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No. 372

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

3,3′-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

(CAS NO. 20325-40-0)

IN F344/N RATS

(DRINKING WATER STUDIES)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF 3,3′-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

(CAS NO. 20325-40-0)

IN F344/N RATS

(DRINKING WATER STUDIES)

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Public Health Service
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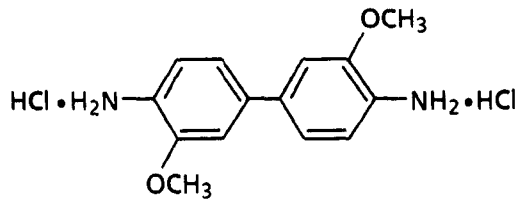

3,3′-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

CAS No. 20325-40-0

$C_{14}H_{16}N_2O_2$•2HCl Molecular weight 317.2

Synonyms: *o*-dianisidine dihydrochloride; 3,3′-dimethoxy-(1,1-biphenyl)-4,4′-diamine dihydrochloride; 3,3′-dimethoxy-4,4′-diaminobiphenyl dihydrochloride

ABSTRACT

3,3′-Dimethoxybenzidine dihydrochloride was evaluated in toxicity and carcinogenicity studies as part of the National Toxicology Program's Benzidine Dye Initiative. This Initiative was designed to evaluate representative benzidine congeners and benzidine congener-derived and benzidine-derived dyes. 3,3′-Dimethoxybenzidine dihydrochloride was nominated for study because of the potential for human exposure during production of bisazobiphenyl dyes and because benzidine, a structurally related chemical, is a known human carcinogen.

Toxicology and carcinogenesis studies were conducted by administering 3,3′-dimethoxybenzidine dihydrochloride (greater than 97.5% pure) in drinking water to groups of F344/N rats of each sex for 14 days, 13 weeks, 9 months, or 21 months. The 21-month studies were intended to last 24 months but were terminated early because of rapidly declining survival due to neoplasia. Studies were performed only in rats because similar studies are being performed in mice at the National Center for Toxicology Research. Genetic toxicology studies were conducted with *Salmonella typhimurium*, Chinese hamster ovary (CHO) cells, and *Drosophila melanogaster*.

Fourteen-Day Studies: All rats receiving drinking water concentrations up to 4,500 ppm lived to the end of the studies. Rats that received water containing 4,500 ppm 3,3′-dimethoxybenzidine dihydrochloride lost weight. Water consumption decreased with increasing concentration of chemical and at 4,500 ppm was less than one-fourth that by the controls. Lymphoid depletion of the thymus in males and hypocellularity of the bone marrow in males and females were seen at the 4,500-ppm concentration, but not at the next lower concentration or in controls.

Thirteen-Week Studies: All rats receiving concentrations up to 2,500 ppm lived to the end of the studies. Final mean body weights of rats given drinking water containing 1,250 or 2,500 ppm 3,3′-dimethoxybenzidine dihydrochloride were 5%-20% lower than those of controls. Water consumption at these concentrations was 40%-60% that consumed by controls. Compound-related effects in rats given water containing 2,500 ppm 3,3′-dimethoxybenzidine dihydrochloride included a mild exacerbation of naturally occurring nephropathy and the presence of a yellow-brown pigment (lipofuscin) in the cytoplasm of thyroid follicular cells. Serum triiodothyronine (T_3) and thyroxin (T_4) concentrations in females receiving 330 ppm or more and T_4 concentrations in males receiving 170 ppm or more were significantly lower than in controls. Thyrotropin (TSH) concentrations were comparable in controls and exposed rats.

Based on the chemical-related nephropathy and reductions in water consumption and body weight gain observed in the 13-week studies, doses for the long-term studies in male and female rats were 0 or 330 ppm 3,3'-dimethoxybenzidine dihydrochloride in drinking water administered for 9 months and 0, 80, 170, or 330 ppm administered for 21 months.

Nine-Month Studies: Ten rats of each sex in the control and 330-ppm groups were evaluated after 9 months. Significant decreases in T_3 and T_4 concentrations were seen in exposed male and female rats. Other lesions seen in exposed rats included foci of alteration in the liver, a carcinoma of the preputial gland in one male, a carcinoma of the clitoral gland in one female, and carcinoma of the Zymbal gland in two males.

Body Weights and Survival in the Twenty-One-Month Studies: The average amount of 3,3'-dimethoxybenzidine dihydrochloride consumed per day was approximately 6, 12, or 21 mg/kg for low, mid, or high dose male rats and 7, 14, or 23 mg/kg for low, mid, or high dose female rats. Mean body weights of male and female rats began to decrease relative to those of controls after about 1 year of exposure at 170 or 330 ppm and were 6%-22% lower for males and 7%-17% lower for females. Survival of rats exposed to 3,3'-dimethoxybenzidine dihydrochloride was reduced because animals were dying with neoplasms or being killed in a moribund condition (survival at 21 months--male: control, 44/60, 73%; low dose, 8/45, 18%; mid dose, 0/75; high dose, 0/60; female: 45/60, 75%; 15/45, 33%; 6/75, 8%; 0/60). Because of these early compound-related deaths, the studies were terminated at 21 months.

Nonneoplastic and Neoplastic Effects in the Twenty-One-Month Studies: Increased incidences of several nonneoplastic lesions were observed in exposed rats, including hematopoietic cell proliferation in the spleen and cystic and centrilobular degeneration and necrosis of the liver. Neoplasms attributed to 3,3'-dimethoxybenzidine dihydrochloride exposure were observed in rats at many tissue sites, including the skin, Zymbal gland, preputial and clitoral glands, oral cavity, small and large intestines, liver, brain, mesothelium, mammary gland, and uterus/cervix. The incidences of these neoplasms in male and female rats are given in the abstract summary table.

Genetic Toxicology: 3,3'-Dimethoxybenzidine was mutagenic in *S. typhimurium* strain TA100 with exogenous metabolic activation and in strain TA98 without activation; a weakly positive response was observed in strain TA1535 with metabolic activation. 3,3'-Dimethoxybenzidine induced sister chromatid exchanges and chromosomal aberrations in CHO cells with and without exogenous metabolic activation. 3,3'-Dimethoxybenzidine did not induce sex-linked recessive lethal mutations in adult male *D. melanogaster* exposed via feeding or injection.

Conclusions: Under the conditions of these 21-month drinking water studies, there was *clear evidence of carcinogenic activity** of 3,3'-dimethoxybenzidine dihydrochloride for male F344/N rats, as indicated by benign and malignant neoplasms of the skin, Zymbal gland, preputial gland, oral cavity, intestine, liver, and mesothelium. Increased incidences of astrocytomas of the brain may have been related to chemical administration. There was *clear evidence of carcinogenic activity* of 3,3'-dimethoxybenzidine dihydrochloride for female F344/N rats, as indicated by benign and malignant neoplasms of the Zymbal gland, clitoral gland, and mammary gland. Increases in neoplasms of the skin, oral cavity, large intestine, liver, and uterus/cervix were also considered to be related to chemical administration of 3,3'-dimethoxybenzidine dihydrochloride.

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*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 9.

SUMMARY OF THE TWENTY-ONE-MONTH DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

Male F344/N Rats	Female F344/N Rats
Drinking water concentration	
0, 80, 170, or 330 ppm 3,3'-dimethoxybenzidine dihydrochloride	0, 80, 170, or 330 ppm 3,3'-dimethoxybenzidine dihydrochloride
Body weights	
Lower than controls	Lower than controls
Survival rates	
44/60; 8/45; 0/75; 0/60 (a)	45/60; 15/45; 6/75; 0/60 (a)
Nonneoplastic effects	
Liver: cystic and centrilobular degeneration and necrosis; spleen: hematopoietic proliferation; lung: histiocytic infiltration; heart: thrombi in the atrium	Liver: cystic and centrilobular degeneration and necrosis; spleen: hematopoietic proliferation; lung: histiocytic infiltration
Neoplastic effects (b)	
Skin--basal cell or sebaceous gland neoplasms: 2/60 (3%); 33/45 (73%); 56/75 (75%); 41/60 (68%) Skin--squamous cell neoplasms: 0/60; 13/45 (29%); 28/75 (37%); 22/60 (37%) Zymbal gland: 0/59; 10/45 (22%); 25/75 (33%); 30/60 (50%) Preputial gland: 16/60 (27%); 12/43 (28%); 33/73 (45%); 29/59 (49%) Palate or tongue: 1/60 (2%); 8/45 (18%); 10/75 (13%); 11/60 (18%) Small intestine: 0/60; 4/45 (9%); 7/75 (9%); 5/60 (8%) Large intestine: 0/60; 1/45 (2%); 8/75 (11%); 8/60 (13%) Liver: 1/60 (2%); 4/45 (9%); 7/74 (9%); 8/60 (13%) Mesothelium: 2/60 (3%); 1/45 (2%); 7/75 (9%); 6/60 (10%) Brain--astrocytomas: 0/60; 2/44 (5%); 3/75 (4%); 1/60 (2%)	Clitoral gland: 7/58 (12%); 27/44 (61%); 48/74 (65%); 41/55 (75%) Zymbal gland: 1/60 (2%); 12/45 (27%); 21/75 (28%); 16/60 (27%) Mammary gland--adenocarcinomas: 1/60 (2%); 2/45 (4%); 14/75 (19%); 20/60 (33%) Skin--basal cell neoplasms: 0/60; 4/45 (9%); 3/75 (4%); 2/60 (3%) Palate or tongue: 2/60 (3%); 2/45 (4%); 6/75 (8%); 5/60 (8%) Large intestine: 0/60; 1/45 (2%); 1/75 (1%); 3/60 (5%) Liver: 0/60; 1/44 (2%); 0/75; 3/60 (5%) Uterus/cervix: 0/60; 4/45 (9%); 2/75 (3%); 2/60 (3%)
Level of evidence of carcinogenic activity	
Clear evidence	Clear evidence

(a) Reduced survival in exposed groups was due to neoplasia.
(b) Number with lesion/total evaluated (percent incidence)

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence including: animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results ("Clear Evidence" and "Some Evidence"); one category for uncertain findings ("Equivocal Evidence"); one category for no observable effects ("No Evidence"); and one category for experiments that because of major flaws cannot be evaluated ("Inadequate Study"). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.

- **Some Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.

- **Equivocal Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.

- **No Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.

- **Inadequate Study of Carcinogenic Activity** is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. This should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- The adequacy of the experimental design and conduct;
- Occurrence of common versus uncommon neoplasia;
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- Combining benign and malignant tumor incidences known or thought to represent stages of progression in the same organ or tissue;
- Latency in tumor induction;
- Multiplicity in site-specific neoplasia;
- Metastases;
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- Survival-adjusted analyses and false positive or false negative concerns;
- Structure-activity correlations; and
- In some cases, genetic toxicology.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of 3,3′-Dimethoxybenzidine Dihydrochloride is based on 13-week studies that began in June 1982 and ended in September 1982 and on 21-month studies that began in March 1983 and ended in December 1984 at Hazleton Laboratories America, Inc. (Vienna, VA).

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on 3,3′-dimethoxybenzidine dihydrochloride on June 27, 1989, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

On June 27, 1989, the draft Technical Report on the toxicology and carcinogenesis studies of 3,3'-dimethoxybenzidine dihydrochloride received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. D. Morgan, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (clear evidence of carcinogenic activity for male and female rats). Dr. Morgan explained that the studies were intended to last 24 months but were terminated after 21 months because of the rapidly declining survival of exposed animals due to neoplasia.

Dr. McKnight, a principal reviewer, agreed with the conclusions. She commented that the statistical analysis for skin tumors would be more accurate if based on the time at which a tumor first appeared in each animal, rather than the time at which each animal died with a tumor. (In these studies, this change of analysis would not affect the conclusions.)

Dr. Popp, the second principal reviewer, agreed with the conclusions. He pointed out that, because the chemical had previously been shown to be carcinogenic in experimental animals, information could be added to the rationale for doing the current studies. Dr. Popp noted the observation of foci in the liver of rats after dosing for 9 months, which suggested the chemical might be a hepatocarcinogen, yet there was a relatively weak liver tumor response at 21 months. Dr. Morgan speculated that the early animal deaths may have sufficiently shortened the time available for progression of foci to detectable tumors.

Dr. Gold, the third principal reviewer, agreed with the conclusions. She also requested that the rationale for performing the current studies be mentioned in light of findings from earlier studies. She opined that some of the earlier studies were not adequate by current standards. Dr. Morgan said that the rationale for the studies would be stated earlier in the Introduction and that the inadequacies of the earlier studies would be noted. Dr. Gold asked that the National Institute for Occupational Safety and Health data from the current National Occupational Exposure Survey be appended to indicate the estimated number of U.S. workers exposed to the chemical (page 13). Dr. Scala questioned the accuracy of the exposure estimates. Dr. H. Matthews, NIEHS, proposed that the number of workers exposed to 3,3'-dimethoxybenzidine was likely to be greater that the survey estimates because NTP studies have shown, at least in animals, that dyes derived from benzidine or its congeners were metabolically reduced in vivo almost completely to the parent compound. Dr. Gold also suggested that the results from the study in mice conducted at the National Center for Toxicological Research be included in the Report (page 19).

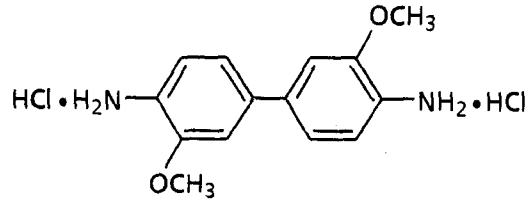
Dr. Mirer said that another rationale for the NTP studies could be that there is no tumor site concordance between humans and animals. Dr. J. Huff, NIEHS, responded that there were no epidemiology studies on this congener to enable determination of concordance. He added that there is a comparable neoplastic site (urinary bladder) in humans and dogs exposed to the parent chemical, benzidine.

Dr. McKnight moved that the Technical Report on 3,3'-dimethoxybenzidine dihydrochloride be accepted with the revisions discussed and the conclusions as written for male and female rats, clear evidence of carcinogenic activity. Dr. Popp seconded the motion, which was accepted unanimously.

I. INTRODUCTION

Use and Production
Exposure
Disposition and Metabolism
Genetic Toxicology
Toxicity and Carcinogenicity Studies
Toxicity and Carcinogenicity of Related Compounds
Study Rationale

I. INTRODUCTION



3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

CAS No. 20325-40-0

$C_{14}H_{16}N_2O_2 \cdot 2HCl$ Molecular weight 317.2

Synonyms: *o*-dianisidine dihydrochloride; 3,3'-dimethoxy-(1,1-biphenyl)-4,4'-diamine dihydrochloride; 3,3'-dimethoxy-4,4'-diaminobiphenyl dihydrochloride

Use and Production

3,3'-Dimethoxybenzidine dihydrochloride is an off-white powder with a melting point of 274° C. 3,3'-Dimethoxybenzidine is used principally as an intermediate in the production of commercial bisazobiphenyl dyes for coloring textiles, paper, plastic, rubber, and leather (Fishbein, 1981). In the synthesis of the bisazobiphenyl dyes, the amine groups of 3,3'-dimethoxybenzidine are chemically linked with other aromatic amines. A small quantity of 3,3'-dimethoxybenzidine is also used as an intermediate in the production of *o*-dianisidine diisocyanate, which is used in isocyanate-based adhesive systems and as a component of polyurethane elastomers (Woolrich and Rye, 1969; Fishbein, 1981).

3,3'-Dimethoxybenzidine has been produced commercially in the United States for at least 50 years (Fishbein, 1981). 3,3'-Dimethoxybenzidine is synthesized by reduction of *o*-nitroanisole to hydrazoanisole, followed by rearrangement of hydrazoanisole with acid to yield 3,3'-dimethoxybenzidine (IARC, 1974).

Domestic production of 3,3'-dimethoxybenzidine was reduced from 367,000 pounds in 1967 to small quantities in 1978 (USEPA, 1980). No information on more recent production volume is available. Approximately 554,000 pounds of 3,3'-dimethoxybenzidine was imported in 1978 (USEPA, 1980) and 106,000 pounds in 1983 (USITC, 1984). The National Institute for Occupational Safety and Health (NIOSH) reported 33 commercially available (United States) dyes synthesized from 3,3'-dimethoxybenzidine (Boeniger, 1980). Production and importation of 3,3'-dimethoxybenzidine-based dyes were estimated at 1,329,000 pounds (presscake basis) in 1979.

Exposure

Occupational exposure to 3,3'-dimethoxybenzidine may occur during the manufacture of those dyes in which 3,3'-dimethoxybenzidine is an intermediate. Exposure to 3,3'-dimethoxybenzidine may occur by inhalation, ingestion, or skin absorption (Meigs et al., 1951, 1954; El-Hawari et al., 1979). Exposure may also occur indirectly during handling of the finished 3,3'-dimethoxybenzidine-based dyes. Residual amounts of 3,3'-dimethoxybenzidine may be present in the finished dyes due to incomplete dye synthesis or breakdown of the dye after production. As discussed below, there is also evidence to suggest that 3,3'-dimethoxybenzidine-based dyes are metabolized back to the parent compound in vivo, resulting in exposure to 3,3'-dimethoxybenzidine.

Exposure to benzidine, benzidine congeners, and derived dyes has been estimated to include approximately 1,000 workers in dye manufacturing and approximately 10,000 workers in the various application industries (DETO, 1980). Because many of these compounds are found concurrently in the same industry, it is difficult to estimate the number of exposed workers and the extent of exposure to 3,3'-dimethoxybenzidine alone.

Exposure of workers to 3,3'-dimethoxybenzidine may also occur in clinical laboratories (IARC, 1974; Collier, 1974). 3,3'-Dimethoxybenzidine is commonly used for detection of blood and for the quantitation of chlorine in water and of glucose by the glucose oxidase method (Collier, 1974). According to a recent National Occupational Exposure Survey (NIOSH unpublished data), approximately 490 clinical laboratory technologists and technicians are exposed to 3,3'-dimethoxybenzidine.

Nonoccupational exposure to 3,3'-dimethoxybenzidine-based dyes may occur through contact with paper, fabrics, and leather to which these dyes have been applied and through the use of dyes packaged for home use and paints that contain 3,3'-dimethoxybenzidine. No estimates of consumer exposure to 3,3'-dimethoxybenzidine alone were found.

3,3'-Dimethoxybenzidine has been found in samples of commercially produced and imported sneezing powders (Giehl and Salger, 1983; Charles et al., 1984). The commercial material is usually a mixture of black pepper and sawdust; however, in some cases, 3,3'-dimethoxybenzidine or benzidine has been used in place of black pepper. These powders have reportedly caused severe poisoning in children, but the symptoms of 3,3'-dimethoxybenzidine poisoning were not described (Charles et al., 1984).

Disposition and Metabolism

Rodgers et al. (1983) reported that after intravenous administration to male F344 rats, [^{14}C]3,3'-dimethoxybenzidine was rapidly and extensively metabolized; less than 2% of the radiolabel could be recovered unchanged 30 minutes after dosing. Seventy percent of the radiolabel was excreted in the bile within 72 hours, and 50% was located in the intestinal tract after 2 hours. Three days after either oral or intravenous administration, 50% of the radiolabel had been excreted in the feces and 30%-40% excreted in the urine; 45% of the radiolabel remaining in the animal was present in the liver in the form of covalently bound metabolites. Analysis of the pooled urine (days 0-3) demonstrated that more than 90% of the urinary radiolabel was in the form of metabolites. Unmetabolized 3,3'-dimethoxybenzidine accounted for 3%-9% of the urinary radiolabel, and acetyldimethoxybenzidine accounted for 5% or less (Figure 1).

Reductive metabolism of 3,3'-dimethoxybenzidine-based dyes may result in formation of 3,3'-dimethoxybenzidine (Figure 2). Azo reduction can be carried out by enzymes in the liver or by azo reductase associated with intestinal bacterial flora. Highly polar compounds are not well absorbed from the gut, and therefore the water-soluble sulfonated dyes would not be expected to be well absorbed by mammals (Walker, 1970). For this reason, reductive cleavage of the benzidine-congener azo dyes is thought to occur primarily through bacterial action in the gastrointestinal tract (Martin and Kennelly, 1981; Cerniglia et al., 1982; Brown and Dietrich, 1983; Bos et al., 1984, 1986). The less polar metabolites could then be absorbed and further metabolized by the liver.

3,3'-Dimethoxybenzidine-based dyes have been shown to be metabolized to 3,3'-dimethoxybenzidine in dogs, rats, and humans. After exposure of dogs and rats to two 3,3'-dimethoxybenzidine-based dyes, 3,3'-dimethoxybenzidine was detected in the urine of both species at levels that were reportedly greater than the amount contributed by 3,3'-dimethoxybenzidine contamination of the dyes (Lynn et al., 1980). Genin (1977) also detected 3,3'-dimethoxybenzidine in the urine of rats exposed to two 3,3'-dimethoxybenzidine-based dyes. In the same study, 3,3'-dimethoxybenzidine was detected in the urine of three workers who dried and ground two 3,3'-dimethoxybenzidine-based dyes. Boeniger (1980) reported finding 3,3'-dimethoxybenzidine in the urine of a person who worked with 3,3'-dimethoxybenzidine-based dyes but not with 3,3'-dimethoxybenzidine itself. The urinary 3,3'-dimethoxybenzidine may have resulted from metabolism of the dyes or from exposure to dyes contaminated with 3,3'-dimethoxybenzidine.

Genetic Toxicology

3,3'-Dimethoxybenzidine has been extensively studied for induction of gene mutations in *Salmonella typhimurium*. The chemical was mutagenic with exogenous metabolic activation in strains TA98, TA100, and TA1538 (Anderson and Styles, 1978; Martin and Kennelly, 1981;

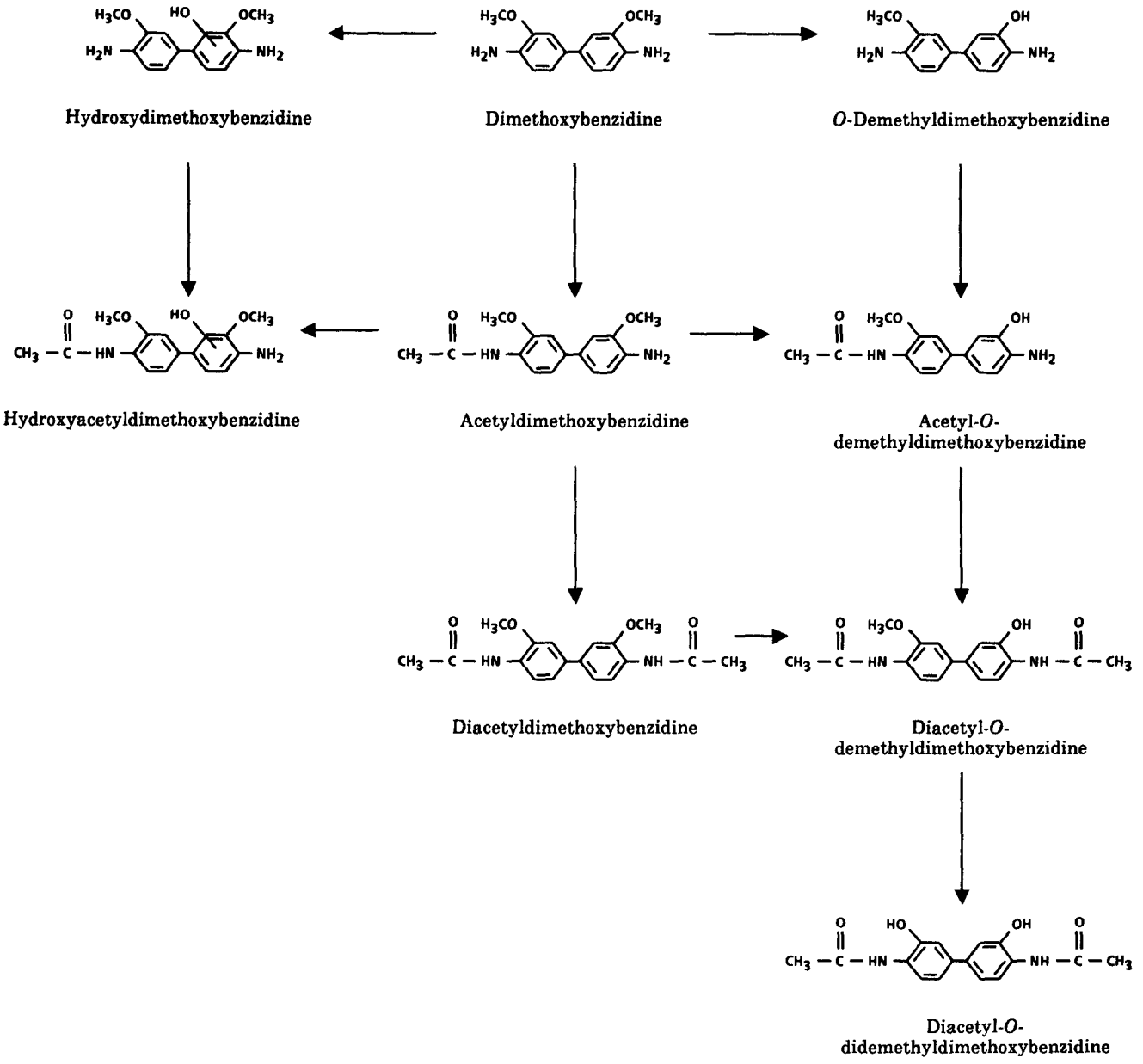


FIGURE 1. PROPOSED METABOLIC PATHWAYS OF 3,3'-DIMETHOXYBENZIDINE
(From Rodgers et al., 1983)

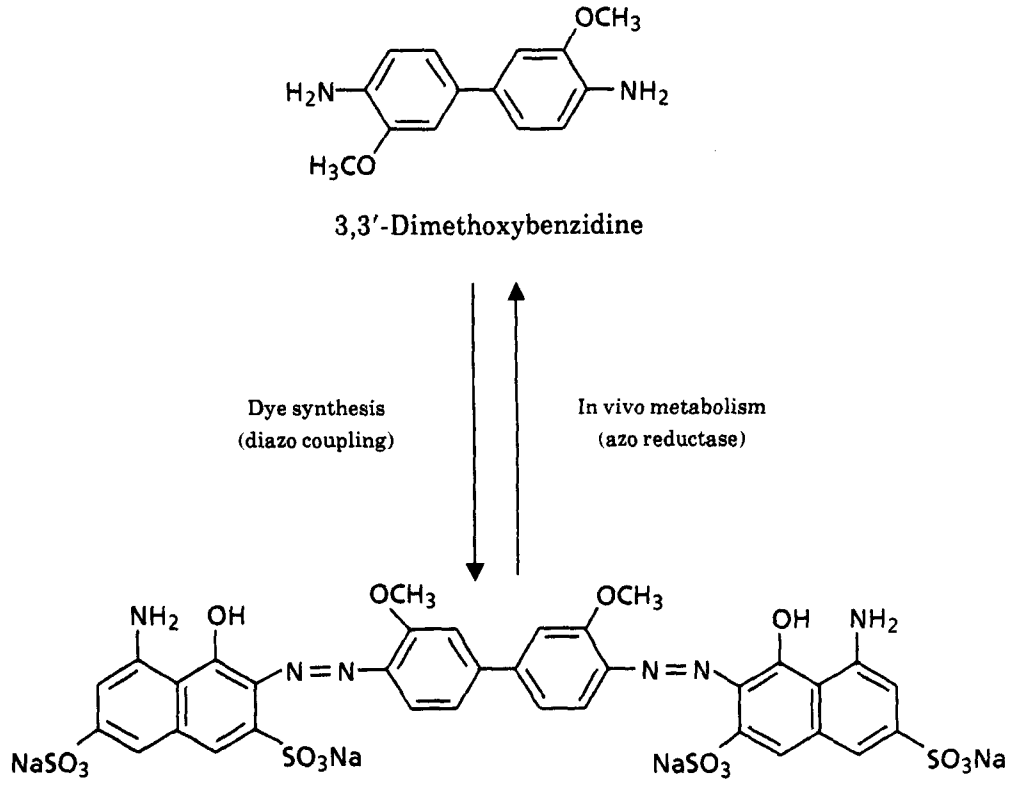


FIGURE 2. FORMATION OF 3,3'-DIMETHOXYBENZIDINE BY REDUCTIVE METABOLISM OF C.I. DIRECT BLUE 15

Probst et al., 1981; Haworth et al., 1983; Rodgers et al., 1983; Reid et al., 1984a,b). Messerly et al. (1987), in a structure-function study of the mutagenic activity of several benzidine derivatives, confirmed the greater activity of 3,3'-dimethoxybenzidine and other substituted aminobiphenyl compounds in *S. typhimurium* TA98 (a strain that mutates via frameshifts) compared with the activity of the chemical in TA100 (a base-substitution strain). The dihydrochloride salt of 3,3'-dimethoxybenzidine also induced gene mutations in *S. typhimurium* TA98 and TA100 (Gregory et al., 1981; Prival et al., 1984; Table H1). Growth inhibition due to induced DNA damage was not observed, however, in *Escherichia coli* treated with 3,3'-dimethoxybenzidine, but this test was performed in the absence of S9 activation (Fluck et al., 1976). Induction of unscheduled DNA synthesis in rat hepatocyte primary cultures treated with 500-1,000 nmol/ml 3,3'-dimethoxybenzidine was reported by Probst et al. (1981). Sister chromatid exchanges were significantly increased in Chinese hamster ovary cells treated with 3,3'-dimethoxybenzidine dihydrochloride with and without S9 metabolic activation (Galloway et al., 1985; Table H2). When originally reported, the results of the chromosomal aberration tests were considered to be negative (Galloway et al., 1985); however, by an updated statistical reanalysis of the chromosomal aberration data (Galloway et al., 1987), the results currently are considered to be weakly positive in the absence of S9 and positive with S9 (Table H3). Negative results were obtained in a *Drosophila melanogaster* sex-linked recessive lethal test in which the chemical was administered by two routes, feeding or injection (Yoon et al., 1985; Table H4).

Mutagenicity data for several metabolites and structural analogs of 3,3'-dimethoxybenzidine are consistent with the positive results in Salmonella and mammalian cell assays seen with 3,3'-dimethoxybenzidine. Benzidine, the parent compound in this series of substituted biphenyls, is positive for induction of gene mutations in *S. typhimurium* TA98, TA100, and TA1538 in the presence of S9 (Ames et al., 1973; Shimizu and Takemura, 1976; Anderson and Styles, 1978; Probst et al., 1981; Baker and Bonin, 1981; Haworth et al., 1983; Reid et al., 1984b) as well as in some strains of *E. coli* with S9 (Venitt and Crofton-Sleigh, 1981; Mohn et al., 1981; Matsushima et al., 1981). Like benzidine, two metabolites of 3,3'-dimethoxybenzidine, *N,N'*diacetyldimethoxybenzidine and *N*-acetyldimethoxybenzidine, were both positive in *S. typhimurium* TA98, TA100, and TA1538 in the presence of S9 activation (Kennelly et al., 1984; Reid et al. 1984b).

Toxicity and Carcinogenicity Studies

In 1980, NIOSH and the Occupational Safety and Health Administration (OSHA) issued a health hazard alert stating that persons working with 3,3'-dimethoxybenzidine-, benzidine-, or 3,3'-dimethylbenzidine-based dyes should be aware of the potential health hazards associated with excess exposure (Boeniger, 1980). In a later report issued to alert workers of the hazards of benzidine-congener dyes, NIOSH stated that workplace exposure to dyes based on 3,3'-dimethoxybenzidine may pose a carcinogenic risk to workers (NIOSH, 1983). These conclusions were based on evidence from animal studies indicating that 3,3'-dimethoxybenzidine is carcinogenic and on preliminary evidence that dyes derived from 3,3'-dimethoxybenzidine may be metabolically converted to the parent compound.

Earlier studies showed that repeated exposure to 3,3'-dimethoxybenzidine results in neoplasms in the gastrointestinal tract, Zymbal gland, skin, and mammary gland of rats and hamsters (Pliss, 1963, 1965; Saffiotti et al., 1967; Hadidian et al., 1968). Although these early studies provided evidence that 3,3'-dimethoxybenzidine is carcinogenic, the use of small numbers of animals, the use of toxic doses, and poor animal survival weakened this evidence. In addition, the doses of 3,3'-dimethoxybenzidine administered in earlier feed studies are questionable, since in the current studies, 3,3'-dimethoxybenzidine was shown to be unstable in rodent feed.

Pliss (1963, 1965) reported on the effects of orally administered 3,3'-dimethoxybenzidine (30 mg, three times per week, via gavage in sunflower oil) in rats. This dose was reduced to 15 mg after 3 weeks because of poor survival. Administration at the lower dose was continued for 13 months. The study was started with 42 rats, and 18 survived through month 14. Two of these 18 animals had neoplasms of the Zymbal gland, and 1 had an ovarian neoplasm. None of the 50 control rats developed neoplasms at the same sites as the exposed rats.

Saffiotti et al. (1967) fed diets containing 1,000 ppm 3,3'-dimethoxybenzidine to Syrian golden hamsters (30 males and 30 females per group) in a lifespan study. A transitional cell carcinoma of the urinary bladder was found in one animal after 144 weeks of exposure. This neoplasm is rare in hamsters and was attributed to 3,3'-dimethoxybenzidine exposure. Sellakumar et al. (1969) conducted a similar study in which a higher dietary concentration of 3,3'-dimethoxybenzidine (10,000 ppm) was administered to hamsters. Forestomach papillomas were detected in 37% of the exposed animals and in only 2% of the controls, but no urinary bladder lesions were detected. This publication is an abstract and does not detail the experimental design or survival data.

Hadidian et al. (1968) administered 3,3'-dimethoxybenzidine by gavage (0.1, 0.3, 1, 3, 10, or 30 mg per animal per day, 5 days per week) to groups of 3 or 14 (10-mg dose only) male and 3 or 15 (10-mg dose only) female F344 rats. The vehicle was a proprietary mixture composed of sodium chloride, sodium carboxymethylcellulose, polysorbate 80, and benzyl alcohol in water. The animals were exposed for 52 weeks and observed for an additional 6 months; necropsies were then performed. Neoplasms occurred as early as day 293, but most were detected at necropsy 18 months after the initial administration of 3,3'-dimethoxybenzidine. A variety of neoplasms were reported, and pooled results for all dosed male and female groups included neoplastic lesions of the urinary bladder (two papillomas), mammary gland (three carcinomas, two fibroadenomas), skin (five carcinomas), intestinal

tract (three carcinomas), and Zymbal gland (eight carcinomas). Incidences of neoplasms were significantly increased over those of the 360 pooled vehicle and untreated control rats.

No epidemiologic data on the occurrence of cancer in workers exposed to 3,3'-dimethoxybenzidine in the absence of other compounds suspected of being carcinogenic were found in the literature. No reports on the carcinogenicity of 3,3'-dimethoxybenzidine-derived dyes in animals or humans were found in the literature.

Toxicity and Carcinogenicity of Related Compounds

Benzidine: 3,3'-Dimethoxybenzidine is a congener of benzidine, a known carcinogen for humans (Scott, 1952; Case et al., 1954; IARC, 1972a; Zavon et al., 1973), rats (Spitz et al., 1950; Griswold et al., 1968), hamsters (Saffiotti et al., 1966), and mice (Bonser et al., 1956; Prokofjeva, 1971; IARC, 1972a; Frith and Dooley, 1976). Benzidine has been shown to produce urinary bladder tumors in as many as 90% of workers who have been exposed for up to 30 years (Scott, 1952). Exposure to benzidine may occur directly or by reductive metabolism of benzidine-based dyes. The carcinogenicity of benzidine has been extensively reviewed (IARC, 1972a, 1982, 1987a; Haley, 1975; USEPA, 1980).

Benzidine exposure has been shown to cause urinary bladder tumors in 1/7 dogs (Spitz et al., 1950); hepatocellular, harderian gland, and lymphoreticular tumors in mice (Bonser et al., 1956; Vesselinovitch et al., 1975; Frith and Dooley, 1976; Littlefield et al., 1983); Zymbal gland, hepatic, and mammary gland carcinomas in rats (Spitz et al., 1950; Griswold et al., 1968); and hepatocellular carcinomas, adenomas, and cholangiomas in hamsters (Saffiotti et al., 1967). In many of the carcinogenicity studies on benzidine, animal survival was poor, primarily because of administration of toxic doses. These studies, however, leave no doubt that benzidine is carcinogenic for laboratory animals.

3,3'-Dimethylbenzidine: 3,3'-Dimethylbenzidine, a methylated congener of benzidine and a structural analog of 3,3'-dimethoxybenzidine, has been shown to be carcinogenic in laboratory animals. In early studies, Spitz et al. (1950) demonstrated the ability of the compound to induce Zymbal gland neoplasms in rats. In a series of experiments, 3,3'-dimethylbenzidine administered subcutaneously to rats was shown to cause neoplasms of the Zymbal gland, small intestine, and mammary gland (Pliss, 1963, 1965; Pliss and Zabezhinsky, 1970). The IARC (1972b) reviewed the literature on 3,3'-dimethylbenzidine and concluded that it was a systemic carcinogen for rats when given subcutaneously.

o-Anisidine: o-Anisidine (2-methoxyaniline) is structurally analogous to one-half the 3,3'-dimethoxybenzidine molecule. o-Anisidine is used in the manufacture of monoazo dyes by diazotization and coupling with other aromatic amines (Noller, 1965). In 103-week studies, o-anisidine hydrochloride was found to be carcinogenic for F344 rats and B6C3F$_1$ mice (NCI, 1978a). Groups of 55 animals of each species and sex received o-anisidine in feed at either 5,000 or 10,000 ppm for rats and 2,500 or 5,000 ppm for mice. Controls consisted of 55 untreated animals of each sex and species. Administration of o-anisidine hydrochloride resulted in transitional cell carcinomas or papillomas of the bladder in each sex of each species, transitional cell carcinomas of the renal pelvis in male rats, and follicular cell neoplasms of the thyroid gland in male rats. Only one control animal had any neoplasms of the urinary system (a transitional cell papilloma of the renal pelvis in a male mouse).

3,3'-Dimethoxybenzidine-4,4'-diisocyanate: 3,3'-Dimethoxybenzidine is a hydrolysis product of 3,3'-dimethoxybenzidine-4,4'-diisocyanate (dianisidine diisocyanate). Although there is presently no known producer of dianisidine diisocyanate, it was produced by one U.S. manufacturer in the 1970's (IARC, 1986). Dianisidine diisocyanate can be used as a component of polyurethane elastomers and in isocyanate-based adhesives (NCI, 1979; IARC, 1986). In 78-week studies, dianisidine diisocyanate was found to be carcinogenic for F344 rats but not for B6C3F$_1$ mice (NCI, 1979). Dianisidine diisocyanate was administered at either of two concentrations to 50 animals of each species and sex. The compound was administered in feed, with the exception of the first 22 weeks of the study in rats when it was administered by gavage. Controls consisted of 20 animals of each sex and species. The doses of dianisidine diisocyanate administered by gavage to rats were 1,500 and 3,000 mg/kg per day, 5 days per week. Dietary

concentrations for rats and mice were 22,000 and 40,000 ppm. Animals were chemically exposed for 78 weeks, followed by an observation period of 26 weeks for rats and 25 weeks for mice. In rats, administration of dianisidine diisocyanate resulted in neoplasms of the skin in males, endometrial stromal polyps in females, and leukemia and malignant lymphomas in each sex. Dianisidine diisocyanate administration was also associated with the development of a combination of squamous cell carcinomas and sebaceous adenocarcinomas of the Zymbal gland and skin of the ear in rats of each sex. There was no evidence of carcinogenicity of dianisidine diisocyanate for B6C3F$_1$ mice.

Study Rationale

Benzidine is known to cause cancer in humans (IARC, 1972a, 1987a), and 3,3'-dimethoxybenzidine, a benzidine congener, is suspected of possessing carcinogenic potential for humans (Fishbein, 1981). Numerous benzidine and benzidine congener-based dyes have been shown to be metabolized to their parent amines in vivo (Rinde and Troll, 1975; Lynn et al., 1980). Consequently, all benzidine-derived and benzidine congener-derived dyes are logical candidates for carcinogenicity evaluation in laboratory animals.

The National Toxicology Program's (NTP's) Benzidine Dye Initiative is a collaborative effort of the National Institute of Environmental Health Sciences, the National Center for Toxicological Research (NCTR), NIOSH, the U.S. Environmental Protection Agency, the Consumer Product Safety Commission, and OSHA, under the aegis of the NTP. The objective of this Initiative was to develop an integrated body of data concerning the metabolism and pharmacokinetics, genetic toxicology, and in vivo carcinogenicity of dyes derived from benzidine, 3,3'-dimethylbenzidine, and 3,3'-dimethoxybenzidine (Table 1). Because studying each of the hundreds of benzidine-based dyes was considered to be impractical, the research program was designed to evaluate representative benzidine congeners and benzidine congener-derived dyes.

3,3'-Dimethoxybenzidine was selected by the collaborating agencies for study in the Initiative to allow comparison of its toxic and carcinogenic effects with those of related chemicals that were studied simultaneously with comparable doses and the same study design. In addition, 3,3'-dimethoxybenzidine was studied to strengthen the evidence for its carcinogenicity. Although results of earlier studies suggested that 3,3'-dimethoxybenzidine was carcinogenic (Pliss, 1963, 1965; Saffiotti et al., 1967; Hadidian et al., 1968), these studies have been criticized because of the use of small groups of animals, the use of toxic doses, poor survival, and the use of parenteral routes of administration (Haley, 1975; DETO, 1980).

TABLE 1. SUMMARY OF THE NATIONAL TOXICOLOGY PROGRAM BENZIDINE CONGENER INITIATIVE

Class/Chemical	Tests (a)
o-Tolidine (3,3'-dimethylbenzidine)	
o-Tolidine	G, P, B
C.I. Direct Red 2	G, M
C.I. Direct Red 39	G, M
C.I. Acid Red 114	G, P, B
C.I. Direct Blue 25	G
C.I. Direct Blue 53	G, M
C.I. Direct Blue 14	G
C.I. Direct Orange 6	G, M
o-Dianisidine (3,3'-dimethoxybenzidine)	
o-Dianisidine	G, P, B
C.I. Direct Blue 15	G, P, B
C.I. Direct Blue 218	G, P, B
C.I. Direct Black 114	G, M
C.I. Direct Yellow 68	G, M
C.I. Direct Blue 8	G, M

(a) G = genetic toxicology; P = pharmacokinetic studies; M = metabolism studies for detection of carcinogens in urine; B = toxicology and carcinogenicity studies.

3,3′-Dimethoxybenzidine dihydrochloride is one of five chemicals being evaluated in the 2-year carcinogenicity studies as part of the Benzidine Dye Initiative. The other chemicals currently being studied are C.I. Direct Blue 15 and C.I. Direct Blue 218 (representative 3,3′-dimethoxybenzidine-based dyes), 3,3′-dimethylbenzidine dihydrochloride (a related benzidine congener), and C.I. Acid Red 114 (a representative 3,3′-dimethylbenzidine-based dye). The oral route of administration was selected for the 3,3′-dimethoxybenzidine dihydrochloride, C.I. Direct Blue 15, 3,3′-dimethylbenzidine dihydrochloride, and C.I. Acid Red 114 studies to maximize the chances of detecting systemic effects associated with chemical administration. These four chemicals were studied with the same study design and with staggered starts over a period of 4 months. Because of the instability of 3,3′-dimethoxybenzidine and 3,3′-dimethylbenzidine in feed, all four chemicals were administered in drinking water.

Long-term studies of 3,3′-dimethoxybenzidine dihydrochloride are being conducted in mice at the NCTR as part of the Benzidine Initiative. Male and female (840 each) BALB/c mice were given 0, 20, 40, 80, 160, 315, or 630 ppm 3,3′-dimethoxybenzidine dihydrochloride in drinking water. Animals were killed after exposure for 13, 26, 39, 52, 78, or 112 weeks, and complete necropsies and histopathologic examinations were performed. 3,3′-Dimethoxybenzidine dihydrochloride was not carcinogenic in BALB/c mice (Schieferstein et al., 1989)

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

CHARACTERIZATION OF FORMULATED DRINKING WATER MIXTURES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

NINE-MONTH AND TWENTY-ONE-MONTH STUDIES

Study Design

Source and Specifications of Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

A single lot of 3,3'-dimethoxybenzidine dihydrochloride (lot no. 11F-5034) was obtained from Sigma Chemical Company (St. Louis, MO) in two batches. Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, MO) (Appendix G). The study chemical in both batches was identified as 3,3'-dimethoxybenzidine dihydrochloride by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Lot no. 11F-5034 was found to be approximately 98% pure, as determined by elemental analysis, Karl Fischer water analysis, potentiometric titration of the two amine groups, thin-layer chromatography, and high-performance liquid chromatography. Comparison of batch no. 1 and batch no. 2 by high-performance liquid chromatography indicated no significant differences between the two batches.

The identity of the chemical at the laboratory was confirmed by infrared spectroscopy. The stability of the study material was monitored by high-performance liquid chromatography and nonaqueous titration of the amine groups. No deterioration of the study material was seen over the course of the studies.

CHARACTERIZATION OF FORMULATED DRINKING WATER MIXTURES

The stability of 3,3'-dimethoxybenzidine dihydrochloride mixed with NIH 07 Rat and Mouse Ration at 200 ppm and stored for 2 weeks at temperatures ranging from −20° C to room temperature was determined. The feed mixtures were extracted and analyzed by gas chromatography using a 3% OV-17 column and flame ionization detection. The formulated diets were found to be unstable under all storage conditions at or above 5° C. Formulated diets stored open to air and light under simulated animal room conditions lost 12.4% or 18.2% of the chemical after 3 or 7 days, respectively. The same feed mixtures stored in the dark in sealed containers lost 1.6%, 8.9%, or 25.7% of the chemical after storage for 2 weeks at −20° C, 5° C, or room temperature.

Because the feed blends of 3,3'-dimethoxybenzidine dihydrochloride were found to be unstable, drinking water was selected as the route of administration for these studies. The 14-day stability of 3,3'-dimethoxybenzidine dihydrochloride in water at 200 ppm (200 µg/ml), stored at room temperature or at 5° C, was determined. The water solutions were diluted with methanol and analyzed by high-performance liquid chromatography with a C_{18} column and ultraviolet detection at 280 nm. The 3,3'-dimethoxybenzidine dihydrochloride/water solutions were found to be stable for at least 14 days when stored in the dark at room temperature or at 5° C. The water solutions were also stable under simulated dosing conditions for at least 48 hours. Drinking water mixtures were prepared two times per week and were used immediately or, for the 21-month studies, stored at room temperature for up to 7 days before being used.

During the 21-month studies, the drinking water mixtures were analyzed at approximately 4-week intervals. For the 3,3'-dimethoxybenzidine dihydrochloride studies, it was estimated that the mixtures were formulated within ±10% of the target concentrations approximately 99% (103/104) of the time throughout the studies (Table G3). Results of periodic referee analysis performed by the analytical chemistry laboratory indicated good agreement with the results from the study laboratory (Table G4).

FOURTEEN-DAY STUDIES

Male and female F344/N rats were obtained from Frederick Cancer Research Facility and were held for 17 days before the studies began. The rats were 7 weeks old when placed on study.

Groups of five rats of each sex received 0, 200, 350, 750, 1,500, or 4,500 ppm 3,3'-dimethoxybenzidine dihydrochloride in drinking water for 14 days.

Animals were housed five per cage. Water and feed were available ad libitum. The rats were observed two times per day and were weighed on days 1, 7 (males) or 4 (females), and 14. A necropsy was performed on all animals. Organ weight to body weight ratios were determined for brain, lung, heart, liver, kidney, right testis, and thymus. Complete histopathologic

examinations were performed on all controls and animals in the 4,500-ppm groups. The spleen, bone marrow (sternum), and thymus in 1,500-ppm males and bone marrow (sternum) in 1,500-ppm females were examined. Further details are presented in Table 2.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to 3,3'-dimethoxybenzidine dihydrochloride and to determine the concentrations to be used in the 2-year studies.

Four-week-old male and female F344/N rats were obtained from Frederick Cancer Research Facility, observed for 14 days, distributed to weight classes, and assigned to dose groups according to a table of random numbers. Rats were 6 weeks old when placed on study.

Groups of 10 rats of each sex received 0, 170, 330, 630, 1,250, or 2,500 ppm 3,3'-dimethoxybenzidine dihydrochloride in drinking water ad libitum for 13 weeks. Rats were housed five per cage. Feed was available ad libitum. Further experimental details are summarized in Table 2.

Animals were observed two times per day; moribund animals were killed. Feed consumption was measured one time per week by cage. Water consumption was measured two times per week. Individual animal weights were recorded one time per week.

Blood was collected from the retro-orbital sinus of all animals at the termination of the studies. Hematocrit values, hemoglobin concentrations, erythrocyte counts, leukocyte counts, and differential leukocyte counts were determined with a Coulter Counter Model S-Plus IV. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals. The liver, kidney (right), heart, brain, lung, thymus, and testis (right) were weighed at necropsy. An accumulation of lipofuscin was observed in the thyroid gland after rats were exposed to 3,3'-dimethoxybenzidine for 13 weeks, suggesting a possible chemical effect on thyroid gland function. Thyroid gland function was further evaluated by analyzing the remaining serum samples for changes in triiodothyronine (T_3), thyroxin (T_4), and thyrotropin (TSH). These indices of thyroid gland injury were also investigated in the 2-year studies. T_3, T_4, TSH, blood urea nitrogen, creatinine, lactic dehydrogenase, sorbitol dehydrogenase, and alanine aminotransferase were measured in serum taken from the abdominal aorta at necropsy. T_3 and T_4 were analyzed with the Tri-Tab RIA Diagnostic Kit and the Tetra-Tab RIA Diagnostic Kit (Nuclear Medical Laboratories). TSH analysis was performed by the method of Ridgway et al. (1973). Histopathologic examinations were performed. Tissues and groups examined are listed in Table 2.

NINE-MONTH AND TWENTY-ONE-MONTH STUDIES

Study Design

The 21-month study was originally designed for 24 months using an animal allocation recommended by Portier and Hoel (1984). Additionally, at 9 months, 10 rats of each sex in control groups and 10 rats of each sex in the 330-ppm groups were killed, and at 15 months, 10 rats of each sex in each dose group were to be killed. Animals to be used for the 9- and 15-month studies were designated before the studies were started. Because of the large number of early deaths in the chemically exposed groups, the 15-month interim kill was canceled and these animals were added to the core groups, resulting in 60 rats in the control groups, 45 in the 80-ppm groups, 75 in the 170-ppm groups, and 60 in the 330-ppm groups. The liver, right kidney, heart, brain, lung, thymus, and right testis were weighed at necropsy. Hematocrit values, hemoglobin concentrations, erythrocyte counts, leukocyte counts, and differential leukocyte counts were determined. T_3, T_4, TSH, blood urea nitrogen, creatinine, lactic dehydrogenase, sorbitol dehydrogenase, and alanine aminotransferase were measured in serum taken from the abdominal aorta at necropsy. Histopathologic examinations were performed.

Source and Specifications of Animals

The male and female F344/N rats used in these studies were produced under strict barrier conditions at Simonsen Laboratories. Breeding stock for the foundation colony at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

Fourteen-Day Studies	Thirteen-Week Studies	Nine-Month and Twenty-One-Month Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
5 males and 5 females	10 males and 10 females	9 mo--10 males and 10 females at 0 or 330 ppm; 21 mo--60 males and 60 females at 0 or 330 ppm; 45 males and 45 females at 80 ppm; 75 males and 75 females at 170 ppm
Doses		
0, 200, 350, 750, 1,500, or 4,500 ppm 3,3'-dimethoxybenzidine dihydrochloride in drinking water	0, 170, 330, 630, 1,250, or 2,500 ppm 3,3'-dimethoxybenzidine dihydrochloride in drinking water	9 mo--0 or 330 ppm 3,3'-dimethoxybenzidine dihydrochloride in drinking water; 21 mo--0, 80, 170, or 330 ppm 3,3'-dimethoxybenzidine dihydrochloride in drinking water
Date of First Dose		
3/19/82	6/17/82	3/29/83
Date of Last Dose		
4/2/82	Male--9/16/82; female--9/19/82	9 mo--12/27/83; 21 mo--12/26/84
Duration of Dosing		
14 consecutive d	13 wk	9 or 21 mo
Type and Frequency of Observation		
Observed at least 2 × d; weighed on d 1 and d 7 (male) or d 4 (female) and at the end of the studies; water consumption recorded 1 × wk	Observed 2 × d; weighed 1 × wk; water consumption determined 2 × wk	Observed 2 × d; weighed 1 × wk for 15 wk and then at least 1 × mo
Necropsy, Histologic Examinations, and Supplemental Analyses		
Necropsy performed on all animals; the following tissues examined histologically for control and high dose groups: adrenal glands, brain, cecum, colon, esophagus, heart and aorta, ileum, kidneys, liver, lungs, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland, prostate/testes or ovaries/uterus, rectum, salivary glands, skin, small intestine, spleen, sternebrae, stomach, thymus, thyroid gland, trachea, urinary bladder, and Zymbal gland. Tissues examined for the 1,500-ppm groups include bone marrow, spleen, sternum, and thymus for males and sternum for females. Organ weights obtained at necropsy	Necropsy performed on all animals; the following tissues examined histologically for control and high dose groups: adrenal glands, brain, cecum, colon, duodenum, epididymis/prostate/testes or ovaries/uterus, esophagus, eyes (if grossly abnormal), gross lesions and tissue masses with regional lymph nodes, heart, ileum, jejunum, kidneys, liver, lungs and mainstem bronchi, mandibular or mesenteric lymph nodes, nasal turbinates, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland, rectum, salivary glands, spinal cord (if neurologic signs present), spleen, sternebrae including marrow, stomach, thymus, thyroid gland, trachea, urinary bladder, and Zymbal gland. Tissues examined in lower dose groups include kidneys, thymus (male only), and thyroid gland at 1,250 ppm and thyroid gland for both males and females at 630 ppm and females at 330 ppm. Hematologic and serum chemical analyses and thyroid hormone determinations performed; organ weights obtained at necropsy	Necropsy and histologic exams performed on all animals; the following tissues were examined: adrenal glands, brain, cecum, colon, esophagus, heart and aorta, ileum, kidneys, liver, lungs, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland, prostate/testes or ovaries/uterus, rectum, salivary glands, skin, small intestine, spleen, sternebrae, stomach, thymus, thyroid gland, trachea, urinary bladder, and Zymbal gland. Hematologic and serum chemical analyses, urinalyses, and thyroid hormone determinations performed at 9 mo; organ weights obtained at necropsy

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

Fourteen-Day Studies	Thirteen-Week Studies	Nine-Month and Twenty-One-Month Studies
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species F344/N rats	F344/N rats	F344/N rats
Animal Source Frederick Cancer Research Facility (Frederick, MD)	Frederick Cancer Research Facility (Frederick, MD)	Simonsen Laboratories (Gilroy, CA)
Study Laboratory Hazleton Laboratories America, Inc.	Hazleton Laboratories America, Inc.	Hazleton Laboratories America, Inc.
Method of Animal Identification Ear tag	Ear punch	Ear tag and ear punch
Time Held Before Study 17 d	14 d	21 d for first shipment and 14 d for second shipment
Age When Placed on Study 7 wk	6 wk	6-7 wk
Age When Killed 9 wk	19 wk	9 mo: 42-43 wk; 21 mo: 98-100 wk
Necropsy Dates 4/2/82	Male--9/17/82; female--9/20/82	9 mo: 12/28/83-1/2/84; 21 mo: 1/3/85-1/4/85 and 1/7/85
Method of Animal Distribution Animals distributed to weight classes and then assigned to cages by one table of random numbers and to groups by another table of random numbers	Same as 14-d studies	Same as 14-d studies
Diet NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as 14-d studies	Same as 14-d studies
Bedding Hardwood chips (P.J. Murphy Forest Products Corp., Mt. Jewuit, PA)	Same as 14-d studies	Same as 14-d studies
Water Tap or formulated water in glass water bottles (Hazleton Systems, Inc., Aberdeen, MD); available ad libitum	Same as 14-d studies	Same as 14-d studies
Cages Polycarbonate (Hazleton Systems, Inc., Aberdeen, MD)	Same as 14-d studies	Same as 14-d studies
Cage Filters Nonwoven fiber filters (National Paper Co., Wilmington, DE)	Same as 14-d studies	Same as 14-d studies
Animals per Cage 5	5	5
Other Chemicals on Study in the Same Room None	None	None

TABLE 2. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

Fourteen-Day Studies	Thirteen-Week Studies	Nine-Month and Twenty-One-Month Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Animal Room Environment		
Temp--72°-77° F; hum--19%-60%; fluorescent light 12 h/d	Temp--70°-75° F (except for 68° F on 6/19/82); hum--41%-82% (except for 32% on 8/29/82); fluorescent light 12 h/d; 10-12 room air changes/h	Temp--65°-81° F; hum--20%-77%; fluorescent light 12 h/d; 9-17 room air changes/h

parents that were transferred from isolators to barrier-maintained rooms. The rats were shipped to the study laboratory at 3-4 weeks of age and were quarantined at the study laboratory for 2 or 3 weeks. Thereafter, a complete necropsy was performed on five animals of each sex to assess their health status. The rodents were placed on study at 6-7 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix C).

Animal Maintenance

The rats were housed five per cage. Feed (Appendix E) and water were available ad libitum. Cages were rotated every 2 weeks during the studies.

Clinical Examinations and Pathology

All animals were observed two times per day. Body weights were recorded one time per week for the first 15 weeks of the studies and then at least one time per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead. In some cases, a particular organ was autolyzed or lost (e.g., intestine or thymus); thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study. During necropsy, all organs and tissues were examined for grossly visible lesions. All major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Tissues examined are listed in Table 2.

When the pathology evaluation was completed by the laboratory pathologist and the pathology data entered into the Toxicology Data Management System, the slides, paraffin blocks, and residual formalin-fixed tissues were sent to the NTP Archives. The slides, blocks, and residual wet tissues were audited for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The slides, individual animal necropsy records, and pathology tables were sent to an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tissues with a tumor diagnosis, all potential target tissues, and all tissues from a randomly selected 10% of the animals were re-evaluated microscopically by a quality assessment pathologist. Target tissues were the oral cavity, intestines, liver, preputial or clitoral gland, Zymbal gland, skin, spleen, bone marrow (male) and mammary gland (female). Nonneoplastic lesions were evaluated for accuracy and consistency of diagnosis only in the potential target tissues, in the randomly selected 10% of animals, and in tissues with unusual incidence patterns or trends.

The quality assessment report and slides were submitted to a Pathology Working Group (PWG) Chairperson, who reviewed microscopically all potential target tissues and any other tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative examples of liver, intestine, Zymbal gland, preputial/clitoral gland,

skin, mammary gland, and brain neoplasms and examples of disagreements in diagnosis between the laboratory and quality assessment pathologists were shown to the PWG. The PWG included the quality assessment pathologist and other pathologists experienced in rodent toxicology, who examined the tissues without knowledge of dose group or previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the diagnosis was changed to reflect the opinion of the PWG. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final pathology data represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Statistical Methods

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found to be dead from other than natural causes; animals dying from natural causes were not 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) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., in this study, oral cavity) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence: In this study, the large numbers of dosed rats that died or were killed in a moribund condition early in the study were considered to be due primarily to skin, preputial gland, clitoral gland, Zymbal gland, and malignant mammary gland tumors. Consequently, for these particular lesions, primary emphasis in the analysis of tumor incidence was given to the life table test (Cox, 1972; Tarone, 1975), a survival-adjusted procedure appropriate for rapidly lethal tumors.

For incidental tumors (i.e., tumors discovered as the result of death from an unrelated cause), one method of analysis used in this study was logistic regression. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). However, markedly reduced survival in exposed animals (due largely to increased incidences of lethal tumors) reduced the power of logistic regression to detect carcinogenic effects in some instances. Hence, although the results of logistic regression analysis are given in the appendixes for informational purposes, in the evaluation of incidental tumors, primary emphasis was given to Cochran-Armitage and Fisher exact tests based on the "effective" number of animals, i.e., the number of animals surviving until observation of the first tumor at that tissue site. These survival-adjusted procedures are recommended by Gart et al. (1979).

Tests of significance include pairwise comparisons of each dosed group with controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described above also were used to evaluate selected nonneoplastic lesions. (For further discussion of these statistical methods, see Haseman, 1984.)

Historical Control Data: Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of tumor incidence. Although the current studies were terminated at month 21, control

tumor incidences from the NTP historical control data base for 24-month studies (Haseman et al., 1984, 1985) are included for those tumors appearing to show compound-related effects.

Analysis of Continuous Variables: Organ weight to body weight ratios and hematology and serum chemistry data from the 14-day and 13-week studies were analyzed by the nonparametric multiple comparison procedures of Dunn (1964) and Shirley (1977); Jonckheere's test (Jonckheere, 1954) was used to evaluate the significance of dose-response trends and to determine whether Dunn's or Shirley's test was more appropriate for pairwise comparisons. For the 9-month studies (in which a single dose group was compared with the controls), Wilcoxon's rank sum test (Hollander and Wolfe, 1973) was used to evaluate organ weight, hematology, serum chemistry, and urinalysis data.

III. RESULTS

RATS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

NINE-MONTH STUDIES

TWENTY-ONE-MONTH STUDIES

Body Weights, Water Consumption, and Clinical Signs

Survival

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III. RESULTS: RATS

FOURTEEN-DAY STUDIES

All rats lived to the end of the studies (Table 3). The final mean body weights of rats that received 4,500 ppm were lower than the initial weights. The final mean body weights of rats that received 1,500 ppm were 4% lower than those of controls. Water consumption decreased as the chemical concentration increased and at 4,500 ppm was less than one-fourth that by the controls. The relative liver and kidney weights were increased, but no microscopic changes were seen in these organs (Table F1). The relative thymus weight for females was significantly lower than that for controls receiving 4,500 ppm, and lymphoid depletion of the spleen in males and females and of the thymus in males was observed. Hypocellularity of the bone marrow was seen at 4,500 ppm (in the groups that lost weight).

THIRTEEN-WEEK STUDIES

All rats lived to the end of the studies (Table 4). Final mean body weights of rats receiving 1,250 or 2,500 ppm were 10% or 20% lower than that of the controls for males and 5% or 11% lower for females. Water consumption at 1,250 or 2,500 ppm was about 60% that by the controls for males and about 45% for females. The relative liver and kidney weights for all groups of dosed male rats, the relative liver weights for females receiving 630 ppm and more, and the relative kidney weights for females receiving 330 ppm and more were significantly greater than those for controls (Table 5). Significant increases in the leukocyte and lymphocyte counts were observed for males receiving 2,500 ppm (Table F2). Segmented neutrophil counts were significantly decreased for males receiving 630 ppm or more and for females receiving 2,500 ppm.

TABLE 3. SURVIVAL, MEAN BODY WEIGHTS, AND WATER CONSUMPTION OF RATS IN THE FOURTEEN-DAY DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Water Consumption (d) Week 1	Week 2
MALE							
0	5/5	175	235	+60		21	22
200	5/5	178	241	+63	103	18	19
350	5/5	176	235	+59	100	16	18
750	5/5	175	232	+57	99	15	16
1,500	5/5	177	225	+48	96	13	14
4,500	5/5	177	141	−36	60	4	5
FEMALE							
0	5/5	136	163	+27		32	30
200	5/5	139	163	+24	100	14	15
350	5/5	138	160	+22	98	14	13
750	5/5	138	156	+18	96	12	12
1,500	5/5	141	157	+16	96	13	15
4,500	5/5	139	135	−4	83	7	6

(a) Number surviving/number initially in group
(b) Initial group mean body weight
(c) Mean body weight change of the group
(d) Milliliters per animal per day

TABLE 4. SURVIVAL, MEAN BODY WEIGHTS, AND WATER CONSUMPTION OF RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Water Consumption (d) Week 7	Week 13
MALE							
0	10/10	132	343	+211		21	21
170	10/10	131	337	+206	98	21	22
330	10/10	129	337	+208	98	17	20
630	10/10	132	332	+200	97	16	17
1,250	10/10	129	310	+181	90	13	14
2,500	10/10	129	276	+147	80	12	12
FEMALE							
0	10/10	103	190	+87		27	25
170	10/10	103	186	+83	98	23	21
330	10/10	103	188	+85	99	29	29
630	10/10	103	183	+80	96	16	14
1,250	10/10	105	180	+75	95	13	11
2,500	10/10	103	169	+66	89	10	10

(a) Number surviving/number initially in group
(b) Initial group mean body weight
(c) Mean body weight change of the group
(d) Milliliters per animal per day

TABLE 5. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

Organ	Control	170 ppm	330 ppm	630 ppm	1,250 ppm	2,500 ppm
MALE						
Necropsy body weight (grams)	326 ± 6.18	319 ± 5.58	325 ± 4.54	318 ± 5.69	**295 ± 5.51	**265 ± 5.45
Liver	25.1 ± 0.20	**27.7 ± 0.19	**27.9 ± 0.21	**29.3 ± 0.30	**31.3 ± 0.35	**32.8 ± 0.58
Brain	5.8 ± 0.10	5.9 ± 0.06	5.8 ± 0.10	6.0 ± 0.09	**6.4 ± 0.11	**6.9 ± 0.11
Heart	2.9 ± 0.04	2.9 ± 0.03	2.8 ± 0.04	2.9 ± 0.06	*3.2 ± 0.10	*3.0 ± 0.06
Right kidney	3.0 ± 0.04	*3.1 ± 0.04	**3.2 ± 0.04	**3.4 ± 0.04	**3.5 ± 0.06	**4.0 ± 0.06
Lungs	3.6 ± 0.09	3.7 ± 0.08	3.5 ± 0.09	3.5 ± 0.05	3.8 ± 0.09	**4.2 ± 0.27
Right testis	4.5 ± 0.10	4.7 ± 0.06	4.6 ± 0.09	4.6 ± 0.08	*4.8 ± 0.08	**5.4 ± 0.07
Thymus	1.1 ± 0.03	*0.9 ± 0.02	**0.9 ± 0.06	**0.9 ± 0.04	**0.8 ± 0.06	**0.8 ± 0.01
FEMALE						
Necropsy body weight (grams)	179 ± 2.20	176 ± 2.22	178 ± 1.65	175 ± 1.46	174 ± 3.44	**164 ± 2.63
Liver	25.9 ± 0.40	26.2 ± 0.36	27.0 ± 0.39	**28.4 ± 0.97	**28.3 ± 0.24	**30.2 ± 0.46
Brain	10.0 ± 0.07	10.1 ± 0.17	9.9 ± 0.07	10.1 ± 0.13	10.2 ± 0.16	**10.6 ± 0.15
Heart	3.2 ± 0.07	3.2 ± 0.03	3.3 ± 0.08	*3.5 ± 0.07	**3.4 ± 0.05	*3.4 ± 0.06
Right kidney	3.2 ± 0.05	3.3 ± 0.05	**3.5 ± 0.05	**3.9 ± 0.06	**4.0 ± 0.09	**4.2 ± 0.05
Lungs	4.7 ± 0.19	4.8 ± 0.13	4.7 ± 0.09	5.0 ± 0.08	4.9 ± 0.08	(b) 4.6 ± 0.06
Thymus	1.3 ± 0.04	1.2 ± 0.04	1.3 ± 0.04	1.4 ± 0.05	1.4 ± 0.03	1.3 ± 0.04

(a) Mean (milligrams per gram) ± standard error for groups of 10 animals, unless otherwise specified. P values are vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Nine animals were weighed.
*P<0.05
**P<0.01

Erythrocyte counts and hematocrit values were significantly decreased by up to 15% in female rats exposed to 630 ppm or more; however, the lack of a concomitant decrease in hemoglobin suggested that these decreases were due to sample hemolysis and were probably not related to chemical exposure. In male rats, a mild increase (<1,000 cells/μl) in total leukocytes was produced by a combination of a mild increase (<1,300/μl) in lymphocytes and a decrease (<400 cells/μl) in neutrophils. None of these changes is biologically relevant. Mild decreases in creatinine (about 20%) were observed in all groups of dosed males and females. These decreases could be produced by loss of muscle mass. Alternatively, decreased concentrations of creatinine can result from substances that interfere with the assay (e.g., bilirubin or hemoglobin).

Compound-related effects seen at 2,500 ppm included mild exacerbation of nephropathy, a condition commonly seen in F344 rats. Nephropathy, characterized by mild tubular regeneration and lymphocytic inflammatory infiltrates, was observed in 10/10 males and 6/10 females. In addition, brown granular pigment was seen in the cytoplasm of the thyroid gland follicular cells of 10/10 males and 10/10 females. The AFIP method for determination of lipofuscin indicated that the pigment was lipofuscin. The mean serum triiodothyronine (T_3) and thyroxin (T_4) concentrations in females receiving 330 ppm or more and the serum T_4 concentrations in males receiving 170 ppm or more were significantly lower than those in controls. The thyrotropin (TSH) concentrations in dosed rats were not significantly different from those in controls (Table F2.)

Dose Selection Rationale: Because of chemical-related exacerbation of nephropathy and decreased water consumption at higher concentrations in short-term studies, drinking water concentrations of 3,3'-dimethoxybenzidine dihydrochloride selected for rats for the 9-month and 2-year (21-month) studies were 80, 170, and 330 ppm.

NINE-MONTH STUDIES

After exposure to 3,3'-dimethoxybenzidine dihydrochloride at 330 ppm for only 9 months, a carcinoma of the preputial gland in one male, focal hyperplasia of the preputial gland in one male, a carcinoma of the clitoral gland in one female, and carcinomas of the Zymbal gland in two males and focal hyperplasia of the Zymbal gland in two males and two females were detected. None of these lesions was observed in control rats. Low dose and mid dose animals were not examined. Other compound-related effects included basophilic and/or eosinophilic foci of altered cells of the liver in 8/10 males and 5/10 females.

The relative kidney and liver weights for males and females receiving 330 ppm were significantly greater than those for controls (Table 6). Significant decreases were seen for T_3 and T_4 concentrations in both male and female rats receiving 330 ppm (Table F3). Decreases in hemoglobin, erythrocyte counts, hematocrit, and mean corpuscular hemoglobin concentrations were observed in exposed rats and were indicative of mild anemia in male rats only. Decreases in lactic dehydrogenase and alanine aminotransferase activity in the 330-ppm groups are not indicative of hepatocellular damage. Urinalysis revealed no evidence of renal damage; there was no apparent effect on the ability to concentrate urine.

TABLE 6. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE NINE-MONTH DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

Organ	Control	330 ppm
MALE		
Body weight (grams)	390 ± 7.7	373 ± 8.4
Brain	5.2 ± 0.12	5.6 ± 0.11
Kidney	6.1 ± 0.11	**7.0 ± 0.12
Liver	25.5 ± 0.40	**28.7 ± 0.67
FEMALE		
Body weight (grams)	232 ± 3.9	223 ± 3.3
Brain	8.0 ± 0.13	8.3 ± 0.15
Kidney	6.2 ± 0.16	**7.3 ± 0.15
Liver	26.9 ± 0.47	**29.7 ± 0.69

(a) Mean ± standard error in milligrams per gram, unless otherwise specified, for groups of 10 animals; P values vs. controls by Wilcoxon's test (Hollander and Wolfe, 1973).
**P<0.01

TWENTY-ONE-MONTH STUDIES

Body Weights, Water Consumption, and Clinical Signs

Mean body weights of high dose male rats were within 6% of those of the controls until week 69 and were 11%-22% lower thereafter; mean body weights of mid dose male rats were within 5% of those of the controls until week 69 and were 6%-14% lower thereafter (Table 7 and Figure 3). Mean body weights of high dose female rats were 9%-11% lower than those of controls after week 53; mean body weights of mid dose female rats were 7%-17% lower than those of controls after week 53. Body weight decreases of 22% for high dose males and 17% for mid dose females occurred in the last week of the studies, and calculations of relative body weights were based on only a few surviving animals. The average daily water consumption per rat by low, mid, and high dose rats was 94%, 97%, and 83% that by controls for males and 99%, 97%, and 78% for females (Tables D1 and D2). The average amount of 3,3'-dimethoxybenzidine dihydrochloride consumed per day was approximately 6, 12, or 21 mg/kg for low, mid, or high dose male rats and 7, 14, or 23 mg/kg for low, mid, or high dose female rats. Clinical signs noted during the studies were limited to increased incidences of tissue masses on the head, over the dorsum, and in the genital area in dosed groups.

TABLE 7. MEAN BODY WEIGHTS OF RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

Week on Study	Control Av. Wt. (grams)	Control Number Weighed	80 ppm Av. Wt. (grams)	80 ppm Wt. (percent of controls)	80 ppm Number Weighed	170 ppm Av. Wt. (grams)	170 ppm Wt. (percent of controls)	170 ppm Number Weighed	330 ppm Av. Wt. (grams)	330 ppm Wt. (percent of controls)	330 ppm Number Weighed
MALE											
1	143	70	143	100	45	143	100	75	140	98	70
2	174	70	175	101	45	174	100	75	167	96	70
3	205	70	210	102	45	206	100	75	204	100	70
4	233	70	227	97	45	230	99	75	223	96	70
5	252	70	249	99	45	250	99	75	242	96	70
6	267	70	264	99	45	265	99	75	256	96	70
7	284	70	278	98	45	281	99	75	273	96	70
9	302	70	300	99	45	301	100	75	294	97	70
10	310	70	308	99	45	315	102	75	311	100	70
11	323	70	321	99	45	320	99	75	315	98	70
12	329	69	322	98	45	331	101	75	322	98	70
13	336	69	329	98	45	335	100	75	328	98	70
14	336	69	332	99	45	337	100	75	333	99	70
15	340	69	338	99	45	345	101	75	332	98	70
17	349	69	346	99	(a) 40	346	99	(a) 70	342	98	(a) 65
21	363	69	363	100	45	358	99	75	360	99	70
25	372	69	375	101	45	372	100	75	374	101	70
29	384	69	384	100	45	379	99	75	375	98	70
33	395	69	394	100	45	387	98	75	387	98	70
37	401	69	395	99	45	395	99	75	385	96	70
41	404	(b) 59	404	100	44	391	97	75	395	98	(b) 59
45	404	59	403	100	44	391	97	73	392	97	57
49	401	59	396	99	44	391	98	72	400	100	55
53	414	59	406	98	42	395	95	70	397	96	53
57	416	59	402	97	42	403	97	68	393	94	53
61	411	59	406	99	42	390	95	65	392	95	48
65	403	59	394	98	42	391	97	62	383	95	41
69	405	58	394	97	42	386	95	57	381	94	39
73	417	57	403	97	38	383	92	48	364	87	30
77	409	55	393	96	37	382	93	41	364	89	24
81	409	55	395	97	31	366	89	19	363	89	5
85	413	53	379	92	28	355	86	13	323	78	4
89	405	50	375	93	16	359	89	4	--	--	--
93	403	45	389	97	8	--	--	--	--	--	--
FEMALE											
1	112	70	114	102	45	111	99	75	111	99	70
2	131	70	129	98	45	127	97	75	126	96	70
3	143	70	144	101	45	142	99	75	143	100	70
4	153	70	152	99	45	149	97	75	148	97	70
5	163	70	161	99	45	158	97	(a) 73	155	95	70
6	168	70	168	100	45	166	99	75	163	97	70
7	179	70	174	97	45	170	95	75	169	94	70
9	187	70	184	98	45	180	96	75	176	94	70
10	189	70	186	98	45	187	99	75	183	97	70
11	193	70	190	98	45	185	96	75	183	95	70
12	193	70	192	99	45	193	100	75	188	97	70
13	198	70	196	99	45	193	97	75	192	97	70
14	199	70	198	99	45	197	99	75	196	98	70
15	204	70	201	99	45	199	98	75	197	97	70
17	209	(a) 45	207	99	45	201	96	(a) 70	202	97	(a) 65
21	218	70	215	99	45	208	95	75	208	95	70
25	223	70	222	100	(a) 44	214	96	75	216	97	70
29	225	70	225	100	45	221	98	75	219	97	70
33	232	70	230	99	45	223	96	74	222	96	70
37	237	70	235	99	45	231	97	74	226	95	69
41	243	(b) 60	242	100	45	234	96	73	232	95	(b) 57
45	251	60	251	100	45	243	97	68	241	96	53
49	262	60	257	98	45	252	96	66	249	95	52
53	277	60	271	98	45	255	92	57	253	91	42
57	284	60	275	97	44	263	93	52	256	90	40
61	294	59	290	99	44	269	91	48	264	90	35
65	303	59	292	96	41	277	91	41	269	89	22
69	307	59	295	96	40	284	93	34	276	90	18
73	318	59	307	97	36	282	89	27	289	91	11
77	319	57	307	96	34	285	89	24	285	89	11
81	324	56	306	94	34	281	87	18	293	90	7
85	324	54	304	94	29	288	89	11	295	91	5
89	331	50	298	90	22	285	86	7	--	--	--
93	336	45	307	91	15	280	83	6	--	--	--

(a) The number of animals weighed was lower than the number of animals surviving.
(b) Interim kill

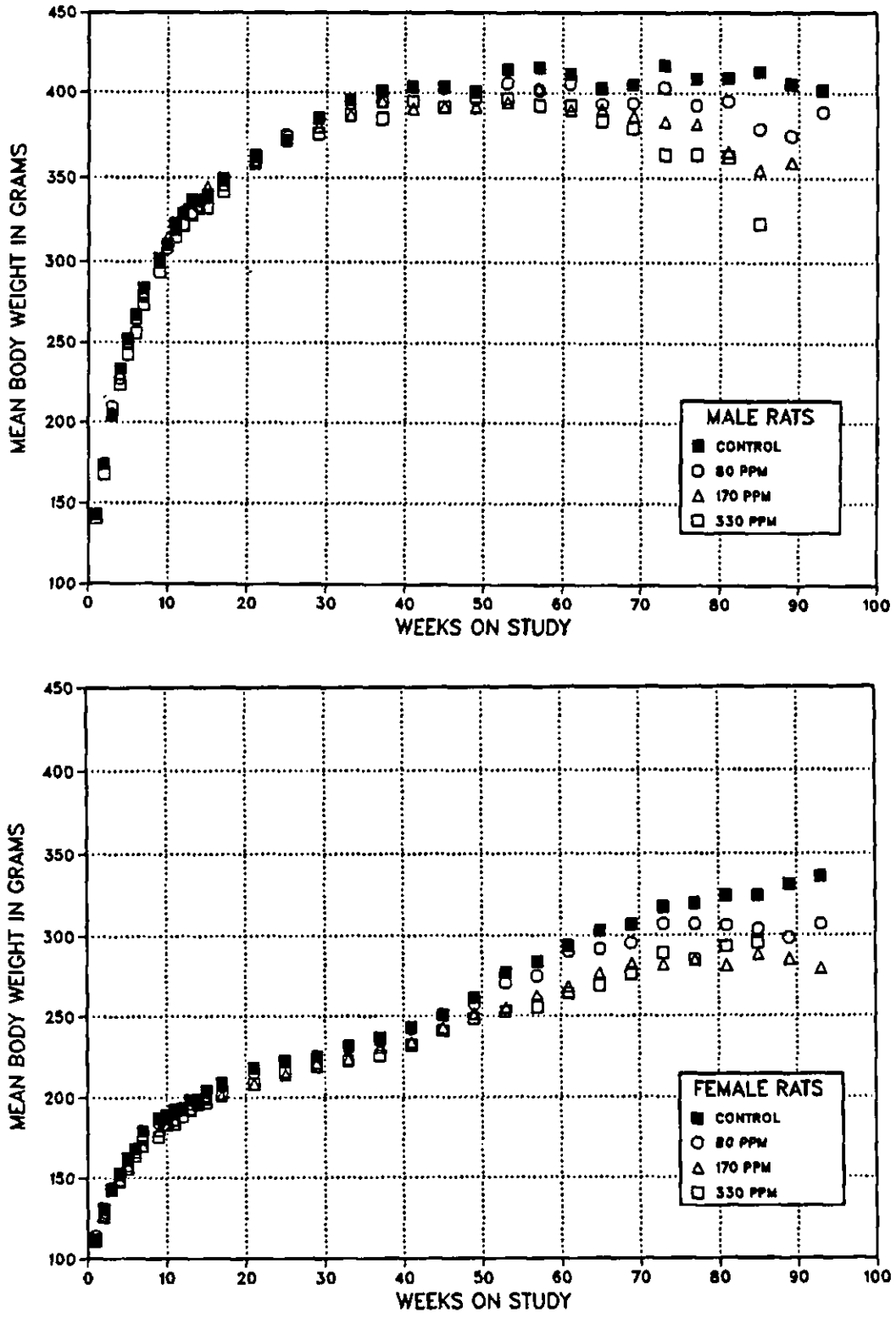


FIGURE 3. GROWTH CURVES FOR RATS GIVEN DRINKING WATER CONTAINING 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE FOR TWENTY-ONE MONTHS

Survival

Estimates of the probabilities of survival for male and female rats given drinking water containing 3,3'-dimethoxybenzidine dihydrochloride at the concentrations used in these studies and for controls are shown in Table 8 and in the Kaplan and Meier curves in Figure 4. The survival of dosed rats was significantly lower than that of controls after day 552 (low dose), 420 (mid dose), or 401 (high dose) for males and day 483 (low dose), 309 (mid dose), or 304 (high dose) for females.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the liver, large intestine, small intestine, Zymbal gland, preputial gland, clitoral gland, oral cavity, skin, mammary gland, brain, uterus, mesothelium, spleen, mesenteric lymph nodes, heart, lung, and bone marrow.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes A and B for male and female rats, respectively.

Liver: The administration of 3,3'-dimethoxybenzidine dihydrochloride in drinking water to

TABLE 8. SURVIVAL OF RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

	Control	80 ppm	170 ppm	330 ppm
MALE (a)				
Animals initially in study	60	45	75	60
Natural deaths	9	9	25	14
Moribund kills	7	28	50	46
Animals surviving until study termination	44	8	0	0
Survival P values (b)	<0.001	<0.001	<0.001	<0.001
FEMALE (a)				
Animals initially in study	60	45	75	60
Natural deaths	5	3	9	9
Moribund kills	10	27	60	51
Animals surviving until study termination	45	15	6	0
Survival P values (b)	<0.001	<0.001	<0.001	<0.001

(a) First day of termination period: male--647; female--648
(b) The result of the life table trend test is in the control column, and the results of the life table pairwise comparisons with the controls are in the dosed columns.

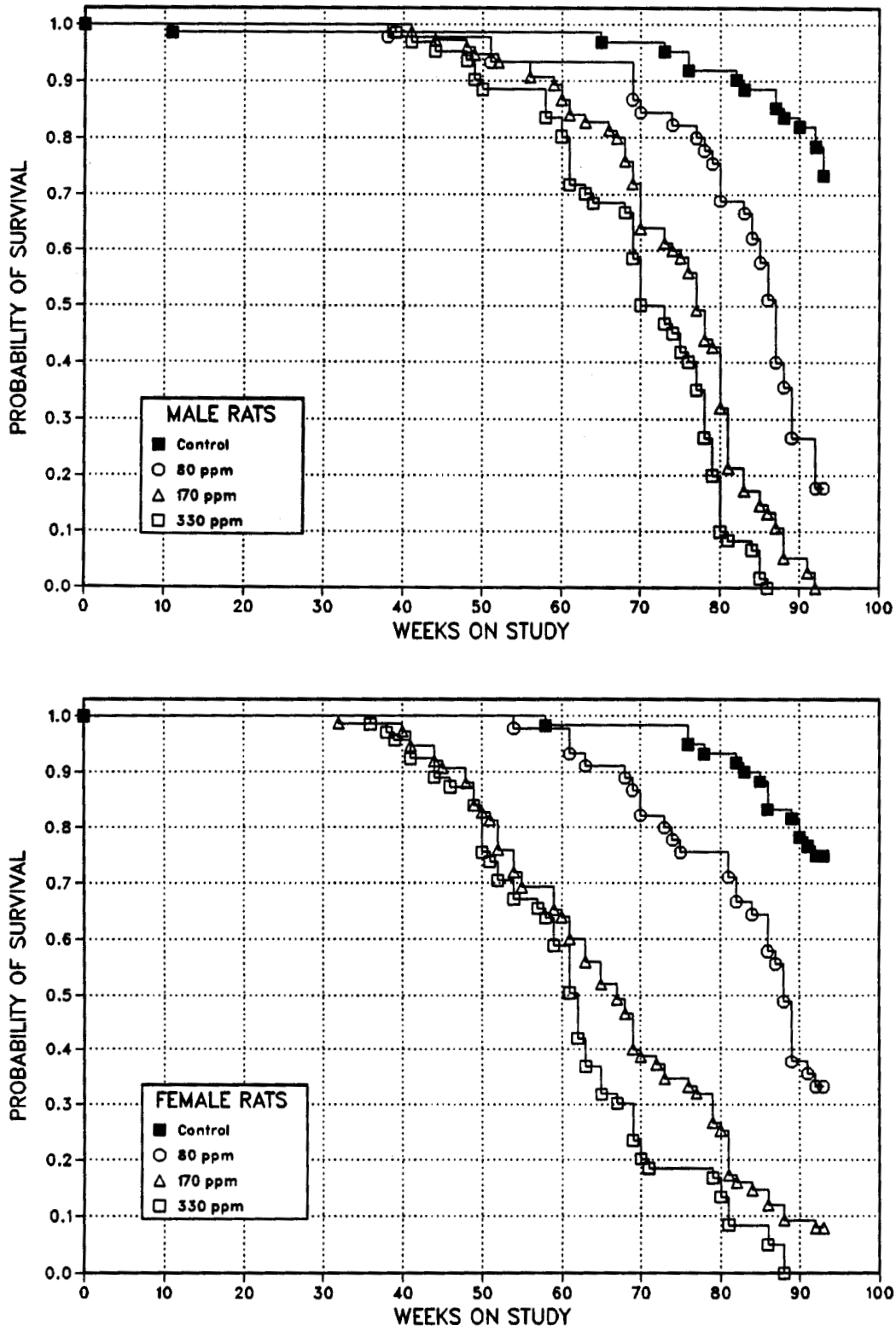


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS GIVEN DRINKING WATER CONTAINING 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE FOR TWENTY-ONE MONTHS

male and female rats caused a variety of degenerative and proliferative lesions in the liver (Table 9); the lesions were generally more severe and the incidences were greater in dosed males than in females. The degenerative lesions consisted of clusters of hepatocytes containing cytoplasmic vacuoles (presumably lipid droplets), generalized centrilobular hepatocellular degeneration, randomly distributed single or multiple foci of necrosis, and foci of multilocular cysts containing granular eosinophilic material or erythrocytes (cystic degeneration or spongiosis hepatis). Hepatocellular regeneration, characterized by poorly circumscribed foci of enlarged cells with deeply staining eosinophilic cytoplasm, occurred in livers with the more severe degenerative lesions.

The incidences of clear cell foci were marginally increased in high dose male rats and dosed female rats. Eosinophilic foci were increased in both dosed male and female rats. Clear cell foci consisted of poorly circumscribed clusters of hepatocytes with pale cytoplasm, whereas eosinophilic foci consisted of cells with eosinophilic cytoplasm. These foci were generally smaller than a hepatic lobule and showed little or no compression of the surrounding parenchyma; the hepatic plates in the foci merged imperceptibly with the normal plates. Neoplastic nodules in males and neoplastic nodules or hepatocellular carcinomas (combined) in males and females occurred with significant positive trends; the incidences in mid and high dose males were significantly greater than that in controls (Table 10). Neoplastic nodules were expansile lesions that were generally larger than a hepatic lobule and compressed the surrounding tissue; the hepatic plates within the neoplastic nodule were not arranged in a normal lobular pattern. The hepatocytes showed altered staining properties and slight nuclear pleomorphism and atypia. The hepatocellular carcinomas were larger masses consisting of hepatocytes in solid clusters or trabeculae several layers thick without a lobular pattern; the hepatocytes generally showed greater cellular atypia and pleomorphism than those within the neoplastic nodules.

Large Intestine (Colon, Cecum, or Rectum): Adenomatous polyps or adenocarcinomas (combined) in male and female rats occurred with significant positive trends; the incidences in mid and high dose males and high dose females were significantly greater than those in controls (Table 11).

TABLE 9. NUMBERS OF RATS WITH SELECTED LIVER LESIONS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

Lesion	Male				Female			
	Control	80 ppm	170 ppm	330 ppm	Control	80 ppm	170 ppm	330 ppm
Number examined	60	45	74	60	60	44	75	60
Clear cell focus	19	11	16	28	7	11	18	*15
Cystic degeneration	13	**23	**34	**28	1	2	1	5
Centrilobular degeneration	0	*4	**9	**10	1	3	*8	5
Eosinophilic focus	6	**15	**35	**38	5	7	**20	**28
Hematopoietic cell proliferation	2	**15	**39	**41	1	**18	**43	**41
Necrosis	4	**15	**18	**17	1	3	**13	**18
Regeneration	5	7	**22	**18	6	3	5	4
Cytoplasmic vacuolization	2	2	7	*10	3	1	4	3
Neoplastic nodule	0	3	**7	**6	0	1	0	2
Hepatocellular carcinoma	1	1	0	2	0	0	0	1

*P<0.05 vs. controls
**P<0.01 vs. controls

TABLE 10. LIVER TUMORS IN RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

	Control	80 ppm (b)	170 ppm (b)	330 ppm (b)
MALE				
Neoplastic Nodule				
Overall Rates	0/60 (0%)	3/45 (7%)	7/74 (9%)	6/60 (10%)
Effective Rates (c)	0/58 (0%)	3/39 (8%)	7/54 (13%)	6/35 (17%)
Terminal Rates	0/44 (0%)	1/8 (13%)	0/0	0/0
Day of First Observation		538	485	485
Cochran-Armitage Trend Test (d)	P=0.002			
Fisher Exact Test (d)		P=0.062	P=0.005	P=0.002
Hepatocellular Carcinoma				
Overall Rates	1/60 (2%)	1/45 (2%)	0/74 (0%)	2/60 (3%)
Neoplastic Nodule or Hepatocellular Carcinoma (e)				
Overall Rates	1/60 (2%)	4/45 (9%)	7/74 (9%)	8/60 (13%)
Effective Rates (c)	1/58 (2%)	4/39 (10%)	7/54 (13%)	8/35 (23%)
Terminal Rates	1/44 (2%)	2/8 (25%)	0/0	0/0
Day of First Observation	647	538	485	485
Cochran-Armitage Trend Test (d)	P=0.001			
Fisher Exact Test (d)		P=0.083	P=0.024	P=0.001
FEMALE				
Neoplastic Nodule				
Overall Rates	0/60 (0%)	1/44 (2%)	0/75 (0%)	2/60 (3%)
Hepatocellular Carcinoma				
Overall Rates	0/60 (0%)	0/44 (0%)	0/75 (0%)	1/60 (2%)
Neoplastic Nodule or Hepatocellular Carcinoma (f)				
Overall Rates	0/60 (0%)	1/44 (2%)	0/75 (0%)	3/60 (5%)
Effective Rates (c)	0/59 (0%)	1/44 (2%)	0/47 (0%)	3/38 (8%)
Terminal Rates	0/45 (0%)	1/15 (7%)	0/6 (0%)	0/0
Day of First Observation		648		408
Cochran-Armitage Trend Test (d)	P=0.022			
Fisher Exact Test (d)		P=0.427	(g)	P=0.057

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) The estimated dose in milligrams per kilograms per day is given in Section III (Body Weights, Water Consumption, and Clinical Signs) and in Appendix D.
(c) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the four groups
(d) Based on effective rates
(e) Historical incidence at study laboratory (mean): 7/100 (7%); historical incidence in NTP studies (mean ± SD): 78/1,591 (5% ± 4%)
(f) Historical incidence at study laboratory (mean): 2/100 (2%); historical incidence in NTP studies (mean ± SD): 37/1,643 (2% ± 3%)
(g) No P value is reported because no tumors were observed in the 170-ppm and control groups.

TABLE 11. TUMORS OF THE LARGE INTESTINE IN RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

	Control	80 ppm	170 ppm	330 ppm
MALE				
Adenomatous Polyp				
Overall Rates	0/60 (0%)	1/45 (2%)	4/75 (5%)	5/60 (8%)
Effective Rates (b)	0/59 (0%)	1/44 (2%)	4/73 (5%)	5/57 (9%)
Terminal Rates	0/44 (0%)	0/8 (0%)	0/0	0/0
Day of First Observation		644	546	332
Cochran-Armitage Trend Test (c)	P=0.013			
Fisher Exact Test (c)		P=0.427	P=0.090	P=0.026
Adenocarcinoma				
Overall Rates	0/60 (0%)	0/45 (0%)	4/75 (5%)	3/60 (5%)
Effective Rates (b)	0/59 (0%)	0/42 (0%)	4/67 (6%)	3/50 (6%)
Terminal Rates	0/44 (0%)	0/8 (0%)	0/0	0/0
Day of First Observation			485	414
Cochran-Armitage Trend Test (c)	P=0.031			
Fisher Exact Test (c)		(d)	P=0.077	P=0.093
Adenomatous Polyp or Adenocarcinoma (e)				
Overall Rates	0/60 (0%)	1/45 (2%)	8/75 (11%)	8/60 (13%)
Effective Rates (b)	0/59 (0%)	1/44 (2%)	8/73 (11%)	8/57 (14%)
Terminal Rates	0/44 (0%)	0/8 (0%)	0/0	0/0
Day of First Observation		644	485	332
Cochran-Armitage Trend Test (c)	P=0.001			
Fisher Exact Test (c)		P=0.427	P=0.007	P=0.003
FEMALE				
Adenomatous Polyp				
Overall Rates	0/60 (0%)	0/45 (0%)	1/75 (1%)	2/60 (3%)
Adenocarcinoma				
Overall Rates	0/60 (0%)	1/45 (2%)	0/75 (0%)	1/60 (2%)
Adenomatous Polyp or Adenocarcinoma (f)				
Overall Rates	0/60 (0%)	1/45 (2%)	1/75 (1%)	3/60 (5%)
Effective Rates (b)	0/59 (0%)	1/44 (2%)	1/48 (2%)	3/35 (9%)
Terminal Rates	0/45 (0%)	1/15 (7%)	0/6 (0%)	0/0
Day of First Observation		648	424	424
Cochran-Armitage Trend Test (c)	P=0.020			
Fisher Exact Test (c)		P=0.427	P=0.449	P=0.049

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the four groups
(c) Based on effective rates
(d) No P value is reported because no tumors were observed in the 80-ppm and control groups.
(e) Historical incidence at study laboratory: 0/96; historical incidence in NTP studies (mean ± SD): 2/1,541 (0.1% ± 0.5%)
(f) Historical incidence at study laboratory: 0/88; historical incidence in NTP studies: 0/1,601

Adenomatous polyps were exophytic, polypoid masses that protruded into the intestinal lumen. These consisted of glandular structures lined by a single layer of columnar epithelial cells with round nuclei and moderately abundant basophilic cytoplasm. These cells were generally well differentiated, but mucous cells were not present. The adenocarcinomas were similar exophytic masses that showed invasion of the intestinal submucosa. The glandular structures composing the adenocarcinomas were generally more irregular, particularly at the site of invasion, and the epithelial cells were less well differentiated with some atypia.

Small Intestine: The incidences of adenocarcinomas in dosed males were significantly greater than that in controls (Table 12). Adenocarcinomas were seen in 0/60 control, 1/45 low dose, 1/75 mid dose, and 2/60 high dose female rats. The adenocarcinomas invaded the intestinal wall and consisted of glandular structures lined by moderately well to poorly differentiated columnar epithelium. Several of the neoplasms contained mucus-secreting cells forming large dilated spaces filled with mucus (cystic mucinous adenocarcinomas).

Zymbal Gland: The Zymbal glands are specialized sebaceous glands anterior and ventral to the external orifices of the ears. The incidences of adenomas, carcinomas, and adenomas or carcinomas (combined) were significantly greater in the dosed groups than in the control groups (Table 13). Some dosed rats had bilateral neoplasms of the Zymbal gland.

Hyperplasia, adenomas, and carcinomas are part of a morphologic continuum. Hyperplasia was a focal lesion of the glandular epithelium characterized by enlarged cells that distorted the normal acinar arrangement. Adenomas were circumscribed masses consisting of poorly formed acini surrounding ductlike structures lined by squamous epithelium. Sebaceous cell differentiation was evident in the neoplastic acini. Carcinomas were generally larger and invaded adjacent soft tissues. The neoplastic cells demonstrated heterogeneous growth patterns with irregular, poorly formed acinar structures, solid masses, and cords with scattered ductlike structures filled with secretory material and cellular debris. The neoplasms exhibited predominantly sebaceous or squamous differentiation, but some neoplasms had prominent components of each.

TABLE 12. TUMORS OF THE SMALL INTESTINE IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

	Control	80 ppm	170 ppm	330 ppm
Adenocarcinoma (b)				
Overall Rates	0/60 (0%)	4/45 (9%)	7/75 (9%)	5/60 (8%)
Effective Rates (c)	0/59 (0%)	4/44 (9%)	7/75 (9%)	5/60 (8%)
Terminal Rates	0/44 (0%)	0/8 (0%)	0/0	0/0
Day of First Observation		354	417	267
Cochran-Armitage Trend Test (d)	P=0.081			
Fisher Exact Test (d)		P=0.031	P=0.015	P=0.030

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of adenomatous polyps or adenocarcinomas (combined) at study laboratory (mean): 1/97 (1%); historical incidence in NTP studies (mean ± SD): 5/1,557 (0.3% ± 0.8%)
(c) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the four groups
(d) Based on effective rates

TABLE 13. ZYMBAL GLAND LESIONS IN RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

	Control	80 ppm	170 ppm	330 ppm
MALE				
Hyperplasia				
Overall Rates	1/59 (2%)	**9/45 (20%)	**13/75 (17%)	**14/60 (23%)
Adenoma				
Overall Rates	0/59 (0%)	4/45 (9%)	11/75 (15%)	9/60 (15%)
Effective Rates (b)	0/58 (0%)	4/44 (9%)	11/71 (15%)	9/53 (17%)
Terminal Rates	0/44 (0%)	1/8 (13%)	0/0	0/0
Day of First Observation		353	391	445
Life Table Tests	P<0.001	P=0.011	P<0.001	P<0.001
Cochran-Armitage Trend Test (c)	P=0.002			
Fisher Exact Test (c)		P=0.032	P<0.001	P<0.001
Carcinoma				
Overall Rates	0/59 (0%)	7/45 (16%)	14/75 (19%)	21/60 (35%)
Effective Rates (b)	0/58 (0%)	7/45 (16%)	14/75 (19%)	21/60 (35%)
Terminal Rates	0/44 (0%)	0/8 (0%)	0/0	0/0
Day of First Observation		262	304	284
Life Table Tests	P<0.001	P=0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (c)	P<0.001			
Fisher Exact Test (c)		P=0.002	P<0.001	P<0.001
Adenoma or Carcinoma (d)				
Overall Rates	0/59 (0%)	10/45 (22%)	25/75 (33%)	30/60 (50%)
Effective Rates (b)	0/58 (0%)	10/45 (22%)	25/75 (33%)	30/60 (50%)
Terminal Rates	0/44 (0%)	1/8 (13%)	0/0	0/0
Day of First Observation		262	304	284
Life Table Tests	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (c)	P<0.001			
Fisher Exact Test (c)		P<0.001	P<0.001	P<0.001
FEMALE				
Hyperplasia				
Overall Rates	0/60 (0%)	*5/45 (11%)	**14/75 (19%)	**13/60 (22%)
Adenoma				
Overall Rates	0/60 (0%)	3/45 (7%)	4/75 (5%)	3/60 (5%)
Effective Rates (b)	0/59 (0%)	3/44 (7%)	4/48 (8%)	3/35 (9%)
Terminal Rates	0/45 (0%)	0/15 (0%)	0/6 (0%)	0/0
Day of First Observation		424	424	424
Life Table Tests	P<0.001	P=0.036	P=0.010	P=0.005
Cochran-Armitage Trend Test (c)	P=0.054			
Fisher Exact Test (c)		P=0.075	P=0.038	P=0.049
Carcinoma				
Overall Rates	1/60 (2%)	10/45 (22%)	17/75 (23%)	13/60 (22%)
Effective Rates (b)	1/60 (2%)	10/45 (22%)	17/74 (23%)	13/59 (22%)
Terminal Rates	0/45 (0%)	0/15 (0%)	1/6 (17%)	0/0
Day of First Observation	402	424	274	262
Life Table Tests	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (c)	P=0.006			
Fisher Exact Test (c)		P<0.001	P<0.001	P<0.001

TABLE 13. ZYMBAL GLAND LESIONS IN RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Control	80 ppm	170 ppm	330 ppm
FEMALE (Continued)				
Adenoma or Carcinoma (e)				
Overall Rates	1/60 (2%)	12/45 (27%)	21/75 (28%)	16/60 (27%)
Effective Rates (b)	1/60 (2%)	12/45 (27%)	21/74 (28%)	16/59 (27%)
Terminal Rates	0/45 (0%)	0/15 (0%)	1/6 (17%)	0/0
Day of First Observation	402	424	274	262
Life Table Tests	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (c)	P=0.002			
Fisher Exact Test (c)		P<0.001	P<0.001	P<0.001

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the four groups
(c) Based on effective rates
(d) Historical incidence at study laboratory (mean): 1/100 (1%); historical incidence in NTP studies (mean ± SD): 19/1,596 (1% ± 2%)
(e) Historical incidence at study laboratory (mean): 1/100 (1%); historical incidence in NTP studies (mean ± SD): 14/1,643 (0.9% ± 2%)
*P<0.05 vs. controls by Fisher exact test
**P<0.01 vs. controls by Fisher exact test

Preputial or Clitoral Gland: The preputial glands of the male rat are modified sebaceous glands bilateral and adjacent to the penis. The clitoral glands of the female are homologous organs located near the base of the clitoris. Ductular ectasia and glandular hyperplasia occurred at increased incidences in dosed male rats but not in the clitoral gland of female rats (Tables 14 and 15). The incidences of carcinomas and adenomas or carcinomas (combined) of the preputial gland in males occurred with significant positive trends; the incidences in the mid and high dose groups were significantly greater than those in the controls. In female rats, the incidences of adenomas, carcinomas, and adenomas or carcinomas (combined) of the clitoral gland were significantly greater in almost all dosed groups than in controls. Bilateral neoplasms of the preputial and clitoral glands occurred in dosed groups of rats.

Hyperplasia, adenomas, and carcinomas of the preputial and clitoral glands are part of a morphologic continuum. Hyperplasia was characterized by clusters of acini consisting of enlarged cells with prominent nuclei. There was some distortion of the acinar arrangement of the cells. Adenomas were circumscribed, expansile lesions exhibiting loss of normal acinar organization. The neoplastic cells were well differentiated and arranged in solid clusters with scattered ductlike structures containing debris. Carcinomas were poorly circumscribed masses with irregular boundaries, often accompanied by inflammation in the surrounding tissue. Overt invasion of the adjacent soft tissue similar to that seen with Zymbal gland carcinomas was generally not observed. The carcinomas exhibited greater heterogeneity of growth pattern and greater cellular pleomorphism and atypia than adenomas.

TABLE 14. PREPUTIAL GLAND LESIONS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

	Control	80 ppm	170 ppm	330 ppm
Ectasia				
Overall Rates	5/60 (8%)	**12/43 (28%)	**25/73 (34%)	**24/59 (41%)
Hyperplasia				
Overall Rates	2/60 (3%)	*7/43 (16%)	*10/73 (14%)	**12/59 (20%)
Adenoma				
Overall Rates	14/60 (23%)	6/43 (14%)	19/73 (26%)	12/59 (20%)
Effective Rates (b)	14/59 (24%)	6/42 (14%)	19/71 (27%)	12/56 (21%)
Terminal Rates	10/44 (23%)	1/8 (13%)	0/0	0/0
Day of First Observation	531	485	333	423
Life Table Tests	P<0.001	P=0.202	P<0.001	P<0.001
Cochran-Armitage Trend Test (c)	P=0.497			
Fisher Exact Test (c)		P=0.179N	P=0.425	P=0.472N
Carcinoma				
Overall Rates	2/60 (3%)	6/43 (14%)	15/73 (21%)	19/59 (32%)
Effective Rates (b)	2/59 (3%)	6/42 (14%)	15/73 (21%)	19/59 (32%)
Terminal Rates	0/44 (0%)	1/8 (13%)	0/0	0/0
Day of First Observation	603	603	284	267
Life Table Tests	P<0.001	P=0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (c)	P<0.001			
Fisher Exact Test (c)		P=0.053	P=0.003	P<0.001
Adenoma or Carcinoma (d)				
Overall Rates	16/60 (27%)	12/43 (28%)	33/73 (45%)	29/59 (49%)
Effective Rates (b)	16/59 (27%)	12/42 (29%)	33/73 (45%)	29/59 (49%)
Terminal Rates	10/44 (23%)	2/8 (25%)	0/0	0/0
Day of First Observation	531	485	284	267
Life Table Tests	P<0.001	P=0.003	P<0.001	P<0.001
Cochran-Armitage Trend Test (c)	P=0.003			
Fisher Exact Test (c)		P=0.523	P=0.025	P=0.011

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the four groups
(c) Based on effective rates
(d) Historical incidence at study laboratory (mean): 5/100 (5%); historical incidence in NTP studies (mean ± SD): 117/1,596 (7% ± 5%)
*P<0.05 vs. controls by Fisher exact test
**P<0.01 vs. controls by Fisher exact test

TABLE 15. CLITORAL GLAND LESIONS IN FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

	Control	80 ppm	170 ppm	330 ppm
Ectasia				
Overall Rates	15/58 (26%)	11/44 (25%)	11/74 (15%)	12/55 (22%)
Hyperplasia				
Overall Rates	4/58 (7%)	*9/44 (20%)	8/74 (11%)	6/55 (11%)
Adenoma				
Overall Rates	5/58 (9%)	15/44 (34%)	13/74 (18%)	16/55 (29%)
Effective Rates (b)	5/58 (9%)	15/44 (34%)	13/73 (18%)	16/55 (29%)
Terminal Rates	5/44 (11%)	7/15 (47%)	0/6 (0%)	0/0
Day of First Observation	648	436	358	262
Life Table Tests	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (c)	P=0.035			
Fisher Exact Test (c)		P=0.002	P=0.102	P=0.005
Carcinoma				
Overall Rates	2/58 (3%)	17/44 (39%)	41/74 (55%)	30/55 (55%)
Effective Rates	2/58 (3%)	17/44 (39%)	41/74 (55%)	30/55 (55%)
Terminal Rates	2/44 (5%)	5/15 (33%)	3/6 (50%)	0/0
Day of First Observation	648	373	220	270
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (c)	P<0.001			
Fisher Exact Test (c)		P<0.001	P<0.001	P<0.001
Adenoma or Carcinoma (d)				
Overall Rates	7/58 (12%)	27/44 (61%)	48/74 (65%)	41/55 (75%)
Effective Rates (b)	7/58 (12%)	27/44 (61%)	48/74 (65%)	41/55 (75%)
Terminal Rates	7/44 (16%)	10/15 (67%)	3/6 (50%)	0/0
Day of First Observation	648	373	220	262
Life Table Tests	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (c)	P<0.001			
Fisher Exact Test (c)		P<0.001	P<0.001	P<0.001

(a) For a complete explanation of the entries in this table, see Table B3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the four groups
(c) Based on effective rates
(d) Historical incidence at study laboratory (mean): 8/100 (8%); historical incidence in NTP studies (mean ± SD): 115/1,643 (7% ± 5%)
*P<0.05 vs. controls by Fisher exact test

Oral Cavity (Palate or Tongue): Squamous papillomas and squamous papillomas or squamous cell carcinomas (combined) of the palate or tongue in males occurred with significant positive trends; the incidences in dosed males were significantly greater than those in controls (Table 16). A few squamous cell papillomas occurred in each of the female dosed and control groups, but squamous cell carcinomas occurred only in the mid and high dose groups. The papillomas consisted of branching papillae arising from the mucosal epithelium and extending into the oral cavity. The papillae had a thickened stratified squamous epithelium overlying a thin core of connective tissue. The squamous cell carcinomas often had exophytic papillary structures similar to the papillomas but showed invasion of the underlying submucosa by cords and clusters of neoplastic squamous epithelium.

Skin: A spectrum of epithelial neoplasms of the skin occurred at markedly increased incidences, primarily in male rats given 3,3'-dimethoxybenzidine dihydrochloride (Tables 17 and 18). The incidences of basal cell adenomas, basal cell carcinomas, squamous cell papillomas, and squamous cell carcinomas in males occurred with significant positive trends; except for basal cell carcinomas in low dose males, the incidences in the dosed groups were significantly greater than those in the controls. Small numbers of sebaceous gland adenomas or carcinomas (combined) occurred in dosed male rats. The incidences of keratoacanthomas were significantly increased in low dose male rats and increased ($P = 0.053$) in mid dose male rats.

Small numbers of basal cell adenomas occurred in dosed groups of female rats but not in controls. A basal cell carcinoma was observed in a single low dose female. The incidence of basal cell adenomas or carcinomas (combined) in low dose female rats was significantly greater than that in controls. Squamous cell papillomas were observed in three mid dose female rats.

The basal cell neoplasms consisted of small basophilic cells arranged in branching cords, solid clusters, or nodules with central cavities. Some exhibited features of hair follicles, whereas others showed sebaceous differentiation. Those with predominantly sebaceous differentiation were diagnosed as sebaceous gland adenomas. The basal cell adenomas were circumscribed masses without local invasion, whereas the carcinomas exhibited cellular anaplasia, necrosis, and/or local invasion. The squamous cell papillomas were typical exophytic growths consisting of branching papillae of stratified squamous epithelium, and the squamous cell carcinomas were composed of cords of well to poorly differentiated squamous epithelium that infiltrated the underlying dermis and subcutaneous tissue.

Mammary Gland: Adenocarcinomas in female rats occurred with a significant positive trend; the incidences in the mid and high dose groups were significantly greater than that in the controls (Table 19). The incidence of adenocarcinomas in high dose female rats was four times the highest observed historical incidence in untreated control female F344/N rats. The incidences of fibroadenomas in dosed females were lower than that in controls, probably because of the reduced survival in the dosed groups.

Brain: Malignant astrocytomas were seen in small numbers of dosed, but not control, rats (Table 20). The historical incidence of astrocytomas in untreated control male F344/N rats is 10/1,590 (0.6%) and in female F344/N rats is 15/1,628 (0.9%).

Uterus: Adenomas or carcinomas (combined) of the uterus or cervix were observed in dosed, but not in control, female rats (Table 21). The incidence of adenomas or carcinomas (combined) in low dose female rats was significantly greater than that in controls.

Mesothelium: Mesotheliomas were marginally increased in male rats (Table 22); the historical incidence of mesotheliomas in untreated control male F344/N rats is 47/1,596 (3%), and the highest observed incidence is 5/50.

TABLE 16. ORAL CAVITY SQUAMOUS CELL LESIONS IN RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

	Control	80 ppm	170 ppm	330 ppm
MALE				
Hyperplasia				
Overall Rates (b)	0/3 (0%)	0/8 (0%)	2/12 (17%)	0/16 (0%)
Papilloma				
Overall Rates (c)	1/60 (2%)	7/45 (16%)	10/75 (13%)	9/60 (15%)
Effective Rates (d)	1/59 (2%)	7/44 (16%)	10/73 (14%)	9/57 (16%)
Terminal Rates (c)	1/44 (2%)	2/8 (25%)	0/0	0/0
Day of First Observation	647	485	333	402
Cochran-Armitage Trend Test (e)	P=0.029			
Fisher Exact Test (e)		P=0.010	P=0.012	P=0.007
Carcinoma				
Overall Rates (c)	0/60 (0%)	1/45 (2%)	0/75 (0%)	2/60 (3%)
Papilloma or Carcinoma (f)				
Overall Rates (c)	1/60 (2%)	8/45 (18%)	10/75 (13%)	11/60 (18%)
Effective Rates (d)	1/59 (2%)	8/44 (18%)	10/73 (14%)	11/57 (19%)
Terminal Rates (c)	1/44 (2%)	2/8 (25%)	0/0	0/0
Day of First Observation	647	485	333	401
Cochran-Armitage Trend Test (e)	P=0.011			
Fisher Exact Test (e)		P=0.004	P=0.012	P=0.002
FEMALE				
Hyperplasia				
Overall Rates (b)	0/2 (0%)	0/3 (0%)	4/11 (36%)	1/5 (20%)
Papilloma				
Overall Rates (c)	2/60 (3%)	2/45 (4%)	3/75 (4%)	3/60 (5%)
Effective Rates (d)	2/59 (3%)	2/44 (5%)	3/52 (6%)	3/38 (8%)
Terminal Rates (c)	2/45 (4%)	1/15 (7%)	0/6 (0%)	0/0
Day of First Observation	648	644	450	408
Cochran-Armitage Trend Test (e)	P=0.214			
Fisher Exact Test (e)		P=0.574	P=0.440	P=0.299
Carcinoma				
Overall Rates (c)	0/60 (0%)	0/45 (0%)	3/75 (4%)	2/60 (3%)
Papilloma or Carcinoma (g)				
Overall Rates (c)	2/60 (3%)	2/45 (4%)	6/75 (8%)	5/60 (8%)
Effective Rates (d)	2/60 (3%)	2/45 (4%)	6/68 (9%)	5/52 (10%)
Terminal Rates (c)	2/45 (4%)	1/15 (7%)	0/6 (0%)	0/0
Day of First Observation	648	644	331	408
Cochran-Armitage Trend Test (e)	P=0.094			
Fisher Exact Test (e)		P=0.576	P=0.181	P=0.164

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) The denominator is the number of animals examined microscopically; the incidences in the dosed groups are not significantly different from that in the controls by the Fisher exact test.
(c) The denominator is the number of animals examined grossly.
(d) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the four groups
(e) Based on effective rates
(f) Historical incidence at study laboratory: 0/100; historical incidence in NTP studies (mean ± SD): 7/1,596 (0.4% ± 1.0%)
(g) Historical incidence at study laboratory: 0/100; historical incidence in NTP studies (mean ± SD): 4/1,643 (0.2% ± 0.7%)

TABLE 17. SKIN BASAL CELL AND SEBACEOUS GLAND TUMORS AND KERATOACANTHOMAS IN RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

	Control	80 ppm	170 ppm	330 ppm
MALE				
Basal Cell Adenoma				
Overall Rates	1/60 (2%)	31/45 (69%)	47/75 (63%)	35/60 (58%)
Effective Rates (b)	1/59 (2%)	31/42 (74%)	47/67 (70%)	35/50 (70%)
Terminal Rates	1/44 (2%)	7/8 (88%)	0/0	0/0
Day of First Observation	647	480	424	419
Life Table Tests	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (c)	P<0.001			
Fisher Exact Test (c)		P<0.001	P<0.001	P<0.001
Basal Cell Carcinoma				
Overall Rates	1/60 (2%)	4/45 (9%)	18/75 (24%)	17/60 (28%)
Effective Rates (b)	1/59 (2%)	4/44 (9%)	18/71 (25%)	17/54 (31%)
Terminal Rates	1/44 (2%)	0/8 (0%)	0/0	0/0
Day of First Observation	647	552	417	344
Life Table Tests	P<0.001	P=0.016	P<0.001	P<0.001
Cochran-Armitage Trend Test (c)	P<0.001			
Fisher Exact Test (c)		P=0.104	P<0.001	P<0.001
Basal Cell Adenoma or Carcinoma				
Overall Rates	2/60 (3%)	32/45 (71%)	54/75 (72%)	40/60 (67%)
Effective Rates (b)	2/59 (3%)	32/44 (73%)	54/71 (76%)	40/54 (74%)
Terminal Rates	2/44 (5%)	7/8 (88%)	0/0	0/0
Day of First Observation	647	480	417	344
Life Table Tests	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (c)	P<0.001			
Fisher Exact Test (c)		P<0.001	P<0.001	P<0.001
Sebaceous Gland Adenoma or Carcinoma				
Overall Rates	0/60 (0%)	2/45 (4%)	3/75 (4%)	2/60 (3%)
Basal Cell Adenoma, Basal Cell Carcinoma, Sebaceous Gland Adenoma, or Sebaceous Gland Carcinoma (d)				
Overall Rates	2/60 (3%)	33/45 (73%)	56/75 (75%)	41/60 (68%)
Effective Rates (b)	2/59 (3%)	33/44 (75%)	56/72 (78%)	41/56 (73%)
Terminal Rates	2/44 (5%)	7/8 (88%)	0/0	0/0
Day of First Observation	647	353	417	337
Life Table Tests	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (c)	P<0.001			
Fisher Exact Test (c)		P<0.001	P<0.001	P<0.001
Keratoacanthoma (e)				
Overall Rates	1/60 (2%)	5/45 (11%)	7/75 (9%)	1/60 (2%)
Effective Rates (b)	1/59 (2%)	5/42 (12%)	7/70 (10%)	1/53 (2%)
Terminal Rates	0/44 (0%)	0/8 (0%)	0/0	0/0
Day of First Observation	573	556	391	546
Life Table Tests	P=0.006	P=0.003	P=0.002	P=0.370
Cochran-Armitage Trend Test (c)	P=0.457N			
Fisher Exact Test (c)		P=0.044	P=0.053	P=0.725N

TABLE 17. SKIN BASAL CELL AND SEBACEOUS GLAND TUMORS AND KERATOACANTHOMAS IN RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Control	80 ppm	170 ppm	330 ppm
FEMALE				
Basal Cell Adenoma				
Overall Rates	0/60 (0%)	3/45 (7%)	3/75 (4%)	2/60 (3%)
Effective Rates (b)	0/59 (0%)	3/44 (7%)	3/48 (6%)	2/35 (6%)
Terminal Rates	0/45 (0%)	3/15 (20%)	0/6 (0%)	0/0
Day of First Observation		648	423	610
Life Table Tests	P<0.001	P=0.009	P=0.006	P<0.001
Cochran-Armitage Trend Test (c)	P=0.155			
Fisher Exact Test (c)		P=0.075	P=0.087	P=0.136
Basal Cell Carcinoma				
Overall Rates	0/60 (0%)	1/45 (2%)	0/75 (0%)	0/60 (0%)
Basal Cell Adenoma or Carcinoma (f)				
Overall Rates	0/60 (0%)	4/45 (9%)	3/75 (4%)	2/60 (3%)
Effective Rates (b)	0/59 (0%)	4/44 (9%)	3/48 (6%)	2/35 (6%)
Terminal Rates	0/45 (0%)	4/15 (27%)	0/6 (0%)	0/0
Day of First Observation		648	423	610
Life Table Tests	P<0.001	P=0.002	P=0.006	P<0.001
Cochran-Armitage Trend Test (c)	P=0.203			
Fisher Exact Test (c)		P=0.031	P=0.087	P=0.136

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the four groups
(c) Based on effective rates
(d) Historical incidence at study laboratory (mean): 2/100 (2%); historical incidence in NTP studies (mean ± SD): 30/1,596 (2% ± 2%)
(e) Historical incidence at study laboratory (mean): 6/100 (6%); historical incidence in NTP studies (mean ± SD): 39/1,596 (2% ± 4%)
(f) Historical incidence at study laboratory: 0/100; historical incidence in NTP studies (mean ± SD): 7/1,643 (0.4% ± 0.8%)

TABLE 18. SKIN SQUAMOUS CELL TUMORS IN RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

	Control	80 ppm	170 ppm	330 ppm
MALE				
Papilloma				
Overall Rates	0/60 (0%)	5/45 (11%)	7/75 (9%)	5/60 (8%)
Effective Rates (b)	0/58 (0%)	5/42 (12%)	7/62 (11%)	5/41 (12%)
Terminal Rates	0/44 (0%)	2/8 (25%)	0/0	0/0
Day of First Observation		515	525	445
Life Table Tests	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (c)	P=0.032			
Fisher Exact Test (c)		P=0.011	P=0.008	P=0.010
Carcinoma				
Overall Rates	0/60 (0%)	9/45 (20%)	24/75 (32%)	21/60 (35%)
Effective Rates (b)	0/59 (0%)	9/42 (21%)	24/65 (37%)	21/48 (44%)
Terminal Rates	0/44 (0%)	2/8 (25%)	0/0	0/0
Day of First Observation		485	424	445
Life Table Tests	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (c)	P<0.001			
Fisher Exact Test (c)		P<0.001	P<0.001	P<0.001
Papilloma or Carcinoma (d)				
Overall Rates	0/60 (0%)	13/45 (29%)	28/75 (37%)	22/60 (37%)
Effective Rates (b)	0/59 (0%)	13/42 (31%)	28/65 (43%)	22/48 (46%)
Terminal Rates	0/44 (0%)	3/8 (38%)	0/0	0/0
Day of First Observation		485	424	445
Life Table Tests	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (c)	P<0.001			
Fisher Exact Test (c)		P<0.001	P<0.001	P<0.001
FEMALE				
Papilloma (e)				
Overall Rates	0/60 (0%)	0/45 (0%)	3/75 (4%)	0/60 (0%)

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the four groups
(c) Based on effective rates
(d) Historical incidence at study laboratory (mean): 3/100 (3%); historical incidence in NTP studies (mean ± SD): 31/1,596 (2% ± 2%)
(e) Historical incidence of papillomas or carcinomas (combined) at study laboratory: 0/100; historical incidence in NTP studies (mean ± SD): 7/1,643 (0.4% ± 0.8%)

TABLE 19. MAMMARY GLAND TUMORS IN FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

	Control	80 ppm	170 ppm	330 ppm
Adenoma				
Overall Rates	0/60 (0%)	1/45 (2%)	0/75 (0%)	2/60 (3%)
Fibroadenoma (b)				
Overall Rates	14/60 (23%)	11/45 (24%)	9/75 (12%)	4/60 (7%)
Effective Rates (c)	14/60 (23%)	11/45 (24%)	9/63 (14%)	4/50 (8%)
Terminal Rates	12/45 (27%)	6/15 (40%)	2/6 (33%)	0/0
Day of First Observation	532	424	476	344
Cochran-Armitage Trend Test (d)	P=0.011N			
Fisher Exact Test (d)		P=0.537	P=0.146N	P=0.026N
Adenocarcinoma (e)				
Overall Rates	1/60 (2%)	2/45 (4%)	14/75 (19%)	20/60 (33%)
Effective Rates (c)	1/60 (2%)	2/45 (4%)	14/73 (19%)	20/57 (35%)
Terminal Rates	1/45 (2%)	0/15 (0%)	2/6 (33%)	0/0
Day of First Observation	648	512	333	284
Life Table Tests	P<0.001	P=0.252	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.393	P<0.001	P<0.001

(a) For a complete explanation of the entries in this table, see Table B3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence at study laboratory (mean): 47/100 (47%); historical incidence in NTP studies (mean ± SD): 520/1,643 (32% ± 12%)
(c) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the four groups
(d) Based on effective rates
(e) Historical incidence at study laboratory (mean): 3/100 (3%); historical incidence in NTP studies (mean ± SD): 49/1,643 (3% ± 2%)

TABLE 20. BRAIN TUMORS IN RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

	Control	80 ppm	170 ppm	330 ppm
MALE				
Malignant Astrocytoma (b)				
Overall Rates	0/60 (0%)	2/44 (5%)	3/75 (4%)	1/60 (2%)
Effective Rates (c)	0/58 (0%)	2/37 (5%)	3/48 (6%)	1/30 (3%)
Terminal Rates	0/44 (0%)	1/7 (14%)	0/0	0/0
Day of First Observation		618	536	506
Cochran-Armitage Trend Test (d)	P=0.247			
Fisher Exact Test (d)		P=0.149	P=0.090	P=0.341
FEMALE				
Malignant Astrocytoma (e)				
Overall Rates	0/60 (0%)	1/45 (2%)	1/75 (1%)	0/60 (0%)

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of astrocytomas at study laboratory (mean): 2/100 (2%); historical incidence in NTP studies (mean ± SD): 10/1,590 (0.6% ± 1%)
(c) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the four groups
(d) Based on effective rates
(e) Historical incidence of astrocytomas at study laboratory (mean): 2/100 (2%); historical incidence in NTP studies (mean ± SD): 15/1,628 (0.9% ± 2%)

TABLE 21. UTERINE TUMORS IN FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

	Control	80 ppm	170 ppm	330 ppm
Adenoma				
Overall Rates	0/60 (0%)	3/45 (7%)	1/75 (1%)	2/60 (3%)
Carcinoma				
Overall Rates	0/60 (0%)	1/45 (2%)	1/75 (1%)	0/60 (0%)
Adenoma or Carcinoma (b)				
Overall Rates	0/60 (0%)	4/45 (9%)	2/75 (3%)	2/60 (3%)
Effective Rates (c)	0/59 (0%)	4/44 (9%)	2/48 (4%)	2/35 (6%)
Terminal Rates	0/45 (0%)	1/15 (7%)	1/6 (17%)	0/0
Day of First Observation		606	424	563
Cochran-Armitage Trend Test (d)	P=0.230			
Fisher Exact Test (d)		P=0.031	P=0.199	P=0.136

(a) For a complete explanation of the entries in this table, see Table B3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence at study laboratory: 0/99; historical incidence in NTP studies (mean ± SD): 12/1,632 (0.7% ± 1%)
(c) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the four groups
(d) Based on effective rates

TABLE 22. MESOTHELIOMAS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

	Control	80 ppm	170 ppm	330 ppm
Mesothelioma (b)				
Overall Rates	2/60 (3%)	1/45 (2%)	7/75 (9%)	6/60 (10%)
Effective Rates (c)	2/59 (3%)	1/44 (2%)	7/72 (10%)	6/56 (11%)
Terminal Rates	1/44 (2%)	0/8 (0%)	0/0	0/0
Day of First Observation	529	483	339	401
Cochran-Armitage Trend Test (d)	P=0.044			
Fisher Exact Test (d)		P=0.610N	P=0.140	P=0.119

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence at study laboratory (mean): 3/100 (3%); historical incidence in NTP studies (mean ± SD): 47/1,596 (3% ± 3%)
(c) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the four groups
(d) Based on effective rates

Spleen: Hematopoietic cell proliferation was observed at increased incidences in dosed rats (male: control, 3/60; low dose, 13/42; mid dose, 43/74; high dose, 38/59; female: 3/60; 22/44; 50/75; 47/60).

Mesenteric Lymph Nodes: Reticulum cell hyperplasia was observed at increased incidences in dosed rats (male: control, 0/59; low dose, 3/42; mid dose, 6/73; high dose, 6/56; female: 2/60; 3/44; 18/75; 18/58).

Heart: Thrombi in the atrium were observed at increased incidences in dosed male rats (male: control, 3/60; low dose, 15/44; mid dose, 27/75; high dose, 23/60; female: 0/60; 1/45; 0/75; 1/60). The increased incidences of atrial thrombosis observed in the heart of exposed males may have been related to compound-caused morbidity, which led to impaired circulation and sludging of blood in the atrial chambers. This effect was not observed in exposed female rats, although there was a similar degree of morbidity.

Lung: Histiocytic cellular infiltration was observed at increased incidences in dosed rats (male: control, 0/60; low dose, 3/44; mid dose, 10/75; high dose, 6/60; female: 0/60; 3/45; 4/75; 18/60).

Bone Marrow: Hyperplasia of myeloid cells was observed at increased incidences in dosed rats (male: control, 2/60; low dose, 3/43; mid dose, 14/74; high dose, 7/60; female: 5/60; 8/45; 9/75; 14/60).

3,3'-Dimethoxybenzidine was tested for induction of gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 in each of three laboratories (Haworth et al., 1983; Table H1). In all laboratories, a response ranging from weakly positive to positive was observed with strain TA100 in trials conducted in the presence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9; likewise, positive results were reported for strain TA98 with S9 in all three laboratories, and one laboratory also observed a significant response in TA98 without S9. A weakly positive response was reported by one of the test laboratories with TA1535 in the presence of induced hamster S9. In cytogenetic tests with Chinese hamster ovary cells conducted in two laboratories, sister chromatid exchanges (SCEs) were induced by 3,3'-dimethoxybenzidine both with and without Aroclor 1254-induced male Sprague Dawley rat liver S9; in one of these two laboratories, the positive responses observed in the SCE trials without S9 occurred under conditions of delayed harvest (3-5 hours additional culture time), but the positive results reported by the second laboratory in the SCE test were observed at lower doses of the study chemical which did not affect cell cycle time (Galloway et al., 1985; Table H2). Results of the chromosomal aberration test were reported to be negative (Galloway et al., 1985); however, recent statistical reanalysis (Galloway et al., 1987) of the chromosomal aberration data has resulted in a change in the call from negative to weakly positive without S9 (Litton Bionetics study) and positive with S9 (Columbia University study) (Table H3). 3,3'-Dimethoxybenzidine was negative for induction of sex-linked recessive lethal mutations in adult male *Drosophila melanogaster* exposed to the chemical by feeding (100 ppm) or injection (200 ppm) (Yoon et al., 1985; Table H4). The methods and results are presented in Appendix H.

IV. DISCUSSION AND CONCLUSIONS

Fourteen-Day and Thirteen-Week Studies
Nine-Month Studies
Twenty-One-Month Studies
Nonneoplastic Lesions
Neoplastic Lesions
Tumor Transplant Study
Oncogene Activation
Related Aromatic Amines
Audit
Conclusions

IV. DISCUSSION AND CONCLUSIONS

Consumption of drinking water containing 3,3'-dimethoxybenzidine dihydrochloride led to highly significant incidences of neoplasms at a variety of sites and to mild toxicity in several organs. Unusual neoplasm sites in 3,3'-dimethoxybenzidine-exposed rats include the skin, Zymbal gland, preputial and clitoral glands, intestine, and oral mucosa. Most genotoxic carcinogens are associated with unusual tumor sites, and the short latency and multiple sites of these tumors are most characteristic of potent genotoxic carcinogens, such as benzidine dyes (NCI, 1978b), benzene (NTP, 1986), 1,3-butadiene (NTP, 1984), and glycidol (NTP, 1990). 3,3'-Dimethoxybenzidine and related aminobiphenyls are mutagenic. 3,3'-Dimethoxybenzidine requires S9 for mutagenic activation in the Salmonella assay, indicating that the chemical is metabolized to a mutagenic species, most likely through *N*-hydroxylation.

Fourteen-Day and Thirteen-Week Studies

In the 14-day and 13-week studies, male and female rats were exposed to 3,3'-dimethoxybenzidine dihydrochloride in drinking water at concentrations ranging from 170 to 4,500 ppm. Animal survival was unaffected, and few toxic effects were observed. Water consumption was decreased with increasing 3,3'-dimethoxybenzidine dihydrochloride concentration in both studies. In the 13-week studies, mean body weight gains were decreased in the two top dose groups. Compound-related effects seen in the top dose groups of male and female rats included increases in relative liver and kidney weights, nephropathy, and lipofuscin accumulation in the thyroid gland.

Dose-related decreases in serum triiodothyronine (T_3) and thyroxin (T_4) without a change in thyrotropin (TSH) are not consistent with a toxic effect on the thyroid gland; this effect was probably due to a change in the amount or binding capacity of the protein carrier for these hormones rather than to a direct effect on the thyroid gland. 3,3'-Dimethoxybenzidine is similar in structure to T_3 and T_4, suggesting that the dose-related decreases in serum T_3 and T_4 may be due to competition with 3,3'-dimethoxybenzidine for the carrier protein.

Based on the chemical-induced nephropathy and on reductions in water consumption and body weight gain observed in the 13-week studies, doses for the long-term studies in male and female rats were 0 or 330 ppm 3,3'-dimethoxybenzidine dihydrochloride administered in drinking water for 9 months and 0, 80, 170, or 330 ppm for 21 months.

Nine-Month Studies

Carcinomas of the preputial, clitoral, and Zymbal glands were observed after chemical exposure for only 9 months. Basophilic and/or eosinophilic foci in the liver and hyperplasia of the preputial and Zymbal glands were also detected in exposed rats. These lesions were not observed in control rats. The short latency of these lesions is unusual and indicative of the carcinogenic potency of 3,3'-dimethoxybenzidine dihydrochloride.

In the 9-month studies, hematologic effects were indicative of a mild anemia in male rats. Serum enzyme changes were slight and were not considered indicative of liver injury. Serum T_3 and T_4 were decreased, with no change in TSH, and as in the 13-week studies, these changes were not considered to be a direct effect on the thyroid gland.

Twenty-One-Month Studies

3,3'-Dimethoxybenzidine dihydrochloride studies were terminated at month 21 because of reduced survival in the dosed groups (see Table 8 and Figure 4). The reduced survival of dosed rats first became noticeable in males during months 14-15 and in females during month 11. For humane reasons, animals with large visible masses or those in a moribund condition, usually due to internal neoplasms, were killed rather than allowed to suffer; this program may have influenced the overall survival profile. Mean body weights of high dose male and female rats were 4%-22% lower than those of controls during the second year.

Nonneoplastic Lesions

Increased hematopoietic cell proliferation in the liver and spleen, coupled with bone marrow hyperplasia in exposed groups, are probably related to inflammation and necrosis associated with neoplasms.

3,3'-Dimethoxybenzidine dihydrochloride appeared to stimulate the reticuloendothelial system. This effect was manifested as reticulum cell hyperplasia of the mesenteric lymph nodes. Although this effect may be compound related, it is probably a nonspecific reaction.

Neoplastic Lesions

There was a highly significant association between the consumption of 3,3'-dimethoxybenzidine dihydrochloride and the development of Zymbal gland adenomas and/or carcinomas in dosed male and female rats. With the exception of a carcinoma in one control female (first observed during week 58), Zymbal gland neoplasms were not observed in control groups. Carcinomas were observed at necropsy in exposed males and females as early as week 38. Neoplasms develop at this site infrequently (1%) in historical control rats (Tables A4d and B4d) and usually only late in life (Solleveld et al., 1984). Benzidine, the parent compound of 3,3'-dimethoxybenzidine, also causes Zymbal gland tumors in rats, and it is a known urinary bladder carcinogen in humans (IARC, 1982, 1987a).

3,3'-Dimethoxybenzidine dihydrochloride had a profound effect on the preputial and clitoral glands in exposed male and female rats, giving rise to a high incidence of carcinomas and/or adenomas. The incidences of preputial or clitoral gland neoplasms in high dose male and female rats were 7 and 10 times higher, respectively, than in untreated historical control F344/N rats. In exposed rats, carcinomas were confirmed histologically at necropsy as early as week 32 (females) and week 39 (males), whereas in controls, carcinomas were not observed until week 87 in males or at the end of the study at month 21 in females. Potential precursor lesions (hyperplasia) occurred in small numbers of exposed animals, possibly because most such lesions had already progressed to neoplasms.

Of 350 chemicals evaluated for carcinogenicity in rats and mice by the National Cancer Institute/National Toxicology Program (NCI/NTP), only 12 were associated with skin neoplasms; 11 of these 12 chemicals were administered orally or by inhalation. In the current study, 72% of male rats administered 3,3'-dimethoxybenzidine dihydrochloride in drinking water were found to have basal cell and/or sebaceous gland neoplasms of the skin, compared with only 3% of controls. In exposed male rats, basal cell neoplasms occurred as early as week 50; squamous cell neoplasms occurred as early as week 61. The basal cell neoplasms often showed differentiation to structures associated with sebaceous glands or hair follicles. Epithelial skin neoplasms were observed at low incidences in exposed female rats; however, those detected were of the same morphologic type as those observed in males and were considered to be related to 3,3'-dimethoxybenzidine dihydrochloride consumption.

Few substances induce epithelial neoplasms of the skin unless they are applied directly. Although 3,3'-dimethoxybenzidine dihydrochloride was administered in drinking water, exposure of skin during grooming was likely. The possibility that skin neoplasms resulted from direct exposure of the skin to 3,3'-dimethoxybenzidine dihydrochloride or its metabolites in saliva was considered. However, these neoplasms were more likely a result of systemic exposure to reactive 3,3'-dimethoxybenzidine metabolites, because most aromatic amines require metabolic activation to have carcinogenic activity (Miller and Miller, 1974, 1977) and because many skin neoplasms were present on the backs of the animals, where grooming is minimal. No reports on the carcinogenicity of 3,3'-dimethoxybenzidine after dermal application were found.

3,3'-Dimethoxybenzidine dihydrochloride exposure led to development of neoplasms of the small and large intestine in male rats. Chemically induced neoplasms of the intestine are uncommon in rats; of 350 chemicals studied by the NCI/NTP, only 7--tribromomethane (NTP, 1989), bromodichloromethane (NTP, 1987), captan, (NCI, 1977a), phenazopyridine hydrochloride (NCI, 1978c), proflavin hydrochloride (NCI, 1977b), chrysotile asbestos (NTP, 1985), and Aroclor® 1254 (NCI, 1978d)--were associated with adenocarcinomas, adenomatous polyps, or intestinal carcinomas in rats.

In the current studies, neoplasms were principally cystic mucinous adenocarcinomas of the small intestine and adenomatous polyps and adenocarcinomas of the large intestine. Polyps in the colon were first observed at week 48, whereas adenocarcinomas in the small intestine first occurred after 39 weeks of chemical

exposure. Adenocarcinomas in the large intestine were also observed in the low, mid, and high dose groups of exposed female rats; although not as numerous as in males, these neoplasms were considered to be related to 3,3'-dimethoxybenzidine dihydrochloride exposure because no adenocarcinomas or adenomatous polyps of the large intestine have been observed in 1,601 untreated historical control female F344/N rats.

Squamous cell neoplasms that occurred on the tongue and palate of exposed male rats were strongly associated with exposure to 3,3'-dimethoxybenzidine dihydrochloride. Taken collectively, the observed number of squamous cell papillomas and carcinomas of the oral cavity (16% of dosed animals) represents a large increase in the incidence of relatively rare neoplasms (0.4% in untreated control male F344/N rats). Squamous cell neoplasms of the oral cavity were also detected in dosed female rats, although at lower incidences, but the incidences still markedly exceeded the historical incidence of 0.2%.

3,3'-Dimethoxybenzidine dihydrochloride consumption led to adenocarcinomas in the mammary gland of females receiving the mid and high doses. The incidence of adenocarcinomas in the high dose group (33%) was four times greater than the highest observed historical incidence in untreated control female F344/N rats. The first neoplasm was observed in a high dose female at week 41, whereas in the female controls, the one adenocarcinoma was observed at termination at week 93. The remarkable increase in adenocarcinomas and decreased time-to-tumor were a direct result of 3,3'-dimethoxybenzidine dihydrochloride exposure.

Intake of 3,3'-dimethoxybenzidine dihydrochloride was associated with increased incidences of hepatocellular neoplasms, principally neoplastic nodules (hepatocellular adenoma), in exposed male rats. Although the increased incidences of neoplasms were not as remarkable in the liver as in the other organs, the dose-related increases in hepatocellular neoplasms in the mid and high dose groups of males and in exposed female rats support the conclusion that 3,3'-dimethoxybenzidine dihydrochloride exposure was responsible for these neoplasms. 3,3'-Dimethoxybenzidine dihydrochloride was also associated with an increase in the incidence of eosinophilic foci in male rats. These foci are believed to be reversible changes that may progress to neoplasia (Maronpot et al., 1986). Because of the relatively high incidences of liver foci observed after exposure to 3,3'-dimethoxybenzidine dihydrochloride for 9 months, higher incidences of liver tumors were expected after exposure for 21 months. The low incidence of liver tumors may have been due in part to the early deaths of many animals because of neoplasia at other sites. In addition, early termination of the studies shortened the time available for liver foci to progress to detectable tumors.

Survival of 3,3'-dimethoxybenzidine dihydrochloride-exposed rats was reduced during the 21-month studies primarily because of moribund animals' being killed with the presence of grossly visible neoplasms of the skin, Zymbal gland, and preputial gland in males and of the Zymbal, clitoral, and mammary glands in females. Tumors of these tissues first appeared in males after 32 weeks of exposure (Zymbal gland) and in females after 32 weeks (clitoral gland).

Early deaths from these neoplasms may have reduced the number of male and female rats at risk for development of tumors at other sites. Mesotheliomas in male rats were associated with 3,3'-dimethoxybenzidine dihydrochloride exposure at the two upper doses. Although increased above that observed in controls, the incidences of these lesions were marginal; however, the lesions might have occurred in more animals if these groups had survived longer. Similarly, in dosed female rats, neoplasms of the skin, oral cavity, intestine, liver, and uterus/cervix occurred at incidences that were only marginally increased; however, the survival of exposed female rats was reduced early in the study by neoplasms of the clitoral, mammary, and Zymbal glands. Because of the low spontaneous incidence of most of these tumors and the chemically related early deaths, neoplasms in these tissues were considered to be related to 3,3'-dimethoxybenzidine dihydrochloride exposure.

The association between 3,3'-dimethoxybenzidine exposure and astrocytomas of the brain in male rats is less strong. The incidence of these tumors was only marginally increased and was not dose related. However, in consideration of the reduced survival of exposed rats and of the low spontaneous occurrence of these tumors,

these neoplasms may have been related to 3,3'-dimethoxybenzidine dihydrochloride exposure.

For these later developing or less rapidly lethal tumors, expression of tumor incidence by the standard convention (the number of tumor-bearing animals at a site divided by the number of animals in which this site was examined) might underestimate the tumor incidence that would have been observed in the absence of early deaths. Therefore, tumor incidence ratios were expressed in terms of the "effective" number of animals actually at risk; i.e., the number of tumor-bearing animals at a particular site divided by the number of animals alive in each group at the time the first tumor was observed at that site in any of the four (control or low, mid, or high dose) groups. These derived incidences were analyzed statistically with the Cochran-Armitage trend test and the Fisher exact test.

Tumor Transplant Study

Because preputial gland neoplasms are usually not overtly aggressive or invasive and rarely metastasize (Goodman et al., 1979; Reznik and Ward, 1981), classification of these neoplasms as benign or malignant is difficult (Maronpot et al., 1988). Studies by Ward and Lynch (1984) showed that malignant preputial/clitoral gland neoplasms from aging F344 rats were transplantable at a higher incidence and with shorter latency periods than benign neoplasms. However, these conclusions were based on a single-passage study with a single carcinoma and four adenomas.

The transplantability of preputial gland neoplasms induced by 3,3'-dimethoxybenzidine dihydrochloride, C.I. Direct Blue 15, or C.I. Acid Red 114 was investigated to provide information on the biologic behavior of these neoplasms (Maronpot et al., 1988; Ulland et al., 1989). All neoplasms selected for transplantation were retrospectively diagnosed as carcinomas, and therefore comparable information was not obtained for preputial gland adenomas. The transplanted preputial gland neoplasms did not become anaplastic or less differentiated over four serial passages; however, the transplants behaved biologically as malignant neoplasms in spite of their well-differentiated morphology. The latency period was short and transplants grew rapidly, reaching 3.0 cm in 7-9 weeks. No differences were observed in morphology or growth of transplants obtained from control or 3,3'-dimethoxybenzidine dihydrochloride-exposed rats. The results of these studies confirm the malignant nature of these preputial gland neoplasms from rats exposed to 3,3'-dimethoxybenzidine dihydrochloride.

Oncogene Activation

Neoplasms obtained from control rats and rats exposed to 3,3'-dimethoxybenzidine dihydrochloride or C.I. Direct Blue 15 (a 3,3'-dimethoxybenzidine-derived dye) were assayed for the presence of activated proto-oncogenes by the NIH 3T3 DNA transfection assay (Anderson et al., 1987). Oncogenes detectable by DNA transfection analysis were present in 21/27 skin, clitoral gland, or preputial gland neoplasms that had been induced by 3,3'-dimethoxybenzidine dihydrochloride or C.I. Direct Blue 15. DNA from both benign and malignant neoplasms was capable of inducing morphologically transformed foci in NIH 3T3 mouse fibroblast cultures.

Thirteen of the chemically induced neoplasm types were of epidermal origin and were classified as basal or squamous cell neoplasms of the skin; activated *ras* oncogenes were detected at a high frequency in these neoplasms (11/13). Histogenetically related neoplasms of the clitoral and preputial glands also had a high frequency of activated *ras* oncogenes (10/14).

It is difficult to compare oncogene activation in spontaneously occurring neoplasms with that in chemical-induced neoplasms because of the substantial difference in the neoplasm types obtained in the two groups. Only 55% (21/38) of the spontaneously occurring neoplasm types were of epithelial cell origin. However, in neoplasms of epithelial cell origin, there is a thirteenfold higher incidence of *ras* gene activation in the chemically induced neoplasms (21/34) than in the spontaneous neoplasms (1/21).

It is possible that chemically induced neoplasms were derived from a common epidermal progenitor stem-cell population that was susceptible to electrophilic attack by activated metabolites of 3,3'-dimethoxybenzidine or C.I. Direct Blue 15. A relatively high percentage (62%) of the chemically induced rat neoplasms contained activated alleles of either H-*ras* or N-*ras*. Those

neoplasms with activated H-*ras* contained point mutations in the 12th, 13th, or 61st codon. The much higher incidence of H-*ras* gene activation and the apparent mutational specificity at codons 13 and 61 of H-*ras* with 3,3'-dimethoxybenzidine exposure suggest that the increased tumor incidence observed in exposed rats is directly related to the genotoxic effect of this chemical.

Related Aromatic Amines

Benzidine and related aromatic amines produce neoplasms in a wide variety of tissues in experimental animals. In humans, exposure to benzidine is associated with cancer of the urinary bladder (Zavon et al., 1973); in mice, however, the liver is the major target organ (Bonser et al., 1956; Vesselinovitch et al., 1975; Littlefield et al., 1983; IARC, 1987a). In rats, benzidine and other aminobiphenyls cause neoplasms in the Zymbal gland, mammary gland, skin, intestine, and liver. These differences in species and target organ specificity may be related to differences in metabolism.

A number of aromatic amines cause neoplasms in the Zymbal gland (Table 23). The Zymbal gland has been reported to be deficient in sulfotransferase activity (Irving et al., 1971) and transacylase activity (Bartsch et al., 1973), but it is capable of hydroxylating compounds via cytochrome P450-dependent enzymatic pathways (Pohl and Fouts, 1983). Susceptibility of a species to the carcinogenic action of aromatic amines depends on the ability of the species to *N*-hydroxylate the amine substituent. *N*-Hydroxylation appears to be a necessary step in the metabolic activation of aromatic amines. *N*-Acyl and *N*-acetyl aromatic amine derivatives require additional activation to reactive esters, which act as ultimate carcinogens (Miller and Miller, 1977). Formation of different esters by different species may result in variations in organ specificity (Cohen, 1983).

Of 350 chemicals evaluated for carcinogenicity in rats and mice by the NCI/NTP, only 14 were associated with Zymbal gland neoplasms in rats. Ten of these 14 chemicals are aryl nitrogen derivatives (nitro, amino, or isocyanate), which were mutagenic for *Salmonella typhimurium*, and produced neoplasms in both rats and mice. In a survey of 222 chemicals evaluated by the NCI/NTP, Ashby and Tennant (1988) reported that only 6 were associated with skin neoplasms after systemic administration. Of these six chemicals, five were aryl nitrogen derivatives and five were among the group of nine chemicals that caused Zymbal gland neoplasms. Although not included in this survey, 3,3'-dimethoxybenzidine dihydrochloride, benzidine, and several other aromatic amines (Table 23) also belong to this group of genotoxic carcinogens that cause Zymbal gland and/or skin neoplasms in rodents.

Audit

The experimental and tabulated data for the NTP Technical Report on 3,3'-dimethoxybenzidine dihydrochloride were examined for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations. As summarized in Appendix I, the audit revealed no major problems with the conduct of the studies or with collection and documentation of the experimental data. No discrepancies were found that influenced the final interpretation of the results of these studies.

Conclusions

Under the conditions of these 21-month drinking water studies, there was *clear evidence of carcinogenic activity** of 3,3'-dimethoxybenzidine dihydrochloride for male F344/N rats, as indicated by benign and malignant neoplasms of the skin, Zymbal gland, preputial gland, oral cavity, intestine, liver, and mesothelium. Increased incidences of astrocytomas of the brain may have been related to chemical administration. There was *clear evidence of carcinogenic activity* of 3,3'-dimethoxybenzidine dihydrochloride for female F344/N rats, as indicated by benign and malignant neoplasms of the Zymbal gland, clitoral gland, and mammary gland. Increases in neoplasms of the skin, oral cavity, large intestine, liver, and uterus/cervix were also considered to be related to chemical administration of 3,3'-dimethoxybenzidine dihydrochloride.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 9.

TABLE 23. STRUCTURAL ANALOGS OF 3,3'-DIMETHOXYBENZIDINE WHICH ARE MUTAGENIC CARCINOGENS FOR RAT ZYMBAL GLAND AND SKIN

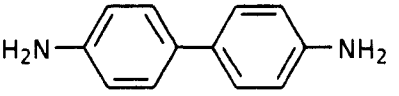
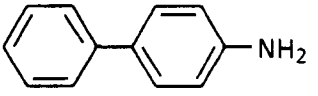
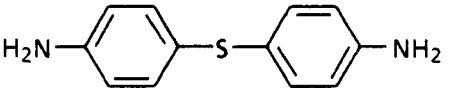
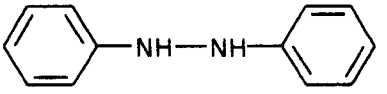
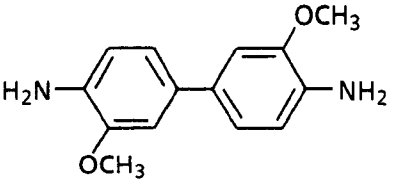
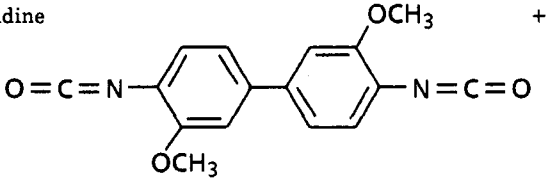
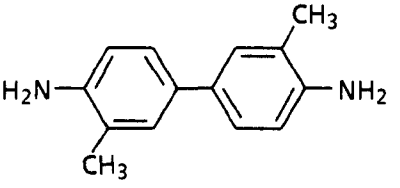
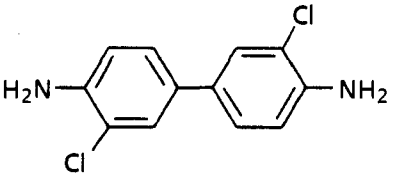
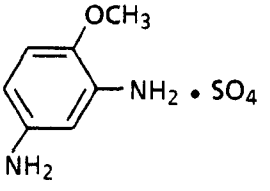
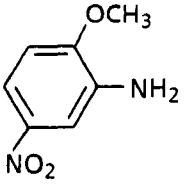
Aromatic Amine	Structure	*Salmonella typhimurium* Assay	Zymbal Gland	Skin	References
Benzidine		+	+	–	IARC, 1987a
4-Aminobiphenyl		+	+	–	IARC, 1987b
4,4'-Thiodianiline		+	+	+	NCI, 1978e
Hydrazobenzene		+	+	–	NCI, 1978f
3,3'-Dimethoxybenzidine		+	+	+	Current studies
3,3'-Dimethoxybenzidine diisocyanate		+	+	+	NCI, 1979

TABLE 23. STRUCTURAL ANALOGS OF 3,3'-DIMETHOXYBENZIDINE WHICH ARE MUTAGENIC CARCINOGENS FOR RAT ZYMBAL GLAND AND SKIN (Continued)

Aromatic Amine	Structure	*Salmonella typhimurium* Assay	Zymbal Gland	Skin	References
3,3'-Dimethylbenzidine		+	+	–	Pliss, 1965
3,3'-Dichlorobenzidine		+	+	+	IARC, 1987c; Lazear and Louie, 1977
2,4-Diaminoanisole sulfate		+	+	+	NCI, 1978g
5-Nitro-*o*-anisidine		+	+	+	NCI, 1978h

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

	Untreated Control	80 ppm	170 ppm	330 ppm
Animals initially in study	70	45	75	70
Animals removed	70	45	75	70
Animals examined histopathologically	60	45	75	60
ALIMENTARY SYSTEM				
Intestine large, cecum	(60)	(42)	(72)	(58)
Adenocarcinoma, cystic, mucinous				1 (2%)
Rectum, mesothelioma malignant, metastatic	1 (2%)			
Intestine large, colon	(60)	(43)	(73)	(58)
Adenocarcinoma			2 (3%)	
Ascending colon, polyp adenomatous		1 (2%)		
Descending colon, adenocarcinoma			2 (3%)	2 (3%)
Descending colon, polyp adenomatous			3 (4%)	4 (7%)
Descending colon, polyp adenomatous, multiple			1 (1%)	
Intestine large, rectum	(59)	(42)	(73)	(58)
Adenocarcinoma				1 (2%)
Polyp adenomatous				1 (2%)
Intestine small, duodenum	(60)	(42)	(70)	(55)
Adenocarcinoma			1 (1%)	
Adenocarcinoma, cystic, mucinous		2 (5%)	1 (1%)	
Ileum, jejunum, mesothelioma malignant, metastatic, testes	1 (2%)			
Jejunum, mesothelioma malignant, metastatic, testes			1 (1%)	
Intestine small, ileum	(59)	(42)	(69)	(57)
Adenocarcinoma				1 (2%)
Intestine small, jejunum	(59)	(41)	(69)	(56)
Adenocarcinoma			1 (1%)	1 (2%)
Adenocarcinoma, cystic, mucinous		2 (5%)	4 (6%)	3 (5%)
Liver	(60)	(45)	(74)	(60)
Hepatocellular carcinoma	1 (2%)	1 (2%)		2 (3%)
Leukemia mononuclear	19 (32%)	16 (36%)	14 (19%)	2 (3%)
Lymphoma malignant histiocytic			1 (1%)	
Mesothelioma malignant, metastatic, testes	1 (2%)			1 (2%)
Mesothelioma malignant, metastatic, multiple, testes			1 (1%)	
Neoplastic nodule		3 (7%)	7 (9%)	4 (7%)
Neoplastic nodule, multiple				2 (3%)
Mesentery	*(60)	*(45)	*(75)	*(60)
Mesothelioma malignant, metastatic, testes	1 (2%)			2 (3%)
Mesothelioma malignant, metastatic, multiple, testes	1 (2%)		3 (4%)	
Sarcoma	1 (2%)			
Schwannoma malignant			2 (3%)	
Pancreas	(60)	(44)	(75)	(60)
Adenocarcinoma, metastatic, multiple, intestine small		1 (2%)		
Leukemia mononuclear	1 (2%)			
Mesothelioma malignant, metastatic, testes	1 (2%)		1 (1%)	1 (2%)
Mesothelioma malignant, metastatic, multiple, testes			1 (1%)	
Acinus, adenoma		2 (5%)		1 (2%)
Pharynx	*(60)	*(45)	*(75)	*(60)
Carcinoma, metastatic, Zymbal gland				1 (2%)
Mucosa, carcinoma, metastatic, skin				1 (2%)
Palate, carcinoma, metastatic, Zymbal gland				1 (2%)
Palate, papilloma squamous		4 (9%)	5 (7%)	3 (5%)
Palate, squamous cell carcinoma				1 (2%)
Salivary glands	(60)	(44)	(75)	(60)
Schwannoma malignant		2 (5%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Untreated Control	80 ppm	170 ppm	330 ppm
ALIMENTARY SYSTEM (Continued)				
Stomach, forestomach	(59)	(44)	(73)	(57)
Leiomyosarcoma			1 (1%)	
Glandular, mesothelioma malignant, metastatic, testes	1 (2%)		1 (1%)	
Tongue	*(60)	*(45)	*(75)	*(60)
Papilloma squamous	1 (2%)	3 (7%)	5 (7%)	7 (12%)
Squamous cell carcinoma		1 (2%)		1 (2%)
Parenchyma, carcinoma	1 (2%)			
CARDIOVASCULAR SYSTEM				
Heart	(60)	(44)	(75)	(60)
Fibrous histiocytoma, metastatic, skin			1 (1%)	
Leukemia mononuclear	4 (7%)	1 (2%)		
Schwannoma benign			1 (1%)	
Schwannoma malignant			1 (1%)	
ENDOCRINE SYSTEM				
Adrenal gland	(60)	(44)	(74)	(60)
Capsule, mesothelioma malignant, metastatic, testes			2 (3%)	
Adrenal gland, cortex	(60)	(44)	(74)	(60)
Leukemia mononuclear	6 (10%)	6 (14%)	2 (3%)	
Bilateral, mesothelioma malignant, metastatic, testes	1 (2%)			
Adrenal gland, medulla	(60)	(44)	(74)	(60)
Leukemia mononuclear	6 (10%)	6 (14%)	2 (3%)	
Pheochromocytoma malignant	2 (3%)	1 (2%)	3 (4%)	
Pheochromocytoma benign	12 (20%)	10 (23%)	16 (22%)	5 (8%)
Bilateral, pheochromocytoma benign	2 (3%)	7 (16%)	7 (9%)	4 (7%)
Islets, pancreatic	(60)	(44)	(75)	(60)
Adenoma	1 (2%)			
Carcinoma		1 (2%)		
Pituitary gland	(58)	(43)	(74)	(59)
Leukemia mononuclear	1 (2%)	2 (5%)		
Schwannoma malignant, metastatic, eye				1 (2%)
Pars distalis, adenoma	2 (3%)	1 (2%)		3 (5%)
Thyroid gland	(60)	(44)	(74)	(60)
C-cell, adenoma	6 (10%)	6 (14%)	5 (7%)	1 (2%)
C-cell, carcinoma		1 (2%)	2 (3%)	1 (2%)
Follicular cell, adenoma				1 (2%)
Follicular cell, carcinoma		1 (2%)		
GENERAL BODY SYSTEM				
Tissue, NOS	*(60)	*(45)	*(75)	*(60)
Mesothelioma malignant, metastatic, testes			1 (1%)	
GENITAL SYSTEM				
Epididymis	(60)	(45)	(75)	(59)
Mesothelioma malignant, metastatic, testes	1 (2%)			
Bilateral, mesothelioma malignant, metastatic, testes	1 (2%)	1 (2%)	6 (8%)	3 (5%)
Preputial gland	(60)	(43)	(73)	(59)
Adenoma	13 (22%)	4 (9%)	17 (23%)	11 (19%)
Carcinoma	2 (3%)	5 (12%)	12 (16%)	17 (29%)
Leukemia mononuclear	1 (2%)			
Bilateral, adenoma	1 (2%)	2 (5%)	2 (3%)	1 (2%)
Bilateral, carcinoma		1 (2%)	3 (4%)	2 (3%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Untreated Control	80 ppm	170 ppm	330 ppm
GENITAL SYSTEM (Continued)				
Prostate	(60)	(44)	(75)	(60)
Adenoma			1 (1%)	
Mesothelioma malignant, metastatic, testes	1 (2%)		1 (1%)	1 (2%)
Mesothelioma malignant, metastatic, multiple, testes			1 (1%)	
Seminal vesicle	(58)	(42)	(58)	(44)
Adenocarcinoma, metastatic, multiple, intestine small		1 (2%)		
Adenoma				1 (2%)
Leukemia mononuclear	1 (2%)			
Mesothelioma malignant, metastatic, testes	1 (2%)		2 (3%)	
Mesothelioma malignant, metastatic, multiple, testes			1 (2%)	
Bilateral, mesothelioma malignant, metastatic, testes	1 (2%)			
Testes	(60)	(45)	(75)	(59)
Mesothelioma benign				1 (2%)
Mesothelioma malignant				1 (2%)
Bilateral, mesothelioma benign				1 (2%)
Bilateral, mesothelioma malignant	2 (3%)	1 (2%)	7 (9%)	3 (5%)
Bilateral, interstitial cell, adenoma	49 (82%)	35 (78%)	51 (68%)	24 (41%)
Interstitial cell, adenoma	8 (13%)	4 (9%)	17 (23%)	18 (31%)
HEMATOPOIETIC SYSTEM				
Bone marrow	(60)	(43)	(74)	(60)
Leukemia mononuclear	2 (3%)		1 (1%)	
Lymph node	(60)	(43)	(75)	(58)
Axillary, mediastinal, basal cell carcinoma, metastatic, skin				1 (2%)
Deep cervical, carcinoma, metastatic, thyroid gland				1 (2%)
Inguinal, carcinoma, metastatic				1 (2%)
Inguinal, iliac, carcinoma, metastatic, preputial gland				1 (2%)
Mediastinal, fibrous histiocytoma, metastatic, skin			1 (1%)	
Mediastinal, leukemia mononuclear	4 (7%)	3 (7%)	1 (1%)	
Pancreatic, leukemia mononuclear	3 (5%)			
Lymph node, mandibular	(60)	(43)	(74)	(58)
Leukemia mononuclear	5 (8%)	5 (12%)	1 (1%)	
Squamous cell carcinoma, metastatic, skin		1 (2%)		
Lymph node, mesenteric	(59)	(42)	(73)	(56)
Leukemia mononuclear	5 (8%)	3 (7%)		
Mediastinal, pancreatic, adenocarcinoma, metastatic, intestine small		1 (2%)		
Spleen	(60)	(42)	(74)	(59)
Basal cell carcinoma, metastatic, skin				1 (2%)
Hemangiosarcoma				1 (2%)
Leukemia mononuclear	19 (32%)	16 (38%)	17 (23%)	4 (7%)
Lymphoma malignant histiocytic			1 (1%)	
Mesothelioma malignant, metastatic, testes	1 (2%)		2 (3%)	1 (2%)
INTEGUMENTARY SYSTEM				
Mammary gland	(56)	(42)	(68)	(56)
Fibroadenoma	1 (2%)		2 (3%)	
Skin	(60)	(45)	(75)	(60)
Basal cell adenoma	1 (2%)	15 (33%)	12 (16%)	10 (17%)
Basal cell adenoma, multiple		16 (36%)	35 (47%)	25 (42%)
Basal cell carcinoma	1 (2%)	3 (7%)	14 (19%)	13 (22%)
Basal cell carcinoma, multiple		1 (2%)	4 (5%)	4 (7%)
Keratoacanthoma	1 (2%)	5 (11%)	7 (9%)	1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Untreated Control	80 ppm	170 ppm	330 ppm
INTEGUMENTARY SYSTEM				
Skin (Continued)	(60)	(45)	(75)	(60)
Papilloma squamous		3 (7%)	7 (9%)	3 (5%)
Papilloma squamous, multiple		2 (4%)		2 (3%)
Squamous cell carcinoma		8 (18%)	15 (20%)	15 (25%)
Squamous cell carcinoma, multiple		1 (2%)	9 (12%)	6 (10%)
Sebaceous gland, adenoma		2 (4%)	2 (3%)	1 (2%)
Sebaceous gland, carcinoma			1 (1%)	1 (2%)
Subcutaneous tissue, carcinoma, metastatic				1 (2%)
Subcutaneous tissue, fibroma		4 (9%)	4 (5%)	1 (2%)
Subcutaneous tissue, fibroma, multiple				1 (2%)
Subcutaneous tissue, fibrosarcoma				1 (2%)
Subcutaneous tissue, fibrous histiocytoma			1 (1%)	
Subcutaneous tissue, neurofibroma		2 (4%)	2 (3%)	2 (3%)
Subcutaneous tissue, sarcoma	2 (3%)			
MUSCULOSKELETAL SYSTEM				
Bone	*(60)	*(45)	*(75)	*(60)
Chordoma		1 (2%)		
Cranium, carcinoma, metastatic, Zymbal gland		1 (2%)		5 (8%)
Cranium, squamous cell carcinoma, metastatic				1 (2%)
Cranium, squamous cell carcinoma, metastatic, skin		1 (2%)		
Skeletal muscle	*(60)	*(45)	*(75)	*(60)
Abdominal, schwannoma malignant, metastatic, mesentery			2 (3%)	
Cervical, carcinoma, metastatic, Zymbal gland				1 (2%)
Thoracic, fibrous histiocytoma, metastatic, skin			1 (1%)	
NERVOUS SYSTEM				
Brain	(60)	(44)	(75)	(60)
Astrocytoma malignant			1 (1%)	
Leukemia mononuclear	3 (5%)	1 (2%)		
Cerebellum, astrocytoma malignant		1 (2%)		
Cerebellum, cerebrum, astrocytoma malignant			1 (1%)	
Cerebrum, astrocytoma malignant		1 (2%)	1 (1%)	1 (2%)
Meninges, cerebrum, perivascular, squamous cell carcinoma, metastatic, skin		1 (2%)		
RESPIRATORY SYSTEM				
Lung	(60)	(44)	(75)	(60)
Adenocarcinoma, metastatic, multiple, intestine small		1 (2%)		
Alveolar/bronchiolar adenoma			2 (3%)	1 (2%)
Basal cell carcinoma, metastatic, multiple, skin		1 (2%)		1 (2%)
Carcinoma, metastatic, preputial gland			1 (1%)	
Carcinoma, metastatic, Zymbal gland		1 (2%)	1 (1%)	1 (2%)
Carcinoma, metastatic, multiple, preputial gland				1 (2%)
Carcinoma, metastatic, multiple, Zymbal gland		1 (2%)		2 (3%)
Fibrosarcoma, metastatic, multiple, skin				1 (2%)
Fibrous histiocytoma, metastatic, skin			1 (1%)	
Leukemia mononuclear	9 (15%)	10 (23%)	8 (11%)	
Lymphoma malignant histiocytic			1 (1%)	
Squamous cell carcinoma, metastatic, skin				2 (3%)
Squamous cell carcinoma, metastatic, multiple, skin		1 (2%)		1 (2%)
Nose	(60)	(44)	(74)	(60)
Adenoma			1 (1%)	
Squamous cell carcinoma, metastatic, skin		1 (2%)		
Submucosa, schwannoma malignant, metastatic, eye				1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Untreated Control	80 ppm	170 ppm	330 ppm
SPECIAL SENSES SYSTEM				
Eye	*(60)	*(45)	*(75)	*(60)
Choroid, conjunctiva, retrobulbar, squamous cell carcinoma, metastatic, skin		1 (2%)		
Optic nerve, schwannoma malignant				1 (2%)
Zymbal gland	(59)	(45)	(75)	(60)
Adenoma		3 (7%)	11 (15%)	9 (15%)
Carcinoma		7 (16%)	13 (17%)	20 (33%)
Bilateral, adenoma		1 (2%)		
Bilateral, carcinoma			1 (1%)	1 (2%)
URINARY SYSTEM				
Kidney	(60)	(44)	(74)	(60)
Adenocarcinoma, metastatic, intestine small		1 (2%)		
Leukemia mononuclear	4 (7%)	1 (2%)	2 (3%)	
Mesothelioma malignant, metastatic, testes	1 (2%)		1 (1%)	1 (2%)
Mesothelioma malignant, metastatic, multiple, testes			1 (1%)	
Bilateral, mesothelioma malignant, metastatic, testes	1 (2%)			
Urinary bladder	(60)	(44)	(75)	(59)
Leukemia mononuclear	1 (2%)			
Mesothelioma malignant, metastatic, testes	1 (2%)		2 (3%)	2 (3%)
SYSTEMIC LESIONS				
Multiple organs	*(60)	*(45)	*(75)	*(60)
Mesothelioma malignant	2 (3%)	1 (2%)	7 (9%)	4 (7%)
Leukemia mononuclear	19 (32%)	17 (38%)	17 (23%)	4 (7%)
Lymphoma malignant histiocytic			1 (1%)	
Mesothelioma benign				2 (3%)
Hemangiosarcoma				1 (2%)
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	70	45	75	70
Interval sacrifice	10			10
Terminal sacrifice	44	8		
Dead	9	9	25	14
Moribund	7	28	50	46
TUMOR SUMMARY				
Total animals with primary neoplasms **	59	45	75	60
Total primary neoplasms	129	194	344	254
Total animals with benign neoplasms	57	43	70	53
Total benign neoplasms	98	135	223	149
Total animals with malignant neoplasms	27	36	66	59
Total malignant neoplasms	31	59	121	105
Total animals with secondary neoplasms ***	2	6	11	19
Total secondary neoplasms	17	16	36	39

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3′-DIMETHOXYBENZIDINE DIHYDROCHLORIDE: UNTREATED CONTROL

WEEKS ON STUDY	011	065	073	076	076	082	083	087	087	088	090	092	092	093	093	093	093	093	093	093	093	093	093	093
CARCASS ID	095	035	045	034	033	065	044	094	135	134	085	055	114	042	115	082	031	032	041	043	051	052	053	054	061
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rectum, mesothelioma malignant, metastatic				X																					
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ileum, jejunum, mesothelioma malignant, metastatic, testes				X																					
Intestine small, ileum	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Leukemia mononuclear			X										X	X	X	X								X	
Mesothelioma malignant, metastatic, testes				X																					
Mesentery				+	+	+			+		+					+			+		+			+	
Mesothelioma malignant, metastatic, testes																								X	
Mesothelioma malignant, metastatic, multiple, testes				X																					
Sarcoma											X														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X												
Mesothelioma malignant, metastatic, testes				X																					
Pharynx																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glandular, mesothelioma malignant, metastatic, testes				X																					
Stomach, glandular	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue										+							+								
Papilloma squamous																	X								
Parenchyma, carcinoma										X															
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X										X	X											
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X											X	X										
Bilateral, mesothelioma malignant, metastatic, testes				X																					
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X											X	X										
Pheochromocytoma malignant								X																	
Pheochromocytoma benign						X			X		X										X				X
Bilateral, pheochromocytoma benign													X												
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Pars distalis, adenoma							X																		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma															X										X
GENERAL BODY SYSTEM																									
None																									

+: Tissue examined microscopically
: Not examined
−: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093
CARCASS ID	062	063	064	071	072	073	074	075	081	083	084	091	092	093	101	102	103	104	105	111	112	113	121	122	123
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rectum, mesothelioma malignant, metastatic																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ileum, jejunum, mesothelioma malignant, metastatic, testes																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma									X																
Leukemia mononuclear		X		X		X	X							X		X	X			X		X	X		
Mesothelioma malignant, metastatic, testes																									
Mesentery	+		+				+								+	+	+		+				+		+
Mesothelioma malignant, metastatic, testes																									
Mesothelioma malignant, metastatic, multiple, testes																									
Sarcoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Mesothelioma malignant, metastatic, testes																									
Pharynx						+																			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glandular, mesothelioma malignant, metastatic, testes																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Papilloma squamous																									
Parenchyma, carcinoma																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X			
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X																		X		X			
Bilateral, mesothelioma malignant, metastatic, testes																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X																		X		X			
Pheochromocytoma malignant							X																		
Pheochromocytoma benign		X	X			X	X											X		X				X	
Bilateral, pheochromocytoma benign					X																				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X											
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X			
Pars distalis, adenoma								X																	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma							X								X							X			X
GENERAL BODY SYSTEM																									
None																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	TOTAL:
CARCASS ID	1 2 4	1 2 5	1 3 1	1 3 2	1 3 3	1 4 1	1 4 2	1 4 3	1 4 4	1 4 5	TISSUES TUMORS
ALIMENTARY SYSTEM											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Intestine large	+	+	+	+	+	+	+	+	+	+	60
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	60
Rectum, mesothelioma malignant, metastatic											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	60
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	59
Intestine small	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	60
Ileum, jejunum, mesothelioma malignant, metastatic, testes											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	59
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	59
Liver	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular carcinoma											1
Leukemia mononuclear	X				X	X					19
Mesothelioma malignant, metastatic, testes											1
Mesentery		+		+	+	+					22
Mesothelioma malignant, metastatic, testes											1
Mesothelioma malignant, metastatic, multiple, testes											1
Sarcoma											1
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											1
Mesothelioma malignant, metastatic, testes											1
Pharynx											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach	M	+	+	+	+	+	+	+	+	+	59
Stomach, forestomach	M	+	+	+	+	+	+	+	+	+	59
Glandular, mesothelioma malignant, metastatic, testes											1
Stomach, glandular	M	+	+	+	+	+	+	+	+	+	58
Tongue											2
Papilloma squamous											1
Parenchyma, carcinoma											1
CARDIOVASCULAR SYSTEM											
Heart	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											4
ENDOCRINE SYSTEM											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											6
Bilateral, mesothelioma malignant, metastatic, testes											1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											6
Pheochromocytoma malignant											2
Pheochromocytoma benign											12
Bilateral, pheochromocytoma benign											2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	60
Adenoma											1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	60
Pituitary gland	+	+	+	+	+	+	+	+	+	+	58
Leukemia mononuclear											1
Pars distalis, adenoma											2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
C-cell, adenoma											6
GENERAL BODY SYSTEM											
None											

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	011	065	073	076	076	082	083	087	087	088	090	092	092	093	093	093	093	093	093	093	093	093	093	093	093
CARCASS ID	095	035	045	034	033	065	044	094	135	134	085	055	114	042	115	082	031	032	041	043	051	052	053	054	061
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes				X																					
Bilateral, mesothelioma malignant, metastatic, testes																								X	
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X			X						X		X									X
Carcinoma									X				X												
Leukemia mononuclear																									
Bilateral, adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes				X																					
Seminal vesicle	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X											
Mesothelioma malignant, metastatic, testes																								X	
Bilateral, mesothelioma malignant, metastatic, testes				X																					
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, mesothelioma malignant				X																				X	
Bilateral, interstitial cell, adenoma					X	X	X	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma				X								X				X									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X											
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear													X	X	X										
Pancreatic, leukemia mononuclear														X	X										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X	X	X										
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X	X	X										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X										X	X	X	X								X	
Mesothelioma malignant, metastatic, testes				X																					
Thymus	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																								X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Basal cell carcinoma																				X					
Keratoacanthoma						X																			
Subcutaneous tissue, sarcoma		X														X									
MUSCULOSKELETAL SYSTEM																									
None																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X											X											
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X										X	X	X	X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																									
Harderian gland																							+		
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X											
Mesothelioma malignant, metastatic, testes																								X	
Bilateral, mesothelioma malignant, metastatic, testes				X																					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X											
Mesothelioma malignant, metastatic, testes				X																					

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093
CARCASS ID	062	063	064	071	072	073	074	075	081	083	084	091	092	093	101	102	103	104	105	111	112	113	121	122	123
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									
Bilateral, mesothelioma malignant, metastatic, testes																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X					X		X	X					X
Carcinoma																									
Leukemia mononuclear																						X			
Bilateral, adenoma											X														
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Mesothelioma malignant, metastatic, testes																									
Bilateral, mesothelioma malignant, metastatic, testes																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, mesothelioma malignant																									
Bilateral, interstitial cell, adenoma	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Interstitial cell, adenoma						X																		X	
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X			
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear																						X			
Pancreatic, leukemia mononuclear																						X			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X			
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X		X	X							X		X	X			X		X	X		
Mesothelioma malignant, metastatic, testes																									
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma					X																				
Basal cell carcinoma																									
Keratoacanthoma																									
Subcutaneous tissue, sarcoma																									
MUSCULOSKELETAL SYSTEM																									
None																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X			
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X												X		X						X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye			+		+											+				+					
Harderian gland																									
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X												X								X			
Mesothelioma malignant, metastatic, testes																									
Bilateral, mesothelioma malignant, metastatic, testes																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Mesothelioma malignant, metastatic, testes																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	TOTAL: TISSUES TUMORS
CARCASS ID	1 2 4	1 2 5	1 3 1	1 3 2	1 3 3	1 4 1	1 4 2	1 4 3	1 4 4	1 4 5	
GENITAL SYSTEM											
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Mesothelioma malignant, metastatic, testes											1
Bilateral, mesothelioma malignant, metastatic, testes											1
Preputial gland	+	+	+	+	+	+	+	+	+	+	60
Adenoma	X				X				X		13
Carcinoma											2
Leukemia mononuclear											1
Bilateral, adenoma											1
Prostate	+	+	+	+	+	+	+	+	+	+	60
Mesothelioma malignant, metastatic, testes											1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	58
Leukemia mononuclear											1
Mesothelioma malignant, metastatic, testes											1
Bilateral, mesothelioma malignant, metastatic, testes											1
Testes	+	+	+	+	+	+	+	+	+	+	60
Bilateral, mesothelioma malignant											2
Bilateral, interstitial cell, adenoma	X	X		X	X		X		X	X	49
Interstitial cell, adenoma			X			X		X			8
HEMATOPOIETIC SYSTEM											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											2
Lymph node	+	+	+	+	+	+	+	+	+	+	60
Mediastinal, leukemia mononuclear											4
Pancreatic, leukemia mononuclear											3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear						X					5
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear						X					5
Spleen	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear	X				X	X					19
Mesothelioma malignant, metastatic, testes											1
Thymus	+	+	M	+	+	+	+	+	+	+	58
INTEGUMENTARY SYSTEM											
Mammary gland	+	+	+	+	+	+	+	+	+	+	56
Fibroadenoma											1
Skin	+	+	+	+	+	+	+	+	+	+	60
Basal cell adenoma											1
Basal cell carcinoma											1
Keratoacanthoma											1
Subcutaneous tissue, sarcoma											2
MUSCULOSKELETAL SYSTEM											
None											
NERVOUS SYSTEM											
Brain	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											3
RESPIRATORY SYSTEM											
Lung	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											9
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60
SPECIAL SENSES SYSTEM											
Eye											4
Harderian gland											1
Zymbal gland	+	+	+	+	+	+	+	+	+	+	59
URINARY SYSTEM											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											4
Mesothelioma malignant, metastatic, testes											1
Bilateral, mesothelioma malignant, metastatic, testes											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											1
Mesothelioma malignant, metastatic, testes											1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3′-DIMETHOXYBENZIDINE DIHYDROCHLORIDE: 80 ppm

WEEKS ON STUDY	038	051	051	069	069	069	070	074	077	078	079	080	080	080	083	084	084	085	085	086	086	086	086	087	087	087
CARCASS ID	315	295	355	294	335	305	334	333	332	314	293	345	354	365	325	353	364	363	344	292	324	323	312	313	362
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Ascending colon, polyp adenomatous																										
Intestine large, rectum	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+
Adenocarcinoma, cystic, mucinous			X																							
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	A	+	+	M	+	+	+	+	+	+
Adenocarcinoma, cystic, mucinous																										
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																										
Leukemia mononuclear								X			X		X	X	X						X		X		X
Neoplastic nodule									X									X								
Mesentery							+		+							+		+				+			+	
Pancreas	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, multiple, intestine small																										
Acinus, adenoma																				X						
Pharynx												+						+								
Palate, papilloma squamous												X						X								
Salivary glands	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																				X						
Stomach	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue							+															+				
Papilloma squamous							X																			
Squamous cell carcinoma																						X				
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																				X						
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X						X					
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X						X					
Pheochromocytoma malignant											X															
Pheochromocytoma benign				X													X				X		X	X	X
Bilateral, pheochromocytoma benign															X			X								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																										
Parathyroid gland	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																					X					
Pars distalis, adenoma																										
Thyroid gland	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma															X											X
C-cell, carcinoma																										
Follicular cell, carcinoma																										
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, mesothelioma malignant, metastatic, testes						X																				
Preputial gland	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																			
Carcinoma																								X		X
Bilateral, adenoma																				X						
Bilateral, carcinoma																									X	
Prostate	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, multiple, intestine small																										
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, mesothelioma malignant						X																				
Bilateral, interstitial cell, adenoma						X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		
Interstitial cell, adenoma				X			X															X				

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 80 ppm (Continued)

WEEKS ON STUDY	087	087	088	088	089	089	089	089	092	092	092	092	093	093	093	093	093	093	093	TOTAL:
CARCASS ID	361	434	311	322	303	304	331	342	375	321	291	301	302	341	351	352	371	372	373	374	TISSUES TUMORS
ALIMENTARY SYSTEM																					
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Ascending colon, polyp adenomatous												X									1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adenocarcinoma, cystic, mucinous												X									2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Adenocarcinoma, cystic, mucinous									X	X											2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Hepatocellular carcinoma																X					1
Leukemia mononuclear	X	X								X	X			X		X	X		X		18
Neoplastic nodule													X								3
Mesentery		+									+						+				9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenocarcinoma, metastatic, multiple, intestine small									X												1
Acinus, adenoma																	X				2
Pharynx												+		+							4
Palate, papilloma squamous												X		X							4
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Schwannoma malignant											X										2
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Tongue			+										+								4
Papilloma squamous			X										X								3
Squamous cell carcinoma																					1
CARDIOVASCULAR SYSTEM																					
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Leukemia mononuclear																					1
ENDOCRINE SYSTEM																					
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Leukemia mononuclear	X	X								X				X							6
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Leukemia mononuclear	X	X								X				X							6
Pheochromocytoma malignant																					1
Pheochromocytoma benign					X									X			X		X		10
Bilateral, pheochromocytoma benign		X	X	X				X	X												7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Carcinoma													X								1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Leukemia mononuclear														X							2
Pars distalis, adenoma															X						1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
C-cell, adenoma	X		X								X						X				6
C-cell, carcinoma									X												1
Follicular cell, carcinoma	X																				1
GENERAL BODY SYSTEM																					
None																					
GENITAL SYSTEM																					
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Bilateral, mesothelioma malignant, metastatic, testes																					1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adenoma					X							X				X					4
Carcinoma										X	X							X			5
Bilateral, adenoma			X																		2
Bilateral, carcinoma																					1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adenocarcinoma, metastatic, multiple, intestine small									X												1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Bilateral, mesothelioma malignant																					1
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X	35
Interstitial cell, adenoma																			X		4

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 80 ppm (Continued)

WEEKS ON STUDY	038	051	051	069	069	069	070	074	077	078	079	080	080	080	083	084	084	085	085	086	086	086	086	087	087	087
CARCASS ID	315	295	355	294	335	305	334	333	332	314	293	345	354	365	325	353	364	363	344	292	324	323	312	313	362
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear											X										X					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X										X		X			
Squamous cell carcinoma, metastatic, skin																		X								
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X										X					
Mediastinal, pancreatic, adenocarcinoma, metastatic, intestine small																										
Spleen	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X			X		X		X						X		X			X
Thymus	+	+	+	+	+	+	+	M	+	A	M	+	+	+	+	+	M	+	+	M	+	+	+	M	M
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma					X		X		X			X	X			X	X	X	X			X				
Basal cell adenoma, multiple															X					X			X			X
Basal cell carcinoma											X															X
Basal cell carcinoma, multiple																						X				
Keratoacanthoma													X													
Papilloma squamous								X																		
Papilloma squamous, multiple									X																	
Squamous cell carcinoma							X										X		X					X		
Squamous cell carcinoma, multiple																										
Sebaceous gland, adenoma		X																								
Subcutaneous tissue, fibroma										X		X	X													
Subcutaneous tissue, neurofibroma																										
MUSCULOSKELETAL SYSTEM																										
Bone					+														+							
Chordoma																										
Cranium, carcinoma, metastatic, Zymbal gland					X																					
Cranium, squamous cell carcinoma, metastatic, skin																			X							
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																		
Cerebellum, astrocytoma malignant																										
Cerebrum, astrocytoma malignant																										
Meninges, cerebrum, perivascular, squamous cell carcinoma, metastatic, skin																			X							
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, multiple, intestine small																										
Basal cell carcinoma, metastatic, multiple, skin																										
Carcinoma, metastatic, Zymbal gland				X																						
Carcinoma, metastatic, multiple, Zymbal gland					X																					
Leukemia mononuclear								X			X		X	X	X						X					
Squamous cell carcinoma, metastatic, multiple, skin																			X							
Nose	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, skin																			X							
Trachea	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
SPECIAL SENSES SYSTEM																										
Eye					+				+										+							
Choroid, conjunctiva, retrobulbar, squamous cell carcinoma, metastatic, skin																			X							
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X			X						X															
Carcinoma	X			X	X	X	X												X							
Bilateral, adenoma																										
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, intestine small																										
Leukemia mononuclear																					X					
Urinary bladder	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 80 ppm (Continued)

WEEKS ON STUDY	087	087	088	088	089	089	089	089	092	092	092	092	093	093	093	093	093	093	093	TOTAL TISSUES TUMORS
CARCASS ID	361	343	311	322	303	304	331	342	375	321	291	301	302	341	351	352	371	373	374	
HEMATOPOIETIC SYSTEM																				
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymph node	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Mediastinal, leukemia mononuclear				X																3
Lymph node, mandibular	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Leukemia mononuclear		X		X																5
Squamous cell carcinoma, metastatic, skin																				1
Lymph node, mesenteric	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Leukemia mononuclear				X																3
Mediastinal, pancreatic, adenocarcinoma, metastatic, intestine small									X											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Leukemia mononuclear	X	X		X					X	X			X		X	X		X		16
Thymus	+	M	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	+	34
INTEGUMENTARY SYSTEM																				
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Basal cell adenoma		X			X	X											X	X		15
Basal cell adenoma, multiple			X	X	X			X		X	X	X	X	X		X			X	16
Basal cell carcinoma								X												3
Basal cell carcinoma, multiple																				1
Keratoacanthoma	X			X						X	X									5
Papilloma squamous				X								X								3
Papilloma squamous, multiple																X				2
Squamous cell carcinoma					X			X			X						X			8
Squamous cell carcinoma, multiple																X				1
Sebaceous gland, adenoma														X						2
Subcutaneous tissue, fibroma												X								4
Subcutaneous tissue, neurofibroma									X	X										2
MUSCULOSKELETAL SYSTEM																				
Bone																	+			3
Chordoma																	X			1
Cranium, carcinoma, metastatic, Zymbal gland																				1
Cranium, squamous cell carcinoma, metastatic, skin																				1
NERVOUS SYSTEM																				
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	44
Leukemia mononuclear																				1
Cerebellum, astrocytoma malignant																X				1
Cerebrum, astrocytoma malignant								X												1
Meninges, cerebrum, perivascular, squamous cell carcinoma, metastatic, skin																				1
RESPIRATORY SYSTEM																				
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenocarcinoma, metastatic, multiple, intestine small									X											1
Basal cell carcinoma, metastatic, multiple, skin								X												1
Carcinoma, metastatic, Zymbal gland																				1
Carcinoma, metastatic, multiple, Zymbal gland																				1
Leukemia mononuclear	X	X								X				X						10
Squamous cell carcinoma, metastatic, multiple, skin																				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Squamous cell carcinoma, metastatic, skin																				1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
SPECIAL SENSES SYSTEM																				
Eye																				3
Choroid, conjunctiva, retrobulbar, squamous cell carcinoma, metastatic, skin																				1
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma																				3
Carcinoma						X														7
Bilateral, adenoma																	X			1
URINARY SYSTEM																				
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenocarcinoma, metastatic, intestine small									X											1
Leukemia mononuclear																				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE: 170 ppm

WEEKS ON STUDY	041	044	048	049	052	056	056	059	060	060	061	061	063	066	066	067	068	068	068	069	069	069	070	070	070	070
CARCASS ID	55 55	47 55	59 55	50 55	61 55	47 44	50 44	52 55	49 55	51 55	53 55	59 44	57 55	61 44	53 44	49 44	58 55	50 33	52 33	52 44	58 44	48 55	54 55	60 55	61 33
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																						X				
Descending colon, adenocarcinoma																										
Descending colon, polyp adenomatous																										
Descending colon, polyp adenomatous, multiple																										
Intestine large, rectum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																										
Adenocarcinoma, cystic, mucinous																							X			
Jejunum, mesothelioma malignant, metastatic, testes																										
Intestine small, ileum	+	+	+	+	+	A	A	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																										
Adenocarcinoma, cystic, mucinous									X																	
Liver	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																					X	X			X	
Lymphoma malignant histiocytic																										
Mesothelioma malignant, metastatic, multiple, testes																										
Neoplastic nodule																							X			
Mesentery			+							+			+	+			+	+	+		+	+				
Mesothelioma malignant, metastatic, multiple, testes																			X							
Schwannoma malignant										X			X													
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																			X							
Mesothelioma malignant, metastatic, multiple, testes																										
Pharynx								+						+												
Palate, papilloma squamous								X						X												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																						X				
Glandular, mesothelioma malignant, metastatic, testes																										
Stomach, glandular	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue			+																							
Papilloma squamous			X																							
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																										
Schwannoma benign																										
Schwannoma malignant																										
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, mesothelioma malignant, metastatic, testes																										
Adrenal gland, cortex	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X				
Adrenal gland, medulla	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																						X				
Pheochromocytoma malignant																										
Pheochromocytoma benign									X											X		X				
Bilateral, pheochromocytoma benign																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																										
C-cell, carcinoma					X																					
GENERAL BODY SYSTEM																										
Tissue, NOS				+																						
Mesothelioma malignant, metastatic, testes				X																						

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 170 ppm (Continued)

WEEKS ON STUDY	070	070	073	073	074	075	078	076	077	077	077	077	078	078	078	078	079	080	080	080	080	080	080
CARCASS ID	564	565	604	583	593	473	544	472	612	582	514	563	513	502	533	543	574	542	512	484	554	581	603	573	492
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Descending colon, adenocarcinoma													X											X	
Descending colon, polyp adenomatous															X										
Descending colon, polyp adenomatous, multiple																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenocarcinoma, cystic, mucinous																									
Jejunum, mesothelioma malignant, metastatic, testes														X											
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenocarcinoma, cystic, mucinous						X			X					X											
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X				X			X				X	X	
Lymphoma malignant histiocytic				X																					
Mesothelioma malignant, metastatic, multiple, testes																						X			
Neoplastic nodule										X										X			X		
Mesentery	+								+				+	+			+			+		+			
Mesothelioma malignant, metastatic, multiple, testes														X								X			
Schwannoma malignant																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									
Mesothelioma malignant, metastatic, multiple, testes																						X			
Pharynx									+							+									
Palate, papilloma squamous									X																
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Glandular, mesothelioma malignant, metastatic, testes														X											
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Tongue												+					+			+					
Papilloma squamous																	X			X					
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin																		X							
Schwannoma benign				X																					
Schwannoma malignant						X																			
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, mesothelioma malignant, metastatic, testes														X								X			
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Pheochromocytoma malignant																								X	
Pheochromocytoma benign	X									X	X		X				X							X	
Bilateral, pheochromocytoma benign			X																						X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma												X													
C-cell, carcinoma																									
GENERAL BODY SYSTEM																									
Tissue, NOS																									
Mesothelioma malignant, metastatic, testes																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 170 ppm (Continued)

WEEKS ON STUDY	080	081	081	081	081	081	081	081	083	083	083	085	085	086	087	087	088	088	088	088	091	091	092	092	TOTAL:
CARCASS ID	562	493	522	551	552	553	483	531	602	482	532	611	471	491	592	572	541	511	521	561	601	571	481	501	591	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	73
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	72
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	73
Adenocarcinoma																			X							2
Descending colon, adenocarcinoma																										2
Descending colon, polyp adenomatous														X				X								3
Descending colon, polyp adenomatous, multiple				X																						1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	73
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	70
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	70
Adenocarcinoma						X																				1
Adenocarcinoma, cystic, mucinous																										1
Jejunum, mesothelioma malignant, metastatic, testes																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	69
Adenocarcinoma				X																						1
Adenocarcinoma, cystic, mucinous																										4
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	74
Leukemia mononuclear	X						X			X									X				X	X		14
Lymphoma malignant histiocytic																										1
Mesothelioma malignant, metastatic, multiple, testes																										1
Neoplastic nodule		X						X					X													7
Mesentery	+	+	+	+		+	+		+		+	+	+					+			+					28
Mesothelioma malignant, metastatic, multiple, testes																										3
Schwannoma malignant																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Mesothelioma malignant, metastatic, testes																										1
Mesothelioma malignant, metastatic, multiple, testes																										1
Pharynx								+							+							+				7
Palate, papilloma squamous								X														X				5
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	73
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	73
Leiomyosarcoma																										1
Glandular, mesothelioma malignant, metastatic, testes																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	72
Tongue														+							+					6
Papilloma squamous														X							X					5
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Fibrous histiocytoma, metastatic, skin																										1
Schwannoma benign																										1
Schwannoma malignant																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	74
Capsule, mesothelioma malignant, metastatic, testes																										2
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	74
Leukemia mononuclear	X																									2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	74
Leukemia mononuclear	X																									2
Pheochromocytoma malignant																			X				X			3
Pheochromocytoma benign			X					X				X		X			X		X				X			16
Bilateral, pheochromocytoma benign									X				X							X		X			X	7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	74
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	74
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	74
C-cell, adenoma				X				X		X											X					5
C-cell, carcinoma																								X		2
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
Mesothelioma malignant, metastatic, testes																										1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 170 ppm (Continued)

WEEKS ON STUDY	041	044	048	049	052	056	056	059	060	060	061	061	063	066	067	068	068	068	069	069	069	070	070	070
CARCASS ID	555	475	595	505	615	474	504	525	495	515	535	594	575	614	534	494	585	503	523	524	584	485	545	605	613
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, mesothelioma malignant, metastatic, testes				X												X			X						
Preputial gland	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X																			X			
Carcinoma	X															X				X				X	X
Bilateral, adenoma																									
Bilateral, carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Mesothelioma malignant, metastatic, testes																									
Mesothelioma malignant, metastatic, multiple, testes																									
Seminal vesicle	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																			X						
Mesothelioma malignant, metastatic, multiple, testes																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, mesothelioma malignant				X												X			X						
Bilateral, interstitial cell, adenoma			X			X		X	X			X		X		X	X				X		X		
Interstitial cell, adenoma								X			X				X	X		X	X	X		X		X	X
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, fibrous histiocytoma, metastatic, skin																									
Mediastinal, leukemia mononuclear																					X				
Lymph node, mandibular		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Lymph node, mesenteric	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																					X	X			X
Lymphoma malignant histiocytic																									
Mesothelioma malignant, metastatic, testes																			X						
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	M	M	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma												X					X						X		X
Basal cell adenoma, multiple																					X				
Basal cell carcinoma									X		X						X							X	
Basal cell carcinoma, multiple																									
Keratoacanthoma							X														X				
Papilloma squamous																									
Squamous cell carcinoma											X											X			
Squamous cell carcinoma, multiple																									
Sebaceous gland, adenoma																			X						
Sebaceous gland, carcinoma																	X								
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrous histiocytoma																									
Subcutaneous tissue, neurofibroma					X																				
MUSCULOSKELETAL SYSTEM																									
Bone																									
Skeletal muscle										+			+												
Abdominal, schwannoma malignant, metastatic, mesentery										X			X												
Thoracic, fibrous histiocytoma, *metastatic, skin*																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Cerebellum, cerebrum, astrocytoma malignant																									
Cerebrum, astrocytoma malignant																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 170 ppm (Continued)

WEEKS ON STUDY	070	070	073	073	074	075	076	076	077	077	077	077	077	078	078	078	078	079	080	080	080	080	080	080
CARCASS ID	564	565	604	583	593	473	544	472	612	582	514	563	513	502	533	543	574	542	512	484	554	581	603	573	492
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, mesothelioma malignant, metastatic, testes														X			X					X			
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma	X						X	X				X	X						X			X		X	
Carcinoma							X										X				X				
Bilateral, adenoma										X															
Bilateral, carcinoma																X									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Mesothelioma malignant, metastatic, testes														X											
Mesothelioma malignant, metastatic, multiple, testes																						X			
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes														X											
Mesothelioma malignant, metastatic, multiple, testes																						X			
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, mesothelioma malignant														X			X	X				X			
Bilateral, interstitial cell, adenoma	X		X		X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma		X		X				X								X									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, fibrous histiocytoma, metastatic, skin																		X							
Mediastinal, leukemia mononuclear																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X				X			X				X	X		
Lymphoma malignant histiocytic				X																					
Mesothelioma malignant, metastatic, testes														X											
Thymus	M	M	M	M	+	+	+	+	M	+	+	+	+	+	M	M	M	M	M	M	+	+	+	+	M
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	M	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Fibroadenoma		X																							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma					X		X				X				X							X			
Basal cell adenoma, multiple	X		X			X						X	X	X		X	X	X	X	X			X	X	X
Basal cell carcinoma			X	X			X							X											
Basal cell carcinoma, multiple					X			X		X															
Keratoacanthoma							X												X						
Papilloma squamous						X				X					X		X								
Squamous cell carcinoma	X				X						X	X						X						X	
Squamous cell carcinoma, multiple																				X	X				
Sebaceous gland, adenoma																									
Sebaceous gland, carcinoma											X														
Subcutaneous tissue, fibroma																				X	X				
Subcutaneous tissue, fibrous histiocytoma																		X							
Subcutaneous tissue, neurofibroma																									
MUSCULOSKELETAL SYSTEM																									
Bone										+															
Skeletal muscle																		+							
Abdominal, schwannoma malignant, metastatic, mesentery																									
Thoracic, fibrous histiocytoma, metastatic, skin																		X							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Cerebellum, cerebrum, astrocytoma malignant											X														
Cerebrum, astrocytoma malignant																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 170 ppm (Continued)

WEEKS ON STUDY	0 8 0	0 8 1	0 8 1	0 8 1	0 8 1	0 8 1	0 8 1	0 8 1	0 8 1	0 8 3	0 8 3	0 8 3	0 8 5	0 8 5	0 8 6	0 8 7	0 8 7	0 8 8	0 8 8	0 8 8	0 8 8	0 8 8	0 9 1	0 9 1	0 9 2	0 9 2	TOTAL:
CARCASS ID	5 6 2	4 9 3	5 2 2	5 5 1	5 5 2	5 5 3	4 8 3	5 3 1	6 0 2	4 8 2	5 3 2	6 1 1	4 7 1	4 9 1	5 9 2	5 7 2	5 4 1	5 1 1	5 2 1	5 6 1	6 0 1	5 7 1	4 8 1	5 0 1	5 9 1	TISSUES TUMORS
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Bilateral, mesothelioma malignant, metastatic, testes																										6
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	73
Adenoma				X						X		X		X		X		X						X		17
Carcinoma		X	X		X			X																		12
Bilateral, adenoma																				X						2
Bilateral, carcinoma						X															X					3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Adenoma																									X	1
Mesothelioma malignant, metastatic, testes																										1
Mesothelioma malignant, metastatic, multiple, testes																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	58
Mesothelioma malignant, metastatic, testes																										2
Mesothelioma malignant, metastatic, multiple, testes																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Bilateral, mesothelioma malignant																										7
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	51
Interstitial cell, adenoma									X			X														17
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	74
Leukemia mononuclear							X																			1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Mediastinal, fibrous histiocytoma, metastatic, skin																										1
Mediastinal, leukemia mononuclear																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	74
Leukemia mononuclear	X																									1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	73
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	74
Leukemia mononuclear	X			X		X	X			X					X				X				X	X		17
Lymphoma malignant histiocytic																										1
Mesothelioma malignant, metastatic, testes																										2
Thymus	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	55
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Fibroadenoma					X																					2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Basal cell adenoma						X				X	X															12
Basal cell adenoma, multiple	X	X		X			X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	35
Basal cell carcinoma		X	X			X			X				X		X											14
Basal cell carcinoma, multiple							X																			4
Keratoacanthoma				X	X																	X				7
Papilloma squamous																		X	X		X					7
Squamous cell carcinoma								X	X				X					X	X					X	X	15
Squamous cell carcinoma, multiple		X	X	X			X				X					X					X					9
Sebaceous gland, adenoma																										2
Sebaceous gland, carcinoma																										1
Subcutaneous tissue, fibroma								X												X						4
Subcutaneous tissue, fibrous histiocytoma																										1
Subcutaneous tissue, neurofibroma																									X	2
MUSCULOSKELETAL SYSTEM																										
Bone																										1
Skeletal muscle																										3
Abdominal, schwannoma malignant, metastatic, mesentery																										2
Thoracic, fibrous histiocytoma, metastatic, skin																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Astrocytoma malignant																								X		1
Cerebellum, cerebrum, astrocytoma malignant																										1
Cerebrum, astrocytoma malignant											X															1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 170 ppm (Continued)

WEEKS ON STUDY	041	044	048	049	052	056	058	059	060	060	061	061	063	066	067	068	068	068	069	069	069	070	070	070	070
CARCASS ID	555	475	595	505	615	474	504	525	495	515	535	594	575	614	534	494	585	503	523	524	584	485	545	605	613
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, preputial gland																									
Carcinoma, metastatic, Zymbal gland												X													
Fibrous histiocytoma, metastatic, skin																									
Leukemia mononuclear																						X			X
Lymphoma malignant histiocytic																									
Nose	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																									
Harderian gland																+									
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X							X		X			X						
Carcinoma		X		X				X				X			X						X				
Bilateral, carcinoma																		X							
URINARY SYSTEM																									
Kidney	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																					X	X			
Mesothelioma malignant, metastatic, testes																									
Mesothelioma malignant, multiple, testes																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 170 ppm (Continued)

WEEKS ON STUDY	070	070	073	073	074	075	076	076	077	077	077	077	077	078	078	078	078	079	080	080	080	080	080	080
CARCASS ID	564	565	604	583	593	473	544	472	612	582	514	563	513	502	533	543	574	542	512	484	554	581	603	573	492
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X						
Carcinoma, metastatic, preputial gland																X									
Carcinoma, metastatic, Zymbal gland																		X							
Fibrous histiocytoma, metastatic, skin																X									
Leukemia mononuclear																									
Lymphoma malignant histiocytic				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																							M		
Harderian gland																									
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X							X														X	
Carcinoma	X	X										X			X										
Bilateral, carcinoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Mesothelioma malignant, metastatic, testes														X											
Mesothelioma malignant, metastatic, multiple, testes																						X			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes														X								X			

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 170 ppm (Continued)

WEEKS ON STUDY	080	081	081	081	081	081	081	081	083	083	083	085	085	086	087	087	088	088	088	088	091	091	092	092	
CARCASS ID	562	493	522	551	552	553	483	531	602	482	532	611	471	491	592	572	541	511	521	561	601	571	481	501	591	TOTAL: TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Alveolar/bronchiolar adenoma		X																								2
Carcinoma, metastatic, preputial gland																										1
Carcinoma, metastatic, Zymbal gland																										1
Fibrous histiocytoma, metastatic, skin																										1
Leukemia mononuclear	X									X									X				X	X		8
Lymphoma malignant histiocytic																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	74
Adenoma												X														1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
SPECIAL SENSES SYSTEM																										
Eye									+											+				+		3
Harderian gland																										1
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Adenoma													X									X	X		X	11
Carcinoma														X						X				X		13
Bilateral, carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	74
Leukemia mononuclear																										2
Mesothelioma malignant, metastatic, testes																										1
Mesothelioma malignant, metastatic, multiple, testes																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Mesothelioma malignant, metastatic, testes																										2

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3′-DIMETHOXYBENZIDINE DIHYDROCHLORIDE: 330 ppm

WEEKS ON STUDY	039	041	044	048	049	049	050	058	058	058	060	060	061	061	061	061	061	063	064	068	069	069	069	069	069
CARCASS ID	785	845	905	875	904	825	805	794	903	855	874	835	793	815	885	895	902	804	865	884	894	803	814	854	893
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Adenocarcinoma, cystic, mucinous																	X								
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Descending colon, adenocarcinoma										X															
Descending colon, polyp adenomatous																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Adenocarcinoma																									
Polyp adenomatous				X																					
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	A	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+
Adenocarcinoma																				X					
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	M	+	+	+
Adenocarcinoma	X																								
Adenocarcinoma, cystic, mucinous																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Leukemia mononuclear																									
Mesothelioma malignant, metastatic, testes								X																	
Neoplastic nodule																									
Neoplastic nodule, multiple																									
Mesentery					+			+																+	
Mesothelioma malignant, metastatic, testes								X																	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes								X																	
Acinus, adenoma																									
Pharynx					+															+					
Carcinoma, metastatic, Zymbal gland																									
Mucosa, carcinoma, metastatic, skin					X																				
Palate, carcinoma, metastatic, Zymbal gland																									
Palate, papilloma squamous																				X					
Palate, squamous cell carcinoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+		+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue									+	+														+	
Papilloma squamous										X														X	
Squamous cell carcinoma									X																
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, eye																			X						
Pars distalis, adenoma													X												X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Bilateral, mesothelioma malignant, metastatic, testes								X													X				
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Adenoma															X		X	X							
Carcinoma	X			X		X	X		X		X										X		X	X	
Bilateral, adenoma																									
Bilateral, carcinoma														X											
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes								X																	
Seminal vesicle	M	M	M	M	+	M	+	M	M	+	M	M	M	+	M	M	M	M	M	M	+	+	+	+	+
Adenoma																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Mesothelioma benign																									
Mesothelioma malignant								X																	
Bilateral, mesothelioma benign																									
Bilateral, mesothelioma malignant																					X				
Bilateral, interstitial cell, adenoma																	X						X		
Interstitial cell, adenoma							X	X	X						X	X			X	X	X				

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 330 ppm (Continued)

WEEKS ON STUDY	070	070	070	070	070	073	073	074	075	075	076	077	077	077	078	078	078	078	078	079	079	079	079	080	080
CARCASS ID	802	883	792	813	791	892	844	873	891	853	864	863	882	801	901	824	843	823	862	812	833	834	852	822	831
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, cystic, mucinous																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Descending colon, adenocarcinoma														X											
Descending colon, polyp adenomatous				X																X			X		
Intestine large, rectum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma														X											
Polyp adenomatous																									
Intestine small	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenocarcinoma, cystic, mucinous									X							X									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																						X			
Leukemia mononuclear							X				X														
Mesothelioma malignant, metastatic, testes																									
Neoplastic nodule		X													X										X
Neoplastic nodule, multiple																					X		X		
Mesentery	+			+								+				+							+		
Mesothelioma malignant, metastatic, testes																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									
Acinus, adenoma																									
Pharynx								+		+															
Carcinoma, metastatic, Zymbal gland																									
Mucosa, carcinoma, metastatic, skin																									
Palate, carcinoma, metastatic, Zymbal gland								X																	
Palate, papilloma squamous																									
Palate, squamous cell carcinoma										X															
Salivary gands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue			+																		+	+			
Papilloma squamous			X																			X			
Squamous cell carcinoma																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign											X	X								X		X			
Bilateral pheochromocytoma benign														X										X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Schwannoma malignant, metastatic, eye																									
Pars distalis, adenoma		X																							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma																									
C cell, carcinoma																									
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, mesothelioma malignant, metastatic, testes																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma	X								X								X				X				
Carcinoma				X	X			X									X		X		X	X		X	
Bilateral, adenoma																									
Bilateral, carcinoma																X									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma benign			X																						
Mesothelioma malignant																									
Bilateral, mesothelioma benign																									
Bilateral, mesothelioma malignant				X																					
Bilateral, interstitial cell, adenoma	X			X			X	X	X	X			X	X		X		X	X	X	X			X	X
Interstitial cell, adenoma		X	X		X						X				X		X					X			

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 330 ppm (Continued)

WEEKS ON STUDY	0 8 0	0 8 0	0 8 0	0 8 0	0 8 1	0 8 4	0 8 5	0 8 5	0 8 5	0 8 6	TOTAL: TISSUES TUMORS
CARCASS ID	8 3 2	8 4 2	8 5 1	8 6 1	8 8 1	8 7 2	8 7 1	8 4 1	8 1 1	8 2 1	
ALIMENTARY SYSTEM											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Intestine large	+	+	+	+	+	+	+	+	+	+	58
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	58
Adenocarcinoma, cystic, mucinous											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	58
Descending colon, adenocarcinoma											2
Descending colon, polyp adenomatous						X					4
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	58
Adenocarcinoma											1
Polyp adenomatous											1
Intestine small	+	+	+	+	+	+	+	+	+	+	58
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	55
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	57
Adenocarcinoma											1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	56
Adenocarcinoma											1
Adenocarcinoma, cystic, mucinous	X										3
Liver	+	+	+	+	+	+	+	+	+	+	60
Hepatocellular carcinoma	X										2
Leukemia mononuclear											2
Mesothelioma malignant, metastatic, testes											1
Neoplastic nodule					X						4
Neoplastic nodule, multiple											2
Mesentery			+		+		+				11
Mesothelioma malignant, metastatic, testes							X				2
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Mesothelioma malignant, metastatic, testes											1
Acinus, adenoma										X	1
Pharynx				+		+		+			7
Carcinoma, metastatic, Zymbal gland						X					1
Mucosa, carcinoma, metastatic, skin											1
Palate, carcinoma, metastatic, Zymbal gland											1
Palate, papilloma squamous				X				X			3
Palate, squamous cell carcinoma											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach	+	+	+	+	+	+	+	+	+	+	59
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	57
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	58
Tongue					+	+		+		+	10
Papilloma squamous					X			X		X	7
Squamous cell carcinoma											1
CARDIOVASCULAR SYSTEM											
Heart	+	+	+	+	+	+	+	+	+	+	60
ENDOCRINE SYSTEM											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	60
Pheochromocytoma benign	X										5
Bilateral, pheochromocytoma benign					X				X		4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	60
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	60
Pituitary gland	+	+	+	+	+	+	+	+	+	+	59
Schwannoma malignant, metastatic, eye											1
Pars distalis, adenoma											3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
C-cell, adenoma								X			1
C-cell, carcinoma				X							1
Follicular cell, adenoma						X					1
GENERAL BODY SYSTEM											
None											
GENITAL SYSTEM											
Epididymis	+	+	+	+	+	+	+	+	+	+	59
Bilateral, mesothelioma malignant, metastatic, testes							X				3
Preputial gland	+	+	+	+	+	+	+	+	+	+	59
Adenoma	X					X	X		X		11
Carcinoma											17
Bilateral, adenoma		X									1
Bilateral, carcinoma											2
Prostate	+	+	+	+	+	+	+	+	+	+	60
Mesothelioma malignant, metastatic, testes											1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	44
Adenoma						X					1
Testes	+	+	+	+	+	+	+	+	+	+	59
Mesothelioma benign											1
Mesothelioma malignant											1
Bilateral, mesothelioma benign					X						1
Bilateral, mesothelioma malignant							X				3
Bilateral, interstitial cell, adenoma	X		X	X			X	X	X	X	24
Interstitial cell, adenoma		X			X	X					18

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 330 ppm (Continued)

WEEKS ON STUDY	039	041	044	048	049	049	050	058	058	058	060	060	061	061	061	061	063	064	068	069	069	069	069	069
CARCASS ID	7855	8455	9055	8755	9044	8255	8055	7944	9033	8558	8744	8355	7933	8155	8855	8952	9024	8044	8654	8844	8944	8033	8144	8544	8993
HEMATOPOIETIC SYSTEM																									
Blood																		+							
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, mediastinal, basal cell carcinoma, metastatic, skin																									
Deep cervical, carcinoma, metastatic, thyroid gland																									
Inguinal, carcinoma, metastatic														X											
Inguinal, iliac, carcinoma, metastatic, preputial gland																								X	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma, metastatic, skin																									
Hemangiosarcoma																									
Leukemia mononuclear																									
Mesothelioma malignant, metastatic, testes								X																	
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	M	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma												X										X	X		
Basal cell adenoma, multiple																		X							X
Basal cell carcinoma							X								X						X				
Basal cell carcinoma, multiple																									X
Keratoacanthoma																									
Papilloma squamous																			X						
Papilloma squamous, multiple																									
Squamous cell carcinoma																			X			X			
Squamous cell carcinoma, multiple																									
Sebaceous gland, adenoma																									
Sebaceous gland, carcinoma					X																				
Subcutaneous tissue, carcinoma, metastatic														X											
Subcutaneous tissue, fibroma																									X
Subcutaneous tissue, fibroma, multiple																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, neurofibroma																X									
MUSCULOSKELETAL SYSTEM																									
Bone																+		+							
Cranium, carcinoma, metastatic, Zymbal gland																X		X							
Cranium, squamous cell carcinoma, metastatic																									
Skeletal muscle																		+							
Cervical, carcinoma, metastatic, Zymbal gland																		X							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cerebrum, astrocytoma malignant																									
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Basal cell carcinoma, metastatic, multiple, skin																									
Carcinoma, metastatic, Zymbal gland			X																						
Carcinoma, metastatic, multiple, Zymbal gland																		X							
Carcinoma, metastatic, multiple, preputial gland														X											
Carcinoma, metastatic, multiple, Zymbal gland										X															
Fibrosarcoma, metastatic, multiple, skin																									
Squamous cell carcinoma, metastatic, skin																									
Squamous cell carcinoma, metastatic, multiple, skin																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Submucosa, schwannoma malignant, metastatic, eye																			X						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear																									
Eye													+						+						
Optic nerve, schwannoma malignant																			X						
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Carcinoma		X	X							X	X	X	X	X				X			X		X		
Bilateral, carcinoma																X									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes								X																	
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Mesothelioma malignant, metastatic, testes								X																	

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 330 ppm (Continued)

WEEKS ON STUDY	070	070	070	070	070	073	073	074	075	075	076	077	077	077	078	078	078	078	078	079	079	079	079	080	080
CARCASS ID	802	883	792	813	791	892	844	873	891	853	864	863	822	801	901	824	843	823	862	812	833	834	852	822	831
HEMATOPOIETIC SYSTEM																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+
Axillary, mediastinal, basal cell carcinoma, metastatic, skin																		X							
Deep cervical, carcinoma, metastatic, thyroid gland																									
Inguinal, carcinoma, metastatic																									
Inguinal, iliac, carcinoma, metastatic, preputial gland																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma, metastatic, skin																		X							
Hemangiosarcoma															X										
Leukemia mononuclear			X				X				X								X						
Mesothelioma malignant, metastatic, testes																									
Thymus	M	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma			X		X			X	X																
Basal cell adenoma, multiple	X	X				X					X	X	X	X	X		X		X	X	X	X	X	X	X
Basal cell carcinoma		X	X					X				X							X					X	
Basal cell carcinoma, multiple				X														X		X					
Keratoacanthoma																		X							
Papilloma squamous													X												X
Papilloma squamous, multiple																						X			
Squamous cell carcinoma		X				X	X			X							X					X	X		X
Squamous cell carcinoma, multiple			X											X						X					
Sebaceous gland, adenoma						X																			
Sebaceous gland, carcinoma																									
Subcutaneous tissue, carcinoma, metastatic																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibroma, multiple																									
Subcutaneous tissue, fibrosarcoma	X																						X		
Subcutaneous tissue, neurofibroma																									
MUSCULOSKELETAL SYSTEM																									
Bone								+		+															+
Cranium, carcinoma, metastatic, Zymbal gland								X																	X
Cranium, squamous cell carcinoma, metastatic										X															
Skeletal muscle																									
Cervical, carcinoma, metastatic, Zymbal gland																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cerebrum, astrocytoma malignant						X																			
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X															
Basal cell carcinoma, metastatic, multiple, skin																		X							
Carcinoma, metastatic, Zymbal gland																									
Carcinoma, metastatic, multiple, Zymbal gland																									
Carcinoma, metastatic, multiple, preputial gland																									
Carcinoma, metastatic, multiple, Zymbal gland																									
Fibrosarcoma, metastatic, multiple, skin	X																								
Squamous cell carcinoma, metastatic, skin																				X					X
Squamous cell carcinoma, metastatic, multiple, skin										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Submucosa, schwannoma malignant, metastatic, eye																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear		+																							
Eye																									
Optic nerve, schwannoma malignant																									
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X						X		X						X					
Carcinoma		X						X							X				X		X	X			X
Bilateral, carcinoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, testes																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 330 ppm (Continued)

WEEKS ON STUDY	0 8 0	0 8 0	0 8 0	0 8 0	0 8 1	0 8 4	0 8 5	0 8 5	0 8 5	0 8 6	TOTAL TISSUES TUMORS
CARCASS ID	8 3 2	8 4 2	8 5 1	8 6 1	8 8 1	8 7 2	8 7 1	8 4 1	8 1 1	8 2 1	
HEMATOPOIETIC SYSTEM											
Blood											1
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node	+	+		+	+	+	+	+	+	+	58
Axillary, mediastinal, basal cell carcinoma, metastatic, skin											1
Deep cervical, carcinoma, metastatic, thyroid gland				X							1
Inguinal, carcinoma, metastatic											1
Inguinal, iliac, carcinoma, metastatic, preputial gland											1
Lymph node, mandibular	+	+		+	+	+	+	+	+	+	58
Lymph node, mesenteric	+	+		+	+	+	+	+	+	+	56
Spleen	+	+	+	+	+	+	+	+	+	+	59
Basal cell carcinoma, metastatic, skin											1
Hemangiosarcoma											1
Leukemia mononuclear											4
Mesothelioma malignant, metastatic, testes											1
Thymus	+	+	+	M	M	+	M	+	+	+	48
INTEGUMENTARY SYSTEM											
Mammary gland	+	+	+	+	+	+	+	+	+	+	56
Skin	+	+	+	+	+	+	+	+	+	+	60
Basal cell adenoma	X	X					X				10
Basal cell adenoma, multiple			X	X	X	X		X	X	X	25
Basal cell carcinoma			X		X	X	X				13
Basal cell carcinoma, multiple											4
Keratoacanthoma											1
Papilloma squamous											3
Papilloma squamous, multiple					X						2
Squamous cell carcinoma	X	X			X		X		X		15
Squamous cell carcinoma, multiple						X		X		X	6
Sebaceous gland, adenoma											1
Sebaceous gland, carcinoma											1
Subcutaneous tissue, carcinoma, metastatic											1
Subcutaneous tissue, fibroma											1
Subcutaneous tissue, fibroma, multiple										X	1
Subcutaneous tissue, fibrosarcoma											1
Subcutaneous tissue, neurofibroma											2
MUSCULOSKELETAL SYSTEM											
Bone						+					6
Cranium, carcinoma, metastatic, Zymbal gland						X					5
Cranium, squamous cell carcinoma, metastatic											1
Skeletal muscle											1
Cervical, carcinoma, metastatic, Zymbal gland											1
NERVOUS SYSTEM											
Brain	+	+	+	+	+	+	+	+	+	+	60
Cerebrum, astrocytoma malignant											1
RESPIRATORY SYSTEM											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma											1
Basal cell carcinoma, metastatic, multiple, skin											1
Carcinoma, metastatic, Zymbal gland											1
Carcinoma, metastatic, multiple, Zymbal gland											1
Carcinoma, metastatic, multiple, preputial gland											1
Carcinoma, metastatic, multiple, Zymbal gland											1
Fibrosarcoma, metastatic, multiple, skin											1
Squamous cell carcinoma, metastatic, skin											2
Squamous cell carcinoma, metastatic, multiple, skin											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Submucosa, schwannoma malignant, metastatic, eye											1
Trachea	+	+	+	+	+	+	+	+	+	+	60
SPECIAL SENSES SYSTEM											
Ear					+						2
Eye											2
Optic nerve, schwannoma malignant											1
Zymbal gland	+	+	+	+	+	+	+	+	+	+	60
Adenoma	X			X	X			X			9
Carcinoma		X				X				X	20
Bilateral, carcinoma											1
URINARY SYSTEM											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Mesothelioma malignant, metastatic, testes											1
Urethra			+								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	59
Mesothelioma malignant, metastatic, testes							X				2

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

	Control	80 ppm	170 ppm	330 ppm
Adrenal Medulla: Pheochromocytoma				
Overall Rates (a)	14/60 (23%)	17/44 (39%)	23/74 (31%)	9/60 (15%)
Effective Rates (b)	14/59 (24%)	17/41 (41%)	23/67 (34%)	9/50 (18%)
Terminal Rates (c)	10/44 (23%)	3/8 (38%)	0/0	0/0
Day of First Observation	573	480	417	527
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P=0.100	P=0.018	P=0.007	P=0.091
Cochran-Armitage Trend Test (d)	P=0.183N			
Fisher Exact Test (d)		P=0.048	P=0.134	P=0.312N
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma				
Overall Rates (a)	15/60 (25%)	18/44 (41%)	23/74 (31%)	9/60 (15%)
Effective Rates (b)	15/59 (25%)	18/41 (44%)	23/67 (34%)	9/50 (18%)
Terminal Rates (c)	10/44 (23%)	3/8 (38%)	0/0	0/0
Day of First Observation	573	480	417	527
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P=0.163	P=0.021	P=0.013	P=0.144
Cochran-Armitage Trend Test (d)	P=0.125N			
Fisher Exact Test (d)		P=0.043	P=0.186	P=0.243N
Brain: Malignant Astrocytoma				
Overall Rates (a)	0/60 (0%)	2/44 (5%)	3/75 (4%)	1/60 (2%)
Effective Rates (b)	0/58 (0%)	2/37 (5%)	3/48 (6%)	1/30 (3%)
Terminal Rates (c)	0/44 (0%)	1/7 (14%)	0/0	0/0
Day of First Observation		618	536	506
Life Table Tests (d)	P=0.002	P=0.021	P=0.004	P=0.372
Logistic Regression Tests (d)	P=0.143	P=0.073	P=0.057	P=0.594
Cochran-Armitage Trend Test (d)	P=0.247			
Fisher Exact Test (d)		P=0.149	P=0.090	P=0.341
Preputial Gland: Adenoma				
Overall Rates (a)	14/60 (23%)	6/43 (14%)	19/73 (26%)	12/59 (20%)
Effective Rates (b)	14/59 (24%)	6/42 (14%)	19/71 (27%)	12/56 (21%)
Terminal Rates (c)	10/44 (23%)	1/8 (13%)	0/0	0/0
Day of First Observation	531	485	333	423
Life Table Tests (d)	P<0.001	P=0.202	P<0.001	P<0.001
Logistic Regression Tests (d)	P=0.076	P=0.307N	P=0.107	P=0.196
Cochran-Armitage Trend Test (d)	P=0.497			
Fisher Exact Test (d)		P=0.179N	P=0.425	P=0.472N
Preputial Gland: Carcinoma				
Overall Rates (a)	2/60 (3%)	6/43 (14%)	15/73 (21%)	19/59 (32%)
Effective Rates (b)	2/59 (3%)	6/42 (14%)	15/73 (21%)	19/59 (32%)
Terminal Rates (c)	0/44 (0%)	1/8 (13%)	0/0	0/0
Day of First Observation	603	603	284	267
Life Table Tests (d)	P<0.001	P=0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.020	P=0.011	P=0.003
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.053	P=0.003	P<0.001
Preputial Gland: Adenoma or Carcinoma				
Overall Rates (a)	16/60 (27%)	12/43 (28%)	33/73 (45%)	29/59 (49%)
Effective Rates (b)	16/59 (27%)	12/42 (29%)	33/73 (45%)	29/59 (49%)
Terminal Rates (c)	10/44 (23%)	2/8 (25%)	0/0	0/0
Day of First Observation	531	485	284	267
Life Table Tests (d)	P<0.001	P=0.003	P<0.001	P<0.001
Logistic Regression Tests (d)	P=0.001	P=0.298	P=0.007	P=0.036
Cochran-Armitage Trend Test (d)	P=0.003			
Fisher Exact Test (d)		P=0.523	P=0.025	P=0.011

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Control	80 ppm	170 ppm	330 ppm
Large Intestine: Adenomatous Polyp				
Overall Rates (e)	0/60 (0%)	1/45 (2%)	4/75 (5%)	5/60 (8%)
Effective Rates (b)	0/59 (0%)	1/44 (2%)	4/73 (5%)	5/57 (9%)
Terminal Rates (c)	0/44 (0%)	0/8 (0%)	0/0	0/0
Day of First Observation		644	546	332
Life Table Tests (d)	P<0.001	P=0.193	P=0.002	P<0.001
Logistic Regression Tests (d)	P=0.005	P=0.238	P=0.030	P=0.069
Cochran-Armitage Trend Test (d)	P=0.013			
Fisher Exact Test (d)		P=0.427	P=0.090	P=0.026
Large Intestine: Adenocarcinoma				
Overall Rates (e)	0/60 (0%)	0/45 (0%)	4/75 (5%)	3/60 (5%)
Effective Rates (b)	0/59 (0%)	0/42 (0%)	4/67 (6%)	3/50 (6%)
Terminal Rates (c)	0/44 (0%)	0/8 (0%)	0/0	0/0
Day of First Observation			485	414
Life Table Tests (d)	P=0.002	(f)	P=0.009	P=0.056
Logistic Regression Tests (d)	P=0.083	(f)	P=0.095	P=0.249
Cochran-Armitage Trend Test (d)	P=0.031			
Fisher Exact Test (d)		(f)	P=0.077	P=0.093
Large Intestine: Adenomatous Polyp or Adenocarcinoma				
Overall Rates (e)	0/60 (0%)	1/45 (2%)	8/75 (11%)	8/60 (13%)
Effective Rates (b)	0/59 (0%)	1/44 (2%)	8/73 (11%)	8/57 (14%)
Terminal Rates (c)	0/44 (0%)	0/8 (0%)	0/0	0/0
Day of First Observation		644	485	332
Life Table Tests (d)	P<0.001	P=0.193	P<0.001	P<0.001
Logistic Regression Tests (d)	P=0.001	P=0.238	P=0.004	P=0.023
Cochran-Armitage Trend Test (d)	P=0.001			
Fisher Exact Test (d)		P=0.427	P=0.007	P=0.003
Small Intestine: Adenocarcinoma				
Overall Rates (e)	0/60 (0%)	4/45 (9%)	7/75 (9%)	5/60 (8%)
Effective Rates (b)	0/59 (0%)	4/44 (9%)	7/75 (9%)	5/60 (8%)
Terminal Rates (c)	0/44 (0%)	0/8 (0%)	0/0	0/0
Day of First Observation		354	417	267
Life Table Tests (d)	P<0.001	P=0.001	P=0.003	P=0.003
Logistic Regression Tests (d)	P=0.169	P=0.043	P=0.043	P=0.100
Cochran-Armitage Trend Test (d)	P=0.081			
Fisher Exact Test (d)		P=0.031	P=0.015	P=0.030
Liver: Neoplastic Nodule				
Overall Rates (a)	0/60 (0%)	3/45 (7%)	7/74 (9%)	6/60 (10%)
Effective Rates (b)	0/58 (0%)	3/39 (8%)	7/54 (13%)	6/35 (17%)
Terminal Rates (c)	0/44 (0%)	1/8 (13%)	0/0	0/0
Day of First Observation		538	485	485
Life Table Tests (d)	P<0.001	P=0.019	P<0.001	P<0.001
Logistic Regression Tests (d)	P=0.005	P=0.078	P=0.019	P=0.007
Cochran-Armitage Trend Test (d)	P=0.002			
Fisher Exact Test (d)		P=0.062	P=0.005	P=0.002
Liver: Neoplastic Nodule or Hepatocellular Carcinoma				
Overall Rates (a)	1/60 (2%)	4/45 (9%)	7/74 (9%)	8/60 (13%)
Effective Rates (b)	1/58 (2%)	4/39 (10%)	7/54 (13%)	8/35 (23%)
Terminal Rates (c)	1/44 (2%)	2/8 (25%)	0/0	0/0
Day of First Observation	647	538	485	485
Life Table Tests (d)	P<0.001	P=0.006	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.072	P=0.044	P=0.002
Cochran-Armitage Trend Test (d)	P=0.001			
Fisher Exact Test (d)		P=0.083	P=0.024	P=0.001

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Control	80 ppm	170 ppm	330 ppm
Palate: Squamous Papilloma				
Overall Rates (e)	0/60 (0%)	4/45 (9%)	5/75 (7%)	3/60 (5%)
Effective Rates (b)	0/59 (0%)	4/42 (10%)	5/68 (7%)	3/50 (6%)
Terminal Rates (c)	0/44 (0%)	1/8 (13%)	0/0	0/0
Day of First Observation		556	408	476
Life Table Tests (d)	P<0.001	P=0.002	P=0.004	P=0.003
Logistic Regression Tests (d)	P=0.157	P=0.023	P=0.098	P=0.092
Cochran-Armitage Trend Test (d)	P=0.188			
Fisher Exact Test (d)		P=0.027	P=0.041	P=0.093
Palate: Squamous Papilloma or Squamous Cell Carcinoma				
Overall Rates (e)	0/60 (0%)	4/45 (9%)	5/75 (7%)	4/60 (7%)
Effective Rates (b)	0/59 (0%)	4/42 (10%)	5/68 (7%)	4/50 (8%)
Terminal Rates (c)	0/44 (0%)	1/8 (13%)	0/0	0/0
Day of First Observation		556	408	476
Life Table Tests (d)	P<0.001	P=0.002	P=0.004	P<0.001
Logistic Regression Tests (d)	P=0.078	P=0.023	P=0.098	P=0.048
Cochran-Armitage Trend Test (d)	P=0.098			
Fisher Exact Test (d)		P=0.027	P=0.041	P=0.041
Tongue: Squamous Papilloma				
Overall Rates (e)	1/60 (2%)	3/45 (7%)	5/75 (7%)	7/60 (12%)
Effective Rates (b)	1/59 (2%)	3/44 (7%)	5/73 (7%)	7/57 (12%)
Terminal Rates (c)	1/44 (2%)	1/8 (13%)	0/0	0/0
Day of First Observation	647	485	333	402
Life Table Tests (d)	P<0.001	P=0.033	P=0.002	P<0.001
Logistic Regression Tests (d)	P=0.014	P=0.212	P=0.185	P=0.023
Cochran-Armitage Trend Test (d)	P=0.023			
Fisher Exact Test (d)		P=0.207	P=0.161	P=0.027
Tongue: Squamous Papilloma or Squamous Cell Carcinoma				
Overall Rates (e)	1/60 (2%)	4/45 (9%)	5/75 (7%)	8/60 (13%)
Effective Rates (b)	1/59 (2%)	4/44 (9%)	5/73 (7%)	8/57 (14%)
Terminal Rates (c)	1/44 (2%)	1/8 (13%)	0/0	0/0
Day of First Observation	647	485	333	401
Life Table Tests (d)	P<0.001	P=0.010	P=0.002	P<0.001
Logistic Regression Tests (d)	P=0.015	P=0.103	P=0.185	P=0.027
Cochran-Armitage Trend Test (d)	P=0.017			
Fisher Exact Test (d)		P=0.104	P=0.161	P=0.014
Oral Cavity: Squamous Papilloma				
Overall Rates (e)	1/60 (2%)	7/45 (16%)	10/75 (13%)	9/60 (15%)
Effective Rates (b)	1/59 (2%)	7/44 (16%)	10/73 (14%)	9/57 (16%)
Terminal Rates (c)	1/44 (2%)	2/8 (25%)	0/0	0/0
Day of First Observation	647	485	333	402
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P=0.015	P=0.009	P=0.028	P=0.007
Cochran-Armitage Trend Test (d)	P=0.029			
Fisher Exact Test (d)		P=0.010	P=0.012	P=0.007
Oral Cavity: Squamous Papilloma or Squamous Cell Carcinoma				
Overall Rates (e)	1/60 (2%)	8/45 (18%)	10/75 (13%)	11/60 (18%)
Effective Rates (b)	1/59 (2%)	8/44 (18%)	10/73 (14%)	11/57 (19%)
Terminal Rates (c)	1/44 (2%)	2/8 (25%)	0/0	0/0
Day of First Observation	647	485	333	401
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P=0.007	P=0.004	P=0.028	P=0.004
Cochran-Armitage Trend Test (d)	P=0.011			
Fisher Exact Test (d)		P=0.004	P=0.012	P=0.002

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Control	80 ppm	170 ppm	330 ppm
Pituitary Gland/Pars Distalis: Adenoma				
Overall Rates (a)	2/58 (3%)	1/43 (2%)	0/74 (0%)	3/59 (5%)
Effective Rates (b)	2/58 (3%)	1/40 (3%)	0/64 (0%)	3/47 (6%)
Terminal Rates (c)	1/44 (2%)	1/8 (13%)	0/0	0/0
Day of First Observation	581	647		423
Life Table Tests (d)	P=0.013	P=0.594	P=0.767N	P=0.091
Logistic Regression Tests (d)	P=0.389	P=0.691N	P=0.344N	P=0.673
Cochran-Armitage Trend Test (d)	P=0.315			
Fisher Exact Test (d)		P=0.638N	P=0.224N	P=0.401
Skin: Basal Cell Adenoma				
Overall Rates (e)	1/60 (2%)	31/45 (69%)	47/75 (63%)	35/60 (58%)
Effective Rates (b)	1/59 (2%)	31/42 (74%)	47/67 (70%)	35/50 (70%)
Terminal Rates (c)	1/44 (2%)	7/8 (88%)	0/0	0/0
Day of First Observation	647	480	424	419
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P<0.001	P<0.001	P<0.001
Skin: Basal Cell Adenoma or Sebaceous Gland Adenoma				
Overall Rates (e)	1/60 (2%)	32/45 (71%)	49/75 (65%)	35/60 (58%)
Effective Rates (b)	1/59 (2%)	32/44 (73%)	49/71 (69%)	35/53 (66%)
Terminal Rates (c)	1/44 (2%)	7/8 (88%)	0/0	0/0
Day of First Observation	647	353	424	419
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P<0.001	P<0.001	P<0.001
Skin: Basal Cell Carcinoma				
Overall Rates (e)	1/60 (2%)	4/45 (9%)	18/75 (24%)	17/60 (28%)
Effective Rates (b)	1/59 (2%)	4/44 (9%)	18/71 (25%)	17/54 (31%)
Terminal Rates (c)	1/44 (2%)	0/8 (0%)	0/0	0/0
Day of First Observation	647	552	417	344
Life Table Tests (d)	P<0.001	P=0.016	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.092	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.104	P<0.001	P<0.001
Skin: Basal Cell Carcinoma or Sebaceous Gland Carcinoma				
Overall Rates (e)	1/60 (2%)	4/45 (9%)	18/75 (24%)	18/60 (30%)
Effective Rates (b)	1/59 (2%)	4/44 (9%)	18/72 (25%)	18/56 (32%)
Terminal Rates (c)	1/44 (2%)	0/8 (0%)	0/0	0/0
Day of First Observation	647	552	417	337
Life Table Tests (d)	P<0.001	P=0.016	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.092	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.104	P<0.001	P<0.001
Skin: Basal Cell Adenoma or Carcinoma				
Overall Rates (e)	2/60 (3%)	32/45 (71%)	54/75 (72%)	40/60 (67%)
Effective Rates (b)	2/59 (3%)	32/44 (73%)	54/71 (76%)	40/54 (74%)
Terminal Rates (c)	2/44 (5%)	7/8 (88%)	0/0	0/0
Day of First Observation	647	480	417	344
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P<0.001	P<0.001	P<0.001

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Control	80 ppm	170 ppm	330 ppm
Skin: Sebaceous Gland Adenoma or Carcinoma				
Overall Rates (e)	0/60 (0%)	2/45 (4%)	3/75 (4%)	2/60 (3%)
Effective Rates (b)	0/59 (0%)	2/44 (5%)	3/72 (4%)	2/56 (4%)
Terminal Rates (c)	0/44 (0%)	1/8 (13%)	0/0	0/0
Day of First Observation		353	472	337
Life Table Tests (d)	P=0.063	P=0.067	P=0.106	P=0.166
Logistic Regression Tests (d)	P=0.509	P=0.210	P=0.253	P=0.397
Cochran-Armitage Trend Test (d)	P=0.250			
Fisher Exact Test (d)		P=0.180	P=0.163	P=0.235
Skin: Basal Cell Adenoma, Basal Cell Carcinoma, Sebaceous Gland Adenoma, or Sebaceous Gland Carcinoma				
Overall Rates (e)	2/60 (3%)	33/45 (73%)	56/75 (75%)	41/60 (68%)
Effective Rates (b)	2/59 (3%)	33/44 (75%)	56/72 (78%)	41/56 (73%)
Terminal Rates (c)	2/44 (5%)	7/8 (88%)	0/0	0/0
Day of First Observation	647	353	417	337
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P<0.001	P<0.001	P<0.001
Skin: Keratoacanthoma				
Overall Rates (e)	1/60 (2%)	5/45 (11%)	7/75 (9%)	1/60 (2%)
Effective Rates (b)	1/59 (2%)	5/42 (12%)	7/70 (10%)	1/53 (2%)
Terminal Rates (c)	0/44 (0%)	0/8 (0%)	0/0	0/0
Day of First Observation	573	556	391	546
Life Table Tests (d)	P=0.006	P=0.003	P=0.002	P=0.370
Logistic Regression Tests (d)	P=0.572N	P=0.041	P=0.103	P=0.814
Cochran-Armitage Trend Test (d)	P=0.457N			
Fisher Exact Test (d)		P=0.044	P=0.053	P=0.725N
Skin: Squamous Papilloma				
Overall Rates (e)	0/60 (0%)	5/45 (11%)	7/75 (9%)	5/60 (8%)
Effective Rates (b)	0/58 (0%)	5/42 (12%)	7/62 (11%)	5/41 (12%)
Terminal Rates (c)	0/44 (0%)	2/8 (25%)	0/0	0/0
Day of First Observation		515	525	445
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P=0.016	P=0.015	P=0.004	P=0.031
Cochran-Armitage Trend Test (d)	P=0.032			
Fisher Exact Test (d)		P=0.011	P=0.008	P=0.010
Skin: Squamous Cell Carcinoma				
Overall Rates (e)	0/60 (0%)	9/45 (20%)	24/75 (32%)	21/60 (35%)
Effective Rates (b)	0/59 (0%)	9/42 (21%)	24/65 (37%)	21/48 (44%)
Terminal Rates (c)	0/44 (0%)	2/8 (25%)	0/0	0/0
Day of First Observation		485	424	445
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P<0.001	P<0.001	P<0.001
Skin: Squamous Papilloma or Squamous Cell Carcinoma				
Overall Rates (e)	0/60 (0%)	13/45 (29%)	28/75 (37%)	22/60 (37%)
Effective Rates (b)	0/59 (0%)	13/42 (31%)	28/65 (43%)	22/48 (46%)
Terminal Rates (c)	0/44 (0%)	3/8 (38%)	0/0	0/0
Day of First Observation		485	424	445
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P<0.001	P<0.001	P<0.001

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Control	80 ppm	170 ppm	330 ppm
Subcutaneous Tissue: Fibroma				
Overall Rates (e)	0/60 (0%)	4/45 (9%)	4/75 (5%)	2/60 (3%)
Effective Rates (b)	0/58 (0%)	4/42 (10%)	4/57 (7%)	2/40 (5%)
Terminal Rates (c)	0/44 (0%)	0/8 (0%)	0/0	0/0
Day of First Observation		546	556	483
Life Table Tests (d)	P=0.002	P=0.009	P=0.003	P=0.016
Logistic Regression Tests (d)	P=0.223	P=0.041	P=0.043	P=0.227
Cochran-Armitage Trend Test (d)	P=0.249			
Fisher Exact Test (d)		P=0.029	P=0.057	P=0.164
Subcutaneous Tissue: Fibroma or Neurofibroma				
Overall Rates (e)	0/60 (0%)	6/45 (13%)	6/75 (8%)	4/60 (7%)
Effective Rates (b)	0/59 (0%)	6/42 (14%)	6/71 (8%)	4/53 (8%)
Terminal Rates (c)	0/44 (0%)	0/8 (0%)	0/0	0/0
Day of First Observation		546	358	424
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P=0.001
Logistic Regression Tests (d)	P=0.115	P=0.006	P=0.032	P=0.093
Cochran-Armitage Trend Test (d)	P=0.196			
Fisher Exact Test (d)		P=0.004	P=0.024	P=0.047
Subcutaneous Tissue: Fibroma or Fibrosarcoma				
Overall Rates (e)	0/60 (0%)	4/45 (9%)	4/75 (5%)	3/60 (5%)
Effective Rates (b)	0/58 (0%)	4/42 (10%)	4/57 (7%)	3/40 (8%)
Terminal Rates (c)	0/44 (0%)	0/8 (0%)	0/0	0/0
Day of First Observation		546	556	483
Life Table Tests (d)	P<0.001	P=0.009	P=0.003	P=0.007
Logistic Regression Tests (d)	P=0.134	P=0.041	P=0.043	P=0.148
Cochran-Armitage Trend Test (d)	P=0.123			
Fisher Exact Test (d)		P=0.029	P=0.057	P=0.065
Subcutaneous Tissue: Fibroma, Neurofibroma, Sarcoma, or Fibrosarcoma				
Overall Rates (e)	2/60 (3%)	6/45 (13%)	6/75 (8%)	5/60 (8%)
Effective Rates (b)	2/59 (3%)	6/42 (14%)	6/71 (8%)	5/53 (9%)
Terminal Rates (c)	0/44 (0%)	0/8 (0%)	0/0	0/0
Day of First Observation	452	546	358	424
Life Table Tests (d)	P<0.001	P=0.004	P=0.002	P=0.006
Logistic Regression Tests (d)	P=0.242	P=0.075	P=0.267	P=0.353
Cochran-Armitage Trend Test (d)	P=0.282			
Fisher Exact Test (d)		P=0.053	P=0.206	P=0.177
Testis: Interstitial Cell Adenoma				
Overall Rates (a)	57/60 (95%)	39/45 (87%)	68/75 (91%)	42/59 (71%)
Effective Rates (b)	57/59 (97%)	39/44 (89%)	68/73 (93%)	42/56 (75%)
Terminal Rates (c)	44/44 (100%)	8/8 (100%)	0/0	0/0
Day of First Observation	529	480	333	344
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P=0.530N	P=0.675	P=0.007	P=0.439
Cochran-Armitage Trend Test (d)	P<0.001N			
Fisher Exact Test (d)		P=0.117N	P=0.317N	P<0.001N
Thyroid Gland: C-Cell Adenoma				
Overall Rates (a)	6/60 (10%)	6/44 (14%)	5/74 (7%)	1/60 (2%)
Effective Rates (b)	6/55 (11%)	6/36 (17%)	5/52 (10%)	1/24 (4%)
Terminal Rates (c)	5/44 (11%)	1/8 (13%)	0/0	0/0
Day of First Observation	645	578	538	592
Life Table Tests (d)	P<0.001	P=0.011	P<0.001	P=0.024
Logistic Regression Tests (d)	P=0.450	P=0.161	P=0.283	P=0.474
Cochran-Armitage Trend Test (d)	P=0.197N			
Fisher Exact Test (d)		P=0.313	P=0.540N	P=0.310N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Control	80 ppm	170 ppm	330 ppm
Thyroid Gland: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	6/60 (10%)	7/44 (16%)	7/74 (9%)	2/60 (3%)
Effective Rates (b)	6/59 (10%)	7/41 (17%)	7/70 (10%)	2/53 (4%)
Terminal Rates (c)	5/44 (11%)	1/8 (13%)	0/0	0/0
Day of First Observation	645	578	358	560
Life Table Tests (d)	P<0.001	P=0.003	P<0.001	P=0.002
Logistic Regression Tests (d)	P=0.389	P=0.075	P=0.288	P=0.254
Cochran-Armitage Trend Test (d)	P=0.087N			
Fisher Exact Test (d)		P=0.238	P=0.600N	P=0.173N
Zymbal Gland: Adenoma				
Overall Rates (a)	0/59 (0%)	4/45 (9%)	11/75 (15%)	9/60 (15%)
Effective Rates (b)	0/58 (0%)	4/44 (9%)	11/71 (15%)	9/53 (17%)
Terminal Rates (c)	0/44 (0%)	1/8 (13%)	0/0	0/0
Day of First Observation		353	391	445
Life Table Tests (d)	P<0.001	P=0.011	P<0.001	P<0.001
Logistic Regression Tests (d)	P=0.006	P=0.050	P=0.004	P=0.001
Cochran-Armitage Trend Test (d)	P=0.002			
Fisher Exact Test (d)		P=0.032	P<0.001	P<0.001
Zymbal Gland: Carcinoma				
Overall Rates (a)	0/59 (0%)	7/45 (16%)	14/75 (19%)	21/60 (35%)
Effective Rates (b)	0/58 (0%)	7/45 (16%)	14/75 (19%)	21/60 (35%)
Terminal Rates (c)	0/44 (0%)	0/8 (0%)	0/0	0/0
Day of First Observation		262	304	284
Life Table Tests (d)	P<0.001	P=0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.006	P=0.005	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.002	P<0.001	P<0.001
Zymbal Gland: Adenoma or Carcinoma				
Overall Rates (a)	0/59 (0%)	10/45 (22%)	25/75 (33%)	30/60 (50%)
Effective Rates (b)	0/58 (0%)	10/45 (22%)	25/75 (33%)	30/60 (50%)
Terminal Rates (c)	0/44 (0%)	1/8 (13%)	0/0	0/0
Day of First Observation		262	304	284
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P<0.001	P<0.001	P<0.001
Hematopoietic System: Mononuclear Leukemia				
Overall Rates (e)	19/60 (32%)	17/45 (38%)	17/75 (23%)	4/60 (7%)
Effective Rates (b)	19/58 (33%)	17/42 (40%)	17/57 (30%)	4/40 (10%)
Terminal Rates (c)	14/44 (32%)	4/8 (50%)	0/0	0/0
Day of First Observation	505	515	483	486
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P=0.033
Logistic Regression Tests (d)	P=0.206N	P=0.108	P=0.199	P=0.303N
Cochran-Armitage Trend Test (d)	P=0.005N			
Fisher Exact Test (d)		P=0.280	P=0.445N	P=0.007N
All Sites: Mesothelioma				
Overall Rates (e)	2/60 (3%)	1/45 (2%)	7/75 (9%)	6/60 (10%)
Effective Rates (b)	2/59 (3%)	1/44 (2%)	7/72 (10%)	6/56 (11%)
Terminal Rates (c)	1/44 (2%)	0/8 (0%)	0/0	0/0
Day of First Observation	529	483	339	401
Life Table Tests (d)	P<0.001	P=0.720	P=0.016	P=0.001
Logistic Regression Tests (d)	P=0.148	P=0.545N	P=0.297	P=0.226
Cochran-Armitage Trend Test (d)	P=0.044			
Fisher Exact Test (d)		P=0.610N	P=0.140	P=0.119

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the four groups
(c) Observed tumor incidence in animals killed at the end of the study
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the effective tumor rates. A negative trend or a lower incidence in a dosed group than in controls is indicated by (N).
(e) Number of tumor-bearing animals/number of animals examined grossly at the site
(f) No P value is reported because no tumors were observed in the dosed and control groups.

TABLE A4a. HISTORICAL INCIDENCE OF LIVER TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Neoplastic Nodule	Hepatocellular Carcinoma	Neoplastic Nodule or Hepatocellular Carcinoma
Historical Incidence at Hazleton Laboratories America, Inc.			
Decabromodiphenyl oxide	1/50	1/50	2/50
Chlorendic acid	2/50	3/50	5/50
TOTAL	3/100 (3.0%)	4/100 (4.0%)	7/100 (7.0%)
Overall Historical Incidence			
TOTAL	65/1,591 (4.1%)	14/1,591 (0.9%)	78/1,591 (4.9%)
SD (b)	4.18%	1.52%	4.34%
Range (c)			
High	6/49	3/50	7/49
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4b. HISTORICAL INCIDENCE OF TUMORS OF THE LARGE INTESTINE IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Adenocarcinomas in Controls
Historical Incidence at Hazleton Laboratories America, Inc.	
Decabromodiphenyl oxide	0/47
Chlorendic acid	0/49
TOTAL	0/96
Overall Historical Incidence	
TOTAL	(b) 2/1,541 (0.1%)
SD (c)	0.50%
Range (d)	
High	1/49
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Mucinous adenocarcinomas; no benign tumors have been observed.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A4c. HISTORICAL INCIDENCE OF TUMORS OF THE SMALL INTESTINE IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Adenocarcinomas in Controls
Historical Incidence at Hazleton Laboratories America, Inc.	
Decabromodiphenyl oxide	(b) 1/49
Chlorendic acid	0/48
TOTAL	1/97 (1.0%)
Overall Historical Incidence	
TOTAL	(c) 5/1,557 (0.3%)
SD (d)	0.77%
Range (e)	
High	1/44
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Carcinoma, NOS
(c) Includes one carcinoma, NOS, three adenocarcinomas, NOS, and one mucinous adenocarcinoma; no benign tumors have been observed.
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE A4d. HISTORICAL INCIDENCE OF ZYMBAL GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Adenomas or Carcinomas in Controls
Historical Incidence at Hazleton Laboratories America, Inc.	
Decabromodiphenyl oxide	0/50
Chlorendic acid	(b) 1/50
TOTAL	(b) 1/100 (1.0%)
Overall Historical Incidence	
TOTAL	(c) 19/1,596 (1.2%)
SD (d)	1.82%
Range (e)	
High	4/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Carcinoma, NOS
(c) Includes 1 papillary adenoma, 11 carcinomas, NOS, and 7 squamous cell carcinomas
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE A4e. HISTORICAL INCIDENCE OF PREPUTIAL GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Hazleton Laboratories America, Inc.			
Decabromodiphenyl oxide	0/50	4/50	4/50
Chlorendic acid	0/50	1/50	1/50
TOTAL	0/100	5/100 (5.0%)	5/100 (5.0%)
Overall Historical Incidence			
TOTAL	68/1,596 (4.3%)	(b) 49/1,596 (3.1%)	(b) 117/1,596 (7.3%)
SD (c)	5.02%	2.84%	5.24%
Range (d)			
High	8/50	5/50	9/50
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes one squamous cell carcinoma and seven adenocarcinomas, NOS
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A4f. HISTORICAL INCIDENCE OF ORAL CAVITY SQUAMOUS CELL TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence at Hazleton Laboratories America, Inc.			
Decabromodiphenyl oxide	0/50	0/50	0/50
Chlorendic acid	0/50	0/50	0/50
TOTAL	0/100	0/100	0/100
Overall Historical Incidence			
TOTAL	(b) 3/1,596 (0.2%)	(c) 4/1,596 (0.3%)	(d) 7/1,596 (0.4%)
SD (e)	0.60%	0.68%	0.99%
Range (f)			
High	1/49	1/49	2/49
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes two tumors of the palate and one of the tongue
(c) Includes two tumors of the palate and two of the oral mucosa
(d) Includes four tumors of the palate, two of the oral mucosa, and one of the tongue
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE A4g. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM BASAL CELL TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Benign	Malignant	Benign or Malignant
Historical Incidence at Hazleton Laboratories America, Inc.			
Decabromodiphenyl oxide	0/50	1/50	1/50
Chlorendic acid	0/50	1/50	1/50
TOTAL	0/100	(b) 2/100 (2.0%)	(b) 2/100 (2.0%)
Overall Historical Incidence			
TOTAL	(c) 20/1,596 (1.3%)	(b) 10/1,596 (0.6%)	(d) 30/1,596 (1.9%)
SD (e)	1.82%	1.07%	2.16%
Range (f)			
High	3/50	2/50	4/50
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Basal cell carcinomas
(c) Includes 11 basal cell adenomas, 4 trichoepitheliomas, 1 adnexal adenoma, and 4 sebaceous gland adenomas
(d) Includes 11 basal cell adenomas, 4 trichoepitheliomas, 1 adnexal adenoma, 4 sebaceous gland adenomas, and 10 basal cell carcinomas
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE A4h. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM KERATOACANTHOMAS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls
Historical Incidence at Hazleton Laboratories America, Inc.	
Decabromodiphenyl oxide	2/50
Chlorendic acid	4/50
TOTAL	6/100 (6.0%)
Overall Historical Incidence	
TOTAL	39/1,596 (2.4%)
SD (b)	3.69%
Range (c)	
High	7/49
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4i. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM SQUAMOUS CELL TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence at Hazleton Laboratories America, Inc.			
Decabromodiphenyl oxide	1/50	1/50	2/50
Chlorendic acid	1/50	0/50	1/50
TOTAL	2/100 (2.0%)	1/100 (1.0%)	3/100 (3.0%)
Overall Historical Incidence			
TOTAL	(b) 21/1,596 (1.3%)	10/1,596 (0.6%)	(b) 31/1,596 (1.9%)
SD (c)	1.50%	1.08%	1.81%
Range (d)			
High	2/49	2/49	3/49
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes one papilloma, NOS
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A4j. HISTORICAL INCIDENCE OF BRAIN GLIAL CELL TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls
Historical Incidence at Hazleton Laboratories America, Inc.	
Decabromodiphenyl oxide	2/50
Chlorendic acid	0/50
TOTAL	(b) 2/100 (2.0%)
Overall Historical Incidence	
TOTAL	(c) 14/1,590 (0.9%)
SD (d)	1.43%
Range (e)	
High	2/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Astrocytomas
(c) Includes 10 astrocytomas, 3 gliomas, NOS, and 1 oligodendroglioma
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE A4k. HISTORICAL INCIDENCE OF MESOTHELIAL TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Mesotheliomas in Controls
Historical Incidence at Hazleton Laboratories America, Inc.	
Decabromodiphenyl oxide	1/50
Chlorendic acid	2/50
TOTAL	(b) 3/100 (3.0%)
Overall Historical Incidence	
TOTAL	(c) 47/1,596 (2.9%)
SD (d)	2.65%
Range (e)	
High	5/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes two malignant mesotheliomas
(c) Includes 11 malignant mesotheliomas
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

	Untreated Control	80 ppm	170 ppm	330 ppm
Animals initially in study	70	45	75	70
Animals removed	70	45	75	70
Animals examined histopathologically	60	45	75	60
ALIMENTARY SYSTEM				
Esophagus	(60)	(44)	(75)	(60)
Hyperkeratosis		1 (2%)		1 (2%)
Inflammation, acute				1 (2%)
Intestine large, cecum	(60)	(42)	(72)	(58)
Congestion			1 (1%)	
Mucosa, necrosis, focal		1 (2%)		
Submucosa, edema		1 (2%)		
Intestine large, colon	(60)	(43)	(73)	(58)
Parasite metazoan			2 (3%)	2 (3%)
Intestine large, rectum	(59)	(42)	(73)	(58)
Parasite metazoan		1 (2%)	4 (5%)	
Intestine small, duodenum	(60)	(42)	(70)	(55)
Mucosa, hyperplasia, diffuse			1 (1%)	
Intestine small, jejunum	(59)	(41)	(69)	(56)
Congestion			1 (1%)	
Necrosis, focal				1 (2%)
Mucosa, hyperplasia, focal			1 (1%)	
Liver	(60)	(45)	(74)	(60)
Basophilic focus	42 (70%)	29 (64%)	48 (65%)	49 (82%)
Clear cell focus	19 (32%)	11 (24%)	16 (22%)	28 (47%)
Degeneration, cystic	7 (12%)	21 (47%)	28 (38%)	15 (25%)
Degeneration, cystic, focal	6 (10%)	1 (2%)	4 (5%)	4 (7%)
Degeneration, cystic, multifocal		1 (2%)	2 (3%)	9 (15%)
Ectasia, multifocal		1 (2%)	1 (1%)	
Eosinophilic focus	6 (10%)	15 (33%)	35 (47%)	38 (63%)
Fatty change	2 (3%)		4 (5%)	3 (5%)
Granuloma	2 (3%)	2 (4%)		3 (5%)
Hematopoietic cell proliferation	2 (3%)	15 (33%)	39 (53%)	41 (68%)
Hepatodiaphragmatic nodule	4 (7%)	3 (7%)	2 (3%)	2 (3%)
Hepatodiaphragmatic nodule, multiple		1 (2%)		
Infarct, chronic	1 (2%)	2 (4%)		
Necrosis, coagulative		1 (2%)	1 (1%)	1 (2%)
Necrosis, focal		1 (2%)	2 (3%)	5 (8%)
Necrosis, multifocal			5 (7%)	5 (8%)
Regeneration, diffuse		1 (2%)	8 (11%)	3 (5%)
Regeneration, focal	4 (7%)	1 (2%)	3 (4%)	5 (8%)
Regeneration, multifocal	1 (2%)	5 (11%)	11 (15%)	10 (17%)
Thrombus		3 (7%)	3 (4%)	7 (12%)
Vacuolization cytoplasmic, focal				3 (5%)
Vacuolization cytoplasmic, multifocal	2 (3%)	2 (4%)	7 (9%)	7 (12%)
Bile duct, hyperplasia	14 (23%)	2 (4%)	6 (8%)	4 (7%)
Caudate lobe, pigmentation			1 (1%)	
Caudate lobe, regeneration			1 (1%)	
Centrilobular, degeneration, diffuse		4 (9%)	9 (12%)	10 (17%)
Centrilobular, necrosis	2 (3%)	3 (7%)	4 (5%)	1 (2%)
Centrilobular, necrosis, diffuse	2 (3%)	7 (16%)	6 (8%)	5 (8%)
Centrilobular, necrosis, focal		1 (2%)		
Centrilobular, necrosis, multifocal		2 (4%)		
Periportal, fibrosis			1 (1%)	1 (2%)
Serosa, hemorrhage	1 (2%)			
Serosa, inflammation, acute				1 (2%)
Mesentery	(22)	(9)	(28)	(11)
Ectasia, focal			1 (4%)	
Inflammation, acute				1 (9%)
Artery, inflammation, chronic	1 (5%)			
Artery, mineralization		1 (11%)		
Fat, necrosis	17 (77%)	8 (89%)	21 (75%)	9 (82%)
Vein, ectasia			1 (4%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Untreated Control	80 ppm	170 ppm	330 ppm
ALIMENTARY SYSTEM (Continued)				
Pancreas	(60)	(44)	(75)	(60)
Atrophy	9 (15%)	4 (9%)	5 (7%)	2 (3%)
Degeneration				1 (2%)
Acinus, hypertrophy, multifocal		1 (2%)		
Pharynx	(1)	(4)	(7)	(7)
Palate, hyperplasia, squamous			1 (14%)	
Palate, hyperplasia, squamous, focal			1 (14%)	
Palate, necrosis	1 (100%)			
Salivary glands	(60)	(44)	(75)	(60)
Atrophy		1 (2%)		
Interlobular, edema		1 (2%)		1 (2%)
Parotid gland, atrophy		1 (2%)		
Stomach, forestomach	(59)	(44)	(73)	(57)
Acanthosis	2 (3%)		2 (3%)	2 (4%)
Acanthosis, diffuse				1 (2%)
Ulcer	1 (2%)			2 (4%)
Ulcer, multifocal				1 (2%)
Stomach, glandular	(58)	(44)	(72)	(58)
Erosion, focal	1 (2%)		2 (3%)	
Erosion, multifocal		5 (11%)	4 (6%)	
Hemorrhage, focal				1 (2%)
Hemorrhage, multifocal			1 (1%)	
Mineralization			1 (1%)	
Necrosis, focal				1 (2%)
Mucosa, muscularis, mineralization		1 (2%)		
Submucosa, hemorrhage, focal	1 (2%)			
Tongue	(2)	(4)	(6)	(10)
Hyperkeratosis, focal				1 (10%)
Necrosis, focal			1 (17%)	
CARDIOVASCULAR SYSTEM				
Heart	(60)	(44)	(75)	(60)
Cardiomyopathy, chronic	47 (78%)	29 (66%)	58 (77%)	42 (70%)
Inflammation, acute, multifocal			1 (1%)	1 (2%)
Mineralization, multifocal	1 (2%)			
Artery, mineralization		1 (2%)		
Atrium, thrombus	3 (5%)	15 (34%)	27 (36%)	23 (38%)
Epicardium, inflammation, chronic active, focal		1 (2%)		
ENDOCRINE SYSTEM				
Adrenal gland, cortex	(60)	(44)	(74)	(60)
Angiectasis, multifocal				1 (2%)
Atrophy			1 (1%)	
Congestion		1 (2%)		
Hyperplasia, focal	3 (5%)	1 (2%)	1 (1%)	
Infarct, chronic				1 (2%)
Necrosis, multifocal			1 (1%)	
Pigmentation			1 (1%)	
Vacuolization cytoplasmic, diffuse			1 (1%)	4 (7%)
Vacuolization cytoplasmic, focal	1 (2%)			
Vacuolization cytoplasmic, multifocal	2 (3%)			
Adrenal gland, medulla	(60)	(44)	(74)	(60)
Atrophy			1 (1%)	
Congestion		1 (2%)		
Hyperplasia	2 (3%)			
Hyperplasia, focal	4 (7%)	4 (9%)	8 (11%)	5 (8%)
Hyperplasia, multifocal	1 (2%)		4 (5%)	5 (8%)
Infarct, chronic				1 (2%)
Pigmentation			1 (1%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Untreated Control	80 ppm	170 ppm	330 ppm
ENDOCRINE SYSTEM (Continued)				
Islets, pancreatic	(60)	(44)	(75)	(60)
Hyperplasia, focal			2 (3%)	
Parathyroid gland	(60)	(43)	(74)	(60)
Hyperplasia		4 (9%)	3 (4%)	
Pituitary gland	(58)	(43)	(74)	(59)
Pigmentation	1 (2%)			
Pars distalis, angiectasis			1 (1%)	
Pars distalis, congestion			1 (1%)	
Pars distalis, cyst		2 (5%)	1 (1%)	1 (2%)
Pars distalis, ectasia, focal	2 (3%)			
Pars distalis, hyperplasia, focal		1 (2%)	1 (1%)	
Pars intermedia, cyst				1 (2%)
Thyroid gland	(60)	(44)	(74)	(60)
C-cell, hyperplasia, focal	6 (10%)	4 (9%)	2 (3%)	2 (3%)
C-cell, hyperplasia, multifocal	1 (2%)			
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Epididymis	(60)	(45)	(75)	(59)
Atypical cells			1 (1%)	
Preputial gland	(60)	(43)	(73)	(59)
Atrophy	4 (7%)	8 (19%)	10 (14%)	7 (12%)
Cyst			1 (1%)	
Ectasia	5 (8%)	12 (28%)	25 (34%)	24 (41%)
Hyperplasia		1 (2%)		
Hyperplasia, focal	1 (2%)	2 (5%)	4 (5%)	8 (14%)
Hyperplasia, squamous	1 (2%)	1 (2%)		
Hyperplasia, squamous, focal		3 (7%)	5 (7%)	4 (7%)
Hyperplasia, squamous, multifocal			1 (1%)	
Inflammation, acute			2 (3%)	1 (2%)
Inflammation, chronic			1 (1%)	1 (2%)
Inflammation, chronic active			2 (3%)	
Prostate	(60)	(44)	(75)	(60)
Hyperplasia, glandular, focal	5 (8%)	2 (5%)	2 (3%)	2 (3%)
Hyperplasia, glandular, multifocal	5 (8%)	4 (9%)	3 (4%)	
Inflammation, acute			2 (3%)	
Inflammation, chronic			1 (1%)	
Inflammation, chronic active	5 (8%)	2 (5%)	11 (15%)	11 (18%)
Seminal vesicle	(58)	(42)	(58)	(44)
Atrophy			1 (2%)	2 (5%)
Inflammation, chronic active			1 (2%)	
Bilateral, atrophy	1 (2%)			
Epithelium, hyperplasia, focal			1 (2%)	
Testes	(60)	(45)	(75)	(59)
Atrophy	3 (5%)	4 (9%)	2 (3%)	4 (7%)
Cyst			1 (1%)	
Degeneration			1 (1%)	2 (3%)
Interstitial cell, hyperplasia	2 (3%)	4 (9%)	14 (19%)	17 (29%)
HEMATOPOIETIC SYSTEM				
Bone marrow	(60)	(43)	(74)	(60)
Hyperplasia	2 (3%)	3 (7%)	14 (19%)	7 (12%)
Hypoplasia			1 (1%)	
Myelofibrosis				3 (5%)
Myelofibrosis, focal		1 (2%)	2 (3%)	2 (3%)
Myeloid cell, hyperplasia		1 (2%)		

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Untreated Control	80 ppm	170 ppm	330 ppm
HEMATOPOIETIC SYSTEM (Continued)				
Lymph node	(60)	(43)	(75)	(58)
Axillary, congestion		1 (2%)		
Axillary, erythrophagocytosis		1 (2%)		
Axillary, hemorrhage			1 (1%)	
Axillary, hyperplasia, lymphoid			1 (1%)	
Bronchial, congestion				1 (2%)
Iliac, hyperplasia, lymphoid			1 (1%)	
Inguinal, hyperplasia, lymphoid				1 (2%)
Inguinal, necrosis			1 (1%)	
Mediastinal, atrophy			2 (3%)	
Mediastinal, congestion		3 (7%)	3 (4%)	1 (2%)
Mediastinal, hemorrhage			2 (3%)	
Mediastinal, hyperplasia, lymphoid		1 (2%)	2 (3%)	3 (5%)
Mediastinal, pigmentation		1 (2%)	2 (3%)	1 (2%)
Pancreatic, congestion				1 (2%)
Pancreatic, hyperplasia, lymphoid		1 (2%)		
Pancreatic, hyperplasia, reticulum cell				1 (2%)
Lymph node, mandibular	(60)	(43)	(74)	(58)
Congestion		1 (2%)	2 (3%)	1 (2%)
Erythrophagocytosis		1 (2%)		
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (1%)	6 (10%)
Hyperplasia, reticulum cell			1 (1%)	
Lymph node, mesenteric	(59)	(42)	(73)	(56)
Congestion		1 (2%)		1 (2%)
Ectasia	1 (2%)			
Hyperplasia, lymphoid	1 (2%)	1 (2%)	2 (3%)	3 (5%)
Hyperplasia, reticulum cell		3 (7%)	6 (8%)	6 (11%)
Spleen	(60)	(42)	(74)	(59)
Angiectasis, focal				2 (3%)
Atrophy	3 (5%)		4 (5%)	4 (7%)
Hematopoietic cell proliferation	3 (5%)	13 (31%)	43 (58%)	38 (64%)
Hyperplasia, megakaryocyte				1 (2%)
Hyperplasia, reticulum cell	2 (3%)		4 (5%)	7 (12%)
Metaplasia				1 (2%)
Necrosis			1 (1%)	
Necrosis, multifocal				1 (2%)
Pigmentation, hemosiderin			1 (1%)	
Thymus	(53)	(34)	(55)	(48)
Atrophy	1 (2%)		1 (2%)	
Edema			1 (2%)	
Hemorrhage				1 (2%)
Epithelial cell, hyperplasia, focal	1 (2%)			
INTEGUMENTARY SYSTEM				
Skin	(60)	(45)	(75)	(60)
Abscess	1 (2%)		1 (1%)	
Acanthosis, focal			1 (1%)	1 (2%)
Acanthosis, multifocal	1 (2%)			
Cyst epithelial inclusion	2 (3%)	2 (4%)	1 (1%)	
Granuloma, focal			1 (1%)	
Hyperkeratosis, focal		1 (2%)	2 (3%)	
Inflammation, chronic, focal		1 (2%)		
Necrosis		1 (2%)		
Dermis, fibrosis				1 (2%)
Dermis, fibrosis, focal			2 (3%)	1 (2%)
Hair follicle, hyperplasia, basal cell, focal		1 (2%)	1 (1%)	3 (5%)
Prepuce, hemorrhage				1 (2%)
Subcutaneous tissue, edema		3 (7%)	3 (4%)	3 (5%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Untreated Control	80 ppm	170 ppm	330 ppm
MUSCULOSKELETAL SYSTEM				
Bone		(3)	(1)	(6)
Cranium, proliferation, focal			1 (100%)	
NERVOUS SYSTEM				
Brain	(60)	(44)	(75)	(60)
Cerebellum, hemorrhage				1 (2%)
Cerebrum, hemorrhage			2 (3%)	
Cerebrum, thrombus, multifocal			1 (1%)	
RESPIRATORY SYSTEM				
Lung	(60)	(44)	(75)	(60)
Congestion		1 (2%)	1 (1%)	1 (2%)
Edema			1 (1%)	
Foreign body	2 (3%)			1 (2%)
Hemorrhage			1 (1%)	1 (2%)
Hyperplasia, lymphoid	49 (82%)	29 (66%)	55 (73%)	52 (87%)
Infiltration cellular, histiocytic		3 (7%)	10 (13%)	6 (10%)
Inflammation, acute, multifocal				1 (2%)
Inflammation, suppurative	1 (2%)			
Pigmentation, focal			1 (1%)	
Thrombus				1 (2%)
Thrombus, multiple		1 (2%)		2 (3%)
Alveolar epithelium, hyperplasia, focal	1 (2%)	1 (2%)	6 (8%)	1 (2%)
Alveolar epithelium, hyperplasia, multifocal		1 (2%)	3 (4%)	3 (5%)
Artery, mediastinum, mineralization		1 (2%)		
Mediastinum, inflammation, acute				1 (2%)
Nose	(60)	(44)	(74)	(60)
Foreign body	1 (2%)			1 (2%)
Fungus	4 (7%)	3 (7%)	9 (12%)	7 (12%)
Hyperkeratosis	2 (3%)		2 (3%)	1 (2%)
Inflammation, acute	6 (10%)	3 (7%)	8 (11%)	4 (7%)
Inflammation, chronic		1 (2%)	2 (3%)	3 (5%)
Necrosis, focal		1 (2%)	2 (3%)	2 (3%)
Necrosis, multifocal			1 (1%)	
Glands, hyperplasia				1 (2%)
Mucosa, hyperplasia			1 (1%)	
Nasolacrimal duct, inflammation, acute				1 (2%)
Submucosa, fibrosis				1 (2%)
SPECIAL SENSES SYSTEM				
Ear				(2)
Canal, hyperplasia, squamous, focal				1 (50%)
Eye	(4)	(3)	(3)	(2)
Cataract	1 (25%)		2 (67%)	
Degeneration	1 (25%)			
Anterior chamber, cornea, inflammation, acute		1 (33%)		
Cornea, inflammation, chronic				1 (50%)
Retina, degeneration	3 (75%)		3 (100%)	
Zymbal gland	(59)	(45)	(75)	(60)
Ectasia	42 (71%)	40 (89%)	53 (71%)	40 (67%)
Ectasia, focal			1 (1%)	
Hyperplasia, diffuse		2 (4%)		
Hyperplasia, focal		3 (7%)	2 (3%)	2 (3%)
Hyperplasia, multifocal	1 (2%)			
Hyperplasia, squamous			1 (1%)	
Hyperplasia, squamous, focal		4 (9%)	10 (13%)	12 (20%)
Hypertrophy, diffuse		1 (2%)		

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Untreated Control	80 ppm	170 ppm	330 ppm
URINARY SYSTEM				
Kidney	(60)	(44)	(74)	(60)
Abscess, multifocal				1 (2%)
Hydronephrosis			1 (1%)	
Infarct, acute				1 (2%)
Infarct, chronic		1 (2%)		
Mineralization		1 (2%)		
Nephropathy, chronic	53 (88%)	36 (82%)	58 (78%)	52 (87%)
Thrombus, multifocal			2 (3%)	
Cortex, infarct, acute			1 (1%)	
Proximal convoluted renal tubule, necrosis, diffuse	1 (2%)		1 (1%)	
Renal tubule, degeneration		1 (2%)		
Renal tubule, mineralization			2 (3%)	
Renal tubule, necrosis, focal				2 (3%)
Renal tubule, pigmentation	1 (2%)	1 (2%)	2 (3%)	3 (5%)
Transitional epithelium, hyperplasia, focal			1 (1%)	1 (2%)
Urethra				(1)
Hyperplasia, squamous, focal				1 (100%)
Urinary bladder	(60)	(44)	(75)	(59)
Edema	1 (2%)			
Hemorrhage			3 (4%)	
Inflammation, acute			3 (4%)	
Necrosis, diffuse			2 (3%)	
Necrosis, focal			1 (1%)	
Mucosa, hyperplasia			2 (3%)	
Serosa, cyst			1 (1%)	

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3′-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

	Untreated Control	80 ppm	170 ppm	330 ppm
Animals initially in study	70	45	75	70
Animals removed	70	45	75	70
Animals examined histopathologically	60	45	75	60
ALIMENTARY SYSTEM				
Intestine large, cecum	(60)	(44)	(75)	(58)
Peyer's patch, leukemia mononuclear	1 (2%)			
Intestine large, colon	(60)	(44)	(75)	(59)
Sarcoma stromal, metastatic, uterus			1 (1%)	
Descending colon, adenocarcinoma		1 (2%)		
Descending colon, polyp adenomatous			1 (1%)	2 (3%)
Intestine large, rectum	(60)	(43)	(74)	(59)
Adenocarcinoma				1 (2%)
Polyp adenomatous				1 (2%)
Intestine small, duodenum	(60)	(43)	(73)	(58)
Adenocarcinoma, cystic, mucinous				1 (2%)
Carcinoma, metastatic, urinary bladder				1 (2%)
Intestine small, jejunum	(60)	(43)	(72)	(58)
Adenocarcinoma, cystic, mucinous		1 (2%)	1 (1%)	1 (2%)
Peyer's patch, leukemia mononuclear	1 (2%)			
Liver	(60)	(44)	(75)	(60)
Carcinoma, metastatic, urinary bladder				1 (2%)
Carcinoma, metastatic, uterus		1 (2%)		
Carcinoma, metastatic, multiple, uterus			1 (1%)	
Hepatocellular carcinoma				1 (2%)
Leukemia mononuclear	20 (33%)	14 (32%)	12 (16%)	4 (7%)
Neoplastic nodule		1 (2%)		
Neoplastic nodule, multiple				2 (3%)
Mesentery	*(60)	*(45)	*(75)	*(60)
Carcinoma, metastatic, multiple, urinary bladder				1 (2%)
Carcinoma, metastatic, multiple, uterus			1 (1%)	
Leukemia mononuclear	1 (2%)			
Sarcoma stromal, metastatic, uterus			1 (1%)	1 (2%)
Pancreas	(60)	(43)	(75)	(59)
Carcinoma, metastatic, urinary bladder				1 (2%)
Leukemia mononuclear	2 (3%)		1 (1%)	
Pharynx	*(60)	*(45)	*(75)	*(60)
Palate, papilloma squamous	1 (2%)		3 (4%)	1 (2%)
Palate, squamous cell carcinoma			1 (1%)	
Salivary glands	(59)	(44)	(75)	(59)
Schwannoma malignant			1 (1%)	
Bilateral, carcinosarcoma		1 (2%)		
Stomach, forestomach	(60)	(44)	(74)	(58)
Leukemia mononuclear	2 (3%)			
Stomach, glandular	(60)	(44)	(75)	(59)
Leukemia mononuclear	2 (3%)			
Tongue	*(60)	*(45)	*(75)	*(60)
Papilloma squamous	1 (2%)	2 (4%)		2 (3%)
Squamous cell carcinoma			2 (3%)	2 (3%)
CARDIOVASCULAR SYSTEM				
Heart	(60)	(45)	(75)	(60)
Leukemia mononuclear	3 (5%)		1 (1%)	
ENDOCRINE SYSTEM				
Adrenal gland, cortex	(60)	(45)	(75)	(60)
Leukemia mononuclear	9 (15%)	4 (9%)	3 (4%)	2 (3%)
Adrenal gland, medulla	(60)	(45)	(74)	(59)
Leukemia mononuclear	9 (15%)	4 (9%)	3 (4%)	2 (3%)
Pheochromocytoma benign	5 (8%)	1 (2%)	1 (1%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF *3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE* (Continued)

	Untreated Control	80 ppm	170 ppm	330 ppm
ENDOCRINE SYSTEM (Continued)				
Pituitary gland	(60)	(45)	(75)	(60)
Adenoma	1 (2%)			
Leukemia mononuclear	2 (3%)	2 (4%)	1 (1%)	1 (2%)
Pars distalis, adenoma	14 (23%)	9 (20%)	5 (7%)	8 (13%)
Pars distalis, carcinoma	2 (3%)			
Thyroid gland	(60)	(44)	(75)	(59)
C-cell, adenoma	4 (7%)	1 (2%)	2 (3%)	1 (2%)
C-cell, carcinoma	1 (2%)		1 (1%)	
Follicular cell, adenoma			1 (1%)	1 (2%)
Follicular cell, carcinoma	2 (3%)	1 (2%)		
GENERAL BODY SYSTEM				
Tissue, NOS	*(60)	*(45)	*(75)	*(60)
Carcinoma, metastatic, uterus			1 (1%)	
GENITAL SYSTEM				
Clitoral gland	(58)	(44)	(74)	(55)
Adenoma	4 (7%)	13 (30%)	12 (16%)	13 (24%)
Carcinoma	2 (3%)	12 (27%)	27 (36%)	26 (47%)
Carcinoma, metastatic, clitoral gland				1 (2%)
Bilateral, adenoma	1 (2%)	2 (5%)	1 (1%)	3 (5%)
Bilateral, carcinoma		5 (11%)	14 (19%)	4 (7%)
Ovary	(60)	(45)	(75)	(58)
Carcinoma, metastatic, urinary bladder				1 (2%)
Leukemia mononuclear	1 (2%)			
Uterus	(60)	(45)	(75)	(59)
Adenoma		3 (7%)		2 (3%)
Carcinoma			1 (1%)	
Deciduoma benign				1 (2%)
Leukemia mononuclear	1 (2%)	1 (2%)		
Polyp stromal	5 (8%)	5 (11%)	6 (8%)	5 (8%)
Polyp stromal, multiple	1 (2%)	3 (7%)	1 (1%)	
Sarcoma stromal	1 (2%)	1 (2%)	2 (3%)	1 (2%)
Cervix, adenoma, papillary			1 (1%)	
Cervix, carcinoma		1 (2%)		
Cervix, sarcoma stromal, metastatic, uterus				1 (2%)
Vagina	*(60)	*(45)	*(75)	*(60)
Mucosa, polyp			1 (1%)	
HEMATOPOIETIC SYSTEM				
Bone marrow	(60)	(45)	(75)	(60)
Leukemia mononuclear	2 (3%)			
Lymph node	(60)	(45)	(75)	(60)
Iliac, leukemia mononuclear	1 (2%)	1 (2%)		
Lumbar, leukemia mononuclear			1 (1%)	
Mediastinal, leukemia mononuclear	7 (12%)	1 (2%)	1 (1%)	
Pancreatic, leukemia mononuclear	4 (7%)	3 (7%)	2 (3%)	
Renal, carcinoma, metastatic, uterus			1 (1%)	
Renal, leukemia mononuclear		1 (2%)		
Thoracic, leukemia mononuclear			1 (1%)	
Lymph node, mandibular	(59)	(44)	(74)	(59)
Carcinoma, metastatic, Zymbal gland		1 (2%)		
Leukemia mononuclear	9 (15%)	5 (11%)	4 (5%)	
Axillary, renal, carcinoma, metastatic			1 (1%)	
Lymph node, mesenteric	(60)	(44)	(75)	(58)
Leukemia mononuclear	10 (17%)	4 (9%)	2 (3%)	1 (2%)
Spleen	(60)	(44)	(75)	(60)
Leukemia mononuclear	21 (35%)	15 (34%)	12 (16%)	4 (7%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Untreated Control	80 ppm	170 ppm	330 ppm
HEMATOPOIETIC SYSTEM (Continued)				
Thymus	(53)	(41)	(68)	(54)
Leukemia mononuclear			1 (1%)	
Lymphoma malignant lymphocytic			1 (1%)	
INTEGUMENTARY SYSTEM				
Mammary gland	(59)	(43)	(75)	(59)
Adenocarcinoma	1 (2%)	2 (5%)	13 (17%)	18 (31%)
Adenocarcinoma, multiple			1 (1%)	2 (3%)
Adenoma		1 (2%)		2 (3%)
Fibroadenoma	12 (20%)	9 (21%)	8 (11%)	4 (7%)
Fibroadenoma, multiple	2 (3%)	2 (5%)	1 (1%)	
Mixed tumor malignant				1 (2%)
Skin	(60)	(45)	(75)	(60)
Basal cell adenoma		3 (7%)	3 (4%)	2 (3%)
Basal cell carcinoma		1 (2%)		
Papilloma squamous			2 (3%)	
Papilloma squamous, multiple			1 (1%)	
Subcutaneous tissue, carcinoma, metastatic			1 (1%)	
Subcutaneous tissue, fibroma		1 (2%)		
Subcutaneous tissue, squamous cell carcinoma, metastatic, pharynx			1 (1%)	
MUSCULOSKELETAL SYSTEM				
Bone	*(60)	*(45)	*(75)	*(60)
Cranium, carcinoma, metastatic, Zymbal gland		1 (2%)		
Skeletal muscle	*(60)	*(45)	*(75)	*(60)
Diaphragm, carcinoma, metastatic, urinary bladder				1 (2%)
Intercostal, leukemia mononuclear			1 (1%)	
NERVOUS SYSTEM				
Brain	(60)	(45)	(75)	(60)
Leukemia mononuclear	3 (5%)			
Cerebellum, astrocytoma malignant			1 (1%)	
Cerebrum, astrocytoma malignant		1 (2%)		
Cerebrum, carcinoma, metastatic, pituitary gland	1 (2%)			
Meninges, cerebrum, nerve, carcinoma, metastatic, Zymbal gland		1 (1%)		
RESPIRATORY SYSTEM				
Lung	(60)	(45)	(75)	(60)
Adenocarcinoma, metastatic, multiple, mammary gland			1 (1%)	
Alveolar/bronchiolar adenoma		1 (2%)	1 (1%)	1 (2%)
Carcinoma, metastatic, clitoral gland			1 (1%)	
Carcinoma, metastatic, uncertain primary site		1 (2%)		
Carcinoma, metastatic, urinary bladder				1 (2%)
Carcinoma, metastatic, multiple, uterus			1 (1%)	
Carcinoma, metastatic, multiple, Zymbal gland			1 (1%)	
Carcinoma, metastatic, metastatic			1 (1%)	
Leukemia mononuclear	9 (15%)	6 (13%)	4 (5%)	1 (2%)
Mixed tumor malignant, metastatic, multiple, mammary gland				1 (2%)
Squamous cell carcinoma, metastatic, pharynx			1 (1%)	
Mediastinum, sarcoma			1 (1%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Untreated Control	80 ppm	170 ppm	330 ppm
SPECIAL SENSES SYSTEM				
Zymbal gland	(60)	(45)	(75)	(60)
Adenoma		3 (7%)	4 (5%)	3 (5%)
Carcinoma	1 (2%)	10 (22%)	17 (23%)	10 (17%)
Bilateral, carcinoma				3 (5%)
URINARY SYSTEM				
Kidney	(60)	(45)	(75)	(60)
Leukemia mononuclear	5 (8%)	1 (2%)	1 (1%)	
Lipoma	2 (3%)			
Renal tubule, adenoma		1 (2%)		
Renal tubule, carcinoma, metastatic, urinary bladder				1 (2%)
Transitional epithelium, carcinoma				1 (2%)
Ureter	*(60)	*(45)	*(75)	*(60)
Carcinoma, metastatic, urinary bladder				1 (2%)
Urinary bladder	(60)	(45)	(75)	(59)
Leukemia mononuclear	1 (2%)			
Sarcoma stromal, metastatic, uterus				1 (2%)
Transitional epithelium, carcinoma				1 (2%)
SYSTEMIC LESIONS				
Multiple organs	*(60)	*(45)	*(75)	*(60)
Leukemia mononuclear	21 (35%)	15 (33%)	12 (16%)	4 (7%)
Lymphoma malignant lymphocytic			1 (1%)	
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	70	45	75	70
Interval sacrifice	10			10
Terminal sacrifice	45	15	6	
Moribund	10	27	60	51
Dead	5	3	9	9
TUMOR SUMMARY				
Total animals with primary neoplasms **	48	42	73	57
Total primary neoplasms	84	113	151	132
Total animals with benign neoplasms	35	30	32	34
Total benign neoplasms	53	61	55	54
Total animals with malignant neoplasms	27	32	68	56
Total malignant neoplasms	31	52	96	78
Total animals with secondary neoplasms ***	1	3	7	4
Total secondary neoplasms	1	4	16	14
Total animals with malignant neoplasms--uncertain primary site		1		

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
*** Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE: UNTREATED CONTROL

WEEKS ON STUDY	058	076	076	078	082	083	085	086	086	086	089	090	090	091	092	093	093	093	093	093	093	093	093	093	093
CARCASS ID	175	215	255	245	205	225	265	235	275	214	274	184	185	204	272	171	172	173	174	181	182	183	191	192	193
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peyer's patch, leukemia mononuclear				X																					
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peyer's patch, leukemia mononuclear				X																					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X	X				X	X	X		X					X						
Mesentery						+			+																
Leukemia mononuclear																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X															
Pharynx																						+			
Palate, papilloma squamous																						X			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X								X													
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X								X													
Tongue																									
Papilloma squamous																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X					X			X											
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X		X				X	X	X		X											
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X		X				X	X	X		X											
Pheochromocytoma benign					X																				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																		
Leukemia mononuclear			X																						
Pars distalis, adenoma					X			X					X		X	X		X		X					X
Pars distalis, carcinoma									X													X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma				X									X												
C-cell, carcinoma								X																	
Follicular cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																X			X						
Bilateral, adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X																						
Polyp stromal																									
Polyp stromal, multiple																									
Sarcoma stromal																			X						
Vagina		+																							
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X													
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, leukemia mononuclear				X																					
Mediastinal, leukemia mononuclear			X	X	X					X				X											
Pancreatic, leukemia mononuclear				X	X						X			X											
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X						X	X		X											
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X					X	X	X		X											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X	X				X	X	X		X					X						
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M

+ Tissue examined microscopically
Not examined
– Present but not examined microscopically
I Insufficient tissue

M Missing
A Autolysis precludes examination
X Incidence of listed morphology

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3
CARCASS ID	1 9 4	1 9 5	2 0 1	2 0 2	2 0 3	2 1 1	2 1 2	2 1 3	2 2 1	2 2 2	2 2 3	2 2 4	2 3 1	2 3 2	2 3 3	2 3 4	2 4 1	2 4 2	2 4 3	2 7 3	2 8 3	2 4 4	2 5 1	2 5 2	2 5 3
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peyer's patch, leukemia mononuclear																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peyer's patch, leukemia mononuclear																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X							X								X		X		X	X		X		
Mesentery			+		+									+							+				
Leukemia mononuclear																					X				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																					X				
Pharynx																									
Palate, papilloma squamous																									
Salivary glands	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Tongue																									
Papilloma squamous																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																					X				
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																					X				
Pheochromocytoma benign			X									X				X									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear																					X				
Pars distalis, adenoma			X																X			X			
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																X									
C-cell, carcinoma																									
Follicular cell, carcinoma																	X					X			
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Adenoma				X					X																
Carcinoma																									
Bilateral, adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Polyp stromal			X																						X
Polyp stromal, multiple																									
Sarcoma stromal																									
Vagina																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																					X				
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, leukemia mononuclear																									
Mediastinal, leukemia mononuclear								X													X				
Pancreatic, leukemia mononuclear																									
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X													X				
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X													X				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X							X								X	X	X		X	X		X		
Thymus	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	TOTAL:
CARCASS ID	2 5 4	2 6 1	2 6 2	2 6 3	2 6 4	2 7 1	2 8 1	2 8 2	2 8 4	2 8 5	TISSUES TUMORS
ALIMENTARY SYSTEM											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Intestine large	+	+	+	+	+	+	+	+	+	+	60
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	60
Peyer's patch, leukemia mononuclear											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	60
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	60
Intestine small	+	+	+	+	+	+	+	+	+	+	60
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	60
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	60
Peyer's patch, leukemia mononuclear											1
Liver	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear					X		X	X	X		20
Mesentery											6
Leukemia mononuclear											1
Pancreas	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											2
Pharynx											1
Palate, papilloma squamous											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	59
Stomach	+	+	+	+	+	+	+	+	+	+	60
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											2
Tongue							+				1
Papilloma squamous							X				1
CARDIOVASCULAR SYSTEM											
Heart	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											3
ENDOCRINE SYSTEM											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear					X						9
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear					X						9
Pheochromocytoma benign										X	5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	60
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	58
Pituitary gland	+	+	+	+	+	+	+	+	+	+	60
Adenoma											1
Leukemia mononuclear											2
Pars distalis, adenoma	X					X				X	14
Pars distalis, carcinoma											2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
C-cell, adenoma		X									4
C-cell, carcinoma											1
Follicular cell, carcinoma											2
GENERAL BODY SYSTEM											
None											
GENITAL SYSTEM											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	58
Adenoma		X					X				4
Carcinoma											2
Bilateral, adenoma									X		1
Ovary	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											1
Uterus	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											1
Polyp stromal			X		X		X				5
Polyp stromal, multiple								X			1
Sarcoma stromal											1
Vagina											1
HEMATOPOIETIC SYSTEM											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											2
Lymph node	+	+	+	+	+	+	+	+	+	+	60
Iliac, leukemia mononuclear											1
Mediastinal, leukemia mononuclear											7
Pancreatic, leukemia mononuclear											4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear					X						9
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear					X						10
Spleen	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear					X		X	X	X		21
Thymus	+	+	+	+	+	+	+	+	+	M	53

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	058	076	076	078	082	083	085	086	086	086	089	090	090	091	092	093	093	093	093	093	093	093	093	093	093
CARCASS ID	175	215	255	245	205	225	265	235	275	214	274	184	185	204	272	171	172	173	174	181	182	183	191	192	193
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																X									
Fibroadenoma			X				X														X			X	X
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone																				+					
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X							X														
Cerebrum, carcinoma, metastatic, pituitary gland																						X			
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X	X					X	X		X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																									
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma	X																								
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X		X								X											
Lipoma																									
Ureter																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X																						

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093	093
CARCASS ID	194	195	201	202	203	211	212	213	221	222	223	224	231	232	233	234	241	242	243	273	283	244	251	252	253
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Fibroadenoma				X	X						X	X								X					
Fibroadenoma, multiple																							X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone										+															
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Cerebrum, carcinoma, metastatic, pituitary gland																									
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																					X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye											+														
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																					X				
Lipoma																									
Ureter											+	+													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: UNTREATED CONTROL (Continued)

WEEKS ON STUDY	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	TOTAL: TISSUES TUMORS
CARCASS ID	2 5 4	2 6 1	2 6 2	2 6 3	2 6 4	2 7 1	2 8 1	2 8 2	2 8 4	2 8 5	
INTEGUMENTARY SYSTEM											
Mammary gland	+	+	+	+	+	+	+	+	+	+	59
Adenocarcinoma											1
Fibroadenoma			X					X			12
Fibroadenoma, multiple					X						2
Skin	+	+	+	+	+	+	+	+	+	+	60
MUSCULOSKELETAL SYSTEM											
Bone											2
NERVOUS SYSTEM											
Brain	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											3
Cerebrum, carcinoma, metastatic, pituitary gland											1
RESPIRATORY SYSTEM											
Lung	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear					X						9
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60
SPECIAL SENSES SYSTEM											
Eye											1
Zymbal gland	+	+	+	+	+	+	+	+	+	+	60
Carcinoma											1
URINARY SYSTEM											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											5
Lipoma	X				X						2
Ureter											2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE: 80 ppm

WEEKS ON STUDY	054	061	061	063	068	069	070	070	073	074	075	081	081	082	082	084	086	086	086	087	088	088	088	088	089	089
CARCASS ID	435	415	434	465	445	405	385	395	464	414	384	545	383	455	425	404	394	453	463	424	413	451	452	393	403
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Descending colon, adenocarcinoma																										
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, cystic, mucinous																										
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uterus																				X						
Leukemia mononuclear												X	X	X				X		X			X			
Neoplastic nodule																										
Mesentery																										
Pancreas	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Pharynx																										
Salivary glands	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, carcinosarcoma																	X									
Stomach	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																										
Papilloma squamous																										
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X											X			
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X											X			
Pheochromocytoma benign																										
Islets, pancreatic	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																							X			
Pars distalis, adenoma									X			X	X								X					
Thyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																					X					
Follicular cell, carcinoma																										
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X			X							X					X					X	X	
Carcinoma								X						X				X						X	X	X
Bilateral, adenoma																										
Bilateral, carcinoma	X																X					X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oviduct																										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X		
Leukemia mononuclear																							X			
Polyp stromal				X						X													X			
Polyp stromal, multiple					X													X								
Sarcoma stromal																										
Cervix, carcinoma																				X						
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, leukemia mononuclear																							X			
Mediastinal, leukemia mononuclear																		X								
Pancreatic, leukemia mononuclear												X											X			
Renal, leukemia mononuclear																							X			
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal gland		X																								
Leukemia mononuclear												X								X			X			
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																				X			X			
Spleen	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X	X	X	X			X		X			X			
Thymus	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 80 ppm (Continued)

WEEKS ON STUDY	0 8 9	0 8 9	0 8 9	0 9 1	0 9 2	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	TOTAL:
CARCASS ID	4 1 2	4 3 2	4 4 4	4 3 3	4 0 1	3 8 1	3 8 2	3 9 1	3 9 2	4 0 2	4 1 1	4 2 1	4 2 2	4 2 3	4 3 1	4 4 1	4 4 2	4 4 3	4 6 1	4 6 2	TISSUES TUMORS
ALIMENTARY SYSTEM																					
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Descending colon, adenocarcinoma														X							1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adenocarcinoma, cystic, mucinous											X										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Carcinoma, metastatic, uterus																					1
Leukemia mononuclear	X			X			X				X	X					X	X		X	14
Neoplastic nodule												X									1
Mesentery	+																				1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Pharynx													+								1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Bilateral, carcinosarcoma																					1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Tongue					+														+		2
Papilloma squamous					X														X		2
CARDIOVASCULAR SYSTEM																					
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																					
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia mononuclear				X								X									4
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia mononuclear				X								X									4
Pheochromocytoma benign											X										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia mononuclear												X									2
Pars distalis, adenoma			X		X			X							X				X		9
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
C-cell, adenoma																					1
Follicular cell, carcinoma																				X	1
GENERAL BODY SYSTEM																					
None																					
GENITAL SYSTEM																					
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenoma				X		X		X			X	X			X				X		13
Carcinoma	X	X	X			X					X			X							12
Bilateral, adenoma					X		X														2
Bilateral, carcinoma										X										X	5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Oviduct																		+			1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma					X	X															3
Leukemia mononuclear																					1
Polyp stromal					X														X		5
Polyp stromal, multiple																		X			3
Sarcoma stromal														X							1
Cervix, carcinoma																					1
HEMATOPOIETIC SYSTEM																					
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Iliac, leukemia mononuclear																					1
Mediastinal, leukemia mononuclear																					1
Pancreatic, leukemia mononuclear				X																	3
Renal, leukemia mononuclear																					1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Carcinoma, metastatic, Zymbal gland																					1
Leukemia mononuclear				X								X									5
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Leukemia mononuclear				X								X									4
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Leukemia mononuclear	X			X			X				X	X					X	X		X	15
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 80 ppm (Continued)

WEEKS ON STUDY	054	061	061	063	068	069	070	070	073	074	075	081	081	082	082	084	086	086	086	087	088	088	088	089	089
CARCASS ID	435	415	434	465	445	405	385	395	464	414	384	454	383	455	425	404	394	453	463	424	413	451	452	393	403
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma										X											X				
Adenoma																									
Fibroadenoma			X		X														X						
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Basal cell carcinoma																									
Subcutaneous tissue, fibroma																									
MUSCULOSKELETAL SYSTEM																									
Bone									+		+			+						+		+			
Cranium, carcinoma, metastatic, Zymbal gland																				X					
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cerebrum, astrocytoma malignant																			X						
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, uncertain primary site											X														
Leukemia mononuclear													X		X			X		X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye								+									+								
Harderian gland								+									+								
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X																						X
Carcinoma		X				X				X		X		X		X		X		X	X				X
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 80 ppm (Continued)

WEEKS ON STUDY	0 8 9	0 8 9	0 8 9	0 9 1	0 9 2	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	0 9 3	TOTAL:
CARCASS ID	4 1 2	4 3 2	4 4 4	4 3 3	4 0 1	3 8 1	3 8 2	3 9 1	3 9 2	4 0 2	4 1 1	4 2 1	4 2 2	4 2 3	4 3 1	4 4 1	4 4 2	4 4 3	4 6 1	4 6 2	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																					
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adenocarcinoma																					2
Adenoma																	X				1
Fibroadenoma							X	X		X	X						X			X	9
Fibroadenoma, multiple			X		X																2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Basal cell adenoma							X			X						X					3
Basal cell carcinoma																		X			1
Subcutaneous tissue, fibroma								X													1
MUSCULOSKELETAL SYSTEM																					
Bone																					5
Cranium, carcinoma, metastatic, Zymbal gland																					1
NERVOUS SYSTEM																					
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Cerebrum, astrocytoma malignant																					1
RESPIRATORY SYSTEM																					
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Alveolar/bronchiolar adenoma								X													1
Carcinoma, metastatic, uncertain primary site																					1
Leukemia mononuclear				X								X									6
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
SPECIAL SENSES SYSTEM																					
Eye	+																				3
Harderian gland																					2
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma			X																		3
Carcinoma																					10
URINARY SYSTEM																					
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia mononuclear				X																	1
Renal tubule, adenoma																X					1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE: 170 ppm

WEEKS ON STUDY	0 3 2	0 4 0	0 4 1	0 4 1	0 4 4	0 4 4	0 4 5	0 4 8	0 4 8	0 4 9	0 4 9	0 4 9	0 5 0	0 5 1	0 5 2	0 5 2	0 5 2	0 5 2	0 5 4	0 5 4	0 5 4	0 5 5	0 5 5	0 5 9	0 5 9
CARCASS ID	7 5 5	6 7 2	6 6 5	6 9 5	6 4 5	7 4 5	7 2 5	7 5 4	7 6 5	6 6 4	7 3 5	7 6 4	7 0 5	7 5 3	6 4 4	6 6 3	7 0 4	6 7 1	6 5 5	6 5 4	7 0 3	6 6 2	7 1 5	6 3 4	6 3 5
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus							X																		
Descending colon, polyp adenomatous																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, cystic, mucinous																							X		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, multiple, uterus																									
Leukemia mononuclear																									
Mesentery							+	+				+	+										+		
Carcinoma, metastatic, multiple, uterus																									
Sarcoma stromal, metastatic, uterus							X																		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Pharynx								+																	
Palate, papilloma squamous																									
Palate, squamous cell carcinoma								X																	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue									+																
Squamous cell carcinoma																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
Tissue, NOS																									
Carcinoma, metastatic, uterus																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X			X							
Carcinoma	X			X		X					X				X	X	X	X	X	X			X		X
Bilateral, adenoma																									
Bilateral, carcinoma			X										X								X				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Polyp stromal																									
Polyp stromal, multiple																									
Sarcoma stromal							X							X											
Cervix, adenoma, papillary																									
Vagina									+																
Mucosa, polyp									X																

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 170 ppm (Continued)

WEEKS ON STUDY	059	060	061	061	061	063	063	063	065	065	065	067	067	068	068	069	069	069	069	069	070	072	073	073	076
CARCASS ID	6611	6894	6625	7002	7683	6775	6885	7224	6774	6443	7444	7343	7552	6884	6993	6224	6891	6992	7223	7443	6223	7442	7551	6553	7441
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus																									
Descending colon, polyp adenomatous				X																					
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Adenocarcinoma, cystic, mucinous																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, multiple, uterus					X																				
Leukemia mononuclear		X								X															
Mesentery					+																				
Carcinoma, metastatic, multiple, uterus					X																				
Sarcoma stromal, metastatic, uterus																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Pharynx											+						+								
Palate, papilloma squamous											X														
Palate, squamous cell carcinoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue			+							+													+		
Squamous cell carcinoma			X																				X		
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X															
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X															
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Pars distalis, adenoma													X	X											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
Tissue, NOS					+																				
Carcinoma, metastatic, uterus					X																				
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X	X		X			X				X		X	X						X				
Carcinoma	X					X	X	X							X	X	X	X	X	X	X				
Bilateral, adenoma																									
Bilateral, carcinoma																								X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma					X																				
Polyp stromal				X			X	X													X				
Polyp stromal, multiple																									
Sarcoma stromal																									
Cervix, adenoma, papillary																									
Vagina																									
Mucosa, polyp																									

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 170 ppm (Continued)

WEEKS ON STUDY	077	079	079	079	079	080	081	081	081	081	081	081	082	084	086	086	088	088	088	092	093	093	093	093	093	093	TOTAL:
CARCASS ID	733	633	701	714	722	641	683	652	713	632	732	762	651	761	642	673	622	721	882	621	631	881	111	112	131		TISSUES TUMORS
ALIMENTARY SYSTEM																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		75
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		75
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		75
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		75
Sarcoma stromal, metastatic, uterus																											1
Descending colon, polyp adenomatous																											1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		74
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		73
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		73
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		72
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		72
Adenocarcinoma, cystic, mucinous																											1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		75
Carcinoma, metastatic, multiple, uterus																											1
Leukemia mononuclear			X	X		X		X		X		X	X									X	X	X			12
Mesentery										+				+													8
Carcinoma, metastatic, multiple, uterus																											1
Sarcoma stromal, metastatic, uterus																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		75
Leukemia mononuclear			X																								1
Pharynx		+									+									+							6
Palate, papilloma squamous											X									X							3
Palate, squamous cell carcinoma																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		75
Schwannoma malignant				X																							1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		75
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		74
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		75
Tongue												+															5
Squamous cell carcinoma																											2
CARDIOVASCULAR SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		75
Leukemia mononuclear			X																								1
ENDOCRINE SYSTEM																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		75
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		75
Leukemia mononuclear			X								X																3
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	74
Leukemia mononuclear			X								X																3
Pheochromocytoma benign								X																			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		75
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+		70
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		75
Leukemia mononuclear									X																		1
Pars distalis, adenoma								X															X		X		5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		75
C-cell, adenoma																					X				X		2
C-cell, carcinoma																	X										1
Follicular cell, adenoma															X												1
GENERAL BODY SYSTEM																											
Tissue, NOS																											1
Carcinoma, metastatic, uterus																											1
GENITAL SYSTEM																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		74
Adenoma											X					X											12
Carcinoma									X							X					X			X			27
Bilateral, adenoma																				X							1
Bilateral, carcinoma		X			X		X	X			X			X	X		X	X					X				14
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		75
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		75
Carcinoma																											1
Polyp stromal									X		X																6
Polyp stromal, multiple						X																					1
Sarcoma stromal																											2
Cervix, adenoma, papillary																										X	1
Vagina																											1
Mucosa, polyp																											1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 170 ppm (Continued)

WEEKS ON STUDY	032	040	041	041	044	044	045	048	048	049	049	049	050	051	052	052	052	052	054	054	054	055	055	055	059	059
CARCASS ID	755	672	665	695	645	745	725	754	765	664	735	764	705	753	644	663	704	671	655	654	703	662	715	634	635
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumbar, leukemia mononuclear																										
Mediastinal, leukemia mononuclear																										
Pancreatic, leukemia mononuclear																										
Renal, carcinoma, metastatic, uterus																										
Thoracic, leukemia mononuclear																										
Lymph node, mandibular	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																										
Axillary, renal, carcinoma, metastatic																										
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																										
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																										
Lymphoma malignant lymphocytic																										
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma									X	X		X														
Adenocarcinoma, multiple																										
Fibroadenoma																										
Fibroadenoma, multiple																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																										
Papilloma squamous																		X								
Papilloma squamous, multiple																										
Subcutaneous tissue, carcinoma, metastatic																										
Subcutaneous tissue, squamous cell carcinoma, metastatic, pharynx								X																		
MUSCULOSKELETAL SYSTEM																										
Bone																										+
Skeletal muscle																										
Intercostal, leukemia mononuclear																										
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cerebellum, astrocytoma malignant																										
Meninges, cerebrum, nerve, carcinoma, metastatic, Zymbal gland																										
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, multiple, mammary gland																										
Alveolar/bronchiolar adenoma																										
Carcinoma, metastatic, clitoral gland													X													
Carcinoma, metastatic, multiple, Zymbal gland																										
Carcinoma, metastatic, multiple, uterus																										
Carcinoma, metastatic, metastatic																										
Leukemia mononuclear																										
Squamous cell carcinoma, metastatic, pharynx								X																		
Mediastinum, sarcoma																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																										
Eye														+			+									
Harderian gland														+												
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Carcinoma		X			X														X		X	X		X		
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																										
Ureter							+																			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 170 ppm (Continued)

WEEKS ON STUDY	059	060	061	061	061	063	063	063	065	065	065	067	067	068	068	069	069	069	069	069	070	072	073	073	076
CARCASS ID	661	694	625	702	763	675	685	724	674	643	744	734	752	684	693	624	691	692	723	743	623	742	751	653	741
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumbar, leukemia mononuclear																									
Mediastinal, leukemia mononuclear																									
Pancreatic, leukemia mononuclear																									
Renal, carcinoma, metastatic, uterus					X																				
Thoracic, leukemia mononuclear																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																
Axillary, renal, carcinoma, metastatic																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X							X																
Thymus	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+
Leukemia mononuclear																									
Lymphoma malignant lymphocytic																X									
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma												X			X				X	X		X			X
Adenocarcinoma, multiple																									
Fibroadenoma														X			X								X
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma			X																						
Papilloma squamous																									
Papilloma squamous, multiple																									
Subcutaneous tissue, carcinoma, metastatic																									
Subcutaneous tissue, squamous cell carcinoma, metastatic, pharynx																									
MUSCULOSKELETAL SYSTEM																									
Bone		+				+	+		+							+								+	
Skeletal muscle																									
Intercostal, leukemia mononuclear																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cerebellum, astrocytoma malignant																									
Meninges, cerebrum, nerve, carcinoma, metastatic, Zymbal gland																									
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, multiple, mammary gland											X														
Alveolar/bronchiolar adenoma								X																	
Carcinoma, metastatic, clitoral gland																									
Carcinoma, metastatic, multiple, Zymbal gland																									
Carcinoma, metastatic, multiple, uterus					X																				
Carcinoma, metastatic, metastatic																									
Leukemia mononuclear									X																
Squamous cell carcinoma, metastatic, pharynx																									
Mediastinum, sarcoma																						X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																									
Harderian gland																									
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X											X									
Carcinoma				X						X	X				X			X							
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X															
Ureter					+																				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 170 ppm (Continued)

WEEKS ON STUDY	07 7	07 9	07 9	07 9	07 9	08 0	08 1	08 1	08 1	08 1	08 1	08 1	08 2	08 4	08 6	08 6	08 8	08 8	09 2	09 3	09 3	09 3	09 3	09 3	TOTAL
CARCASS ID	73 3	63 3	70 1	71 4	72 2	64 1	68 3	65 2	71 3	63 2	73 2	76 2	65 1	76 1	64 2	67 3	62 2	72 1	68 2	62 1	63 1	68 1	71 1	71 2	73 1	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Lumbar, leukemia mononuclear			X																							1
Mediastinal, leukemia mononuclear			X																							1
Pancreatic, leukemia mononuclear			X			X																				2
Renal, carcinoma, metastatic, uterus																										1
Thoracic, leukemia mononuclear			X																							1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	74
Leukemia mononuclear			X			X						X														4
Axillary, renal, carcinoma, metastatic									X																	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Leukemia mononuclear			X			X																				2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Leukemia mononuclear			X	X		X		X		X		X	X								X	X	X			12
Thymus	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	68
Leukemia mononuclear			X																							1
Lymphoma malignant lymphocytic																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Adenocarcinoma										X					X					X			X			13
Adenocarcinoma, multiple									X																	1
Fibroadenoma								X			X						X			X				X		8
Fibroadenoma, multiple																X										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Basal cell adenoma																X			X							3
Papilloma squamous								X																		2
Papilloma squamous, multiple																			X							1
Subcutaneous tissue, carcinoma, metastatic									X																	1
Subcutaneous tissue, squamous cell carcinoma, metastatic, pharynx																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+																									8
Skeletal muscle			+																							1
Intercostal, leukemia mononuclear			X																							1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Cerebellum, astrocytoma malignant																				X						1
Meninges, cerebrum, nerve, carcinoma, metastatic, Zymbal gland													X													1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Adenocarcinoma, metastatic, multiple, mammary gland																										1
Alveolar/bronchiolar adenoma																										1
Carcinoma, metastatic, clitoral gland																										1
Carcinoma, metastatic, multiple, Zymbal gland													X													1
Carcinoma, metastatic, multiple, uterus																										1
Carcinoma, metastatic, metastatic									X																	1
Leukemia mononuclear			X			X						X														4
Squamous cell carcinoma, metastatic, pharynx																										1
Mediastinum, sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
SPECIAL SENSES SYSTEM																										
Eye													+	+			+									5
Harderian gland																										1
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Adenoma						X	X																			4
Carcinoma					X			X				X	X			X					X					17
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75
Leukemia mononuclear																										1
Ureter																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	75

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE: 330 ppm

WEEKS ON STUDY	036	038	039	041	041	044	044	046	049	049	050	050	050	050	050	051	052	052	054	054	054	057	058	059	059	059
CARCASS ID	094 5	094 4	099 5	101 5	097 5	100 5	101 4	099 4	093 5	096 5	095 5	098 4	098 5	102 4	102 5	096 3	093 4	094 3	099 5	098 4	093 3	102 3	095 2	095 3	100 4
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Descending colon, polyp adenomatous																									
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Polyp adenomatous																									
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, cystic, mucinous																									
Carcinoma, metastatic, urinary bladder																		X							
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, cystic, mucinous																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, urinary bladder																		X							
Hepatocellular carcinoma																									
Leukemia mononuclear																									
Neoplastic nodule, multiple																							X		
Mesentery																+		+				+			
Carcinoma, metastatic, multiple, urinary bladder																		X							
Sarcoma stromal, metastatic, uterus																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, urinary bladder																		X							
Pharynx																									+
Palate, papilloma squamous																									X
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Papilloma squamous																									
Squamous cell carcinoma																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Pars distalis, adenoma																							X		
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenoma		X					X		X			X										X			
Carcinoma			X		X	X	X	X	X	X	X	X	X		X		X		X	X					
Carcinoma, metastatic, clitoral gland																	X								
Bilateral, adenoma																									
Bilateral, carcinoma																							X		
Ovary	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, urinary bladder																		X							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Deciduoma benign																									
Polyp stromal																				X					
Sarcoma stromal																									
Cervix, sarcoma stromal, metastatic, uterus																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 330 ppm (Continued)

WEEKS ON STUDY	061	061	061	061	061	062	062	062	062	062	063	063	063	065	065	065	067	069	069	069	069	070	070	071	079
CARCASS ID	1035	0942	0974	1003	1013	0993	0951	0962	0992	1012	0961	1011	1022	1002	0932	1001	0973	0982	0983	1034	1045	0931	1044	1043	0972
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Descending colon, polyp adenomatous				X			X																		
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Polyp adenomatous							X																		
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Adenocarcinoma, cystic, mucinous																									
Carcinoma, metastatic, urinary bladder																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenocarcinoma, cystic, mucinous															X										
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, urinary bladder																									
Hepatocellular carcinoma																									
Leukemia mononuclear						X										X									
Neoplastic nodule, multiple																									
Mesentery						+								+											
Carcinoma, metastatic, multiple, urinary bladder																									
Sarcoma stromal, metastatic, uterus														X											
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Carcinoma, metastatic, urinary bladder																									
Pharynx																									
Palate, papilloma squamous																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue							+																+		
Papilloma squamous																									
Squamous cell carcinoma							X																X		
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Adrenal gland, medulla	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Pars distalis, adenoma													X		X	X					X	X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma												X													
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M
Adenoma						X	X					X										X	X		
Carcinoma				X						X	X	X	X					X		X	X	X			
Carcinoma, metastatic, clitoral gland																									
Bilateral, adenoma																									
Bilateral, carcinoma					X				X																
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Carcinoma, metastatic, urinary bladder																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Adenoma																									
Deciduoma benign										X															
Polyp stromal										X													X		
Sarcoma stromal														X											
Cervix, sarcoma stromal, metastatic, uterus														X											
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X										X									
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	M	+	+	+	+

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 330 ppm (Continued)

WEEKS ON STUDY	0 8 0	0 8 0	0 8 1	0 8 1	0 8 1	0 8 6	0 8 6	0 8 8	0 8 8	0 8 8	TOTAL: TISSUES TUMORS
CARCASS ID	0 9 9 1	1 0 2 1	1 0 4 2	1 0 3 2	1 0 3 3	0 9 8 1	1 0 4 1	0 9 4 1	0 9 7 1	1 0 3 1	
ALIMENTARY SYSTEM											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Intestine large	+	+	+	+	+	+	+	+	+	+	59
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	58
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	59
Descending colon, polyp adenomatous											2
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	59
Adenocarcinoma				X							1
Polyp adenomatous											1
Intestine small	+	+	+	+	+	+	+	+	+	+	59
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	58
Adenocarcinoma, cystic, mucinous					X						1
Carcinoma, metastatic, urinary bladder											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	58
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	58
Adenocarcinoma, cystic, mucinous											1
Liver	+	+	+	+	+	+	+	+	+	+	60
Carcinoma, metastatic, urinary bladder											1
Hepatocellular carcinoma							X				1
Leukemia mononuclear	X									X	4
Neoplastic nodule, multiple									X		2
Mesentery				+				+			7
Carcinoma, metastatic, multiple, urinary bladder											1
Sarcoma stromal, metastatic, uterus											1
Pancreas	+	+	+	+	+	+	+	+	+	+	59
Carcinoma, metastatic, urinary bladder											1
Pharynx									+		2
Palate, papilloma squamous											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	59
Stomach	+	+	+	+	+	+	+	+	+	+	59
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	58
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	59
Tongue							+		+		4
Papilloma squamous							X		X		2
Squamous cell carcinoma											2
CARDIOVASCULAR SYSTEM											
Heart	+	+	+	+	+	+	+	+	+	+	60
ENDOCRINE SYSTEM											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear	X									X	2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear	X									X	2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	59
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	59
Pituitary gland	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear	X										1
Pars distalis, adenoma						X			X		8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	59
C-cell, adenoma											1
Follicular cell, adenoma					X						1
GENERAL BODY SYSTEM											
None											
GENITAL SYSTEM											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	55
Adenoma		X				X				X	13
Carcinoma			X	X			X				26
Carcinoma, metastatic, clitoral gland											1
Bilateral, adenoma	X							X	X		3
Bilateral, carcinoma					X						4
Ovary	+	+	+	+	+	+	+	+	+	+	58
Carcinoma, metastatic, urinary bladder											1
Uterus	+	+	+	+	+	+	+	+	+	+	59
Adenoma				X						X	2
Deciduoma benign											1
Polyp stromal		X		X							5
Sarcoma stromal											1
Cervix, sarcoma stromal, metastatic, uterus											1
HEMATOPOIETIC SYSTEM											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node	+	+	+	+	+	+	+	+	+	+	60
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	59
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	58
Leukemia mononuclear										X	1
Spleen	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear	X									X	4
Thymus	+	M	+	+	+	+	+	+	+	+	54

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 330 ppm (Continued)

WEEKS ON STUDY	036	038	039	041	041	044	044	046	049	049	050	050	050	050	050	051	052	052	054	054	057	058	059	059	059
CARCASS ID	09445	09444	09955	10155	09775	10055	10144	09944	09935	09665	09555	09664	09885	10244	10255	09633	09343	09443	09543	09844	09933	10233	09952	09953	10044
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma				X							X		X	X					X						
Adenocarcinoma, multiple																									
Adenoma																								X	
Fibroadenoma														X											
Mixed tumor malignant																X									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
MUSCULOSKELETAL SYSTEM																									
Bone																									
Skeletal muscle																		+							
Diaphragm, carcinoma, metastatic, urinary bladder																		X							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, urinary bladder																		X							
Leukemia mononuclear																									
Mixed tumor malignant, metastatic, multiple, mammary gland																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																									
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma		X							X						X			X				X		X	X
Bilateral, carcinoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma, metastatic, urinary bladder																		X							
Transitional epithelium, carcinoma																					X				
Ureter																		+							
Carcinoma, metastatic, urinary bladder																		X							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus																									
Transitional epithelium, carcinoma																		X							

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 330 ppm (Continued)

WEEKS ON STUDY	061	061	061	061	062	062	062	062	062	063	063	063	065	065	065	067	069	069	069	069	070	070	071	079
CARCASS ID	10351	09422	09744	10103	10133	09933	09951	09622	09922	10122	09611	10111	10222	10022	09322	10101	09733	09822	09833	10334	10445	09931	10444	10433	09972
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma		X	X	X	X			X		X			X					X		X				X	
Adenocarcinoma, multiple																									
Adenoma																									
Fibroadenoma																			X	X					
Mixed tumor malignant																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
MUSCULOSKELETAL SYSTEM																									
Bone								+										+							
Skeletal muscle																									
Diaphragm, carcinoma, metastatic, urinary bladder																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X						
Carcinoma, metastatic, urinary bladder																									
Leukemia mononuclear															X										
Mixed tumor malignant, metastatic, multiple, mammary gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																									
Zymbal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X													X							
Carcinoma																			X			X			
Bilateral, carcinoma	X														X					X					
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma, metastatic, urinary bladder																									
Transitional epithelium, carcinoma																									
Ureter																									
Carcinoma, metastatic, urinary bladder																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus													X												
Transitional epithelium, carcinoma																									

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 330 ppm (Continued)

WEEKS ON STUDY	0 8 0	0 8 0	0 8 1	0 8 1	0 8 1	0 8 6	0 8 6	0 8 8	0 8 8	0 8 8	TOTAL: TISSUES TUMORS
CARCASS ID	0 9 9 1	1 0 2 1	1 0 4 2	1 0 3 2	1 0 3 3	0 9 8 1	1 0 4 1	0 9 4 1	0 9 7 1	1 0 3 1	
INTEGUMENTARY SYSTEM											
Mammary gland	+	+	+	+	+	+	+	+	+	+	59
Adenocarcinoma					X			X	X		18
Adenocarcinoma, multiple			X			X					2
Adenoma								X			2
Fibroadenoma									X		4
Mixed tumor malignant											1
Skin	+	+	+	+	+	+	+	+	+	+	60
Basal cell adenoma								X	X		2
MUSCULOSKELETAL SYSTEM											
Bone					+					+	4
Skeletal muscle											1
Diaphragm, carcinoma, metastatic, urinary bladder											1
NERVOUS SYSTEM											
Brain	+	+	+	+	+	+	+	+	+	+	60
RESPIRATORY SYSTEM											
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma											1
Carcinoma, metastatic, urinary bladder											1
Leukemia mononuclear											1
Mixed tumor malignant, metastatic, multiple, mammary gland											1
Nose	+	+	+	+	+	+	+	+	+	+	60
Trachea	+	+	+	+	+	+	+	+	+	+	60
SPECIAL SENSES SYSTEM											
Harderian gland									+		1
Zymbal gland	+	+	+	+	+	+	+	+	+	+	60
Adenoma						X					3
Carcinoma							X				10
Bilateral, carcinoma											3
URINARY SYSTEM											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Renal tubule, carcinoma, metastatic, urinary bladder											1
Transitional epithelium, carcinoma											1
Ureter											1
Carcinoma, metastatic, urinary bladder											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	59
Sarcoma stromal, metastatic, uterus											1
Transitional epithelium, carcinoma											1

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

	Control	80 ppm	170 ppm	330 ppm
Adrenal Medulla: Pheochromocytoma				
Overall Rates (a)	5/60 (8%)	1/45 (2%)	1/74 (1%)	0/59 (0%)
Effective Rates (b)	5/56 (9%)	1/34 (3%)	1/18 (6%)	0/8 (0%)
Terminal Rates (c)	4/45 (9%)	1/15 (7%)	0/5 (0%)	0/0
Day of First Observation	574	648	562	
Life Table Tests (d)	P=0.601N	P=0.462N	P=0.652	P=0.936N
Logistic Regression Tests (d)	P=0.247N	P=0.298N	P=0.470N	P=0.490N
Cochran-Armitage Trend Test (d)	P=0.027N			
Fisher Exact Test (d)		P=0.261N	P=0.546N	P=0.501N
Clitoral Gland: Adenoma				
Overall Rates (a)	5/58 (9%)	15/44 (34%)	13/74 (18%)	16/55 (29%)
Effective Rates (b)	5/58 (9%)	15/44 (34%)	13/73 (18%)	16/55 (29%)
Terminal Rates (c)	**5/44 (11%)**	7/15 (47%)	0/6 (0%)	0/0
Day of First Observation	648	436	358	262
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P=0.002	P<0.001	P=0.133	P<0.001
Cochran-Armitage Trend Test (d)	P=0.035			
Fisher Exact Test (d)		P=0.002	P=0.102	P=0.005
Clitoral Gland: Carcinoma				
Overall Rates (a)	2/58 (3%)	17/44 (39%)	41/74 (55%)	30/55 (55%)
Effective Rates (b)	2/58 (3%)	17/44 (39%)	41/74 (55%)	30/55 (55%)
Terminal Rates (c)	2/44 (5%)	5/15 (33%)	3/6 (50%)	0/0
Day of First Observation	648	373	220	270
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P<0.001	P<0.001	P=0.004
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P<0.001	P<0.001	P<0.001
Clitoral Gland: Adenoma or Carcinoma				
Overall Rates (a)	7/58 (12%)	27/44 (61%)	48/74 (65%)	41/55 (75%)
Effective Rates (b)	7/58 (12%)	27/44 (61%)	48/74 (65%)	41/55 (75%)
Terminal Rates (c)	7/44 (16%)	10/15 (67%)	3/6 (50%)	0/0
Day of First Observation	648	373	220	262
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P<0.001	P<0.001	P<0.001
Large Intestine: Adenomatous Polyp or Adenocarcinoma				
Overall Rates (e)	0/60 (0%)	1/45 (2%)	1/75 (1%)	3/60 (5%)
Effective Rates (b)	0/59 (0%)	1/44 (2%)	1/48 (2%)	3/35 (9%)
Terminal Rates (c)	0/45 (0%)	1/15 (7%)	0/6 (0%)	0/0
Day of First Observation		648	424	424
Life Table Tests (d)	P=0.001	P=0.282	P=0.455	P=0.011
Logistic Regression Tests (d)	P=0.051	P=0.282	P=0.886	P=0.163
Cochran-Armitage Trend Test (d)	P=0.020			
Fisher Exact Test (d)		P=0.427	P=0.449	P=0.049
Liver: Neoplastic Nodule or Hepatocellular Carcinoma				
Overall Rates (a)	0/60 (0%)	1/44 (2%)	0/75 (0%)	3/60 (5%)
Effective Rates (b)	0/59 (0%)	1/44 (2%)	0/47 (0%)	3/38 (8%)
Terminal Rates (c)	0/45 (0%)	1/15 (7%)	0/6 (0%)	0/0
Day of First Observation		648		408
Life Table Tests (d)	P<0.001	P=0.282	(f)	P<0.001
Logistic Regression Tests (d)	P=0.002	P=0.282	(f)	P=0.013
Cochran-Armitage Trend Test (d)	P=0.022			
Fisher Exact Test (d)		P=0.427	(f)	P=0.057

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Control	80 ppm	170 ppm	330 ppm
Mammary Gland: Fibroadenoma				
Overall Rates (e)	14/60 (23%)	11/45 (24%)	9/75 (12%)	4/60 (7%)
Effective Rates (b)	14/60 (23%)	11/45 (24%)	9/63 (14%)	4/50 (8%)
Terminal Rates (c)	12/45 (27%)	6/15 (40%)	2/6 (33%)	0/0
Day of First Observation	532	424	476	344
Life Table Tests (d)	P<0.001	P=0.038	P=0.003	P=0.006
Logistic Regression Tests (d)	P=0.503	P=0.383	P=0.248	P=0.525N
Cochran-Armitage Trend Test (d)	P=0.011N			
Fisher Exact Test (d)		P=0.537	P=0.146N	P=0.026N
Mammary Gland: Adenoma or Fibroadenoma				
Overall Rates (e)	14/60 (23%)	11/45 (24%)	9/75 (12%)	6/60 (10%)
Effective Rates (b)	14/60 (23%)	11/45 (24%)	9/63 (14%)	6/50 (12%)
Terminal Rates (c)	12/45 (27%)	6/15 (40%)	2/6 (33%)	0/0
Day of First Observation	532	424	476	344
Life Table Tests (d)	P<0.001	P=0.038	P=0.003	P<0.001
Logistic Regression Tests (d)	P=0.252	P=0.383	P=0.248	P=0.553
Cochran-Armitage Trend Test (d)	P=0.044N			
Fisher Exact Test (d)		P=0.537	P=0.146N	P=0.098N
Mammary Gland: Adenocarcinoma				
Overall Rates (e)	1/60 (2%)	2/45 (4%)	14/75 (19%)	20/60 (33%)
Effective Rates (b)	1/60 (2%)	2/45 (4%)	14/73 (19%)	20/57 (35%)
Terminal Rates (c)	1/45 (2%)	0/15 (0%)	2/6 (33%)	0/0
Day of First Observation	648	512	333	284
Life Table Tests (d)	P<0.001	P=0.252	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.468	P=0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.393	P<0.001	P<0.001
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma				
Overall Rates (e)	15/60 (25%)	13/45 (29%)	21/75 (28%)	22/60 (37%)
Effective Rates (b)	15/60 (25%)	13/45 (29%)	21/73 (29%)	22/57 (39%)
Terminal Rates (c)	13/45 (29%)	6/15 (40%)	3/6 (50%)	0/0
Day of First Observation	532	424	333	284
Life Table Tests (d)	P<0.001	P=0.016	P<0.001	P<0.001
Logistic Regression Tests (d)	P=0.001	P=0.294	P=0.024	P=0.030
Cochran-Armitage Trend Test (d)	P=0.068			
Fisher Exact Test (d)		P=0.410	P=0.387	P=0.083
Palate: Squamous Papilloma				
Overall Rates (e)	1/60 (2%)	0/45 (0%)	3/75 (4%)	1/60 (2%)
Effective Rates (b)	1/59 (2%)	0/44 (0%)	3/52 (6%)	1/38 (3%)
Terminal Rates (c)	1/45 (2%)	0/15 (0%)	0/6 (0%)	0/0
Day of First Observation	648		450	408
Life Table Tests (d)	P=0.027	P=0.718N	P=0.021	P=0.412
Logistic Regression Tests (d)	P=0.341	P=0.718N	P=0.158	P=0.884N
Cochran-Armitage Trend Test (d)	P=0.330			
Fisher Exact Test (d)		P=0.573N	P=0.263	P=0.633
Palate: Squamous Papilloma or Squamous Cell Carcinoma				
Overall Rates (e)	1/60 (2%)	0/45 (0%)	4/75 (5%)	1/60 (2%)
Effective Rates (b)	1/60 (2%)	0/45 (0%)	4/68 (6%)	1/52 (2%)
Terminal Rates (c)	1/45 (2%)	0/15 (0%)	0/6 (0%)	0/0
Day of First Observation	648		331	408
Life Table Tests (d)	P=0.039	P=0.718N	P=0.013	P=0.412
Logistic Regression Tests (d)	P=0.543	P=0.718N	P=0.238	P=0.884N
Cochran-Armitage Trend Test (d)	P=0.408			
Fisher Exact Test (d)		P=0.571N	P=0.224	P=0.715

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Control	80 ppm	170 ppm	330 ppm
Tongue: Squamous Papilloma or Squamous Cell Carcinoma				
Overall Rates (e)	1/60 (2%)	2/45 (4%)	2/75 (3%)	4/60 (7%)
Effective Rates (b)	1/59 (2%)	2/44 (5%)	2/48 (4%)	4/35 (11%)
Terminal Rates (c)	1/45 (2%)	1/15 (7%)	0/6 (0%)	0/0
Day of First Observation	648	644	423	431
Life Table Tests (d)	P<0.001	P=0.161	P=0.209	P<0.001
Logistic Regression Tests (d)	P=0.011	P=0.178	P=0.677	P=0.012
Cochran-Armitage Trend Test (d)	P=0.037			
Fisher Exact Test (d)		P=0.390	P=0.422	P=0.062
Oral Cavity: Squamous Papilloma				
Overall Rates (e)	2/60 (3%)	2/45 (4%)	3/75 (4%)	3/60 (5%)
Effective Rates (b)	2/59 (3%)	2/44 (5%)	3/52 (6%)	3/38 (8%)
Terminal Rates (c)	2/45 (4%)	1/15 (7%)	0/6 (0%)	0/0
Day of First Observation	648	644	450	408
Life Table Tests (d)	P<0.001	P=0.283	P=0.040	P<0.001
Logistic Regression Tests (d)	P=0.018	P=0.306	P=0.257	P=0.062
Cochran-Armitage Trend Test (d)	P=0.214			
Fisher Exact Test (d)		P=0.574	P=0.440	P=0.299
Oral Cavity: Squamous Cell Carcinoma				
Overall Rates (e)	0/60 (0%)	0/45 (0%)	3/75 (4%)	2/60 (3%)
Effective Rates (b)	0/60 (0%)	0/45 (0%)	3/68 (4%)	2/52 (4%)
Terminal Rates (c)	0/45 (0%)	0/15 (0%)	0/6 (0%)	0/0
Day of First Observation			331	431
Life Table Tests (d)	P=0.016	(f)	P=0.078	P=0.055
Logistic Regression Tests (d)	P=0.339	(f)	P=0.527	P=0.429
Cochran-Armitage Trend Test (d)	P=0.082			
Fisher Exact Test (d)		(f)	P=0.147	P=0.213
Oral Cavity: Squamous Papilloma or Squamous Cell Carcinoma				
Overall Rates (e)	2/60 (3%)	2/45 (4%)	6/75 (8%)	5/60 (8%)
Effective Rates (b)	2/60 (3%)	2/45 (4%)	6/68 (9%)	5/52 (10%)
Terminal Rates (c)	2/45 (4%)	1/15 (7%)	0/6 (0%)	0/0
Day of First Observation	648	644	331	408
Life Table Tests (d)	P<0.001	P=0.283	P=0.004	P<0.001
Logistic Regression Tests (d)	P=0.028	P=0.306	P=0.212	P=0.028
Cochran-Armitage Trend Test (d)	P=0.094			
Fisher Exact Test (d)		P=0.576	P=0.181	P=0.164
Pituitary Gland/Pars Distalis: Adenoma				
Overall Rates (a)	15/60 (25%)	9/45 (20%)	5/75 (7%)	8/60 (13%)
Effective Rates (b)	15/59 (25%)	9/44 (20%)	5/53 (9%)	8/38 (21%)
Terminal Rates (c)	10/45 (22%)	3/15 (20%)	2/6 (33%)	0/0
Day of First Observation	574	505	468	408
Life Table Tests (d)	P<0.001	P=0.212	P=0.190	P<0.001
Logistic Regression Tests (d)	P=0.242	P=0.528N	P=0.375N	P=0.388
Cochran-Armitage Trend Test (d)	P=0.224N			
Fisher Exact Test (d)		P=0.364N	P=0.024N	P=0.405N
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma				
Overall Rates (a)	17/60 (28%)	9/45 (20%)	5/75 (7%)	8/60 (13%)
Effective Rates (b)	17/59 (29%)	9/44 (20%)	5/52 (10%)	8/38 (21%)
Terminal Rates (c)	11/45 (24%)	3/15 (20%)	2/6 (33%)	0/0
Day of First Observation	574	505	468	408
Life Table Tests (d)	P<0.001	P=0.309	P=0.252	P<0.001
Logistic Regression Tests (d)	P=0.351	P=0.375N	P=0.255N	P=0.497
Cochran-Armitage Trend Test (d)	P=0.131N			
Fisher Exact Test (d)		P=0.232N	P=0.010N	P=0.271N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Control	80 ppm	170 ppm	330 ppm
Skin: Basal Cell Adenoma				
Overall Rates (e)	0/60 (0%)	3/45 (7%)	3/75 (4%)	2/60 (3%)
Effective Rates (b)	0/59 (0%)	3/44 (7%)	3/48 (6%)	2/35 (6%)
Terminal Rates (c)	0/45 (0%)	3/15 (20%)	0/6 (0%)	0/0
Day of First Observation		648	423	610
Life Table Tests (d)	P<0.001	P=0.009	P=0.006	P<0.001
Logistic Regression Tests (d)	P=0.003	P=0.009	P=0.058	P=0.001
Cochran-Armitage Trend Test (d)	P=0.155			
Fisher Exact Test (d)		P=0.075	P=0.087	P=0.136
Skin: Basal Cell Adenoma or Carcinoma				
Overall Rates (e)	0/60 (0%)	4/45 (9%)	3/75 (4%)	2/60 (3%)
Effective Rates (b)	0/59 (0%)	4/44 (9%)	3/48 (6%)	2/35 (6%)
Terminal Rates (c)	0/45 (0%)	4/15 (27%)	0/6 (0%)	0/0
Day of First Observation		648	423	610
Life Table Tests (d)	P<0.001	P=0.002	P=0.006	P<0.001
Logistic Regression Tests (d)	P=0.003	P=0.002	P=0.058	P=0.001
Cochran-Armitage Trend Test (d)	P=0.203			
Fisher Exact Test (d)		P=0.031	P=0.087	P=0.136
Thyroid Gland: C-Cell Adenoma				
Overall Rates (a)	4/60 (7%)	1/44 (2%)	2/75 (3%)	1/59 (2%)
Effective Rates (b)	4/59 (7%)	1/41 (2%)	2/45 (4%)	1/25 (4%)
Terminal Rates (c)	2/45 (4%)	0/15 (0%)	2/6 (33%)	0/0
Day of First Observation	543	616	648	436
Life Table Tests (d)	P=0.094	P=0.514N	P=0.235	P=0.472
Logistic Regression Tests (d)	P=0.589	P=0.288N	P=0.497	P=0.410N
Cochran-Armitage Trend Test (d)	P=0.407N			
Fisher Exact Test (d)		P=0.314N	P=0.475N	P=0.531N
Thyroid Gland: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	5/60 (8%)	1/44 (2%)	3/75 (4%)	1/59 (2%)
Effective Rates (b)	5/59 (8%)	1/41 (2%)	3/45 (7%)	1/25 (4%)
Terminal Rates (c)	2/45 (4%)	0/15 (0%)	2/6 (33%)	0/0
Day of First Observation	543	616	616	436
Life Table Tests (d)	P=0.066	P=0.388N	P=0.094	P=0.518
Logistic Regression Tests (d)	P=0.580	P=0.176N	P=0.369	P=0.276N
Cochran-Armitage Trend Test (d)	P=0.354N			
Fisher Exact Test (d)		P=0.210N	P=0.517N	P=0.419N
Uterus: Adenoma				
Overall Rates (e)	0/60 (0%)	3/45 (7%)	1/75 (1%)	2/60 (3%)
Effective Rates (b)	0/56 (0%)	3/34 (9%)	1/19 (5%)	2/8 (25%)
Terminal Rates (c)	0/45 (0%)	1/15 (7%)	1/6 (17%)	0/0
Day of First Observation		618	648	563
Life Table Tests (d)	P<0.001	P=0.014	P=0.118	P<0.001
Logistic Regression Tests (d)	P=0.001	P=0.029	P=0.118	P=0.010
Cochran-Armitage Trend Test (d)	P=0.007			
Fisher Exact Test (d)		P=0.051	P=0.253	P=0.014
Uterus: Adenoma or Carcinoma				
Overall Rates (e)	0/60 (0%)	4/45 (9%)	2/75 (3%)	2/60 (3%)
Effective Rates (b)	0/59 (0%)	4/44 (9%)	2/48 (4%)	2/35 (6%)
Terminal Rates (c)	0/45 (0%)	1/15 (7%)	1/6 (17%)	0/0
Day of First Observation		606	424	563
Life Table Tests (d)	P<0.001	P=0.005	P=0.056	P<0.001
Logistic Regression Tests (d)	P=0.020	P=0.013	P=0.228	P=0.010
Cochran-Armitage Trend Test (d)	P=0.230			
Fisher Exact Test (d)		P=0.031	P=0.199	P=0.136

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Control	80 ppm	170 ppm	330 ppm
Uterus: Stromal Polyp				
Overall Rates (e)	6/60 (10%)	8/45 (18%)	7/75 (9%)	5/60 (8%)
Effective Rates (b)	6/60 (10%)	8/45 (18%)	7/57 (12%)	5/42 (12%)
Terminal Rates (c)	6/45 (13%)	2/15 (13%)	0/6 (0%)	0/0
Day of First Observation	648	436	424	378
Life Table Tests (d)	P<0.001	P=0.020	P=0.009	P<0.001
Logistic Regression Tests (d)	P=0.433	P=0.214	P=0.397	P=0.234
Cochran-Armitage Trend Test (d)	P=0.542			
Fisher Exact Test (d)		P=0.192	P=0.460	P=0.501
Zymbal Gland: Adenoma				
Overall Rates (a)	0/60 (0%)	3/45 (7%)	4/75 (5%)	3/60 (5%)
Effective Rates (b)	0/59 (0%)	3/44 (7%)	4/48 (8%)	3/35 (9%)
Terminal Rates (c)	0/45 (0%)	0/15 (0%)	0/6 (0%)	0/0
Day of First Observation		424	424	424
Life Table Tests (d)	P<0.001	P=0.036	P=0.010	P=0.005
Logistic Regression Tests (d)	P=0.137	P=0.150	P=0.090	P=0.071
Cochran-Armitage Trend Test (d)	P=0.054			
Fisher Exact Test (d)		P=0.075	P=0.038	P=0.049
Zymbal Gland: Carcinoma				
Overall Rates (a)	1/60 (2%)	10/45 (22%)	17/75 (23%)	13/60 (22%)
Effective Rates (b)	1/60 (2%)	10/45 (22%)	17/74 (23%)	13/59 (22%)
Terminal Rates (c)	0/45 (0%)	0/15 (0%)	1/6 (17%)	0/0
Day of First Observation	402	424	274	262
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P=0.187	P=0.013	P=0.011	P=0.145
Cochran-Armitage Trend Test (d)	P=0.006			
Fisher Exact Test (d)		P<0.001	P<0.001	P<0.001
Zymbal Gland: Adenoma or Carcinoma				
Overall Rates (a)	1/60 (2%)	12/45 (27%)	21/75 (28%)	16/60 (27%)
Effective Rates (b)	1/60 (2%)	12/45 (27%)	21/74 (28%)	16/59 (27%)
Terminal Rates (c)	0/45 (0%)	0/15 (0%)	1/6 (17%)	0/0
Day of First Observation	402	424	274	262
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P=0.068	P=0.005	P=0.001	P=0.019
Cochran-Armitage Trend Test (d)	P=0.002			
Fisher Exact Test (d)		P<0.001	P<0.001	P<0.001
Hematopoietic System: Mononuclear Leukemia				
Overall Rates (e)	21/60 (35%)	15/45 (33%)	12/75 (16%)	4/60 (7%)
Effective Rates (b)	21/59 (36%)	15/44 (34%)	12/49 (24%)	4/35 (11%)
Terminal Rates (c)	13/45 (29%)	6/15 (40%)	3/6 (50%)	0/0
Day of First Observation	532	562	419	430
Life Table Tests (d)	P<0.001	P=0.052	P=0.003	P=0.019
Logistic Regression Tests (d)	P=0.351N	P=0.479	P=0.548	P=0.180N
Cochran-Armitage Trend Test (d)	P=0.005N			
Fisher Exact Test (d)		P=0.521N	P=0.150N	P=0.008N

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Number of tumor-bearing animals/effective number of animals, i.e., number of animals alive at the first occurrence of tumors in any of the four groups
(c) Observed tumor incidence in animals killed at the end of the study
(d) Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the effective tumor rates. A negative trend or a lower incidence in a dosed group than in controls is indicated by (N).
(e) Number of tumor-bearing animals/number of animals examined grossly at the site
(f) No P value is reported because no tumors were observed in the dosed and control groups.

TABLE B4a. HISTORICAL INCIDENCE OF LIVER TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls	
	Neoplastic Nodule	Neoplastic Nodule or Hepatocellular Carcinoma
Historical Incidence at Hazleton Laboratories America, Inc.		
Decabromodiphenyl oxide	1/50	1/50
Chlorendic acid	1/50	1/50
TOTAL	2/100 (2.0%)	2/100 (2.0%)
Overall Historical Incidence		
TOTAL	34/1,643 (2.1%)	37/1,643 (2.3%)
SD (b)	2.62%	2.73%
Range (c)		
High	5/50	5/50
Low	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE B4b. HISTORICAL INCIDENCE OF TUMORS OF THE LARGE INTESTINE IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls
Historical Incidence at Hazleton Laboratories America, Inc.	
TOTAL	0/88
Overall Historical Incidence	
TOTAL	0/1,601

(a) Data as of May 12, 1988, for studies of at least 104 weeks

TABLE B4c. HISTORICAL INCIDENCE OF TUMORS OF THE SMALL INTESTINE IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls
Historical Incidence at Hazleton Laboratories America, Inc.	
TOTAL	0/99
Overall Historical Incidence	
TOTAL	0/1,611

(a) Data as of May 12, 1988, for studies of at least 104 weeks

TABLE B4d. HISTORICAL INCIDENCE OF ZYMBAL GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Carcinomas in Controls
Historical Incidence at Hazleton Laboratories America, Inc.	
Decabromodiphenyl oxide	0/50
Chlorendic acid	1/50
TOTAL	1/100 (1.0%)
Overall Historical Incidence	
TOTAL	(b) 14/1,643 (0.9%)
SD (c)	1.50%
Range (d)	
High	3/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes four carcinomas, NOS, seven squamous cell carcinomas, one adenocarcinoma, NOS, and two adenosquamous carcinomas; no benign tumors have been observed.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B4e. HISTORICAL INCIDENCE OF CLITORAL GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Hazleton Laboratories America, Inc.			
Decabromodiphenyl oxide	0/50	4/50	4/50
Chlorendic acid	0/50	4/50	4/50
TOTAL	0/100	8/100 (8.0%)	8/100 (8.0%)
Overall Historical Incidence			
TOTAL	62/1,643 (3.8%)	(b) 53/1,643 (3.2%)	(b) 115/1,643 (7.0%)
SD (c)	4.36%	3.49%	4.86%
Range (d)			
High	10/50	6/49	10/50
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes three squamous cell carcinomas and four adenocarcinomas, NOS
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B4f. HISTORICAL INCIDENCE OF ORAL CAVITY SQUAMOUS CELL TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Papillomas or Carcinomas in Controls
Historical Incidence at Hazleton Laboratories America, Inc.	
Decabromodiphenyl oxide	0/50
Chlorendic acid	0/50
TOTAL	0/100
Overall Historical Incidence	
TOTAL	(b) 4/1,643 (0.2%)
SD (c)	0.66%
Range (d)	
High	1/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) All tumors were observed in the tongue.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B4g. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM BASAL CELL TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Benign	Malignant	Benign or Malignant
Historical Incidence at Hazleton Laboratories America, Inc.			
Decabromodiphenyl oxide	0/50	0/50	0/50
Chlorendic acid	0/50	0/50	0/50
TOTAL	0/100	0/100	0/100
Overall Historical Incidence			
TOTAL	(b) 3/1,643 (0.2%)	(c) 4/1,643 (0.2%)	(d) 7/1,643 (0.4%)
SD (e)	0.58%	0.66%	0.83%
Range (f)			
High	1/50	1/50	1/50
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes one trichoepithelioma and two basal cell tumors
(c) Basal cell carcinoma
(d) Includes one trichoepithelioma, two benign basal cell tumors, and one basal cell carcinoma
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE B4h. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM SQUAMOUS CELL TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence at Hazleton Laboratories America, Inc.			
Decabromodiphenyl oxide	0/50	0/50	0/50
Chlorendic acid	0/50	0/50	0/50
TOTAL	0/100	0/100	0/100
Overall Historical Incidence			
TOTAL	(b) 4/1,643 (0.2%)	3/1,643 (0.2%)	(b) 7/1,643 (0.4%)
SD (c)	0.66%	0.59%	0.83%
Range (d)			
High	1/50	1/49	1/49
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes two papillomas, NOS
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B4i. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Fibroadenoma	Adenocarcinoma	Fibroadenoma or Adenocarcinoma
Historical Incidence at Hazleton Laboratories America, Inc.			
Decabromodiphenyl oxide	24/50	2/50	25/50
Chlorendic acid	23/50	1/50	24/50
TOTAL	47/100 (47.0%)	3/100 (3.0%)	49/100 (49.0%)
Overall Historical Incidence			
TOTAL	(b) 520/1,643 (31.6%)	(c) 49/1,643 (3.0%)	(b,c) 552/1,643 (33.6%)
SD (d)	12.23%	2.07%	11.95%
Range (e)			
High	30/50	4/50	32/50
Low	5/50	0/50	6/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes 11 adenomas, NOS, 2 cystadenomas, NOS, and 1 papillary cystadenoma, NOS
(c) Includes two carcinomas, NOS, two papillary adenocarcinomas, and one papillary cystadenocarcinoma, NOS
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE B4j. HISTORICAL INCIDENCE OF BRAIN GLIAL CELL TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Astrocytomas in Controls
Historical Incidence at Hazleton Laboratories America, Inc.	
Decabromodiphenyl oxide	2/50
Chlorendic acid	0/50
TOTAL	2/100 (2.0%)
Overall Historical Incidence	
TOTAL	(b) 19/1,628 (1.2%)
SD (c)	1.51%
Range (d)	
High	3/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes four oligodendrogliomas
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B4k. HISTORICAL INCIDENCE OF UTERINE GLANDULAR TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Adenocarcinoma	Adenoma or Adenocarcinoma
Historical Incidence at Hazleton Laboratories America, Inc.			
Decabromodiphenyl oxide	0/49	0/49	0/49
Chlorendic acid	0/50	0/50	0/50
TOTAL	0/99	0/99	0/99
Overall Historical Incidence			
TOTAL	5/1,632 (0.3%)	(b) 7/1,632 (0.4%)	(b) 12/1,632 (0.7%)
SD (c)	0.75%	0.99%	1.44%
Range (d)			
High	1/45	2/50	2/45
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes one carcinoma, NOS, and one papillary adenocarcinoma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

	Untreated Control	80 ppm	170 ppm	330 ppm
Animals initially in study	70	45	75	70
Animals removed	70	45	75	70
Animals examined histopathologically	60	45	75	60
ALIMENTARY SYSTEM				
Intestine large, cecum	(60)	(44)	(75)	(58)
Hemorrhage, focal			1 (1%)	1 (2%)
Parasite metazoan		1 (2%)		
Submucosa, inflammation, acute				1 (2%)
Intestine large, colon	(60)	(44)	(75)	(59)
Parasite metazoan		1 (2%)	1 (1%)	1 (2%)
Descending colon, hemorrhage, focal			1 (1%)	
Muscularis, mineralization				1 (2%)
Intestine large, rectum	(60)	(43)	(74)	(59)
Parasite metazoan			3 (4%)	3 (5%)
Liver	(60)	(44)	(75)	(60)
Angiectasis	1 (2%)			
Angiectasis, focal	1 (2%)	1 (2%)		
Basophilic focus	44 (73%)	34 (77%)	54 (72%)	48 (80%)
Clear cell focus	7 (12%)	11 (25%)	18 (24%)	15 (25%)
Cyst				1 (2%)
Degeneration, cystic	1 (2%)	2 (5%)		3 (5%)
Degeneration, cystic, focal			1 (1%)	2 (3%)
Eosinophilic focus	5 (8%)	7 (16%)	20 (27%)	28 (47%)
Fatty change	1 (2%)	1 (2%)	4 (5%)	1 (2%)
Granuloma	10 (17%)	3 (7%)	7 (9%)	5 (8%)
Hematopoietic cell proliferation	1 (2%)	18 (41%)	43 (57%)	41 (68%)
Hepatodiaphragmatic nodule	5 (8%)	6 (14%)	4 (5%)	1 (2%)
Hepatodiaphragmatic nodule, multiple	1 (2%)		1 (1%)	
Necrosis, coagulative			1 (1%)	3 (5%)
Necrosis, focal			5 (7%)	9 (15%)
Necrosis, multifocal		1 (2%)	1 (1%)	1 (2%)
Pigmentation		1 (2%)		
Regeneration, diffuse	6 (10%)	2 (5%)	2 (3%)	1 (2%)
Regeneration, focal			1 (1%)	
Regeneration, multifocal		1 (2%)	2 (3%)	3 (5%)
Thrombus				1 (2%)
Vacuolization cytoplasmic, diffuse			3 (4%)	1 (2%)
Vacuolization cytoplasmic, focal	1 (2%)	1 (2%)		2 (3%)
Vacuolization cytoplasmic, multifocal	2 (3%)		1 (1%)	
Bile duct, hyperplasia	1 (2%)	1 (2%)	2 (3%)	
Bile duct, inflammation, chronic				1 (2%)
Centrilobular, degeneration	1 (2%)	1 (2%)	1 (1%)	1 (2%)
Centrilobular, degeneration, diffuse		2 (5%)	7 (9%)	4 (7%)
Centrilobular, necrosis	1 (2%)	1 (2%)	1 (1%)	
Centrilobular, necrosis, diffuse		1 (2%)	5 (7%)	5 (8%)
Kupffer cell, pigmentation				1 (2%)
Mesentery	(6)	(1)	(8)	(7)
Fat, accessory spleen			1 (13%)	
Fat, necrosis	6 (100%)	1 (100%)	5 (63%)	5 (71%)
Pancreas	(60)	(43)	(75)	(59)
Atrophy	4 (7%)	4 (9%)	4 (5%)	
Hemorrhage, focal				1 (2%)
Pharynx	(1)	(1)	(6)	(2)
Mucosa, palate, hyperplasia, focal			2 (33%)	1 (50%)
Palate, hyperkeratosis, focal		1 (100%)		
Salivary glands	(59)	(44)	(75)	(59)
Atrophy	1 (2%)		2 (3%)	
Inflammation, chronic		1 (2%)		
Stomach, forestomach	(60)	(44)	(74)	(58)
Acanthosis			3 (4%)	1 (2%)
Hyperkeratosis			1 (1%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Untreated Control	80 ppm	170 ppm	330 ppm
ALIMENTARY SYSTEM (Continued)				
Stomach, glandular	(60)	(44)	(75)	(59)
Erosion, focal		1 (2%)	1 (1%)	2 (3%)
Erosion, multifocal			1 (1%)	
Inflammation, acute				1 (2%)
Mineralization				2 (3%)
Necrosis, multifocal			1 (1%)	
Tongue	(1)	(2)	(5)	(4)
Hyperplasia, focal			2 (40%)	
CARDIOVASCULAR SYSTEM				
Heart	(60)	(45)	(75)	(60)
Cardiomyopathy, chronic	25 (42%)	17 (38%)	21 (28%)	17 (28%)
Artery, mineralization, multifocal				1 (2%)
Atrium, thrombus		1 (2%)		1 (2%)
Epicardium, inflammation, chronic				1 (2%)
ENDOCRINE SYSTEM				
Adrenal gland, cortex	(60)	(45)	(75)	(60)
Congestion			1 (1%)	
Degeneration, focal	1 (2%)	1 (2%)		
Ectasia			1 (1%)	
Hematopoietic cell proliferation				1 (2%)
Hyperplasia, focal	5 (8%)	1 (2%)		
Hyperplasia, multifocal			1 (1%)	
Hypertrophy, focal	2 (3%)	3 (7%)	1 (1%)	1 (2%)
Hypertrophy, multifocal			1 (1%)	
Infiltration cellular, lymphocytic				1 (2%)
Necrosis, focal				1 (2%)
Vacuolization cytoplasmic, diffuse			1 (1%)	3 (5%)
Vacuolization cytoplasmic, focal	2 (3%)			1 (2%)
Adrenal gland, medulla	(60)	(45)	(74)	(59)
Hematopoietic cell proliferation			1 (1%)	1 (2%)
Hyperplasia, focal	5 (8%)		1 (1%)	3 (5%)
Hyperplasia, multifocal	1 (2%)			
Parathyroid gland	(58)	(43)	(70)	(59)
Hyperplasia				1 (2%)
Pituitary gland	(60)	(45)	(75)	(60)
Pigmentation			1 (1%)	
Pars distalis, angiectasis	3 (5%)	4 (9%)	3 (4%)	1 (2%)
Pars distalis, cyst	14 (23%)	10 (22%)	17 (23%)	19 (32%)
Pars distalis, hemorrhage	1 (2%)			
Pars distalis, hyperplasia	1 (2%)			
Pars distalis, hyperplasia, diffuse	1 (2%)	2 (4%)		
Pars distalis, hyperplasia, focal	5 (8%)	4 (9%)	7 (9%)	2 (3%)
Pars distalis, hyperplasia, multifocal	1 (2%)		1 (1%)	
Pars distalis, necrosis, focal			1 (1%)	1 (2%)
Pars distalis, pigmentation, focal				1 (2%)
Pars intermedia, cyst				1 (2%)
Thyroid gland	(60)	(44)	(75)	(59)
C-cell, hyperplasia, focal	6 (10%)	4 (9%)	1 (1%)	3 (5%)
C-cell, hyperplasia, multifocal		1 (2%)		
GENERAL BODY SYSTEM				
None				

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Untreated Control	80 ppm	170 ppm	330 ppm
GENITAL SYSTEM				
Clitoral gland	(58)	(44)	(74)	(55)
Atrophy	3 (5%)		2 (3%)	2 (4%)
Cyst			1 (1%)	
Ectasia	15 (26%)	11 (25%)	11 (15%)	12 (22%)
Hyperplasia, focal	3 (5%)	4 (9%)	7 (9%)	5 (9%)
Hyperplasia, multifocal		2 (5%)		
Hyperplasia, squamous, focal	1 (2%)	2 (5%)		1 (2%)
Hyperplasia, squamous, multifocal		1 (2%)	1 (1%)	
Inflammation, acute		1 (2%)		
Inflammation, chronic	1 (2%)			
Inflammation, chronic active			1 (1%)	
Necrosis		1 (2%)		
Ovary	(60)	(45)	(75)	(58)
Cyst	6 (10%)	7 (16%)	4 (5%)	4 (7%)
Bilateral, cyst	1 (2%)			
Germinal epithelium, hyperplasia, papillary, focal	1 (2%)			
Oviduct		(1)		
Thrombus		1 (100%)		
Uterus	(60)	(45)	(75)	(59)
Cyst	1 (2%)			
Fibrosis			2 (3%)	
Hydrometra	3 (5%)	1 (2%)	4 (5%)	2 (3%)
Inflammation, acute		1 (2%)		
Thrombus		1 (2%)		
Bilateral, hydrometra		1 (2%)		
Cervix, cyst	2 (3%)			
Cervix, fibrosis	11 (18%)	3 (7%)	1 (1%)	
Cervix, prolapse	1 (2%)			
Endometrium, cyst	1 (2%)	2 (4%)	6 (8%)	3 (5%)
Vagina	(1)		(1)	
Thrombus, multiple	1 (100%)			
HEMATOPOIETIC SYSTEM				
Bone marrow	(60)	(45)	(75)	(60)
Hyperplasia	5 (8%)	8 (18%)	9 (12%)	14 (23%)
Hypoplasia	2 (3%)			
Myelofibrosis	1 (2%)	1 (2%)	1 (1%)	
Lymph node	(60)	(45)	(75)	(60)
Axillary, hyperplasia, lymphoid				3 (5%)
Mediastinal, congestion				1 (2%)
Mediastinal, erythrophagocytosis		1 (2%)		
Mediastinal, hemorrhage			1 (1%)	2 (3%)
Mediastinal, hyperplasia, lymphoid	1 (2%)			4 (7%)
Mediastinal, infiltration cellular, histiocytic		1 (2%)		1 (2%)
Mediastinal, pigmentation	1 (2%)			
Pancreatic, congestion				1 (2%)
Pancreatic, hyperplasia, lymphoid				2 (3%)
Pancreatic, pigmentation	1 (2%)		1 (1%)	
Lymph node, mandibular	(59)	(44)	(74)	(59)
Congestion			3 (4%)	
Hemorrhage			1 (1%)	1 (2%)
Hyperplasia, lymphoid	2 (3%)	3 (7%)	3 (4%)	4 (7%)
Hyperplasia, reticulum cell		1 (2%)	1 (1%)	
Lymph node, mesenteric	(60)	(44)	(75)	(58)
Atrophy			1 (1%)	2 (3%)
Erythrophagocytosis				1 (2%)
Hemorrhage			1 (1%)	
Hyperplasia, lymphoid			1 (1%)	
Hyperplasia, reticulum cell	2 (3%)	3 (7%)	18 (24%)	18 (31%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Untreated Control	80 ppm	170 ppm	330 ppm
HEMATOPOIETIC SYSTEM (Continued)				
Spleen	(60)	(44)	(75)	(60)
Atrophy			1 (1%)	2 (3%)
Hematopoietic cell proliferation	3 (5%)	22 (50%)	50 (67%)	47 (78%)
Hemorrhage, focal			1 (1%)	
Hyperplasia, reticulum cell		1 (2%)		
Infarct			1 (1%)	
Pigmentation	5 (8%)	1 (2%)	1 (1%)	2 (3%)
Thymus	(53)	(41)	(68)	(54)
Atrophy			1 (1%)	
Congestion			1 (1%)	
Hemorrhage, focal			2 (3%)	
Epithelial cell, hyperplasia	1 (2%)			
INTEGUMENTARY SYSTEM				
Mammary gland	(59)	(43)	(75)	(59)
Galactocele	2 (3%)	1 (2%)		1 (2%)
Duct, ectasia	16 (27%)	7 (16%)	12 (16%)	5 (8%)
Skin	(60)	(45)	(75)	(60)
Acanthosis				1 (2%)
Inflammation, chronic				1 (2%)
Hair follicle, hyperplasia, basal cell, multifocal		1 (2%)		
Subcutaneous tissue, abscess, focal		1 (2%)		
MUSCULOSKELETAL SYSTEM				
Bone	(2)	(5)	(8)	(4)
Sternum, osteopetrosis	2 (100%)	4 (80%)	7 (88%)	4 (100%)
NERVOUS SYSTEM				
Brain	(60)	(45)	(75)	(60)
Cerebrum, compression	8 (13%)	2 (4%)		
Cerebrum, necrosis, focal				1 (2%)
Meninges, infiltration cellular, mononuclear cell			1 (1%)	
RESPIRATORY SYSTEM				
Lung	(60)	(45)	(75)	(60)
Congestion				1 (2%)
Foreign body				1 (2%)
Hemorrhage, focal	1 (2%)			
Hyperplasia, lymphoid	45 (75%)	31 (69%)	60 (80%)	53 (88%)
Infiltration cellular, histiocytic		3 (7%)	4 (5%)	18 (30%)
Inflammation, acute, multifocal				1 (2%)
Inflammation, suppurative, focal				1 (2%)
Parasite metazoan				1 (2%)
Thrombus			1 (1%)	
Alveolar epithelium, hyperplasia, focal	5 (8%)	1 (2%)	5 (7%)	2 (3%)
Alveolar epithelium, hyperplasia, multifocal		1 (2%)		
Alveolus, pigmentation			2 (3%)	
Bronchiole, hyperplasia, multifocal				1 (2%)
Nose	(60)	(45)	(75)	(60)
Fungus		2 (4%)		2 (3%)
Hyperkeratosis, focal				1 (2%)
Inflammation, acute	1 (2%)	1 (2%)	2 (3%)	
Inflammation, chronic				1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (Continued)

	Untreated Control	80 ppm	170 ppm	330 ppm
SPECIAL SENSES SYSTEM				
Eye	(1)	(3)	(5)	
Cataract		2 (67%)	3 (60%)	
Inflammation, chronic active			1 (20%)	
Synechia		1 (33%)	1 (20%)	
Cornea, necrosis			1 (20%)	
Retina, degeneration		2 (67%)	3 (60%)	
Harderian gland		(2)	(1)	(1)
Inflammation, chronic		1 (50%)	1 (100%)	1 (100%)
Zymbal gland	(60)	(45)	(75)	(60)
Ectasia	12 (20%)	21 (47%)	29 (39%)	15 (25%)
Hyperplasia, focal		2 (4%)	6 (8%)	5 (8%)
Hyperplasia, multifocal			1 (1%)	
Hyperplasia, squamous, focal		3 (7%)	7 (9%)	8 (13%)
URINARY SYSTEM				
Kidney	(60)	(45)	(75)	(60)
Atrophy			1 (1%)	
Hydronephrosis			3 (4%)	
Infarct, chronic	1 (2%)	2 (4%)	1 (1%)	
Inflammation, chronic active		1 (2%)		
Inflammation, suppurative				1 (2%)
Nephropathy, chronic	50 (83%)	28 (62%)	38 (51%)	37 (62%)
Cortex, cyst		1 (2%)		2 (3%)
Medulla, inflammation, acute		1 (2%)		
Pelvis, dilatation				1 (2%)
Renal tubule, degeneration, hyaline		2 (4%)		
Renal tubule, dilatation		1 (2%)		
Renal tubule, mineralization				2 (3%)
Renal tubule, necrosis, focal				1 (2%)
Renal tubule, pigmentation	2 (3%)		5 (7%)	7 (12%)
Renal tubule, vacuolization cytoplasmic		1 (2%)		1 (2%)
Transitional epithelium, hyperplasia, focal			1 (1%)	
Ureter	(2)		(2)	(1)
Dilatation			2 (100%)	1 (100%)
Urinary bladder	(60)	(45)	(75)	(59)
Hemorrhage	1 (2%)		1 (1%)	

APPENDIX C

SENTINEL ANIMAL PROGRAM

APPENDIX C. SENTINEL ANIMAL PROGRAM

Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals are untreated, and these animals and the study animals are both subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Fifteen F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Data from animals surviving 21 months were collected from 5/60 randomly selected control animals of each sex. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the antibody titers. The following tests were performed:

Hemagglutination Inhibition	ELISA
PVM (6,12,18 mo)	RCV/SDA (rat coronavirus/sialodacryoadenitis virus)
KRV (Kilham rat virus)	Sendai (21 mo)
H-1 (Toolan's H-1 virus)	PVM (21 mo)
Sendai (6,12,18 mo)	*M. arth.* (*Mycoplasma arthriditis*) (21 mo)
	M. pul. (*Mycoplasma pulmonis*) (21 mo)

Results

Results are presented in Table C1.

TABLE C1. MURINE ANTIBODY DETERMINATIONS FOR RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
6	10/10	PVM
	10/10	Sendai
	10/10	RCV/SDA
12	10/10	PVM
	9/10	Sendai
	6/10	RCV/SDA
18	9/9	PVM
	3/9	Sendai
	8/9	RCV/SDA
21	10/10	PVM
	8/10	Sendai
	7/10	RCV/SDA

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the control animals just before they were killed; samples were sent to Microbiological Associates, Inc. (Bethesda, MD) for determination of antibody titers.

APPENDIX D

WATER AND COMPOUND CONSUMPTION BY RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDIES OF 3,3′-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

TABLE D1. WATER AND COMPOUND CONSUMPTION BY MALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

	Control		80 ppm			170 ppm			330 ppm		
Week	Grams Water/ Day (a)	Body Weight (grams)	Grams Water/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Water/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Water/ Day (a)	Body Weight (grams)	Dose/ Day (b)
4	24	233	25	227	8.8	23	230	17	19	223	28
5	25	252	24	249	7.7	22	250	15	18	242	25
9	25	302	21	300	5.6	22	301	12	20	294	22
10	26	310	26	308	6.8	24	315	13	20	311	21
12	25	329	24	322	6.0	21	331	11	19	322	19
13	22	336	24	329	5.8	22	335	11	19	328	19
17	25	349	25	346	5.8	23	346	11	19	342	18
21	28	363	25	363	5.5	28	358	13	20	360	18
25	25	372	24	375	5.1	23	372	11	20	374	18
29	28	384	24	384	5.0	23	379	10	23	375	20
33	32	395	25	394	5.1	30	387	13	21	387	18
37	27	401	27	395	5.5	26	395	11	23	385	20
41	25	404	23	404	4.6	23	391	10	20	395	17
45	26	404	25	403	5.0	23	391	10	21	392	18
49	28	401	23	396	4.6	24	391	10	21	398	17
53	30	414	25	406	4.9	29	395	12	22	397	18
57	27	416	25	402	5.0	24	403	10	21	393	18
61	24	411	22	406	4.3	23	390	10	20	392	17
65	25	403	21	394	4.3	23	391	10	20	383	17
69	29	405	24	394	4.9	25	386	11	21	380	18
73	22	417	21	403	4.2	22	383	10	20	364	18
77	26	409	27	393	5.5	26	382	12	39	364	35
81	26	409	24	395	4.9	32	366	15	33	363	30
85	26	413	23	379	4.9	34	355	16	29	323	30
89	38	405	48	375	10.2	51	359	24			
Mean	26.6	373	25.0	366	5.6	25.8	359	12	22.0	354	21
SD (c)	3.3		5.1		1.4	6.2		3.2	4.9		5.0
CV (d)	12.3		20.2		25.4	24.1		25.7	22.2		23.8

(a) Grams of water consumed per animal per day; not corrected for wastage.
(b) Estimated milligrams of 3,3'-dimethoxybenzidine dihydrochloride consumed per day per kilogram of body weight
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

TABLE D2. WATER AND COMPOUND CONSUMPTION BY FEMALE RATS IN THE TWENTY-ONE-MONTH DRINKING WATER STUDY OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

	Control		80 ppm			170 ppm			330 ppm		
Week	Grams Water/ Day (a)	Body Weight (grams)	Grams Water/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Water/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Water/ Day (a)	Body Weight (grams)	Dose/ Day (b)
4	19	153	19	152	10.0	19	149	22	14	148	31
5	18	163	17	161	8.4	16	158	17	12	155	26
9	20	187	19	184	8.3	21	180	20	14	176	26
10	23	189	25	186	10.8	19	187	17	13	183	23
12	18	193	22	192	9.2	20	193	18	14	188	25
13	17	198	16	196	6.5	14	193	12	12	192	21
17	21	209	19	207	7.3	18	201	15	12	202	20
21	23	218	20	215	7.4	19	208	16	13	208	21
25	21	223	18	222	6.5	16	214	13	12	216	18
29	26	225	22	225	7.8	19	221	15	13	219	20
33	25	232	21	230	7.3	24	223	18	14	222	21
37	21	237	19	235	6.5	17	231	13	16	226	23
41	20	243	19	242	6.3	18	234	13	14	232	20
45	20	251	17	251	5.4	19	243	13	15	241	21
49	20	262	18	257	5.6	17	252	11	16	249	21
53	20	277	19	271	5.6	19	255	13	16	253	21
57	20	284	19	275	5.5	18	263	12	17	256	22
61	17	294	17	290	4.7	18	269	11	17	264	21
65	16	303	15	292	4.1	16	277	10	15	269	18
69	17	307	17	295	4.6	19	283	11	16	276	19
73	17	318	16	307	4.2	19	282	11	16	289	18
77	19	319	27	307	7.0	22	285	13	22	285	25
81	20	324	19	306	5.0	25	281	15	24	293	27
85	18	324	19	304	5.0	25	288	15	29	295	32
89	27	331	38	298	10.2	27	285	16			
Mean	20.1	251	19.9	244	6.8	19.4	234	14	15.7	231	23
SD (d)	2.9		4.6		1.9	3.1		3.1	4.1		3.8
CV (d)	14.2		23.3		28.1	16.2		21.2	26.0		16.5

(a) Grams of water consumed per animal per day; not corrected for wastage.
(b) Estimated milligrams of 3,3'-dimethoxybenzidine dihydrochloride consumed per day per kilogram of body weight
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

APPENDIX E

INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Pelleted Diet: January 1983 to December 1984

(Manufactured by Zeigler Bros., Inc., Gardners, PA)

TABLE E1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

Ingredients (b)	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

(a) NCI, 1976; NIH, 1978
(b) Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE E2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 µg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

(a) Per ton (2,000 lb) of finished product

TABLE E3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (percent by weight)	22.78 ± 0.84	21.3-24.9	24
Crude fat (percent by weight)	5.29 ± 0.75	3.3-6.5	24
Crude fiber (percent by weight)	3.45 ± 0.28	2.8-3.8	24
Ash (percent by weight)	6.67 ± 0.40	6.2-7.3	24
Amino Acids (percent of total diet)			
Arginine	1.320 ± 0.072	1.310-1.390	5
Cystine	0.319 ± 0.088	0.218-0.400	5
Glycine	1.146 ± 0.063	1.060-1.210	5
Histidine	0.571 ± 0.026	0.531-0.603	5
Isoleucine	0.914 ± 0.030	0.881-0.944	5
Leucine	1.946 ± 0.056	1.850-1.990	5
Lysine	1.280 ± 0.067	1.200-1.370	5
Methionine	0.436 ± 0.165	0.306-0.699	5
Phenylalanine	0.938 ± 0.158	0.665-1.050	5
Threonine	0.855 ± 0.035	0.824-0.898	5
Tryptophan	0.277 ± 0.221	0.156-0.671	5
Tyrosine	0.618 ± 0.086	0.564-0.769	5
Valine	1.108 ± 0.043	1.050-1.170	5
Essential Fatty Acids (percent of total diet)			
Linoleic	2.290 ± 0.313	1.83-2.52	5
Linolenic	0.258 ± 0.040	0.210-0.308	5
Vitamins			
Vitamin A (IU/kg)	12,379 ± 4,800	4,100-24,000	24
Vitamin D (IU/kg)	4,450 ± 1,382	3,000-6,300	4
α-Tocopherol (ppm)	43.58 ± 6.92	31.1-48.0	5
Thiamine (ppm)	19.10 ± 3.78	12.0-27.0	24
Riboflavin (ppm)	7.6 ± 0.85	6.10-8.20	5
Niacin (ppm)	97.8 ± 31.68	65.0-150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0-34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60-8.80	5
Folic acid (ppm)	2.62 ± 0.89	1.80-3.70	5
Biotin (ppm)	0.254 ± 0.053	0.19-0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6-38.0	5
Choline (ppm)	3,122 ± 416.8	2,400-3,430	5
Minerals			
Calcium (percent)	1.26 ± 0.14	0.95-1.54	24
Phosphorus (percent)	0.96 ± 0.06	0.87-1.10	24
Potassium (percent)	0.900 ± 0.098	0.772-0.971	3
Chloride (percent)	0.513 ± 0.114	0.380-0.635	5
Sodium (percent)	0.323 ± 0.043	0.258-0.371	5
Magnesium (percent)	0.167 ± 0.012	0.151-0.181	5
Sulfur (percent)	0.304 ± 0.064	0.268-0.420	5
Iron (ppm)	410.3 ± 94.04	262.0-523.0	5
Manganese (ppm)	90.29 ± 7.15	81.7-99.4	5
Zinc (ppm)	52.78 ± 4.94	46.1-58.2	5
Copper (ppm)	10.72 ± 2.76	8.09-15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44-2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490-0.780	4

TABLE E4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.56 ± 0.18	0.17-0.77	24
Cadmium (ppm) (a)	<0.10		24
Lead (ppm)	0.60 ± 0.23	0.33-1.32	24
Mercury (ppm) (a)	<0.05		24
Selenium (ppm)	0.33 ± 0.06	0.21-0.42	24
Aflatoxins (ppb)	<5.0		24
Nitrate nitrogen (ppm) (b)	9.71 ± 4.98	0.10-22.0	24
Nitrite nitrogen (ppm) (b)	1.02 ± 1.68	0.10-7.20	24
BHA (ppm) (c)	2.13 ± 0.61	2.00-5.00	24
BHT (ppm) (c)	2.17 ± 1.67	1.00-4.00	24
Aerobic plate count (CFU/g) (d)	48,263 ± 38,232	7,100-130,000	24
Coliform (MPN/g) (e)	41.42 ± 102	3.00-460	24
E. coli (MPN/g) (f)	3.04 ± 0.20	<3.00-4.00	24
Total nitrosamines (ppb) (g)	5.77 ± 5.82	1.80-30.90	24
N-Nitrosodimethylamine (ppb) (g)	4.76 ± 5.84	0.80-30.00	24
N-Nitrosopyrrolidine (ppb) (g)	1.02 ± 0.20	0.90-1.70	24
Pesticides (ppm)			
α-BHC (a,h)	<0.01		24
β-BHC (a)	<0.02		24
γ-BHC (a)	<0.01		24
δ-BHC (a)	<0.01		24
Heptachlor (a)	<0.01		24
Aldrin (a)	<0.01		24
Heptachlor epoxide (a)	<0.01		24
DDE (a)	<0.01		24
DDD (a)	<0.01		24
DDT (a)	<0.01		24
HCB (a)	<0.01		24
Mirex (a)	<0.01		24
Methoxychlor (a)	<0.05		24
Dieldrin (a)	<0.01		24
Endrin (a)	<0.01		24
Telodrin (a)	<0.01		24
Chlordane (a)	<0.05		24
Toxaphene (a)	<0.1		24
Estimated PCBs (a)	<0.2		24
Ronnel (a)	<0.01		24
Ethion (a)	<0.02		24
Trithion (a)	<0.05		24
Diazinon (a)	<0.1		24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (i)	0.10 ± 0.09	0.05-0.45	24
Endosulfan I (a)	<0.01		24
Endosulfan II (a)	<0.01		24
Endosulfan sulfate (a)	<0.03		24

(a) All values were less than the detection limit, given in the table as the mean.
(b) Source of contamination: alfalfa, grains, and fish meal
(c) Source of contamination: soy oil and fish meal
(d) CFU = colony-forming unit
(e) MPN = most probable number
(f) One lot dated October contained 4 MPN/g.
(g) All values were corrected for percent recovery.
(h) BHC = hexachlorocyclohexane or benzene hexachloride
(i) Thirteen lots contained more than 0.05 ppm.

APPENDIX F

ORGAN WEIGHTS IN THE FOURTEEN-DAY DRINKING WATER STUDIES AND RESULTS OF HEMATOLOGY AND SERUM CHEMISTRY ANALYSES IN THE THIRTEEN-WEEK AND NINE-MONTH DRINKING WATER STUDIES OF 3,3′-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

TABLE F1. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE FOURTEEN-DAY DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

Organ	Control	200 ppm	350 ppm	750 ppm	1,500 ppm	4,500 ppm
MALE						
Final body weight (grams)	235 ± 1.2	241 ± 6.2	235 ± 4.0	232 ± 7.2	225 ± 9.9	**141 ± 4.2
Brain	7.3 ± 0.11	7.6 ± 0.22	7.6 ± 0.08	7.5 ± 0.12	7.8 ± 0.27	**11.9 ± 0.43
Lungs	4.0 ± 0.09	4.3 ± 0.16	4.2 ± 0.10	4.2 ± 0.09	4.1 ± 0.09	**5.5 ± 0.29
Heart	2.8 ± 0.08	3.1 ± 0.23	2.9 ± 0.08	3.0 ± 0.15	3.0 ± 0.03	**3.3 ± 0.07
Liver	43.4 ± 0.74	*46.7 ± 0.41	45.0 ± 0.70	**48.2 ± 0.45	**51.5 ± 0.41	**47.8 ± 3.60
Kidney	3.5 ± 0.08	3.9 ± 0.27	*3.9 ± 0.15	*3.8 ± 0.10	**4.0 ± 0.09	**5.1 ± 0.25
Right testis	5.3 ± 0.15	5.4 ± 0.24	5.3 ± 0.08	5.6 ± 0.14	5.6 ± 0.13	**7.7 ± 0.26
Thymus	1.5 ± 0.06	1.9 ± 0.30	1.6 ± 0.06	1.6 ± 0.04	1.6 ± 0.12	0.8 ± 0.14
FEMALE						
Final body weight (grams)	163 ± 4.2	163 ± 4.1	160 ± 1.9	156 ± 2.9	157 ± 4.2	**135 ± 3.3
Brain	10.2 ± 0.34	10.4 ± 0.26	11.0 ± 0.40	10.6 ± 0.21	10.4 ± 0.26	*11.9 ± 0.49
Lungs	4.8 ± 0.22	5.0 ± 0.12	5.2 ± 0.42	4.9 ± 0.08	4.9 ± 0.08	5.2 ± 0.13
Heart	3.2 ± 0.13	3.5 ± 0.15	3.7 ± 0.29	2.8 ± 0.24	3.3 ± 0.19	3.2 ± 0.08
Liver	37.0 ± 0.95	39.2 ± 0.96	37.9 ± 1.16	39.3 ± 0.46	**41.1 ± 0.57	**45.6 ± 1.50
Kidney	3.7 ± 0.15	3.7 ± 0.23	3.7 ± 0.08	3.9 ± 0.08	*4.1 ± 0.13	**4.6 ± 0.23
Thymus	2.2 ± 0.10	2.3 ± 0.10	2.4 ± 0.24	2.1 ± 0.08	2.0 ± 0.07	**1.7 ± 0.10

(a) Mean ± standard error in milligrams per gram (unless otherwise specified) for groups of five animals; P values are vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
*P<0.05
**P<0.01

TABLE F2. HEMATOLOGY AND SERUM CHEMISTRY DATA FOR RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

Analysis	Control	170 ppm	330 ppm	630 ppm	1,250 ppm	2,500 ppm
MALE						
Leukocytes (10^3/mm^3)	6.32 ± 0.259	5.83 ± 0.203	6.15 ± 0.226	7.00 ± 0.508	6.43 ± 0.272	*7.20 ± 0.186
Lymphocytes (10^3/mm^3)	4.82 ± 0.243	4.66 ± 0.240	5.00 ± 0.178	*5.89 ± 0.513	5.40 ± 0.271	**6.18 ± 0.255
Segmented neutrophils (10^3/mm^3)	1.40 ± 0.122	1.11 ± 0.092	1.03 ± 0.089	*1.01 ± 0.065	**0.94 ± 0.054	**0.98 ± 0.135
Monocytes (10^3/mm^3)	0.03 ± 0.011	0.03 ± 0.012	0.03 ± 0.015	0.04 ± 0.017	0.04 ± 0.017	0.02 ± 0.011
Eosinophils (10^3/mm^3)	0.07 ± 0.025	0.03 ± 0.018	0.08 ± 0.021	0.05 ± 0.019	0.05 ± 0.015	0.02 ± 0.011
Hematocrit (percent)	41.9 ± 0.50	42.5 ± 0.50	41.6 ± 0.59	42.9 ± 1.03	41.7 ± 0.43	41.8 ± 0.55
Hemoglobin (g/dl)	16.9 ± 0.20	17.0 ± 0.15	16.6 ± 0.18	16.5 ± 0.33	16.5 ± 0.15	16.9 ± 0.20
Erythrocyte (10^6/mm^3)	8.11 ± 0.103	8.26 ± 0.100	8.22 ± 0.104	8.40 ± 0.195	8.16 ± 0.089	7.95 ± 0.122
BUN (mg/dl)	18.0 ± 0.47	17.8 ± 0.55	17.7 ± 0.63	18.6 ± 0.81	18.6 ± 0.93	19.1 ± 1.16
Serum creatinine (mg/dl)	0.67 ± 0.015	**0.58 ± 0.013	**0.57 ± 0.015	**0.50 ± 0.030	**0.61 ± 0.028	**0.56 ± 0.034
LDH (IU/liter)	565 ± 96.2	*863 ± 76.5	*890 ± 74.9	699 ± 77.2	779 ± 49.2	**1,306 ± 137.9
SDH (IU/liter)	7.2 ± 0.66	6.5 ± 0.43	7.0 ± 0.39	6.9 ± 0.46	*9.6 ± 0.72	*10.1 ± 1.20
ALAT (IU/liter)	36.8 ± 2.10	33.7 ± 2.23	34.5 ± 1.56	30.5 ± 1.42	32.9 ± 0.96	38.7 ± 3.98
T_3 (ng/dl)	67.0 ± 2.68	67.0 ± 4.41	69.1 ± 3.31	65.9 ± 2.46	65.5 ± 1.85	58.6 ± 3.13
T_4 (micrograms/dl)	4.0 ± 0.14	*3.4 ± 0.22	*3.6 ± 0.16	**2.9 ± 0.14	**3.4 ± 0.16	**2.8 ± 0.19
Thyrotropin (ng/ml)	(b) 609 ± 55.3	(c) 527 ± 39.2	(d) 639 ± 74.4	592 ± 27.0	(c) 668 ± 74.0	(d) 476 ± 52.3
FEMALE						
Leukocytes (10^3/mm^3)	5.62 ± 0.297	5.33 ± 0.345	4.91 ± 0.294	5.29 ± 0.250	4.92 ± 0.215	5.63 ± 0.250
Lymphocytes(10^3/mm^3)	4.48 ± 0.236	4.28 ± 0.255	3.98 ± 0.269	4.37 ± 0.244	4.15 ± 0.198	4.88 ± 0.264
Segmented neutrophils (10^3/mm^3)	1.02 ± 0.136	0.96 ± 0.100	0.88 ± 0.109	0.87 ± 0.079	0.72 ± 0.081	*0.69 ± 0.073
Monocytes (10^3/mm^3)	0.01 ± 0.010	0.02 ± 0.009	0.00 ± 0.000	0.01 ± 0.007	0.01 ± 0.007	0.01 ± 0.009
Eosinophils (10^3/mm^3)	0.10 ± 0.026	0.07 ± 0.017	0.05 ± 0.014	*0.03 ± 0.012	*0.04 ± 0.011	0.05 ± 0.014
Hematocrit (percent)	47.6 ± 0.76	46.1 ± 0.48	46.1 ± 0.89	**44.0 ± 0.59	**43.3 ± 0.95	**40.6 ± 0.67
Hemoglobin (g/dl)	16.6 ± 0.14	16.2 ± 0.13	16.4 ± 0.26	*16.1 ± 0.17	16.2 ± 0.23	16.1 ± 0.17
Erythrocytes (10^6/mm^3)	8.85 ± 0.121	*8.55 ± 0.070	8.59 ± 0.159	**8.23 ± 0.108	**8.15 ± 0.158	**7.56 ± 0.133
BUN (mg/dl)	18.4 ± 1.06	17.6 ± 0.31	17.9 ± 0.57	18.6 ± 0.81	19.2 ± 1.05	20.5 ± 1.42
Serum creatinine (mg/dl)	0.71 ± 0.031	*0.62 ± 0.025	*0.61 ± 0.038	**(c) 0.54 ± 0.029	*0.62 ± 0.025	**0.57 ± 0.021
LDH (IU/liter)	529 ± 39.2	713 ± 81.3	488 ± 43.1	(c) 558 ± 39.9	471 ± 57.4	613 ± 18.4
SDH (IU/liter)	5.7 ± 0.91	4.3 ± 0.26	7.8 ± 1.95	9.6 ± 1.97	6.9 ± 0.92	*8.0 ± 0.73
ALAT (IU/liter)	28.7 ± 1.65	26.0 ± 1.70	27.9 ± 2.64	31.3 ± 2.31	26.0 ± 1.53	29.7 ± 0.87
T_3 (ng/dl)	98.4 ± 2.16	97.7 ± 4.54	**79.4 ± 3.63	**68.3 ± 2.87	**63.3 ± 2.01	**57.2 ± 2.49
T_4 (micrograms/dl)	3.9 ± 0.17	3.4 ± 0.17	*3.2 ± 0.23	**2.4 ± 0.05	**(d) 2.0 ± 0.17	**2.0 ± 0.14
Thyrotropin (ng/ml)	(b) 461 ± 21.7	(e) 697 ± 62.9	(d) 730 ± 79.2	(f) 606 ± 47.8	(d) 962 ± 246.1	(c) 605 ± 138.8

(a) Mean ± standard error for groups of 10 animals, unless otherwise specified. P values are vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
BUN = blood urea nitrogen; LDH = lactic dehydrogenase; SDH = sorbitol dehydrogenase; ALAT = serum alanine aminotransferase; T_3 = triiodothyronine; T_4 = thyroxin.
(b) Five animals were examined.
(c) Nine animals were examined.
(d) Eight animals were examined.
(e) Six animals were examined.
(f) Seven animals were examined.
*$P<0.05$
**$P<0.01$

TABLE F3. HEMATOLOGY, SERUM CHEMISTRY, AND URINALYSIS DATA FOR RATS IN THE NINE-MONTH DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (a)

Analysis	Male		Female	
	Control	330 ppm	Control	330 ppm
Leukocytes (1,000/µl)	6.2 ± 0.23	*(b) 4.7 ± 0.47	3.0 ± 0.09	**5.0 ± 1.52
Lymphocytes (1,000/µl)	3.9 ± 0.24	**(b) 2.7 ± 0.27	2.0 ± 0.07	**2.5 ± 0.15
Segmented neutrophils (1,000/µl)	1.9 ± 0.19	(b) 1.8 ± 0.30	0.8 ± 0.07	2.2 ± 1.29
Monocytes (1,000/µl)	0.25 ± 0.036	(b) 0.19 ± 0.034	0.10 ± 0.017	0.19 ± 0.064
Eosinophils (1,000/µl)	0.13 ± 0.032	**(b) 0.02 ± 0.011	0.03 ± 0.010	0.06 ± 0.036
Hematocrit (percent)	49.5 ± 0.56	(b) 44.6 ± 2.87	47.8 ± 0.52	46.5 ± 1.39
Hemoglobin (g/dl)	17.2 ± 0.17	*(b) 14.8 ± 0.98	15.9 ± 0.18	15.3 ± 0.47
Mean corpuscular hemoglobin (pg)	17.8 ± 0.08	(b) 17.5 ± 0.15	18.4 ± 0.08	18.6 ± 0.18
Mean corpuscular hemoglobin concentration (g/dl)	34.7 ± 0.18	**(b) 33.3 ± 0.28	33.2 ± 0.13	32.9 ± 0.09
Mean cell volume (μ^3)	51.1 ± 0.16	(b) 52.4 ± 0.57	55.4 ± 0.15	*56.4 ± 0.61
Erythrocytes (10^6/µl)	9.6 ± 0.09	*(b) 8.5 ± 0.53	8.6 ± 0.08	8.3 ± 0.30
Alanine aminotransferase (IU/liter)	72.8 ± 7.42	53.7 ± 8.42	45.4 ± 6.51	**23.7 ± 1.59
Blood urea nitrogen (mg/dl)	19.9 ± 0.28	20.6 ± 0.69	19.7 ± 0.65	20.0 ± 0.45
Serum creatinine (mg/dl)	0.78 ± 0.053	0.69 ± 0.023	0.73 ± 0.026	0.68 ± 0.020
Lactic dehydrogenase (IU/liter)	866 ± 42.8	**513 ± 101	448 ± 40.6	*314 ± 43.2
Sorbitol dehydrogenase (IU/liter)	16.8 ± 2.02	23.3 ± 4.90	13.3 ± 2.73	8.6 ± 1.81
Serum glucose (mg/dl)	171 ± 5.7	159 ± 6.4	133 ± 2.9	135 ± 4.7
Serum osmolality (MOS/kg)	321 ± 1.3	*313 ± 2.8	312 ± 2.3	310 ± 2.6
Triiodothyronine (ng/dl)	93.1 ± 5.54	**67.2 ± 2.84	157 ± 7.4	**117 ± 7.9
Thyroxin (ng/dl)	3,400 ± 130	**2,400 ± 150	3,800 ± 180	*3,100 ± 190
Thyrotropin (ng/dl)	811 ± 26.4	838 ± 24.9	748 ± 41.0	810 ± 49.2
Urinary creatinine excretion (mg/16 h)	7.0 ± 0.62	(b) 6.8 ± 0.61	5.1 ± 0.18	**(c) 2.8 ± 0.37
Osmolality ratio (urine/serum)	9.4 ± 0.89	10.9 ± 0.61	5.2 ± 0.61	**(d) 11.5 ± 0.44
Urinary creatinine (mg/dl)	417 ± 42.2	(b) 492 ± 53.7	170 ± 22.9	**(c) 333 ± 16.5
Urine osmolality (MOS/kg)	3,017 ± 284	3,430 ± 200	1,603 ± 187	**(d) 3,604 ± 121
Urine pH	6.3 ± 0.08	6.3 ± 0.08	6.3 ± 0.08	(b) 6.1 ± 0.07
Urine volume (ml/16 h)	2.0 ± 0.42	1.4 ± 0.21	3.5 ± 0.42	**0.8 ± 0.08

(a) Mean ± standard error for groups of 10 animals, unless otherwise specified; P values vs. controls by Wilcoxon's test (Hollander and Wolfe, 1973).
(b) Nine animals were examined.
(c) Eight animals were examined.
(d) Six animals were examined.
*$P<0.05$
**$P<0.01$

APPENDIX G

CHEMICAL CHARACTERIZATION, ANALYSIS, AND PREPARATION OF FORMULATED DRINKING WATER MIXTURES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE FOR THE TOXICOLOGY STUDIES

APPENDIX G. CHEMICAL CHARACTERIZATION

Procurement and Characterization of 3,3'-Dimethoxybenzidine Dihydrochloride

A single lot of 3,3'-dimethoxybenzidine dihydrochloride (lot no. 11F-5034) was obtained from Sigma Chemical Company (St. Louis, MO) in two batches: batch no. 1 on February 2, 1981, and batch no. 2 on October 14, 1981. Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on the analyses performed in support of the 3,3'-dimethoxybenzidine dihydrochloride studies are on file at the National Institute of Environmental Health Sciences.

The study chemical in both batches was identified as 3,3'-dimethoxybenzidine dihydrochloride by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure and with literature references (Sadtler Standard Spectra), except for a minor impurity peak in the nuclear magnetic resonance spectrum and a small unresolved absorbance between 400 and 350 nm in the ultraviolet/visible spectrum.

The purity of lot no. 11F-5034 was determined by elemental analysis, Karl Fischer water analysis, potentiometric titration of the two amine groups in a glacial acetic acid:acetone medium containing mercury (II) acetate with 0.1 N perchloric acid, thin-layer chromatography, and high-performance liquid chromatography. Thin-layer chromatography was performed with chloroform:methyl ethyl ketone:methanol:concentrated ammonium hydroxide (50:30:19:1) on silica gel plates (system 1) and methanol:water:concentrated ammonium hydroxide (80:18:2) on Whatman $KC_{18}F$ plates (system 2). High-performance liquid chromatography was performed by ultraviolet detection at 280 nm with a Waters μBondapak C_{18} column and a solvent system of aqueous 5 mM heptanesulfonic acid sodium salt adjusted to pH 2 with concentrated phosphoric acid:5 mM heptanesulfonic acid sodium salt in methanol with the same volume of phosphoric acid (80:20) (batch no. 1) or aqueous 10 mM heptanesulfonic acid adjusted to pH 2.1 with concentrated phosphoric acid:10 mM heptanesulfonic acid in methanol containing the same volume of phosphoric acid (61:39) (batch no. 2), with detection at 254 nm.

For batch no. 1, the results of elemental analysis for carbon, hydrogen, chlorine, and nitrogen were in agreement with the theoretical values. The presence of 0.66% water was determined by Karl Fischer analysis. Nonaqueous titration of the two amine groups indicated a purity of 97.5%. Thin-layer chromatography indicated a trace impurity at the origin by each system. High-performance liquid chromatography indicated no impurities with individual peak areas greater than or equal to 0.1% of the major peak area.

For batch no. 2, the results of elemental analysis for hydrogen were slightly high. Karl Fischer analysis indicated the presence of 1.1% water. Nonaqueous titration indicated a purity of 98.1%. A trace impurity was observed at the origin by both thin-layer chromatographic systems. High-performance liquid chromatography indicated one impurity with a relative area 0.10% that of the major peak. Comparison of batch no. 1 and batch no. 2 by high-performance liquid chromatography indicated no significant differences between the two batches.

Stability studies performed by high-performance liquid chromatography with the same system as before, but with a solvent ratio of 76:24 and with acetanilide added to the methanol-based solvent as an internal standard, indicated that 3,3'-dimethoxybenzidine dihydrochloride was stable as a bulk chemical when stored protected from light at temperatures up to 60° C. The samples stored at 60° C were different in appearance, indicating possible decomposition. During the 21-month studies, the stability of the bulk chemical was confirmed by high-performance liquid chromatography and nonaqueous titration of the amine groups.

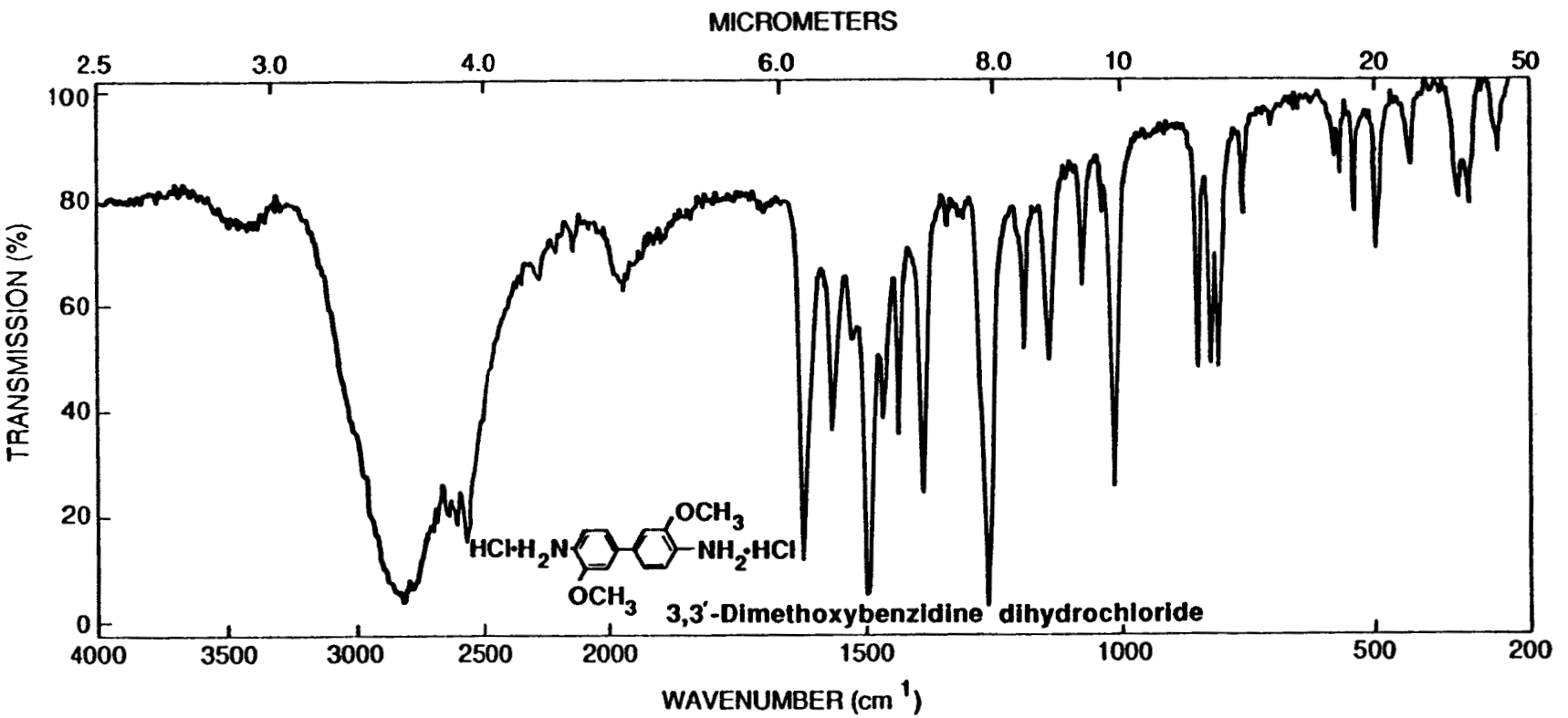

FIGURE G1. INFRARED ABSORPTION SPECTRUM OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (LOT NO. 11F-5034)

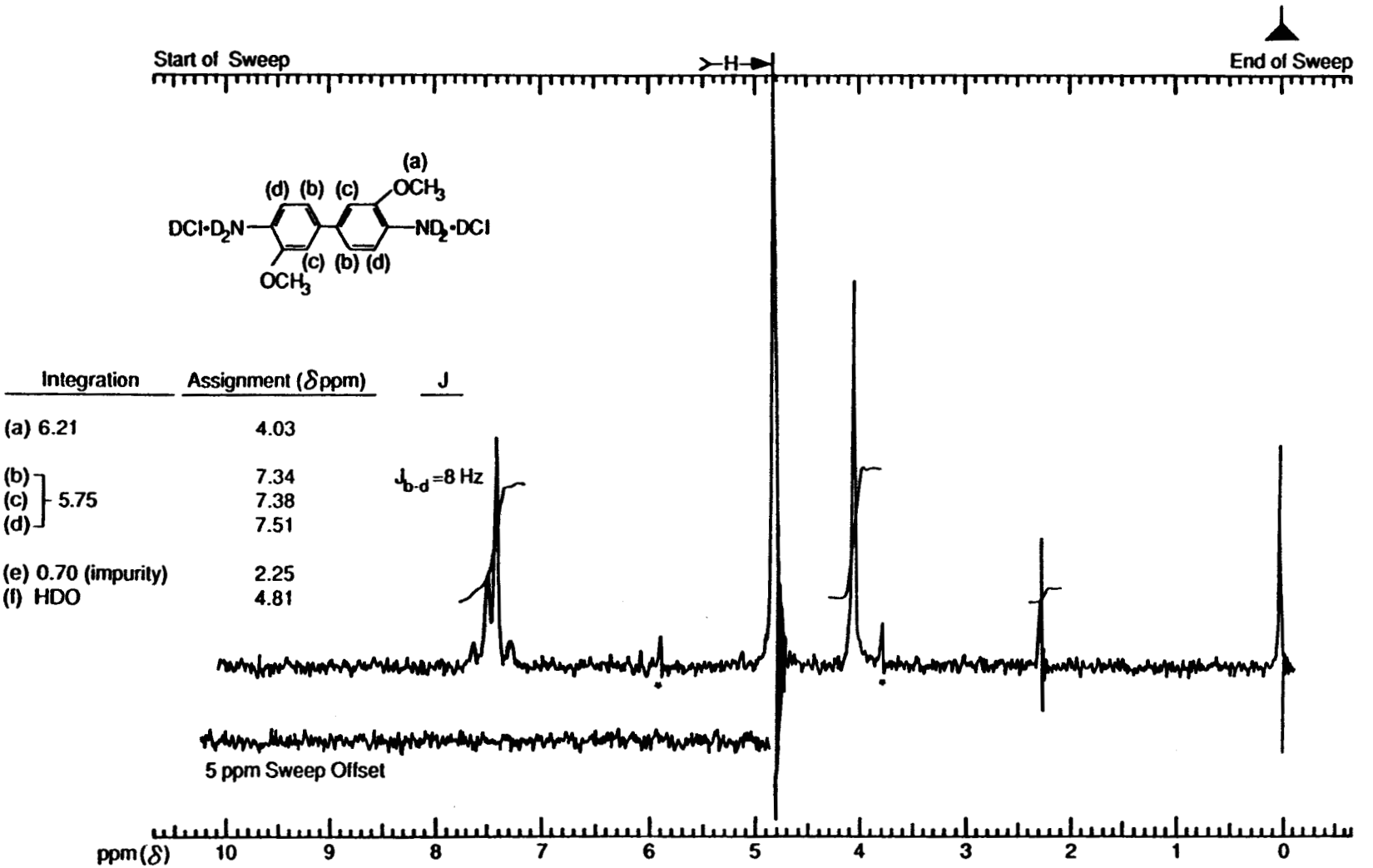

FIGURE G2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE (LOT NO. 11F-5034)

The stability of 3,3'-dimethoxybenzidine dihydrochloride in feed (200 ppm) was determined by extracting the stored feed samples with methanol:10% sodium hydroxide (19:1) followed by neutralization with 0.5 N hydrochloric acid, washing with cyclohexane, adjusting to basic pH with 10 N sodium hydroxide, and extraction with methylene chloride. The methylene chloride extract was analyzed by gas chromatography with a 3% OV-17 column and flame ionization detection. 3,3'-Dimethylbenzidine was used as an internal standard. 3,3'-Dimethoxybenzidine dihydrochloride was unstable in NIH 07 Rat and Mouse Ration (200 ppm) under all storage conditions at or above 5° C. Formulated diets stored open to air and light under simulated dosing conditions lost 12% or 18% of the chemical after 3 or 7 days, respectively. The same feed stored in the dark in sealed containers lost 2%, 9%, or 26% of the chemical after storage for 14 days at −20° C, 5° C, or room temperature. Based on these results, drinking water was selected as the route of chemical administration.

Preparation and Characterization of Formulated Drinking Water Mixtures

The appropriate amounts of 3,3'-dimethoxybenzidine dihydrochloride and tap or distilled (21 month) water were mixed (w/v) to give the desired concentrations (Table G1). The stability of 3,3'-dimethoxybenzidine dihydrochloride in drinking water (200 ppm) was determined by high-performance liquid chromatography on a Waters μBondapak C_{18} column and a Whatman Co:PELL ODS guard column with detection at 280 nm after filtration of the solution through a 0.5-μ filter and with propiophenone as an internal standard. The mobile phase was water:methanol (55:45) containing 0.06 N sodium bromide. 3,3'-Dimethoxybenzidine dihydrochloride was found to be stable in water solutions after 14 days' storage at room temperature in the dark in sealed containers. Storage of the solutions in rat cage water bottles exposed to normal room light for 48 hours had no measurable effect on stability. Drinking water mixtures were prepared two times per week and were used immediately or, for the 21-month studies, stored for up to 7 days at room temperature before being used.

Periodic analysis of formulated 3,3'-dimethoxybenzidine dihydrochloride/drinking water mixtures was conducted at the study laboratory and the analytical chemistry laboratory by ultraviolet spectroscopy at 294 nm. Drinking water mixtures were analyzed 1 week before the studies began and three times during the 13-week studies (Table G2). Results of triplicate analysis by the analytical chemistry laboratory (653 ppm) of the 630-ppm drinking water mixture of June 9, 1982, indicated good agreement with those of the study laboratory (650 ppm).

During the 21-month studies, the drinking water mixtures were analyzed at approximately 4-week intervals. Data on the number of times that concentrations were within specifications can be extrapolated to indicate the frequency with which mixtures were formulated within the specified ±10% of the target concentrations. For the 3,3'-dimethoxybenzidine dihydrochloride studies, the mixtures were formulated within ±10% of the target concentrations approximately 99% (103/104) of the time throughout the studies (Table G3). Results of periodic referee analysis performed by the analytical chemistry laboratory indicated good agreement with the results from the study laboratory (Table G4).

TABLE G1. PREPARATION AND STORAGE OF FORMULATED DRINKING WATER MIXTURES IN THE DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

Fourteen-Day Studies	Thirteen-Week Studies	Nine-Month and Twenty-One-Month Studies
Preparation		
Weighed amount of 3,3'-dimethoxybenzidine dihydrochloride was placed in a carboy and transferred to a compound preparation area. The appropriate amount of tap water was added, and the solution was mixed continuously with an electric stirrer until the chemical dissolved	Same as 14-d studies	Weighed amount of 3,3'-dimethoxybenzidine dihydrochloride was placed in a container. The appropriate amount of distilled water was added, and the solution was mixed continuously with an electric stirrer until the chemical dissolved. For part of the studies, some mixtures for mid and high doses were shaken by hand
Maximum Storage Time		
Up to 4 d in drinking water bottles	Same as 14-d studies	7 d before being placed in drinking water bottles; up to 4 d in drinking water bottles
Storage Conditions		
In the dark at room temperature	Same as 14-d studies	Same as 14-d studies

TABLE G2. RESULTS OF ANALYSIS OF FORMULATED DRINKING WATER MIXTURES IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

Date Mixed	Concentration of 3,3'-Dimethoxybenzidine Dihydrochloride in Drinking Water (ppm)		Determined as a Percent of Target
	Target	Determined (a)	
(b) 06/09/82	170	(c) 190	114.1
	330	356	107.9
	630	650	103.7
	1,250	1,290	103.3
	2,500	2,620	105.0
(b) 06/10/82	170	(d) 183	94.7
(e) 06/17/82	170	161	94.7
	330	333	100.9
	630	628	99.7
	1,250	1,287	103.0
	2,500	2,560	101.4
08/02/82	170	180	105.9
	330	310	93.9
	630	660	104.8
	1,250	1,300	104.0
	2,500	2,590	103.6
(e) 08/02/82	170	180	105.9
	330	280	84.8
	630	660	104.8
	1,250	1,230	98.4
	2,500	2,530	101.2

(a) Results of duplicate analysis
(b) One week before start of studies
(c) Out of specifications; not used in the studies.
(d) Remix
(e) Animal-room samples

TABLE G3. RESULTS OF ANALYSIS OF FORMULATED DRINKING WATER MIXTURES IN THE TWENTY-ONE-MONTH DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

Date Mixed	Determined Concentration of 3,3'-Dimethoxybenzidine Dihydrochloride in Water for Target Concentration (ppm) (a)				
	80	170	170	330	330
03/22/83	83	163	172	326	321
04/15/83	79	170	(b) 193	327	320
04/18/83			(c) 164		
05/13/83	80	170	170	340	330
06/10/83	80	170	180	340	330
07/08/83	84	178	170	329	326
08/05/83	79	165	166	318	319
09/02/83	78	167	164	323	324
09/30/83	79	171	169	334	325
10/28/83	82	173	168	328	301
11/29/83	80	172	169	330	350
12/20/83	74	164	161	319	322
01/20/84	80	165	165	320	
02/17/84	79	170	169	340	
03/16/84	77	166	165	328	
04/13/84	78	172	174	338	
05/11/84	77	169	167	330	
06/08/84	79	181	183	332	
07/06/84	80	173	172	331	
08/03/84	78	170	167	342	
09/04/84	83	173	171	334	
09/28/84	80	170	167	333	
10/26/84	76	167	169	329	
11/27/84	77	165		325	
12/18/84	79	172			
Mean (ppm)	79	170	171	330	324
Standard deviation	2.3	4.3	7.0	6.8	11.6
Coefficient of variation (percent)	2.9	2.5	4.1	2.1	3.6
Range (ppm)	74-84	163-181	161-193	318-342	301-350
Number of samples	24	24	22	23	11

(a) Results of duplicate analysis
(b) Out of specifications; not used in the studies.
(c) Remix; not included in the mean.

TABLE G4. RESULTS OF REFEREE ANALYSIS OF FORMULATED DRINKING WATER MIXTURES IN THE TWENTY-ONE-MONTH DRINKING WATER STUDIES OF 3,3'-DIMETHOXYBENZIDINE DIHYDROCHLORIDE

Date Mixed	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory (a)	Referee Laboratory (b)
03/22/83	80	83	80.7
09/02/83	170	167	169
02/17/84	330	340	336
08/03/84	170	170	171

(a) Results of duplicate analysis
(b) Results of triplicate analysis

APPENDIX H

GENETIC TOXICOLOGY OF

3,3′-DIMETHOXYBENZIDINE

APPENDIX H. GENETIC TOXICOLOGY

METHODS

Salmonella Protocol: Testing was performed as reported by Ames et al. (1975) with modifications listed below and described in greater detail by Haworth et al. (1983). Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver) for 20 minutes at 37° C before the addition of soft agar supplemented with L-histidine and D-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

Chemicals were tested in four strains. Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of the study chemical. The high dose was limited by toxicity or solubility but did not exceed 10 mg/plate.

A positive response was defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response was defined as an increase in revertants which was not dose related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A response was considered negative when no increase in revertant colonies was observed after chemical treatment.

Chinese Hamster Ovary Cytogenetics Assays: Testing was performed as reported by Galloway et al. (1985) and is described briefly below. Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). Chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine (BrdU)-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited by toxicity or solubility but did not exceed 5 mg/ml.

In the SCE test without S9, CHO cells were incubated for 26 hours with the study chemical in McCoy's 5A medium supplemented with 10% fetal bovine serum, L-glutamine (2 mM), and antibiotics. BrdU was added 2 hours after culture initiation. After 26 hours, the medium containing the study chemical was removed and replaced with fresh medium plus BrdU and colcemid, and incubation was continued for 2 more hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with the chemical, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no study chemical; incubation proceeded for an additional 26 hours, with colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9.

In the chromosomal aberration test without S9, cells were incubated in McCoy's 5A medium with the study chemical for 8 hours; colcemid was added, and incubation was continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the chromosomal aberration test with S9, cells were treated with the study chemical and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10 hours in fresh medium, with colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

For the SCE test, if significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable cells. The harvest time for the chromosomal aberration test was based on the cell cycle information obtained in the SCE test; if cell cycle delay was anticipated, the incubation period was extended approximately 5 hours.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. For the SCE test, 50 second-division metaphase cells were usually scored for frequency of SCEs per cell from each dose; 200 first-division metaphase cells were scored at each dose for the chromosomal aberration test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCEs, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P<0.003$) trend test or a significantly increased dose point ($P<0.05$) was sufficient to indicate a chemical effect.

Drosophila Melanogaster Protocol: The assays for gene mutation and chromosomal translocation induction were performed as described by Yoon et al. (1985). Study chemicals were supplied as coded aliquots from Radian Corporation (Austin, TX). Initially, study chemicals were assayed in the sex-linked recessive lethal (SLRL) test by feeding to adult Canton-S wild-type males that were no more than 24 hours old. If no response was obtained, the chemical was retested by injection into adult males. If either route of administration produced a positive result, the chemical was assayed for induction of reciprocal translocations (RTs) by using the same method of exposure. If, because of the physical nature of the chemical, feeding experiments were not possible, injection was selected as the method of study chemical administration, and a positive result was followed by an RT test.

To administer a chemical by injection, a glass Pasteur pipette is drawn out in a flame to a microfine filament and the tip is broken off to allow delivery of the test solution. Injection is either done manually by attaching a rubber bulb to the other end of the pipette and forcing through sufficient solution to slightly distend the abdomen of the fly (0.2-0.3 µl) or by attaching the pipette to a microinjector that automatically delivers a calibrated volume. Flies are anesthetized with ether and immobilized on a strip of double-stick tape; injection into the thorax under the wing is performed with the aid of a dissecting microscope.

Toxicity tests attempted to set concentrations of study chemical at a level that would produce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. For the SLRL test, exposure by feeding was done by allowing Canton-S males (10-20 flies per vial) to feed for 72 hours on a solution of the study chemical in 5% sucrose. In the injection experiments, 24- to 72-hour-old Canton-S males were given a solution of the chemical dissolved in 0.7% saline or peanut oil and allowed 24 hours to recover. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days; sample sperm from successive matings were treated as successively earlier postmeiotic stages. F_1 heterozygous females were allowed to mate with their siblings and then were placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. At least two experiments were performed for each study chemical, resulting in the testing of some 5,000 treated and 5,000 control chromosomes. The only exceptions occurred when the results of the first experiment were clearly positive (induced frequency of recessive lethal mutations equal to or greater than 1%); then, the second trial was not run.

Recessive lethal data were analyzed by the normal test (Margolin et al., 1983). A test result was considered to be positive if the P value was less than 0.01 and the mutation frequency in the tested group was greater than 0.10% or if the P value was less than 0.05 and the frequency in the treatment group was greater than 0.15%. A test was considered to be inconclusive if (a) the P value was between 0.05 and 0.01 but the frequency in the treatment group was between 0.10% and 0.15% or (b) the P value was between 0.10 and 0.05 but the frequency in the treatment group was greater than 0.10%. A result was considered to be negative if the P value was greater than 0.10 or if the frequency in the treatment group was less than 0.10%.

RESULTS

3,3′-Dimethoxybenzidine was tested for induction of gene mutations in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 in each of three laboratories (Haworth et al., 1983; Table H1). In all laboratories, a response ranging from weakly positive to positive was observed with strain TA100 in trials conducted in the presence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9; likewise, positive results were reported for strain TA98 with S9 in all three laboratories, and one laboratory also observed a significant response in TA98 without S9. A weakly positive response was reported by one of the test laboratories with TA1535 in the presence of induced hamster S9. In cytogenetic tests with CHO cells conducted in two laboratories, SCEs were induced by 3,3′-dimethoxybenzidine both with and without Aroclor 1254-induced male Sprague Dawley rat liver S9; in one of these two laboratories, the positive responses observed in the SCE trials without S9 occurred under conditions of delayed harvest (3-5 hours additional culture time), but the positive results reported by the second laboratory in the SCE test were observed at lower doses of the study chemical which did not affect cell cycle time (Galloway et al., 1985; Table H2). Results of the chromosomal aberration test were reported to be negative (Galloway et al., 1985); however, recent statistical reanalysis (Galloway et al., 1987) of the chromosomal aberration data has resulted in a change in the call from negative to weakly positive without S9 (Litton Bionetics study) and positive with S9 (Columbia University study) (Table H3). 3,3′-Dimethoxybenzidine was negative for induction of sex-linked recessive lethal mutations in adult male *D. melanogaster* exposed to the chemical by feeding (100 ppm) or injection (200 ppm) (Yoon et al., 1985; Table H4).

TABLE H1. MUTAGENICITY OF 3,3'-DIMETHOXYBENZIDINE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b)		
Study performed at Case Western Reserve University				
		−S9	+S9 (hamster)	+S9 (rat)
TA100	0	116 ± 6.1	170 ± 7.4	147 ± 7.6
	10	130 ± 10.7	167 ± 10.1	184 ± 7.5
	33	138 ± 6.4	180 ± 14.5	220 ± 2.5
	100	127 ± 13.7	191 ± 10.1	202 ± 7.5
	333	126 ± 11.9	190 ± 7.5	228 ± 2.3
	1,000	147 ± 3.5	200 ± 12.5	244 ± 1.7
Trial summary		Negative	Negative	Weakly positive
Positive control (c)		435 ± 5.2	798 ± 97.5	466 ±129.7
TA1535	0	11 ± 3.4	10 ± 0.3	15 ± 2.7
	10	12 ± 1.0	11 ± 0.7	18 ± 1.0
	33	11 ± 1.7	10 ± 0.3	17 ± 2.2
	100	13 ± 0.3	10 ± 1.5	13 ± 3.8
	333	11 ± 0.3	12 ± 1.5	19 ± 1.5
	1,000	17 ± 0.9	11 ± 0.9	19 ± 1.8
Trial summary		Negative	Negative	Negative
Positive control (c)		447 ± 41.6	70 ± 9.9	34 ± 2.5
TA1537	0	14 ± 1.2	9 ± 2.4	14 ± 2.6
	10	14 ± 1.5	11 ± 1.5	11 ± 0.3
	33	12 ± 2.3	16 ± 1.8	15 ± 1.9
	100	12 ± 1.8	12 ± 1.3	14 ± 1.5
	333	11 ± 3.5	15 ± 1.8	10 ± 2.0
	1,000	13 ± 1.5	21 ± 2.1	20 ± 4.1
Trial summary		Negative	Equivocal	Negative
Positive control (c)		140 ± 11	80 ± 20.6	35 ± 7.0

		−S9		+S9 (hamster)	+S9 (rat)	
		Trial 1	Trial 2		Trial 1	Trial 2
TA98	0	15 ± 3.7	24 ± 1.8	22 ± 2.1	29 ± 0.6	35 ± 4.0
	10	9 ± 2.4	--	43 ± 4.6	47 ± 18.0	--
	33	11 ± 1.8	28 ± 3.0	51 ± 3.4	67 ± 3.2	66 ± 4.7
	66	--	19 ± 3.5	--	--	79 ± 5.8
	100	13 ± 2.0	21 ± 4.1	49 ± 7.1	111 ± 6.2	68 ± 9.5
	166	--	21 ± 2.8	--	--	96 ± 9.0
	333	13 ± 1.8	27 ± 3.5	54 ± 18.3	148 ± 5.3	127 ± 30.6
	1,000	13 ± 1.7	--	76 ± 10.3	148 ± 1.8	--
Trial summary		Negative	Negative	Positive	Positive	Positive
Positive control (c)		195 ± 4.9	231 ± 42.0	878 ± 20.0	302 ± 13.6	324 ± 45.6

TABLE H1. MUTAGENICITY OF 3,3′-DIMETHOXYBENZIDINE IN *SALMONELLA TYPHIMURIUM* (Continued)

Strain	Dose (µg/plate)	Revertants/Plate (b)				
Study performed at SRI International						
		−S9	+S9 (hamster)		+S9 (rat)	
			Trial 1	Trial 2	Trial 1	Trial 2
TA100	0	97 ± 3.2	133 ± 2.2	84 ± 5.2	125 ± 10.8	95 ± 2.6
	10	--	--	101 ± 2.3	--	154 ± 7.0
	33.3	--	--	119 ± 5.1	--	198 ± 12.4
	100	76 ± 5.0	161 ± 11.8	133 ± 6.3	305 ± 23.8	297 ± 2.3
	333.3	83 ± 3.6	186 ± 15.5	137 ± 11.0	394 ± 42.8	335 ± 15.3
	1,000	86 ± 7.3	173 ± 9.6	148 ± 5.2	302 ± 4.2	282 ± 5.2
	3,333.3	(d) 85 ± 4.9	(d) 190 ± 3.2	--	(d) 251 ± 11.0	--
	10,000	(d) 103 ± 4.5	(d) 206 ± 3.9	--	(d) 224 ± 9.9	--
Trial summary		Negative	Weakly positive	Weakly positive	Positive	Positive
Positive control (c)		263 ± 22.9	1,563 ± 23.4	1,960 ± 98.5	893 ± 31.5	1,022 ± 31.8
		−S9	+S9 (hamster)		+S9 (rat)	
			Trial 1	Trial 2		
TA1535	0	25 ± 2.6	10 ± 1.2	9 ± 0.9	12 ± 2.6	
	100	10 ± 5.5	14 ± 2.7	14 ± 1.9	12 ± 3.3	
	333.3	12 ± 2.3	15 ± 3.2	15 ± 1.0	14 ± 0.3	
	1,000	23 ± 3.9	15 ± 0.0	16 ± 5.4	20 ± 2.6	
	3,333.3	(d) 28 ± 2.7	(d) 25 ± 2.6	(d) 21 ± 2.3	(d) 18 ± 1.2	
	10,000	(d) 26 ± 3.5	(d) 30 ± 2.2	(d) 19 ± 3.6	(d) 26 ± 1.2	
Trial summary		Negative	Positive	Equivocal	Equivocal	
Positive control (c)		334 ± 52.4	424 ± 16.7	223 ± 7.9	288 ± 3.7	
TA1537	0	12 ± 2.5	34 ± 1.5	21 ± 1.2	26 ± 1.7	
	100	13 ± 1.9	31 ± 1.9	23 ± 2.3	29 ± 6.0	
	333.3	11 ± 1.2	27 ± 4.5	29 ± 4.9	26 ± 6.4	
	1,000	11 ± 1.8	32 ± 2.9	21 ± 3.8	22 ± 2.5	
	3,333.3	(d) 15 ± 1.8	(d) 39 ± 3.7	(d) 30 ± 1.8	(d) 20 ± 2.3	
	10,000	(d) 12 ± 0.3	(d) 40 ± 2.3	(d) 29 ± 3.8	(d) 15 ± 1.8	
Trial summary		Negative	Negative	Negative	Negative	
Positive control (c)		729 ± 105.3	462 ± 13.5	439 ± 24.2	293 ± 9.6	
		−S9	+S9 (hamster)		+S9 (rat)	
			Trial 1	Trial 2	Trial 1	Trial 2
TA98	0	21 ± 3.5	43 ± 1.7	33 ± 1.8	35 ± 4.0	23 ± 1.7
	10	--	--	60 ± 6.2	--	196 ± 9.2
	33.3	--	--	90 ± 1.3	--	423 ± 9.0
	100	17 ± 1.8	141 ± 2.9	143 ± 5.6	663 ± 28.3	727 ± 27.4
	333.3	28 ± 2.5	213 ± 10.5	225 ± 0.3	905 ± 28.8	891 ± 40.1
	1,000	28 ± 5.9	239 ± 12.3	253 ± 9.3	720 ± 46.3	665 ± 17.0
	3,333.3	(d) 25 ± 1.5	(d) 365 ± 23.2	--	(d) 484 ± 32.8	--
	10,000	(d) 24 ± 3.2	(d) 464 ± 27.4	--	(d) 489 ± 27.1	--
Trial summary		Negative	Positive	Positive	Positive	Positive
Positive control (c)		373 ± 9.1	1,528 ± 6.1	1,331 ± 51.6	698 ± 37.4	716 ± 58.9

TABLE H1. MUTAGENICITY OF 3,3'-DIMETHOXYBENZIDINE IN *SALMONELLA TYPHIMURIUM* (Continued)

Strain	Dose (µg/plate)	Revertants/Plate (b)					
Study performed at EG&G Mason Research Institute							
		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA100	0	116 ± 2.0	138 ± 1.5	111 ± 5.5	114 ± 9.5	114 ± 6.6	113 ± 3.5
	5	--	140 ± 2.1	--	116 ± 5.8	--	119 ± 9.8
	25	--	135 ± 11.3	--	127 ± 9.4	--	135 ± 5.0
	50	--	151 ± 9.8	--	142 ± 0.0	--	165 ± 5.2
	100	88 ± 5.5	149 ± 2.9	117 ± 3.3	141 ± 4.8	168 ± 14.5	173 ± 4.8
	333	110 ± 8.7	148 ± 3.7	118 ± 2.9	193 ± 10.9	178 ± 5.4	214 ± 6.1
	1,000	115 ± 8.7	154 ± 4.5	112 ± 2.3	158 ± 2.0	151 ± 5.9	164 ± 9.0
	3,333	102 ± 3.7	(d) 178 ± 7.0	105 ± 6.8	(d) 147 ± 11.6	(e) 120 ± 5.9	(d) 151 ± 2.9
	10,000	(e) 71 ± 1.9	(d) 125 ± 53.7	(e) 80 ± 1.0	(d) 95 ± 41.0	(e) 110 ± 4.7	(d) 98 ± 40.8
Trial summary		Negative	Negative	Negative	Weakly positive	Equivocal	Weakly positive
Positive control (c)		1,028 ± 31.9	2,042 ± 43.0	2,314 ± 59.0	1,147 ± 58.0	1,290 ± 53.3	777 ± 9.0
TA1535	0	13 ± 0.0	27 ± 4.0	7 ± 1.0	12 ± 2.1	11 ± 3.0	8 ± 1.8
	5	--	35 ± 5.9	--	14 ± 1.5	--	11 ± 1.9
	25	--	32 ± 1.0	--	14 ± 1.8	--	5 ± 0.9
	50	--	30 ± 5.6	--	10 ± 2.6	--	12 ± 1.2
	100	16 ± 0.6	28 ± 4.2	8 ± 1.5	10 ± 1.7	9 ± 1.3	12 ± 1.5
	333	15 ± 2.3	32 ± 3.2	10 ± 1.5	12 ± 2.6	10 ± 2.0	14 ± 2.6
	1,000	14 ± 1.9	34 ± 0.7	10 ± 1.5	14 ± 2.0	10 ± 1.5	15 ± 2.8
	3,333	13 ± 1.5	(e) 26 ± 4.4	14 ± 2.3	(d) 15 ± 2.0	12 ± 2.3	(d) 17 ± 1.0
	10,000	(e) 10 ± 1.7	(e) 18 ± 7.7	(e) 10 ± 0.9	(d) 11 ± 5.0	(e) 15 ± 1.5	(d) 15 ± 6.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		807 ± 71.9	1,488 ± 35.3	165 ± 9.4	103 ± 0.6	104 ± 10.4	98 ± 5.0
		−S9+	S9 (hamster)	+S9 (rat)			
TA1537	0	8 ± 0.3	7 ± 1.8	6 ± 0.6			
	100	7 ± 2.4	9 ± 2.9	7 ± 0.3			
	333	4 ± 0.7	10 ± 2.7	8 ± 1.3			
	1,000	5 ± 0.6	11 ± 1.2	6 ± 0.3			
	3,333	4 ± 0.3	6 ± 1.2	8 ± 1.9			
	10,000	(e) 6 ± 1.9	(e) 5 ± 0.3	(e) 8 ± 2.1			
Trial summary		Negative	Negative	Negative			
Positive control (c)		731 ± 234	289 ± 9.0	133 ± 5.2			
		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA98	0	21 ± 4.4	29 ± 1.9	21 ± 1.8	33 ± 1.3	22 ± 3.5	27 ± 4.3
	5	--	28 ± 2.7	--	41 ± 4.7	--	62 ± 6.7
	25	--	35 ± 2.9	--	59 ± 5.0	--	174 ± 1.2
	50	--	44 ± 0.7	--	75 ± 3.9	--	269 ± 5.4
	100	35 ± 0.9	57 ± 2.0	84 ± 3.2	73 ± 3.8	282 ± 7.5	366 ± 14.6
	333	53 ± 3.6	84 ± 4.1	106 ± 4.8	131 ± 6.7	326 ± 29.3	464 ± 19.2
	1,000	71 ± 8.5	193 ± 16.3	84 ± 3.3	116 ± 3.5	206 ± 17.6	340 ± 5.3
	3,333	81 ± 10.1	(e) 219 ± 7.5	85 ± 2.5	(d) 141 ± 6.4	146 ± 16.3	(d) 212 ± 8.8
	10,000	(e) 56 ± 3.1	(e) 136 ± 60.0	(e) 63 ± 0.7	(d) 109 ± 47.2	(e) 125 ± 8.6	(d) 129 ± 56.3
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control (c)		1,508 ± 39.9	1,913 ± 39.7	2,694 ± 59.4	1,166 ± 31.5	1,320 ± 72.4	1,112 ± 60.9

TABLE H1. MUTAGENICITY OF 3,3'-DIMETHOXYBENZIDINE IN *SALMONELLA TYPHIMURIUM* (Continued)

(a) The detailed protocol is presented by Haworth et al. (1983). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 μg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.
(d) Precipitate on plate
(e) Slight toxicity

TABLE H2. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY 3,3'-DIMETHOXYBENZIDINE (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
Study performed at Litton Bionetics, Inc.								
-S9 (c)								
Trial 1--Summary: Positive								
Dimethyl sulfoxide		50	1,048	351	0.33	7.0	26.0	
3,3'-Dimethoxybenzidine	6.25	32	660	195	0.30	6.1	26.0	87.1
	12.5	50	1,043	382	0.37	7.6	26.0	108.6
	50	45	950	361	0.38	8.0	26.0	114.3
	100	50	1,035	516	0.50	10.3	29.0	147.1
Triethylenemelamine	0.015	15	313	409	1.31	27.3	26.0	390.0
Trial 2--Summary: Positive								
Dimethyl sulfoxide		50	1,012	428	0.42	8.6	26.5	
3,3'-Dimethoxybenzidine	12.5	50	986	477	0.48	9.5	26.5	110.5
	25	50	1,013	464	0.46	9.3	26.5	108.1
	50	50	1,008	314	0.31	6.3	26.5	73.3
	100	50	1,019	557	0.55	11.1	(d) 31.5	129.1
	150	9	184	200	1.09	22.8	(d) 31.5	265.5
Triethylenemelamine	15	50	1,030	2,436	2.37	48.7	26.5	566.3
+S9 (e)--Summary: Positive								
Dimethyl sulfoxide		50	1,048	304	0.29	6.1	26.0	
3,3'-Dimethoxybenzidine	125	50	1,040	310	0.30	6.2	26.0	101.6
	250	50	1,046	300	0.29	6.0	26.0	98.4
	500	50	1,039	461	0.44	9.2	26.0	150.8
	2,500	50	1,034	384	0.37	7.7	26.0	126.2
	5,000	50	1,037	480	0.46	9.6	29.0	157.4
Cyclophosphamide	1.5	50	1,047	1,943	1.86	38.9	29.0	637.7
Study performed at Columbia University								
-S9 (c)								
Trial 1--Summary: Weakly positive								
Dimethyl sulfoxide		50	1,048	424	0.4	8.5	26.0	
3,3'-Dimethoxybenzidine	0.005	50	1,050	432	0.41	8.6	26.0	101.2
	0.05	50	1,046	394	0.38	7.9	26.0	92.9
	0.5	50	1,048	415	0.40	8.3	26.0	97.6
	5	50	1,043	474	0.46	9.5	26.0	111.8
	50	50	1,043	727	0.70	14.5	26.0	170.6
Triethylenemelamine	0.025	50	1,051	2,429	2.31	48.6	26.0	571.8

TABLE H2. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY 3,3'-DIMETHOXYBENZIDINE (Continued)

Compound	Dose (µg/ml)	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
Study performed at Columbia University (Continued)								
Trial 2--Summary: Positive								
Dimethyl sulfoxide		50	1,050	422	0.4	8.4	26.0	
3,3'-Dimethoxybenzidine	0.5	50	1,049	425	0.41	8.5	26.0	101.2
	1.6	50	1,049	456	0.43	9.1	26.0	108.3
	5	50	1,049	515	0.49	10.3	26.0	122.6
	16	50	1,048	598	0.57	12.0	26.0	142.9
	50	50	1,047	825	0.79	16.5	26.0	196.4
Triethylenemelamine	0.025	50	1,050	2,661	2.53	53.2	26.0	633.3
+S9 (e)								
Trial 1--Summary: Negative								
Dimethyl sulfoxide		50	1,052	368	0.35	7.4	26.0	
3,3'-Dimethoxybenzidine	0.005	50	1,053	443	0.42	8.9	26.0	120.3
	0.05	50	1,047	406	0.39	8.1	26.0	109.5
	0.5	50	1,048	405	0.39	8.1	26.0	109.5
	5	50	1,050	419	0.40	8.4	26.0	113.5
	50	50	1,049	433	0.41	8.7	26.0	117.6
Cyclophosphamide	1.5	50	1,049	1,706	1.63	34.1	26.0	460.8
Trial 2--Summary: Positive								
Dimethyl sulfoxide		50	1,049	450	0.43	9.0	26.0	
3,3'-Dimethoxybenzidine	50	50	1,048	418	0.40	8.4	26.0	93.3
	160	50	1,048	461	0.44	9.2	26.0	102.2
	500	50	1,049	465	0.44	9.3	26.0	103.3
	1,600	50	1,048	546	0.52	10.9	26.0	121.1
	5,000	50	1,049	719	0.69	14.4	26.0	160.0
Cyclophosphamide	1.5	50	1,050	1,957	1.86	39.1	26.0	434.4

(a) SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as described in (c) and (e) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air dried, and stained.
(b) SCEs/cell of culture exposed to study chemical relative to those of culture exposed to solvent
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) Because some chemicals induce a delay in the cell division cycle, harvest times are occasionally extended to maximize the proportion of second division cells available for analysis.
(e) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE H3. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY 3,3'-DIMETHOXYBENZIDINE (a)

	−S9 (b)					+S9 (c)			
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Study performed at Litton Bionetics, Inc.									
Trial 1--Harvest time: 10 h					Harvest time: 10.5 h				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	2	0.02	2.0		100	2	0.02	2.0
3,3'-Dimethoxybenzidine					3,3'-Dimethoxybenzidine				
6.25	100	8	0.08	2.0	125	100	1	0.01	1.0
12.5	100	4	0.04	4.0	250	100	4	0.04	4.0
25	100	6	0.06	4.0	500	100	0	0.00	0.0
50	100	1	0.01	1.0	2,500	100	2	0.02	2.0
100	100	2	0.02	2.0	5,000	100	4	0.04	3.0
200	100	12	0.12	*11.0					
Summary: Weakly positive					Summary: Negative				
Triethylenemelamine					Cyclophosphamide				
0.25	49	61	1.24	69.0	25	100	73	0.73	45.0
Study performed at Columbia University									
Trial 1--Harvest time: 14 h					Harvest time: 14 h				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	0	0	0.0		100	0	0	0.0
3,3'-Dimethoxybenzidine					3,3'-Dimethoxybenzidine				
0.005	100	1	0.01	1.0	0.005	100	3	0.03	3.0
0.05	100	4	0.04	3.0	0.05	100	4	0.04	3.0
0.5	100	3	0.03	3.0	0.5	100	7	0.07	*5.0
5	100	3	0.03	3.0	5	100	6	0.06	*6.0
50	100	3	0.03	3.0	50	100	6	0.06	*5.0
Summary: Negative					Summary: Positive				
Triethylenemelamine					Cyclophosphamide				
0.25	100	46	0.46	30.0	25	100	90	0.90	55.0
Trial 2--Harvest time: 14 h									
Dimethyl sulfoxide									
	100	1	0.01	1.0					
3,3'-Dimethoxybenzidine									
50	100	3	0.03	3.0					
160	100	3	0.03	3.0					
500	100	3	0.03	2.0					
1,600	100	6	0.06	6.0					
5,000	100	7	0.07	6.0					
Summary: Negative									
Triethylenemelamine									
25	100	35	0.35	26.0					

TABLE H3. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY 3,3'-DIMETHOXYBENZIDINE (Continued)

(a) Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as indicated in (b) and (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.
*P<0.05

TABLE H4. INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN *DROSOPHILA MELANOGASTER* BY 3,3'-DIMETHOXYBENZIDINE (a)

Route of Exposure	Dose (ppm)	Incidence of Deaths (percent)	Incidence of Sterility (percent)	No. of Lethals/No. of X Chromosomes Tested Mating 1	Mating 2	Mating 3	Overall Total (b)
Feeding	100	0	0	2/2,295	1/2,266	0/2,191	3/6,752 (0.04%)
	0			1/3,410	1/3,375	1/3,127	3/9,912 (0.03%)
Injection	200	0	0	0/1,700	0/1,570	0/1,481	0/4,751 (0.00%)
	0			0/1,360	2/1,291	0/1,213	2/3,864 (0.05%)

(a) Study performed at the University of Wisconsin–Madison. A detailed protocol of the sex-linked recessive lethal assay and data are presented by Yoon et al. (1985). Exposure by feeding was done by allowing 24-hour-old Canton-S males to feed for 3 days on a solution of the study chemical dissolved in 5% sucrose. In the injection experiments, 24-hour-old Canton-S males were treated with a solution of the chemical dissolved in 0.7% saline and allowed 24 hours to recover. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three broods of 3, 2, and 2 days; sample sperm from successive matings were treated as spermatozoa (mating 1), spermatids (mating 2), and spermatocytes (mating 3). F_1 heterozygous females were crossed to their siblings and placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters; no clusters were found. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. Results were not significant at the 5% level (Margolin et al., 1983).
(b) Combined total of number of lethal mutations/number of X chromosomes tested for three mating trials

APPENDIX I

AUDIT SUMMARY

APPENDIX I. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and draft NTP Technical Report for the 2-year studies of 3,3'-dimethoxybenzidine dihydrochloride in rats were audited for the National Institute of Environmental Health Sciences (NIEHS) at the National Toxicology Program (NTP) Archives by quality assurance, resource-support contractors. The audit included review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All inlife records including protocol, correspondence, animal husbandry, environmental conditions, dosing, animal identification, external masses, mortality, and serology.
(3) Body weight and clinical observation data; all data were scanned before individual data for a random 10% sample of animals in each study group were reviewed in detail.
(4) All chemistry records.
(5) All postmortem records for individual animals concerning date of death, disposition code, condition code, tissue accountability, correlation of masses or clinical signs recorded at or near the last inlife observation with gross observations and microscopic diagnoses, consis-tency of data entry on necropsy record forms, and correlation between gross observations and microscopic diagnoses.
(6) All wet tissue bags for inventory and residual wet tissues from a random 20% sample of animals in each study group, plus other relevant cases, to evaluate the integrity of individual animal identity and the thoroughness of necropsy and trimming procedure performance.
(7) Blocks and slides of tissues from a random 20% sample of animals from each study group, plus animals with less than complete or correct identification, to examine for proper inventory, labeling, matching of tissue sections, and preservation.
(8) All microscopic diagnoses for a random 10% sample of animals, plus 100% of the changes in diagnoses made to preliminary pathology tables, to verify their incorporation into the final pathology tables.
(9) The extent of correlation between the data, factual information, and procedures for the 2-year studies as presented in the draft Technical Report and the study records available at the NTP Archives.

Procedures and events for the exposure phase of the studies were documented adequately by the archival records, with the exception that some or all of the records for room air change rate, room light cycle, source of bedding and cages, study chemical receipt and disposal, original chemistry notebook pages, and statistical analysis of some primary tumors were not present. Review of the records indicated that protocol-specified procedures for animal care were followed adequately. Records that documented the administration of doses to animals were complete and accurate. Recalculation of approximately 20% of the group mean body weight values in the Technical Report showed 30/31 to be correct. Review of water consumption records detected a few data entry errors of small magnitude. The correlation between observations of external masses recorded both during the last few months of life and at necropsy was good (785/799 correlated). The date of animal removal correlated with the date of necropsy for all 362 early-death animals. The reason for animal removal recorded during life correlated with the disposition code recorded at necropsy for each rat.

Individual animal identifiers (ear tags) were present and correct in the residual-tissue bags for 80/81 rats examined. Review of the entire data trail for the one rat with an incorrect identifier indicated that the integrity of individual animal identity had been maintained. The audit detected 17 untrimmed potential lesions among the wet tissues of 56 rats examined. Additional histopathology work on the residual livers of all study animals by a pathology-support contractor detected 76 untrimmed lesions, which, when evaluated, resulted in the diagnosis of 7 neoplasms in male rats which had not been identified previously, no additional neoplasms in female rats, and about 30 new nonneoplastic lesions in male and female rats. The additional diagnoses were not incorporated into the tables of the Technical Report; the missing neoplastic diagnoses included nodules in the liver of one control (CM61), one low dose (LM167), and one high dose (HM424) male rats; adenocarcinomas in the colon of one low dose (LM171) and two mid dose (MM231 and MM284) male rats; and an adenometous polyp in one mid dose (MM245, multiple) male rat.

Intestinal segments were incompletely opened for 8/25 rats; however, there were no apparent untrimmed potential lesions evident by external examination of residual tissues for the gastrointestinal tract. Twenty-seven gross observations made at necropsy did not have a corresponding microscopic diagnosis. Tissue sections on blocks and slides matched each other properly. All but two post-Pathology Working Group changes in diagnoses had been incorporated into the final pathology tables.

Full details about these and other findings are presented in audit reports that are on file at NIEHS. This summary describes the extent to which the data and factual information presented in the Technical Report are supported by records at the NTP Archives.

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