOID | | 6 (12%) | |
| CIRCULATORY SYSTEM | | | |
| #MYOCARDIUM | (50) | (49) | (47) |
| ABSCESS, NOS | | | 1 (2%) |
| *LINGUAL ARTERY | (50) | (50) | (50) |
| INFLAMMATION, CHRONIC | | 1 (2%) | |
| *PANCREATIC ARTERY, | (50) | (50) | (50) |
| INFLAMMATION, CHRONIC | | 1 (2%) | |
| #LIVER | (50) | (48) | (47) |
| THROMBOSIS, NOS | 1 (2%) | | |
| #UTERUS/ENDOMETRIUM | (50) | (49) | (45) |
| THROMBOSIS, NOS | | 1 (2%) | |
| DIGESTIVE SYSTEM | | | |
| *PALATE | (50) | (50) | (50) |
| NECROSIS, FOCAL | | 1 (2%) | |
| #SALIVARY GLAND | (47) | (46) | (42) |
| INFLAMMATION, CHRONIC | | 2 (4%) | |
| #LIVER | (50) | (48) | (47) |
| DILATATION, NOS | | 1 (2%) | |
| INFLAMMATION, FOCAL | 1 (2%) | | |
| PELIOSIS HEPATIS | | 1 (2%) | |
| NECROSIS, FOCAL | | 3 (6%) | 2 (4%) |
| INFARCT, NOS | 1 (2%) | | |
| FOCAL CELLULAR CHANGE | 2 (4%) | 1 (2%) | |
| #LIVER/KUPFFER CELL | (50) | (48) | (47) |
| HYPERPLASIA, FOCAL | | 1 (2%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| *GALLBLADDER | (50) | (50) | (50) |
| CALCULUS, NOS | 1 (2%) | | |
| CYST, NOS | | | 1 (2%) |
| #BILE DUCT | (50) | (48) | (47) |
| HYPERPLASIA, NOS | 1 (2%) | | |
| #PANCREAS | (48) | (48) | (43) |
| CYSTIC DUCTS | 2 (4%) | 1 (2%) | |
| NECROSIS, NOS | | | 1 (2%) |
| NECROSIS, FOCAL | | 1 (2%) | |
| METAMORPHOSIS FATTY | 2 (4%) | | |
| *PHARYNX | (50) | (50) | (50) |
| HYPERPLASIA, FOCAL | | 1 (2%) | 2 (4%) |
| ACANTHOSIS | | | 1 (2%) |
| #ESOPHAGUS | (47) | (48) | (44) |
| HYPERKERATOSIS | | | 2 (5%) |
| #STOMACH | (50) | (48) | (46) |
| CYST, NOS | | 1 (2%) | |
| HEMORRHAGE | | | 2 (4%) |
| INFLAMMATION, CHRONIC | | 2 (4%) | 4 (9%) |
| NECROSIS, FOCAL | | 1 (2%) | 3 (7%) |
| HYPERPLASIA, FOCAL | | 1 (2%) | |
| HYPERKERATOSIS | | 20 (42%) | 24 (52%) |
| ACANTHOSIS | | 12 (25%) | 18 (39%) |
| #COLON | (49) | (46) | (39) |
| NEMATODIASIS | 1 (2%) | | |
| URINARY SYSTEM | | | |
| #KIDNEY | (50) | (49) | (46) |
| INFLAMMATION, CHRONIC | 1 (2%) | 1 (2%) | |
| CALCIFICATION, NOS | | | 2 (4%) |
| HYPERPLASIA, FOCAL | | 1 (2%) | |
| #KIDNEY/PELVIS | (50) | (49) | (46) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| #URINARY BLADDER | (48) | (47) | (40) |
| DISTENTION | 1 (2%) | | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (48) | (44) | (28) |
| CYST, NOS | 1 (2%) | | |
| HYPERPLASIA, NOS | 1 (2%) | | |
| HYPERPLASIA, FOCAL | | 2 (5%) | |
| ANGIECTASIS | | 1 (2%) | |
| #ADRENAL | (48) | (49) | (44) |
| CONGESTION, NOS | | | 1 (2%) |
| HEMORRHAGE | | 1 (2%) | 1 (2%) |
| ANGIECTASIS | | | 2 (5%) |
| #ADRENAL CORTEX | (48) | (49) | (44) |
| HYPERPLASIA, FOCAL | | | 1 (2%) |
| #PARATHYROID | (26) | (21) | (20) |
| CYST, NOS | 1 (4%) | | |
| #PANCREATIC ISLETS | (48) | (48) | (43) |
| HYPERPLASIA, NOS | | 1 (2%) | |
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (50) | (50) | (50) |
| GALACTOCELE | | 1 (2%) | |
| FIBROSIS | | | 1 (2%) |
| HYPERPLASIA, EPITHELIAL | 1 (2%) | | |
| LACTATION | 4 (8%) | | |
| *VAGINA | (50) | (50) | (50) |
| EDEMA, NOS | 3 (6%) | | |
| INFLAMMATION, SUPPURATIVE | 3 (6%) | | |
| INFLAMMATION, CHRONIC | | 1 (2%) | 1 (2%) |
| ACANTHOSIS | | 1 (2%) | |
| #UTERUS | (50) | (49) | (45) |
| HYDROMETRA | 2 (4%) | 1 (2%) | 2 (4%) |
| #CERVIX UTERI | (50) | (49) | (45) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| INFLAMMATION, CHRONIC | | 1 (2%) | |
| #UTERUS/ENDOMETRIUM | (50) | (49) | (45) |
| CYST, NOS | | | 11 (24%) |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

## TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| HEMORRHAGE | | 1 (2%) | |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| HYPERPLASIA, CYSTIC | 41 (82%) | 44 (90%) | 6 (13%) |
| ANGIECTASIS | | 1 (2%) | |
| #ENDOMETRIAL GLAND | (50) | (49) | (45) |
| CYST, NOS | 2 (4%) | | |
| #OVARY | (48) | (46) | (29) |
| CYST, NOS | | 1 (2%) | |
| CYSTIC FOLLICLES | 5 (10%) | | |
| FOLLICULAR CYST, NOS | 1 (2%) | 2 (4%) | 1 (3%) |
| PAROVARIAN CYST | 7 (15%) | 1 (2%) | |
| INFLAMMATION, CHRONIC | | | 1 (3%) |
| NERVOUS SYSTEM | | | |
| #CEREBRUM | (50) | (49) | (46) |
| HEMORRHAGE | | | 2 (4%) |
| GLIOSIS | | 1 (2%) | |
| NECROSIS, NOS | | | 1 (2%) |
| NECROSIS, FOCAL | | | 2 (4%) |
| #BRAIN | (50) | (49) | (46) |
| CALCIFICATION, FOCAL | 7 (14%) | | |
| #CEREBELLUM | (50) | (49) | (46) |
| NECROSIS, NOS | | | 1 (2%) |
| SPECIAL SENSE ORGANS | | | |
| *EYE | (50) | (50) | (50) |
| PUS | | | 1 (2%) |
| CATARACT | | 2 (4%) | |
| PHTHISIS BULBI | | 2 (4%) | 1 (2%) |
| *EYE/CORNEA | (50) | (50) | (50) |
| INFLAMMATION, FOCAL | 2 (4%) | | |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| *EYELID | (50) | (50) | (50) |
| NECROSIS, FOCAL | | | 1 (2%) |
| HYPERPLASIA, NOS | | 1 (2%) | |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

**TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)**

| | UNTREATED CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ACANTHOSIS | | 2 (4%) | |
| *HARDERIAN GLAND | (50) | (50) | (50) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| HYPERPLASIA, FOCAL | | 2 (4%) | |
| MUSCULOSKELETAL SYSTEM | | | |
| *STERNUM | (50) | (50) | (50) |
| FIBROUS OSTEODYSTROPHY | | 39 (78%) | 1 (2%) |
| BODY CAVITIES | | | |
| *MEDIASTINUM | (50) | (50) | (50) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | 1 (2%) | |
| *ABDOMINAL CAVITY | (50) | (50) | (50) |
| INFLAMMATION, SUPPURATIVE | | 1 (2%) | |
| NECROSIS, FAT | | 1 (2%) | |
| ANGIECTASIS | | 1 (2%) | |
| *PERITONEUM | (50) | (50) | (50) |
| INFLAMMATION, GRANULOMATOUS | 1 (2%) | | |
| *MESENTERY | (50) | (50) | (50) |
| LYMPHOCYTIC INFLAMMATORY INFILTR | | 1 (2%) | |
| ALL OTHER SYSTEMS | | | |
| NONE | | | |
| SPECIAL MORPHOLOGY SUMMARY | | | |
| AUTO/NECROPSY/HISTO PERF | | 1 | 2 |
| AUTO/NECROPSY/NO HISTO | | 1 | 3 |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

# APPENDIX E

## ANALYSIS OF 1,2-DIBROMO-3-CHLOROPROPANE

## Appendix E

### Analysis of 1,2-Dibromo-3-chloropropane at Midwest Research Institute

### A. ELEMENTAL ANALYSIS

| Element | C | H | Br | Cl |
|---|---|---|---|---|
| Theory | 15.24 | 2.13 | 67.62 | 15.00 |
| Determined | 15.33 | 2.10 | 67.87 | 14.82 |

### B. VAPOR-PHASE CHROMATOGRAPHY

Instrument: Tracor MT 220
Detector: Flame ionization

1. System 1

Column: 10% Carbowax 20 M on 80/100 Chromosorb W AW, 1.8 m x 4 mm I.D., glass
Inlet temperature: 200°C
Detector temperature: 235°C
Oven temperature program: 10 minutes at 50°C, then 50° to 200°C at 10°C/minute

Results: Major peak and seven impurities.

| Peak | Retention Time (min.) | Retention Time (relative to 1,2-dibromo-3-chloropropane) | Area (relative to 1,2-dibromo-3-chloropropane) |
|---|---|---|---|
| 1 | 10.1 | 0.55 | 1.0 |
| 2 | 12.4 | 0.67 | 0.1 |
| 3 | 13.2 | 0.72 | 0.4 |
| 4 | 13.8 | 0.74 | 0.06 |
| 5 | 15.2 | 0.82 | 0.4 |
| 6 | 16.4 | 0.89 | 0.3 |
| 7 | 17.8 | 0.96 | 2.2 |
| 8 | 18.5 | 1.00 | 100 |

2. System 2

Column: 3% Apolar 10°C on 80/100 Gas Chrom Q, 1.8 m x 2 mm I.D., glass
Inlet temperature: 200°C
Detector temperature: 250°C
Oven temperature program: 2 minutes at 50°C, then 50° to 225°C at 10°C/minute.
Results: Major peak and four impurities.

| Peak | Retention Time (min.) | Retention Time (relative to 1,2-dibromo-3-chloropropane) | Area (relative to 1,2-dibromo-3-chloropropane) |
|---|---|---|---|
| 1 | 4.6 | 0.59 | 0.6 |
| 2 | 5.9 | 0.76 | 0.3 |
| 3 | 7.8 | 1.0 | 100 |
| 4 | 9.0 | 1.2 | 0.05 |
| 5 | 10.1 | 1.3 | 0.07 |

C. SPECTRAL DATA

| | Determined | Literature Values |
|---|---|---|
| 1. Infrared | | |
| a. | System 1: liquid spectrum<br>Instrument: Beckman IR-12<br>Cell: Neat between NaCl plates<br>Results: See Figure 9 | Consistent with literature spectrum (Sadtler Standard Spectra) |
| b. | System 2: gas spectrum<br>Instrument: Beckman IR-12<br>Cell: 10 cm gas cell with windows<br>Spectrum scan: 1300-700 $cm^{-1}$<br>Results: See Figure 10 | Consistent with literature spectrum (Sadtler Standard Spectra) |
| 2. Nuclear Magnetic Resonance | | |
| | Instrument: Varian HA-100<br>Solvent: Neat, tetramethylsilane added<br>Assignments: See Figures 11 and 12 | Major peaks consistent with literature spectrum (Sadtler Standard Spectra) |

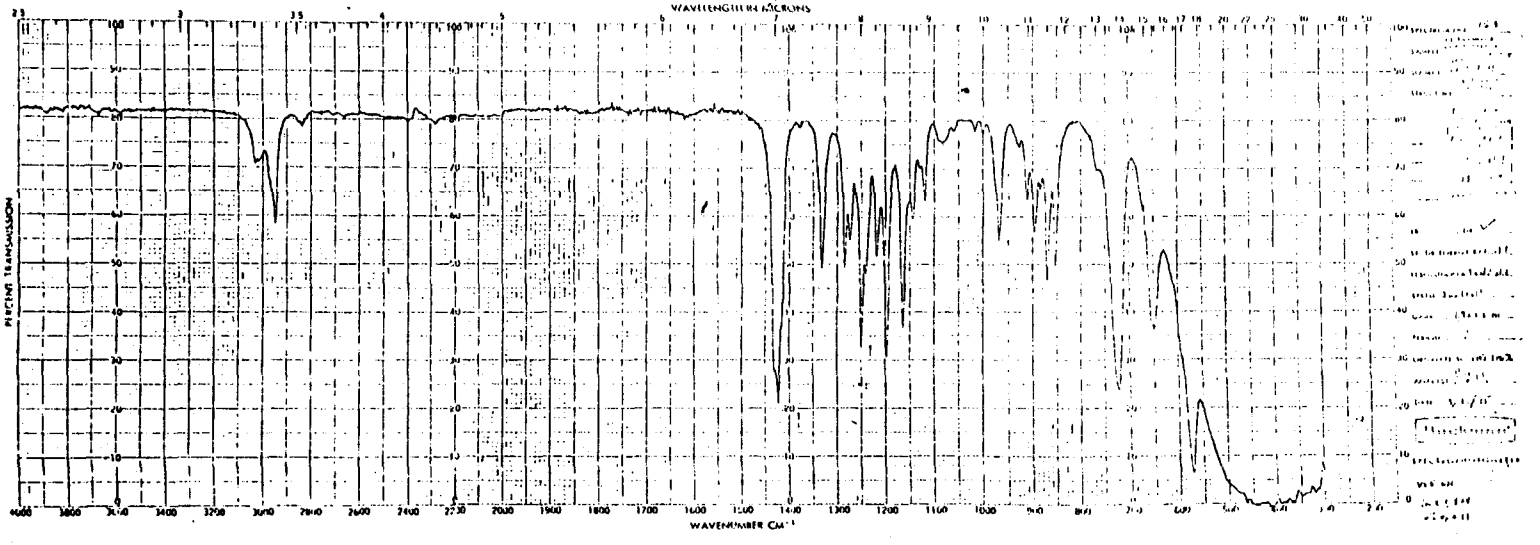

**Figure 9. Infrared Absorption Spectrum (Liquid) of 1, 2-Dibromo-3-Chloropropane**

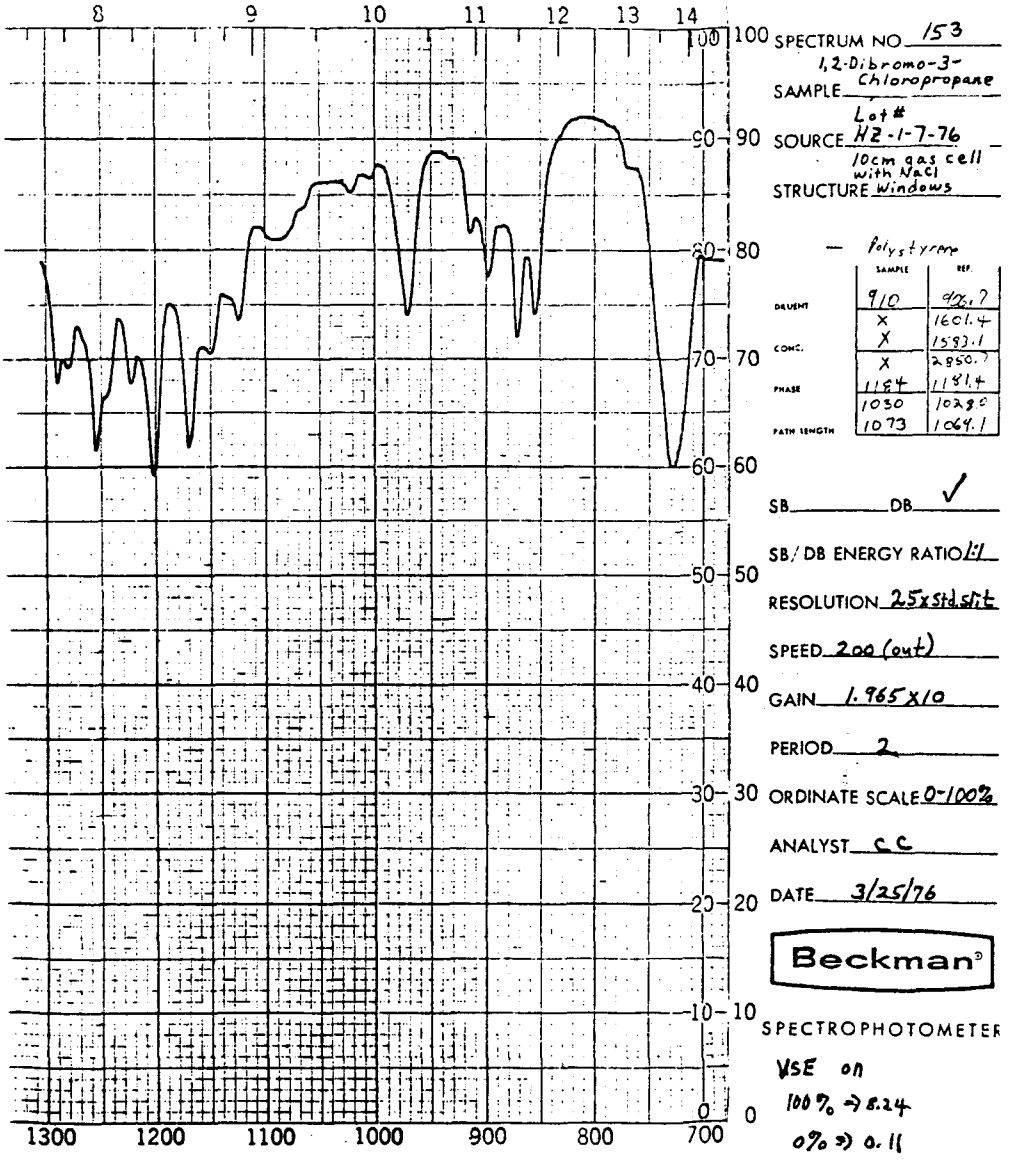


**Figure 10. Infrared Absorption Spectrum (Gas) of 1, 2-Dibromo-3-Chloropropane**

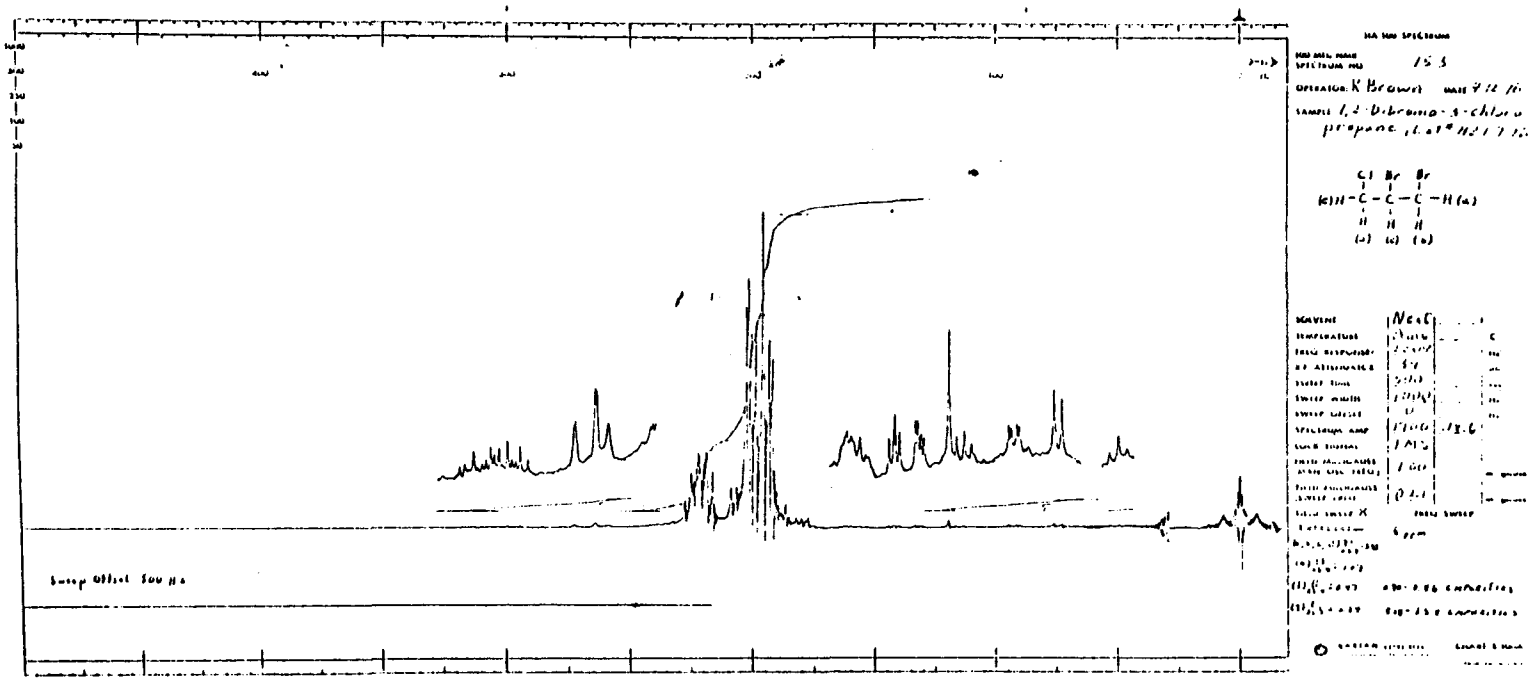

**Figure 11. Nuclear Magnetic Resonance of 1, 2-Dibromo-3-Chloropropane**

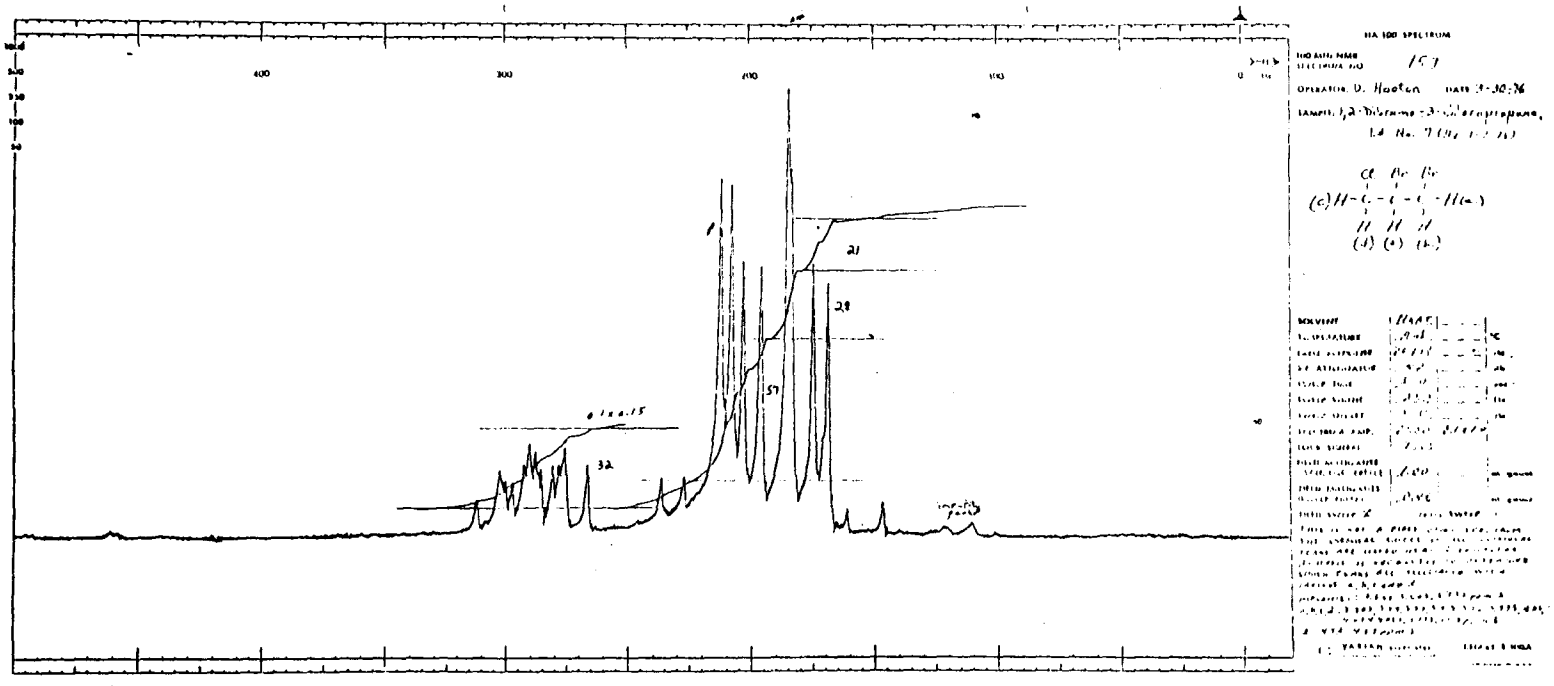

**Figure 12. Nuclear Magnetic Resonance of 1, 2-Dibromo-3-Chloropropane (Enlarged Scale)**

This is not a first order spectrum. The chemical shifts of individual peaks are listed here. A computer analysis is necessary to determine which peaks are associated with protons a, b, c, and d.

(a, b, c, d) 3.805, 3.84, 3.87, 3.913, 3.92, 3.975, 4.01, 4.034, 4.055, 4.133, and 4.178 ppm.
(e) 4.32-4.57 ppm.
(f) impurities 0.90-3.73 ppm.
(g) impurities 4.58-6.54 ppm.

Integration ratios: (a,b,c,d) 3.93
(e) 1.07
(f) 0.47*
(g) 0.34*

*Integration probably high in (f) and (g) because of normal baseline noise.

# APPENDIX F

## ANALYSIS OF 1,2-DIBROMO-3-CHLOROPROPANE RESIDUE AND COMPARISON WITH A STORED SAMPLE

## Appendix F

### Analysis of 1,2-Dibromo-3-chloropropane Residue and Comparison with a Stored Sample

### A. VAPOR-PHASE CHROMATOGRAPHY

Instrument: Tracor MT 220
Detector: Flame ionization
Inlet temperature: 200°C
Detector temperature: 250°C
Carrier gas: Nitrogen
Carrier flow: 70 ml/min

#### 1. DETECTION OF IMPURITIES

##### a. System 1

Column: 20% SP 2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m x 4 mm I.D., glass
Oven temperature program: 50°C, 5 min; 50° to 170°C at 10°C/min
Sample injected: 3 µl neat liquid diluted to 1% in methanol to quantitate major peak

(1) Residue from inhalation studies

Results: Major peak and 12 impurities. One of these has an area that is 1% of the major peak. The areas of the others total 1.4% of the major peak.

| Peak | Retention Time (min.) | Retention Time (Relative to Dibromochloropropane) | Area (Percent of Dibromochloropropane) |
|---|---|---|---|
| 1 | 1.5 | 0.11 | 0.02 |
| 2 | 9.9 | 0.74 | 0.1 |
| 3 | 11.8 | 0.88 | 0.3 |
| 4 | 12.2 | 0.91 | 0.3 |
| 5 | 13.4 | 1.00 | 100 |
| 6 | 14.4 | 1.07 | 0.09 |
| 7 | 14.9 | 1.11 | 0.01 |
| 8 | 15.2 | 1.13 | 0.01 |
| 9 | 15.6 | 1.16 | 0.004 |
| 10 | 15.9 | 1.18 | 0.3 |
| 11 | 17.1 | 1.28 | 0.07 |
| 12 | 21.4 | 1.60 | 0.2 |
| 13 | 28.6 | 2.13 | 1 |

(2) Sample stored at Hazleton Laboratories

Results: Major peak and 17 impurities. The area of each impurity is less than 1% of the major peak. The areas of the impurities total 3.9% of the major peak.

| Peak | Retention Time (min.) | Retention Time (Relative to Dibromochloropropane) | Area (Percent of Dibromochloropropane) |
|---|---|---|---|
| 1 | 1.3 | 0.10 | 0.09 |
| 2 | 1.6 | 0.12 | 0.7 |
| 3 | 1.8 | 0.13 | 0.05 |
| 4 | 5.5 | 0.41 | 0.6 |
| 5 | 9.2 | 0.68 | 0.1 |
| 6 | 9.5 | 0.71 | 0.07 |
| 7 | 9.8 | 0.73 | 0.3 |
| 8 | 11.8 | 0.88 | 0.5 |
| 9 | 12.4 | 0.92 | 0.3 |
| 10 | 13.4 | 1.00 | 100 |
| 11 | 14.7 | 1.07 | 0.07 |
| 12 | 16.2 | 1.16 | <0.01 |
| 13 | 15.8 | 1.18 | 0.2 |
| 14 | 16.2 | 1.20 | 0.01 |
| 15 | 16.3 | 1.21 | 0.01 |
| 16 | 17.0 | 1.26 | 0.05 |
| 17 | 17.2 | 1.28 | 0.2 |
| 18 | 28.2 | 2.10 | 0.7 |

Conclusions: The only obvious difference between the two samples is that the sample stored at Hazleton and not aerated contains more and larger volatile impurities which elute before the major peak.

b. System 2

Column: 10% Carbowax 20 M-TPA on 80/100 Chromosorb W (AW), 1.8 m x 4 mm I.D., glass
Oven temperature program: 50°C, 10 min; 50° to 200°C at 10°C/min.
Sample injected: 4 µl neat liquid diluted to 1% in methanol to quantitate major peak

(1) Residue from inhalation studies

Results: Major peak and 13 impurities. One impurity is 3% of the major peak, one 2%, and one 1%. The others total 0.5% of the major peak.

| Peak | Retention Time (min.) | Retention Time (Relative to Dibromochloropropane) | Area (Percent of Dibromochloropropane) |
|---|---|---|---|
| 1 | 12.6 - 13.5 | 0.68 | 0.003 |
| 2 | 14.2 | 0.73 | 0.004 |
| 3 | 14.7 | 0.76 | 0.04 |
| 4 | 15.0 | 0.79 | 0.01 |
| 5 | 15.7 | 0.81 | 0.1 |
| 6 | 15.9 | 0.85 | 0.2 |
| 7 | 16.1 | 0.87 | shoulder $<$0.03 |
| 8 | 17.4 | 0.94 | 3 |
| 9 | 18.6 | 1.00 | 100 |
| 10 | 19.0 | 1.02 | 2 |
| 11 | 19.7 | 1.06 | 0.03 |
| 12 | 19.9 | 1.07 | 0.03 |
| 13 | 20.1 | 1.08 | 0.03 |
| 14 | 24.6 | 1.32 | 1 |

(2) Sample stored at Hazleton Laboratories

Results: Major peak and 18 impurities. One of these has two shoulders, and the total area of the peak and two shoulders is 2% of the major peak. A second apparently homogeneous peak has an area of 2%. The areas of the other impurities total 2.5% of the major peak.

| Peak | Retention Time (min.) | Retention Time (Relative to Dibromochloropropane) | Area (Percent of Dibromochloropropane) |
|---|---|---|---|
| 1 | 2.1 | 0.11 | 0.03 |
| 2 | 3.0 | 0.16 | 0.7 |
| 3 | 13.1 | 0.69 | 0.005 |
| 4 | 13.3 | 0.70 | 0.002 |
| 5 | 14.1 | 0.75 | 0.7 |
| 6 | 14.6 | 0.77 | shoulder |
| 7 | 14.9 | 0.79 | 0.2 |
| 8 | 15.2 | 0.80 | 0.4 |
| 9 | 15.4 | 0.81 | shoulder |

| Peak | Retention Time (min.) | Retention Time (Relative to Dibromochloropropane) | Area (Percent of Dibromochloropropane) |
|---|---|---|---|
| 10 | 16.1 | 0.85 | 0.3 |
| 11 | 16.4 | 0.87 | shoulder |
| 12 | 17.5 | 0.93 | shoulder |
| 13 | 17.7 | 0.94 | 2 |
| 14 | 17.9 | 0.95 | shoulder |
| 15 | 18.9 | 1.00 | 100 |
| 16 | 19.3 | 1.02 | 2 |
| 17 | 19.6 | 1.04 | 0.06 |
| 18 | 20.0 | 1.06 | 0.05 |
| 19 | 20.5 | 1.08 | 0.03 |

Conclusions: The residue from the inhalation study contains a 1% impurity not observed in the sample stored at Hazleton which elutes much later than the major peak. Another difference between the two samples is that the sample stored at Hazleton and not aerated contains more and larger volatile impurities which elute before the major peak.

2. QUANTITATIONS COMPARED WITH STANDARDS

a. Quantitation Of Major Component (1,2-Dibromo-3-chloropropane)

Column: 20% SP 2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m x 4 mm I.D., glass
Oven temperature program: 100°C, isothermal
Sample injected: 7 µl 0.45% v/v in methanol
Standard: Nemagon soil fum. AC-4010 99.8%, Shell Chemical Company, Agricultural Division
Results: (a) Residue from inhalation studies: 106.9±5.6%
(b) Sample stored at Hazleton Laboratories: 102.8±5.5%

b. Quantitation Of β-Epichlorohydrin

Column: 20% SP 2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m x 4 mm I.D., glass
Oven temperature program: 50°C, isothermal
Sample injected: 6 µl neat 1,2-dibromo-3-chloropropane and 6 *1 0.02% and 0.5% v/v β-epichlorohydrin in methanol
Results: (a) Residue from inhalation studies: 0.026±0.005(δ)%
(b) Sample stored at Hazleton Laboratories: 0.22±0.03(δ)%

## B. VAPOR-PHASE CHROMATOGRAPHY/MASS SPECTROMETRY

Instrument: Varian MAT CH4B mass spectrometer interfaced via a Watson-Biemann helium separator to a Tracor MT 2000 MF vapor-phase chromatograph. Data processed by a Varian 620/i computer.
Inlet temperature: 170°C
Carrier gas: Helium
Carrier flow: 30 ml/min.

### 1. System 1

Column: 20% SP 2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m x 4 mm I.D., glass
Oven temperature program: 50°C, 5 min; 50° to 170°C at 10°C/minute
Sample: 1,2-Dibromo-3-chloropropane stored at Hazleton Laboratories
Sample injected: 0.4 µl neat liquid
Results: Major peak and 13 minor peaks and two shoulders on falling edge of major peak (see Tables F1 and F2).

### 2. System 2

Column: 5% Carbowax 20M-TPA on 80/100 Supelcoport, 1.8 m x 2 mm I.D., glass
Oven temperature program: 50°C, 5 min.; 50° to 170°C at 10°C/min.
Inlet temperature: 170°C
Sample: Residue from inhalation studies
Sample injected: 2 µl neat liquid
Results: Major peak and 20 impurities. Four of the impurities were detected by the total ion current monitor but were too small to obtain good spectra. The retention times are recorded for these in Table F3, but no mass spectral data for them are reported in Table F4.

Table F1. Vapor-Phase Chromatography Data (System 1) DBCP

| Peak | Retention Time (min.) | Retention Time (Relative to Dibromochloropropane) | Corresponding Peak by FID Section IA 2A (Tenative) |
|---|---|---|---|
| 1 | 3.7 | 0.21 | 1 |
| 2 | 4.4 | 0.24 | 2 |
| 3 | 4.9 | 0.27 | 3 |
| 4 | 10.5 | 0.58 | not detected (< 0.01%) |
| 5 | 11.0 | 0.61 | 4 |
| 6 | 12.5 | 0.69 | 5 |
| 7 | 13.5 | 0.75 | 6 |
| 8. | 14.1 | 0.78 | 7 |
| 9 | 16.2 | 0.90 | 8 |
| 10 | 16.7 | 0.93 | 9 |
| 11 | 18.0 | 1.00 | 10 |
| 12 | shoulder 20.0 | 1.11 | 11 |
| 13 | shoulder 21.2 | 1.18 | 13 |
| 14 | 25.3 | 1.41 | 16 |
| 15 | 31.0 | 1.72 | 17 |
| 16 | 52.8 | 2.93 | 18 |

Table F2. Mass Spectrometry Data (System 1) DBCP

| Peak | Mass | Percent of Base Peak | Possible Identity | Literature Mass | Literature Percent of Base Peak |
|---|---|---|---|---|---|
| 1 | 63 | 100 | Unknown | | |
| | 78 | 45 | | | |
| | 65 | 32 | | | |
| | 64 | 12 | | | |
| | 80 | 9 | | | |
| | 62 | 9 | | | |
| | 47 | 7 | | | |
| | 91 | 6 | | | |
| 2 | 41 | >100 | 3-Chloro- | 41(a) | 100 (100,100) |
| | 39 | >100 | propene or | 39 | 44 (62,51) |
| | 76 | 100 | 1- or 2- | 76 | 39 (42,52) |
| | 78 | 33 | chloropropene | 78 | 12 (14,17) |
| | 40 | 38 | | 40 | 7 (14,9) |
| | 38 | 21 | | 38 | 7 (12,10) |
| | 37 | 15 | | 37 | 6 (10,9) |
| | 27 | 31 | | 27 | 6 for 3-chloro |
| | 75 | 10 | | 75 | 7 for 1-chloro |
| | 37 | 15 | | 37 | 9 for 2-chloro |
| 3 | 63 | 100 | Unknown | | |
| | 64 | 67 | | | |
| | 49 | 55 | | | |
| | 55 | 34 | | | |
| | 65 | 31 | | | |
| | 51 | 18 | | | |
| | 83 | 17 | | | |
| | 85 | 15 | | | |
| 4 | 63 | 100 | 1,2-Dichloro- | 63 | 100(a) |
| | 62 | 66 | propane | 62 | 71 |
| | 27 | 54 | | 27 | 59 |
| | 41 | 71 | | 41 | 49 |
| | 39 | 41 | | 39 | 32 |
| | 65 | 32 | | 65 | 31 |
| | 76 | 15 | | 76 | 27 |
| | 64 | 24 | | 64 | 25 |

Table F2. Mass Spectrometry Data (System 1) DBCP

(Continued)

| Peak | Mass | Percent of Base Peak | Possible Identity | Literature | |
|---|---|---|---|---|---|
| | | | | Mass | Percent of Base Peak |
| 5 | 57 | 100 | Epichlor- | 57 | 100(a) |
| | 27 | 86 | hydrin | 27 | 39 |
| | 29 | 50 | | 29 | 31 |
| | 49 | 44 | | 49 | 25 |
| | 31 | 37 | | 31 | 22 |
| | 62 | 30 | | 62 | 18 |
| | 28 | 100 | | 28 | 16 |
| | 51 | 15 | | 51 | 8 |
| 6 | 77 | 100 | Unknown | | |
| | 79 | 29 | | | |
| | 49 | 8 | | | |
| | 57 | 6 | | | |
| | 63 | 5 | | | |
| | 64 | 5 | | | |
| | 62 | 5 | | | |
| | 78 | 3 | | | |
| 7 | 107 | 100 | 1,2-Dibromo- | 107 | 100(a) |
| | 109 | 95 | ethane | 109 | 95 |
| | 27 | 86 | | 27 | 54 |
| | 28 | 328 | | 28 | 11 |
| | 26 | 18 | | 26 | 8 |
| | 93 | 4 | | 93 | 5 |
| | 188 | 2 | | 188 | 5 |
| | 95 | 4 | | 95 | 4 |
| 8 | 75 | 100 | Unknown | | |
| | 77 | 59 | | | |
| | 56 | 30 | | | |
| | 49 | 27 | | | |
| | 55 | 25 | | | |
| | 76 | 23 | | | |
| | 158 | 18 | | | |
| | 156 | 16 | | | |
| 9 | 76 | 100 | Unknown | | |
| | 78 | 36 | | | |
| | 49 | 7 | | | |
| | 61 | 11 | | | |
| | 42 | 12 | | | |

Table F2. Mass Spectrometry Data (System 1) DBCP

(Continued)

| Peak | Mass | Percent of Base Peak | Possible Identity | Literature | |
|---|---|---|---|---|---|
| | | | | Mass | Percent of Base Peak |
| 10 | 75 | 100 | Unknown | | |
| | 77 | 27 | | | |
| | 107 | 12 | | | |
| | 109 | 11 | | | |
| 11 | 157 | 100 | 1,2-Dibromo- | 157 | 100(a) |
| | 155 | 67 | 3-chloropro- | 155 | 78 |
| | 75 | 42 | pane | 75 | 46 |
| | 159 | 21 | | 159 | 25 |
| | 39 | 19 | | 39 | 24 |
| | 77 | 11 | | 77 | 16 |
| | 49 | 6 | | 49 | 10 |
| | 93 | 6 | | 93 | 10 |
| 12 | 201 | 100 | Unknown | | |
| | 199 | 50 | | | |
| | 187 | 38 | | | |
| | 203 | 38 | | | |
| | 169 | 25 | | | |
| | 189 | 25 | | | |
| | 194 | 12 | | | |
| | 196 | 12 | | | |
| 13 | 191 | 100 | 1,1,1-Tri- | 109 | 100(b) |
| | 189 | 87 | chloro-3- | 107 | 38 |
| | 109 | 64 | bromopro- | 111 | 42 |
| | 107 | 26 | pane | 191 | 83 |
| | 111 | 43 | | 189 | 52 |
| | 193 | 62 | | 193 | 38 |
| | 129 | 52 | | 129 | 16 |
| | 83 | 43 | | 83 | 13 |
| 14 | 75 | 100 | Unknown | | |
| | 235 | 40 | | | |
| | 77 | 33 | | | |
| | 237 | 28 | | | |
| | 82 | 26 | | | |
| | 80 | 25 | | | |

Table F2. Mass Spectrometry Data (System 1) DBCP

(Continued)

| Peak | Mass | Percent of Base Peak | Possible Identity | Literature | |
|---|---|---|---|---|---|
| | | | | Mass | Percent of Base Peak |
| 15 | 81 | 100 | Unknown | | |
| | 55 | 59 | | | |
| | 80 | 58 | | | |
| | 67 | 55 | | | |
| | 82 | 47 | | | |
| | 75 | 40 | | | |
| | 117 | 39 | | | |
| | 56 | 34 | | | |
| 16 | 197 | 100 | Unknown | | |
| | 195 | 56 | | | |
| | 159 | 39 | | | |
| | 161 | 33 | | | |
| | 199 | 28 | | | |
| | 231 | 17 | | | |
| | 233 | 17 | | | |
| | 253 | 17 | | | |

(a) Eight Peak Index (1970)
(b) Cyphernetics Computer Search

Table F3. Vapor-Phase Chromatography Data (System 2) DBCP

| Peak | Retention Time (min) | Retention Time (Relative to Dibromochloropropane) | Corresponding Peak by FID (Tentative) |
|---|---|---|---|
| 1 | 4.3 | 0.2 | 1 |
| 2 | 6.6 | 0.3 | 2 |
| 3 | 8.2 | 0.4 | not detected (<0.002%) |
| 4 | 9.2 | 0.5 | 3 |
| 5 | 10.1 | 0.5 | 4 |
| 6 | 12.2 | 0.6 | 5 |
| 7 | 13.8 | 0.7 | not detected (<0.002%) |
| 8 | 15.9 | 0.8 | 6 |
| 9 | 17.5 | 0.9 | 8 |
| 10 | 18.1 | 0.9 | not detected (possible unresolved shoulder) |
| 11 | 20.1 | 1.00 | 9 |
| 12 | 21.5 | 1.1 | not detected (possible unresolved shoulder) |
| 13 | 22.0 | 1.1 | 10 |
| 14 | 23.2 | 1.2 | 11 |
| 15 | 24.7 | 1.2 | not detected (<0.03%) |
| 16 | 25.2 | 1.3 | not detected (<0.03%) |
| 17 | 26.8 | 1.3 | 12 |
| 18 | 27.8 | 1.4 | not detected (<0.03%) |
| 19 | 32.5 | 1.6 | 13 |
| 20 | >45 | > 2.2 | 14 |
| 21 | >45 | > 2.2 | not detected (<0.03%) |

Table F4. Mass Spectrometry Data (System 2) DBCP

| Peak | Mass | Percent of Base Peak | Possible Identity | Literature Mass | Literature Percent of Base Peak |
|---|---|---|---|---|---|
| 1 | 77 | 100 | Unknown | | |
| | 82 | 83 | | | |
| | 80 | 81 | | | |
| | 79 | 40 | | | |
| | 55 | 26 | | | |
| | 81 | 23 | | | |
| 2 | 57 | 100 | Epichloro- | 57 | 100 |
| | 27 | 63 | hydrin(a) | 27 | 96 |
| | 29 | 35 | | 29 | 71 |
| | 31 | 25 | | 31 | 39 |
| | 49 | 27 | | 49 | 34 |
| | 26 | 13 | | 26 | 30 |
| | 15 | 11 | | 15 | 22 |
| | 62 | 16 | | 62 | 19 |
| 3 | 80 | 100 | Unknown | | |
| | 82 | 77 | | | |
| | 123 | 56 | | | |
| | 121 | 53 | | | |
| | 55 | 30 | | | |
| | 81 | 25 | | | |
| | 79 | 22 | | | |
| | 98 | 17 | | | |
| 4 | 107 | 100 | 1,2-Dibromo- | 107 | 100 |
| | 109 | 81 | ethane(a) | 109 | 95 |
| | 27 | >100 | | 27 | 54 |
| | 28 | >100 | | 28 | 11 |
| | 26 | 26 | | 26 | 8 |
| | 93 | < 18 | | 93 | 5 |
| | 188 | < 18 | | 188 | 5 |
| | 95 | < 18 | | 95 | 4 |
| 5 | 75 | 100 | Unknown | | |
| | 77 | 33 | | | |
| | 82 | 24 | | | |
| | 80 | 23 | | | |

Table F4. Mass Spectrometry Data (System 2) DBCP (Continued)

| Peak | Mass | Percent of Base Peak | Possible Identity | Literature Mass | Literature Percent of Base Peak |
|---|---|---|---|---|---|
| 5 (continued) | 49 | 17 | Unknown | | |
| | 156 | 9 | | | |
| | 154 | 6 | | | |
| 6 | 41 | 100 | 1-Chloro-3- | 41 | 100 |
| | 77 | 74 | bromopropane(a) | 77 | 77 |
| | 158 | 27 | | 158 | 56 |
| | 76 | 45 | | 76 | 46 |
| | 156 | 24 | | 156 | 44 |
| | 27 | 25 | | 27 | 29 |
| | 79 | 22 | | 79 | 26 |
| | 39 | 19 | | 39 | 26 |
| 7 | 75 | 100 | Unknown | | |
| | 77 | 28 | | | |
| | 49 | 15 | | | |
| | 82 | 12 | | | |
| | 80 | 12 | | | |
| | 56 | 10 | | | |
| 8 | 26 | 100 | Unknown | | |
| | 157 | 79 | | | |
| | 80 | 77 | | | |
| | 155 | 61 | | | |
| | 82 | 55 | | | |
| | 38 | 51 | | | |
| | 159 | 19 | | | |
| 9 Shoulder on rising edge | 81 | 100 | Unknown | | |
| | 79 | 37 | | | |
| 9 | 157 | 100 | Unknown | | |
| | 39 | 79 | | | |
| | 41 | 79 | | | |
| | 155 | 71 | | | |
| | 75 | 60 | | | |
| | 77 | 40 | | | |
| | 159 | 25 | | | |
| | 76 | 9 | | | |

Table F4. Mass Spectrometry Data (System 2) DBCP

(Continued)

| Peak | Mass | Percent of Base Peak | Possible Identity | Literature Mass | Literature Percent of Base Peak |
|---|---|---|---|---|---|
| 10 | 111 | 100 | 2-Bromo- | 111 | 100 |
| | 113 | 67 | 1,2-dichloro- | 113 | 64 |
| | 75 | 68 | propane(a) | 75 | 46 |
| | 39 | 11 | | 39 | 26 |
| | 143 | 9 | | 143 | 15 |
| | 49 | 33 | | 49 | 15 |
| | 77 | 10 | | 77 | 15 |
| | 141 | 7 | | 141 | 12 |
| 11 | | | 1,2-Dibromo-3-chloropropane | | |
| 12 | 108 | 100 | 2,3-Dibromo- | 108 | 100 |
| | 106 | 88 | 1-propanol(b) | 106 | 83 |
| | 138 | 24 | | 138 | 68 |
| | 31 | 19 | | 31 | 68 |
| | 136 | 28 | | 136 | 67 |
| | 137 | 3 | | 137 | 67 |
| | 139 | < 3 | | 139 | 64 |
| | 29 | 10 | | 29 | 52 |
| 13 | 235 | 100 | Unknown | | |
| | 237 | 76 | | | |
| | 233 | 43 | | | |
| | 129 | 30 | | | |
| | 127 | 23 | | | |
| 14 | 41 | 100 | Unknown | | |
| | 81 | 73 | | | |
| | 117 | 43 | | | |
| | 55 | 42 | | | |
| | 67 | 37 | | | |
| | 103 | 17 | | | |
| | 119 | 15 | | | |
| 15-18 | Spectra too weak | | Unknown | | |

Table F4. Mass Spectrometry Data (System 2) DBCP

(Continued)

| Peak | Mass | Percent of Base Peak | Possible Identity | Literature | |
|---|---|---|---|---|---|
| | | | | Mass | Percent of Base Peak |
| 19 | 41 | 100 | Unknown | | |
| | 79 | 68 | | | |
| | 115 | 54 | | | |
| | 151 | 30 | | | |
| | 197 | 28 | | | |
| | 195 | 22 | | | |
| | 117 | 21 | | | |
| | 119 | 20 | | | |
| 20 | 81 | 100 | Unknown | | |
| | 241 | 21 | | | |
| | 243 | 10 | | | |
| | 321 | 3 | | | |
| | 323 | 3 | | | |
| 21 | 75 | 100 | Unknown | | |
| | 155 | 71 | | | |
| | 157 | 59 | | | |
| | 197 | 58 | | | |
| | 195 | 40 | | | |

(a) Cyphernetics
(b) Eight Peak Index (1970)

No matching spectra were found in the Eight Peak Index of Mass Spectra, or in the Cyphernetics Computer Search system for peaks No. 8, 9, 13, or 20 which constitute 0.2%, 3.0%, 2.0%, and 1%, respectively, of the major peak. An attempt was made to assign the major fragments in the mass spectra of these compounds by comparison of the isotope ratios with those calculated by computer as shown in Table F5.

C. CONCLUSIONS

No method was found to differentiate between HBr, $Br_2$, HCl and $Cl_2$. The total acidity as HBr in the residue from the inhalation studies was less than 0.002%. Vapor-phase chromatography of the residue from the inhalation studies indicated 13 impurities with one system. One of these had an area 3% of that of the major peak, one 2%, and 1%. The others totaled 0.5% of the major peak. Analysis of the sample stored at Hazleton with this system did not indicate the 1% impurity which elutes much later than the major peak but indicated more and larger volatile impurites which elute before the major peak. A total of 18 impurities were observed. One of these had two shoulders, and the total area of the peak and shoulders was 2% of the major peak. A second apparently homogeneous peak had an area of 2%. The areas of the other impurities totaled 2.5% of the major peak.

A second vapor-phase chromatography system indicated 12 impurities in the residue from the inhalation studies. One of these had an area 1% of the major peak. The areas of the others totaled 1.4% of the major peak. Analysis of the sample stored at Hazleton with this system indicated more and larger volatile impurities which elute before the major peak. A total of 17 impurities were observed. The area of each impurity was less than 1% of the major peak, and the areas of the impurities totaled 3.9%.

Vapor-phase chromatography/mass spectrometry with the first system described above detected 20 impurities in the residue sample. Four of these were too weak to obtain good spectra. Mass spectra are reported for the other impurities. The two largest impurities could not be identified. A tentative assignment of some of the clusters in the fragmentation pattern indicates that they are also bromochloropropanes. The impurities which were identified and their area percent in the sample stored at Hazleton and in the residue from the inhalation studies respectively are: epichlorohydrin, 0.7%, 0.04%; 1,2-dibromoethane, less than 0.7% (unresolved shoulder), 0.004%; 1-chloro-3-bromopropane, less than 0.4% (unresolved shoulder), 0.1%; 2-bromo-1,2-dichloropropane, no discrete peak in either sample, probably an unresolved shoulder; 2,3-dibromo-1-propanol, no discrete peak in either sample with flame ionization detection. The following impurities were identified by vapor-phase chromatography/mass spectrometry with the second system (compound area percent in sample stored at Hazleton, area percent in residue from inhalation studies): 3- (or 1- or 2-)-chloropropene 0.7%, 0.02%; 1,2-dichloropropane, not detected (less than 0.01%); detected (less than 0.01%); epichlorohydrin, 0.6%, not detected (less than 0.01%); 1,2-dibromoethane, 0.07%, not detected (less than 0.01%); 1,1,1-trichloro-3-bromopropane, 0.2%, 0.3%. Mass spectra are also reported for those compounds which could not be identified.

Table F5. Isotope Ratios: DBCP

| Peak | Mass | Relative Intensity | Tentative Assignment | Computer Calculation Mass | Computer Calculation Relative Intensity |
|---|---|---|---|---|---|
| 8 | 155 | 77 | $C_3H_5BrCl$ | 155 | 77 |
| | 157 | 100 | | 157 | 100 |
| | 159 | 24 | | 159 | 24 |
| | 80 | 100 | Unknown | | |
| | 82 | 71 | | | |
| | 36 | 100 | HCl | 36 | 100 |
| | 38 | 51 | | 38 | 33 |
| 9 | 155 | 71 | $C_3H_5BrCl$ | 155 | 77 |
| | 157 | 100 | | 157 | 100 |
| | 159 | 25 | | 159 | 24 |
| | 75 | 100 | Unknown | | |
| | 76 | 15 | | | |
| | 77 | 66 | | | |
| 13 | 233 | 43 | $C_3H_4Br_2Cl$ | 233 | 44 |
| | 235 | 100 | | 235 | 100 |
| | 237 | 76 | | 237 | 70 |
| | 171 | 50 | $CHBr_2$ | 171 | 51 |
| | 173 | 100 | | 173 | 100 |
| | 175 | 53 | | 175 | 49 |
| | 127 | 75 | CHBr | 127 | 77 |
| | 129 | 100 | | 129 | 100 |
| 20 | 321 | 100 | $C_6H_3OBr_2Cl_2$ | 321 | 100 |
| | 323 | 88 | | 323 | 90 |
| | 239 | 50 | $C_6H_9Br_2$ | 239 | 51 |
| | 241 | 100 | | 241 | 100 |
| | 243 | 49 | | 243 | 49 |
| | 79 | 27 | Unknown | | |
| | 81 | 100 | | | |

# APPENDIX G

## ANALYSIS OF CHAMBER CONCENTRATIONS OF 1,2-DIBROMO-3-CHLOROPROPANE

## Appendix G

### Analysis of Chamber Concentrations of 1,2-Dibromo-3-chloropropane

Concentrations of 1,2-dibromo-3-chloropropane (DBCP) in the chambers were determined by gas chromatography using a Varian 600-D gas chromatograph equipped with an electron capture detector. The chromatograph was calibrated each day using newly prepared standards of DBCP.

Samples were obtained for analysis from a closed-loop system sample line which was allowed a 1-hour equilibration period prior to sampling. Samples were pulled from a septum in the sample line using Tomac syringes with lock tip and 20 gauge stainless steel needles. The gas samples were discharged into sealed, evacuated, 15-ml test tubes containing 1.0 ml of isopropanol (IPA). The tube contents were then mixed using a Vortex® mixer for at least one minute. Measured aliquots of the IPA solutions from each tube were then injected directly into the gas chromatograph for analysis. A 6-inch x 1/8-inch O.D. stainless steel column packed with 6% FFAP Porapak® Q 80/100 mesh was used with an isothermal column and detector temperature of 165°C. Nitrogen was the carrier gas.

Chamber concentrations (reported as ppm) were determined by injecting measured aliquots of prepared sample, measuring the peak-height response, and determining the equivalent weight from the appropriate standard curve. The weight thus found (ng) was divided by the equivalent volume of gas injected to yield the chamber concentration (mg/cc) of DBCP. This value, divided by the appropriate DBCP constant factor (9.65 ng/cc), gives the reported chamber concentrations in parts per million (ppm). Mean chamber concentrations are presented in Table G1.

Table G1. Chamber Concentrations of 1,2-Dibromo-3-chloropropane

| Theoretical Concentration (ppm) | Number of Samples | Sample Analytical Mean (ppm) | Coefficient of Variation (%) | Range (ppm) |
|---|---|---|---|---|
| 0.6 | 102 | 0.592 | 13.5 | 0.40 - 1.05 |
| 3.0 | 84 | 2.87 | 14.6 | 1.57 - 3.83 |

☆U.S. GOVERNMENT PRINTING OFFICE: 1982-361-132:539

NIH Publication No. 82-1762
March 1982