NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 299

TOXICOLOGY AND CARCINOGENESIS STUDIES OF C.I. DISPERSE BLUE 1

(A commercial dye containing approximately 50% 1,4,5,8-tetraaminoanthraquinone, 30% other compounds structurally related to 1,4,5,8-tetraaminoanthraquinone, and 20% water)

(CAS NO. 2475-45-8)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

The NTP is made up of four charter DHHS agencies: the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

NTP TECHNICAL REPORT

ON THE

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NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

May 1986

NTP TR 299

NIH Publication No. 86-2555

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

NOTE TO THE READER

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for testing in the NTP Carcinogenesis Program are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical has the potential for hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

Five categories of interpretative conclusions were adopted for use in June 1983 in the Technical Reports series to specifically emphasize consistency and the concept of actual evidence of carcinogenicity. For each definitive study result (male rats, female rats, male mice, female mice), one of the following quintet will be 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 Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit an increased incidence of a combination of malignant and benign neoplasms where each increases with dose.
- **Some Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues, or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.
- **Equivocal Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related marginal increase of neoplasms.
- **No Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenicity** demonstrates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

> The term *chemical carcinogenesis* generally means the induction by chemicals of neoplasms not usually observed, the earlier induction by chemicals of neoplasms that are commonly observed, or the induction by chemicals of more neoplasms than are generally found. Different mechanisms may be involved in these situations. Etymologically, the term *carcinogenesis* means induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports, the words *tumor* and *neoplasm* are used interchangeably.

This study was initiated by the National Cancer Institute's Carcinogenesis Bioassay Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for peer review.

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP. Comments and questions about the National Toxicology Program Technical Reports on Toxicology and Carcinogenesis Studies should be directed to Dr. J.E. Huff, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3780).

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

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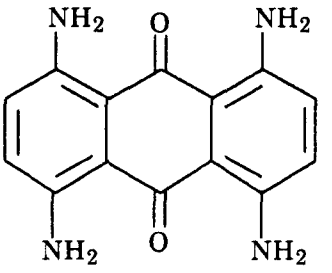

C.I. DISPERSE BLUE 1

CAS No. 2475-45-8

$C_{14}H_{12}N_4O_2$ Molecular weight 268.27

Synonyms: C.I. 64500; 1,4,5,8-Tetraamino-9,10-anthracenedione; 1,4,5,8-Tetraaminoanthraquinone

ABSTRACT

C.I. Disperse Blue 1, a component of several semipermanent hair dyes, was studied as a commercial-grade product (minus lignosulfonate dispersants) containing approximately 50% 1,4,5,8-tetraamino-anthraquinone, 30% other compounds structurally related to 1,4,5,8-tetraaminoanthraquinone, and 20% water. C.I. Disperse Blue 1 was studied for toxicity and carcinogenicity in single-administration gavage, 14-day feed, 13-week feed, and 104-week feed studies. All studies used F344/N rats and $B6C3F_1$ mice.

In the single-administration gavage studies, no deaths occurred within 14 days at doses up to 3,000 mg/kg C.I. Disperse Blue 1 in rats or up to 2,000 mg/kg in mice. In the 14-day feed studies, rats and mice received dietary concentrations of up to 50,000 ppm. All male rats survived, and 2/5 female rats in the 50,000-ppm group died. All mice receiving 25,000 ppm or more died. Three of five male and 2/5 female mice in the 12,500-ppm groups died.

In the 13-week studies, diets containing concentrations up to 20,000 ppm C.I. Disperse Blue 1 were fed to rats, and diets containing concentrations up to 10,000 ppm were fed to mice. No compound-related deaths of rats occurred; however, pathologic changes occurred at 2,500 ppm and higher and included urinary tract calculi, urinary bladder inflammation, hyperplasia of the urinary bladder transitional epithelium, and nephrosis. Compound-related deaths occurred at 10,000 ppm in mice of each sex. Pathologic changes included chronic inflammation and hyperplasia of the urinary bladder transitional epithelium and urinary tract calculi at dietary concentrations of 2,500 ppm and higher and nephrosis, myocardial necrosis, and testicular degeneration at 10,000 ppm. The renal lesions at 5,000 ppm were considered to be potentially life threatening. These composite findings from the short-term studies were used to identify target organs and to help select dietary concentrations for the longer term studies.

In the 2-year studies in rats, groups of 50 animals of each sex were administered C.I. Disperse Blue 1 at dietary concentrations of 0, 1,250, 2,500, or 5,000 ppm. These dietary concentrations corresponded to 0, 45, 95, and 217 mg/kg per day for males and 0, 56, 111, and 240 mg/kg per day for females. Survival of males and females in the 5,000-ppm groups and males in the 2,500-ppm group was significantly reduced. Final body weights, as percent of controls, were: male--low dose 100%; mid dose, 94%; high dose, 85%; female--low dose, 99%; mid dose, 94%; high dose, 87%.

Compound-related effects of feeding diets containing C.I. Disperse Blue 1 for 104 weeks to F344/N rats included urinary bladder neoplasms and calculi at the incidences noted in the table. Positive statistical associations existed between the presence of calculi and transitional cell neoplasms of the urinary bladder in male and female rats, leiomyomas or leiomyosarcomas (combined) in female rats, and squamous cell neoplasms in male rats.

The increased incidence of pancreatic islet cell adenomas or carcinomas (combined) in high dose male rats was significant by survival-adjusted analyses (overall incidences: control, 1/49; low dose, 2/50; mid dose, 5/50; high dose, 3/50).

In the 2-year studies in mice, 50 animals of each sex were administered diets containing C.I. Disperse Blue 1 at 0, 600, 1,200, or 2,500 ppm. These dietary concentrations corresponded to doses of 0, 112, 239, and 540 mg/kg per day for males and 0, 108, 235, and 520 mg/kg per day for females. Survival was comparable among control and dosed male or female mice. Final body weights, as percent of controls, were as follows: male--low dose, 97%; mid dose, 98%; high dose, 101%; female--low dose, 110%; mid dose, 104%; high dose, 91%.

The incidences of hepatocellular adenomas or carcinomas (combined) were increased for dosed male mice (9/50; 21/50; 20/50; 16/50) and for low dose female mice (3/50; 13/49; 3/50; 4/50). Alveolar/bronchiolar adenomas or carcinomas (combined) occurred with an increased incidence in high dose male mice (4/50; 9/49; 5/50; 11/50).

Urinary Bladder Lesion (a)	Dose Group			
	Control	1,250 ppm	2,500 ppm	5,000 ppm
MALE RATS				
Squamous cell papilloma or carcinoma	0/49	0/50	2/50	(b) 4/49
Transitional cell papilloma or carcinoma	0/49	0/50	(c) 10/50	(c) 11/49
Leiomyoma or leiomyosarcoma	0/49	0/50	(c) 7/50	(c) 41/49
Calculi (d)	0/49	0/50	(c) 16/50	(c) 21/49
FEMALE RATS				
Squamous cell papilloma or carcinoma	0/48	0/50	1/50	(c) 11/48
Transitional cell papilloma or carcinoma	0/48	0/50	(c) 15/50	(c) 21/48
Leiomyoma or leiomyosarcoma	0/48	0/50	3/50	(c) 26/48
Calculi (d)	0/48	0/50	(c) 12/50	(c) 37/48

(a) All lesions noted had significant positive trends ($P<0.05$).
(b) Significant by life table test only ($P<0.05$)
(c) Significant vs control at $P< 0.05$
(d) Gross calculi as detected at necropsy

Several nonneoplastic effects were detected in the kidneys of mid dose and high dose male and high dose female rats and of all dosed groups of male and female mice. These effects on the kidney included calculi, hydronephrosis, and epithelial hyperplasia in rats and casts and renal tubular degeneration in mice.

C.I. Disperse Blue 1 was studied for mutagenicity in *Salmonella typhimurium* in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9. C.I. Disperse Blue 1 was mutagenic in strain TA1535 in the presence of S9 and in strains TA97 and TA98 in the presence or absence of S9; it was not mutagenic in strain TA100.

An audit of the experimental data was conducted for the 2-year toxicology and carcinogenesis studies of C.I. Disperse Blue 1. No data discrepancies were found that influenced the final interpretations.

Under the conditions of these feed studies of C.I. Disperse Blue 1, there was *clear evidence of carcinogenicity** for male and female F344/N rats as shown by the increased occurrence of transitional cell papillomas and carcinomas, of leiomyomas and leiomyosarcomas, and of squamous cell papillomas and carcinomas of the urinary bladder. Urinary bladder calculi were observed in the groups of rats in which urinary bladder neoplasms were increased. Positive associations existed between the presence of calculi and transitional cell neoplasms in male and female rats, leiomyomas or leiomyosarcomas (combined) in female rats, and squamous cell neoplasms in male rats. A marginally increased occurrence of pancreatic islet cell adenomas or carcinomas (combined) was observed in male rats exposed to C.I. Disperse Blue 1. There was *equivocal evidence of carcinogenicity* of C.I. Disperse Blue 1 in male $B6C3F_1$ mice as shown by marginally increased incidences of hepatocellular adenomas or carcinomas (combined) in dosed male mice and a marginally increased occurrence of alveolar/bronchiolar adenomas or carcinomas (combined) in high dose male mice. There was *no evidence of carcinogenicity* of C.I. Disperse Blue 1 in female $B6C3F_1$ mice.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of C.I. Disperse Blue 1 is based on the 13-week studies that began in May 1979 and ended in August 1979 and the 2-year studies that began in March 1980 and ended in March 1982 at Southern Research Institute.

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The members of the Peer Review Panel who evaluated the draft Technical Report on C.I. Disperse Blue 1 on March 29, 1985, 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 C.I. DISPERSE BLUE 1

On March 29, 1985, the draft Technical Report on the toxicology and carcinogenesis studies of C.I. Disperse Blue 1 received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting began at 9:00 a.m. in the Conference Center, Building 101, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. E. Rauckman, NTP, began by reviewing the study design, results, and proposed conclusions. Dr. Kociba, a principal reviewer, agreed with most of the conclusions in rats. He stated, however, that interpretation of the data on pancreatic tumors in male rats should be based on use of historical control incidence data. Dr. Rauckman replied that the Program gives more weight to concurrent control values than to historical control values, and there was a good dose response if allowance was made for reduced survival at the high dose. Dr. Kociba stated that the conclusions in mice should be reevaluated after historical control incidences of lung and liver tumors and early mortality in male concurrent control mice were factored in. He said that the doses selected for the 2-year studies in both species were higher than warranted based on the type and magnitude of toxicity observed in the 13-week studies.

As a second principal reviewer, Dr. Crowley agreed with the conclusions on the rat studies but thought that the data in mice were, at most, equivocal evidence of carcinogenicity and that consideration should be given to an assessment of no evidence of carcinogenicity.

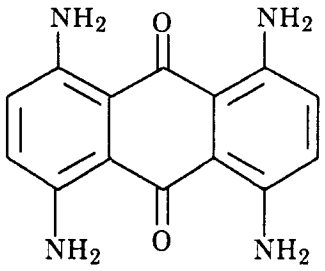
As a third principal reviewer, Dr. Kotelchuck agreed with the conclusions, noting that they were all appropriate even if the high dose animals were excluded.

Most of the discussion dealt with the proposed levels of evidence from the studies in mice (equivocal evidence of carcinogenicity in both sexes). Dr. Rauckman said that the level of evidence chosen for male mice was based on comparison with concurrent controls along with a reasonable dose response if reduced survival at the high dose was considered. In female mice, the low dose incidence of hepatocellular adenomas or carcinomas was greater than that ever observed Programwide in controls. Dr. Kociba emphasized that concurrent control values for liver (both sexes) and lung lesions (males) were low, whereas historical control values are variable, thus making it difficult to attribute causality to chemical administration. Both Dr. Kotelchuck and Dr. Hooper supported greater weight being given to concurrent control values. Dr. J. Haseman, NIEHS, noted that the increases in liver tumors were seen in both sexes at the low dose. Dr. J. Huff, NIEHS/NTP, commented that the chemical is mutagenic, and in other long-term studies, various anthraquinone derivatives have been shown to induce lung and liver tumors.

Dr. Hooper moved that the conclusion of clear evidence of carcinogenicity in male and female rats be accepted as written. Dr. Swenberg seconded the motion, and it was approved unanimously. Dr. Hooper moved that the conclusion of equivocal evidence of carcinogenicity in male mice be accepted as written. Dr. Kotelchuck seconded that motion, and it was approved with six affirmative votes; there were four negative votes (Dr. Crowley, Dr. Kociba, Dr. Purchase, and Dr. Swenberg). Dr. Hooper moved that the conclusion of no evidence of carcinogenicity in female mice be accepted. Dr. Swenberg seconded the motion, and it was approved with seven affirmative votes; there were two negative votes (Dr. Harper and Dr. Kotelchuck) and one abstention (Dr. Turnbull).

I. INTRODUCTION

I. INTRODUCTION



C.I. DISPERSE BLUE 1

CAS No. 2475-45-8

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Synonyms: C.I. 64500; 1,4,5,8-Tetraamino-9,10-anthracenedione; 1,4,5,8-Tetraaminoanthraquinone

Background, Use, and Production

C.I. Disperse Blue 1 (containing approximately 50% 1,4,5,8-tetraaminoanthraquinone, 30% other compounds structurally related to 1,4,5,8-tetraaminoanthraquinone, and 20% water) is a blue-black microcrystalline material used as a disperse dye. Commercial preparations contain approximately equal amounts of dyestuff and lignosulfonate dispersants. The material has a melting point of 332° C (Clairol Research Laboratories) and a low (3 ppm) solubility in water. In the United States, C.I. Disperse Blue 1 is used in semipermanent hair color formulations at concentrations of less than 1%. The solubility of C.I. Disperse Blue 1 in these preparations (approximately 500 ppm) is considerably greater than its solubility in water. Over 3 million people in the United States use hair color preparations containing C.I. Disperse Blue 1, and 4-6 $\times$ 10^6 g of material are imported for this purpose annually (personal communication to NTP, Dr. C. Burnett, Clairol Research Laboratories, November 27, 1984).

Mutagenicity

Brown and Brown (1976) demonstrated that C.I. Disperse Blue 1 was mutagenic in strain TA1537 of *Salmonella typhimurium* in the presence or absence of Aroclor 1254-induced rat liver S9. The NTP found that C.I. Disperse Blue 1 was mutagenic in strains TA1535, TA97, and TA98 of *S. typhimurium* in the presence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9 and in strains TA97 and TA98 in the absence of S9; it was not mutagenic in strain TA100 (Appendix M).

Toxicity

No data on the toxicity, metabolism, pharmacokinetics, or tissue distribution of C.I. Disperse Blue 1 per se were located in the literature (NLM, 1984); however, some studies have been conducted with mixtures containing C.I. Disperse Blue 1. Wernick et al. (1975) studied a formulation containing 15 dyes and dye intermediates and 10 base chemicals at the highest levels found in any formulation of the Clairol "Loving Care"® line of hair colors. This mixture, which contained 0.61% C.I. Disperse Blue 1, was fed to dogs and rats in the diet. No adverse effects were observed in dogs that received the mixture at doses of 19.5 or 97.5 mg/kg per day for 2 years. In rats that received the diet at 1,950 or 7,800 ppm, fertility, gestation, lactation, and offspring viability indices were similar to those of control animals, and no teratogenic effects were noted when the mixture was fed to pregnant rats. The mixture was also administered by gavage to pregnant rabbits from day 6 to day 18 of gestation at doses of 19.5 or 97.5 mg/kg per day. No teratogenic effects were observed.

Toxicity of Structurally Related Compounds

C.I. Disperse Blue 1 is structurally related to 2-aminoanthraquinone (Figure 1), which was found to be carcinogenic in male F344/N rats, causing neoplastic nodules or hepatocellular carcinomas (combined) of the liver, and in $B6C3F_1$ mice, causing hepatocellular carcinomas in each sex and malignant lymphomas in female mice (NCI, 1978a). The highest concentrations used in these experiments were 6,900 ppm for male rats, 2,000 ppm for female rats, and 10,000 ppm for mice of either sex.

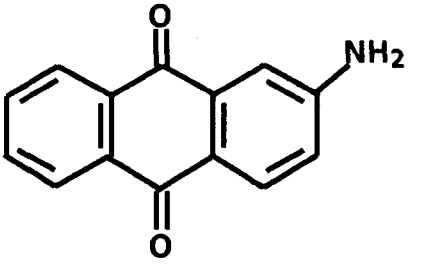
1-Amino-2-methylanthraquinone (Figure 1) was tested for carcinogenicity and was found to cause an increased occurrence of hepatocellular carcinomas in F344/N rats of each sex and of hepatocellular carcinomas or neoplastic liver nodules (combined) in female $B6C3F_1$ mice; in addition, the compound produced a significant increase in kidney neoplasms in male rats (NCI, 1978b). Dietary concentrations for male rats were 1,000 or 2,000 ppm, and the concentration (time-weighted average) for mice was 600 ppm in feed.

2-Methyl-1-nitroanthraquinone (Figure 1) was found to cause hepatocellular carcinomas and neoplastic nodules in male F344/N rats; increased incidences of subcutaneous fibromas were also observed in each sex (NCI, 1978c). In female rats, there was an increased incidence of papillomas and transitional cell papillomas or sarcomas (combined) of the urinary bladder (control, 0/46; low dose, 3/43, 7%; high dose, 4/44, 9%). The compound was administered to groups of 50 animals for 78 weeks at concentrations of 600 or 1,200 ppm in feed; the animals were observed for 31 weeks and then killed. 2-Methyl-1-nitroanthraquinone was also found to produce hemangiosarcomas in $B6C3F_1$ mice of each sex at dietary concentrations of 300 and 600 ppm (Murthy et al., 1977).

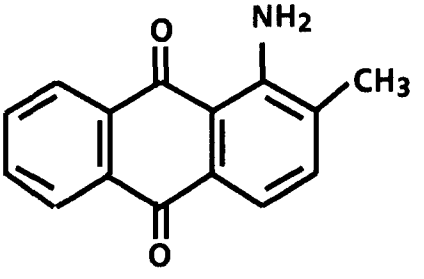
A monograph on aromatic amines has been published by the International Agency for Research on Cancer (IARC, 1982), which includes information about hair dye preparations. Epidemiologic studies concerning the relationships between human cancer and either employment as a hairdresser or the personal use of hair dyes were evaluated. However, these data were considered inconclusive.

Study Rationale

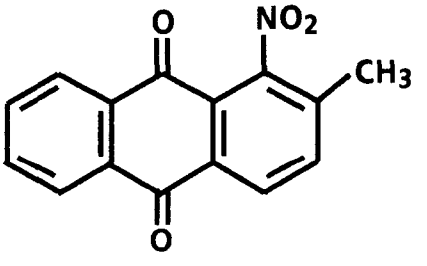
C.I. Disperse Blue 1 is one of five semipermanent hair dyes selected for toxicologic and carcinogenic assessment in a class study of hair color materials. Results of studies of HC Blue No. 1, HC Blue No. 2, and HC Red No. 3 have been reported (NTP, 1985a,b; 1986). HC Blue No. 1 (2,2'((4-(methylamino)-3-nitrophenyl)imino)bis(ethanol), CAS No. 2784-94-3) was found to cause follicular cell adenomas of the thyroid gland in male $B63CF_1$ mice and hepatocellular carcinomas in $B63CF_1$ mice of each sex. Marginal increases in the incidence of alveolar/bronchiolar adenomas or carcinomas (combined) in female F344/N rats and in the incidence of hepatocellular neoplastic nodules or carcinomas (combined) in male F344/N rats were also observed. HC Blue No. 2 (2,2'((4-((2-hydroxyethyl)amino)-3-nitrophenyl)imino)bis(ethanol), CAS No. 33229-34-4) was not found to cause significantly increased compound-related incidences of any neoplasm in F344/N rats or $B6C3F_1$ mice of either sex. An increased incidence of hepatocellular adenomas or carcinomas (combined) was seen in the high dose group of male mice given HC Red. No. 3 (2-((4-amino-2-nitrophenyl)amino)ethanol, CAS No. 2871-01-4). C.I. Acid Orange 3 is still under study.



2-Aminoanthraquinone



1-Amino-2-methylanthraquinone



2-Methyl-1-nitroanthraquinone

FIGURE 1. STRUCTURES OF ANTHRAQUINONES RELATED TO 1,4,5,8-TETRAAMINOANTHRAQUINONE

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF C.I. DISPERSE BLUE 1

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

- Study Design
- Source and Specifications of Animals
- Animal Maintenance
- Clinical Examinations and Pathology
- Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF C.I. DISPERSE BLUE 1

C.I. Disperse Blue 1 (1,4,5,8-tetraaminoanthraquinone) was obtained in two lots from Clairol Research Laboratories (Table 1). Purity and identity determinations were conducted on both lots by the analytical chemistry laboratory (Midwest Research Institute) (Appendix G).

The identity of C.I. Disperse Blue 1 was confirmed by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy (Appendix G). The infrared and nuclear magnetic resonance spectroscopic data were consistent with those expected for the structure of C.I. Disperse Blue 1 and the spectra of the dye provided by Clairol. The visible spectra at 630 nm indicated that lot no. 4351828 had a greater dye content than did a purified sample supplied separately by Clairol.

The purity of the two lots was determined by elemental analysis, water analysis, titration of the amine groups, thin-layer chromatography, and high-performance liquid chromatography (Appendix G). For lot no. 4351828, results of the analyses for water content (19.5%), amine titration (62.9% of the remaining 80.5%), and chromatography, which detected a minimum of four major impurities (more than 1%), indicated that the study material is a complex mixture of components resembling C.I. Disperse Blue 1 in structure and that it contains approximately 50% C.I. Disperse Blue 1, 19.5% water, and 30% other impurities. Discussions of the results with the supplier indicated that this finding is typical for the dye used in commerce. Supplemental analyses conducted on lot no. 4351828 after completion of the animal studies showed that the study material contained no detectable nitrosamines (detection limit 0.2 ppm). In addition, analysis by gas chromatography/mass spectroscopy indicated that the two major impurities present in the study material were an isomer of tetraaminoanthraquinone, present at a concentration of approximately 25%, and a nitrotriaminoanthraquinone isomer, present at approximately 6% (Appendix G).

Results of a heat stability study performed by the analytical chemistry laboratory indicated that the compound should be stored at $-20°$ C (Appendix G). The study chemical was stored at $-20°$ C at the study laboratory. Periodic characterization of C.I. Disperse Blue 1 by infrared and ultraviolet/visible spectroscopy indicated that no detectable deterioration occurred over the course of the studies (Appendix G).

TABLE 1. IDENTITY AND SOURCE OF LOTS USED IN THE STUDIES OF C.I. DISPERSE BLUE 1

	Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers	3460777	4351828	4351828	4351828
Supplier	BASF Aktiengesellschaft supplied by Clairol Research Laboratories (Stamford, CT)	Same as the single-administration studies	Same as the single-administration studies	Same as the single-administration studies

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

The homogeneity of a formulated diet mixture was demonstrated by the analytical chemistry laboratory (Appendix H). Further studies indicated that the C.I. Disperse Blue 1 was stable in feed when stored for 2 weeks at temperatures of 25° C or below.

Formulated diets were prepared by adding a dry premix (approximately equal amounts of feed and C.I. Disperse Blue 1) to the appropriate amount of feed (Table 2; Appendix H). The mixture then was blended for 15 minutes. The formulated diets were held at 5° C until use and used within 13 days after they were mixed.

Periodic analyses for C.I. Disperse Blue 1 in formulated diets were performed to confirm that the chemical was administered to animals at the correct concentrations. The method of analysis involved a methanolic extraction and spectrophotometric quantitation (Appendix I). Because 18/102 samples tested were not within 10% of the target concentration (Table 3; Appendix J), the data can be extrapolated to indicate that 82% of the mixes were formulated within the specified ± 10% of the target concentrations.

TABLE 2. PREPARATION AND STORAGE OF DOSE MIXTURES AND FORMULATED DIETS IN THE STUDIES OF C.I. DISPERSE BLUE 1

	Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation	Mixed by hand in corn oil vehicle until a uniform consistency was achieved, then sonicated	A premix of chemical and feed was sandwiched between two layers of feed in a 16-qt V-blender and mixed for 15 minutes	Same as the 14-d studies	Same as the 14-d studies
Maximum Storage Time	1 wk	1 wk	1 wk	13 d
Storage Conditions	5° C	5° C	5° C	5° C

TABLE 3. SUMMARY OF RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1

	Target Concentration				
	600 ppm	1,200 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Mean (ppm)	549	1,089	1,203	2,367	4,766
Standard deviation	48.8	108.2	89.3	136.6	204.2
Coefficient of variation (percent)	8.9	9.9	7.4	5.8	4.3
Range (ppm)	462-627	920-1,250	980-1,410	2,100-2,640	4,400-5,060
Number of samples	13	12	25	25	27

II. MATERIALS AND METHODS

SINGLE-ADMINISTRATION STUDIES

Single-administration studies were conducted to evaluate the acute toxicity of C.I. Disperse Blue 1 and to help determine dietary concentrations for 14-day studies. Groups of five F344/N rats of each sex were administered a single dose of 188, 375, 750, 1,500, or 3,000 mg/kg C.I. Disperse Blue 1 in corn oil by gavage. Groups of five $B6C3F_1$ mice of each sex were administered 125, 250, 500, 1,000, or 2,000 mg/kg. The animals were housed five per cage. Feed and water were available ad libitum. All animals were killed on day 16. Details of animal maintenance and dosing are given in Table 4.

FOURTEEN-DAY STUDIES

Fourteen-day studies were conducted to characterize short-term toxicity and to set doses for the 13-week studies. Groups of five F344/N rats and $B6C3F_1$ mice of each sex were fed diets containing C.I. Disperse Blue 1 at 0, 3,100, 6,200, 12,500, 25,000, or 50,000 ppm for 14 consecutive days. The animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance and dosing are given in Table 4.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative effects of repeated administration of C.I. Disperse Blue 1 and to determine the concentrations to be used in the 2-year studies.

Three- to four-week old F344/N rats and $B6C3F_1$ mice of each sex were obtained from Harlan Industries 14 days before being placed on study. Groups of 10 rats of each sex were fed diets containing 0, 1,200, 2,500, 5,000, 10,000, or 20,000 ppm C.I. Disperse Blue 1 for 13 weeks. Groups of 10 mice of each sex were fed diets containing 0, 600, 1,200, 2,500, 5,000, or 10,000 ppm. Animals were housed five per cage. Feed and water were available ad libitum. Animals were checked twice daily; moribund animals were killed. Feed consumption was measured weekly by cage. Individual animal weights were recorded weekly. Further experimental details are summarized in Table 4.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Groups and tissues examined are listed in Table 4.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were fed diets containing 0, 1,250, 2,500, or 5,000 ppm C.I. Disperse Blue 1 for 103 weeks. Groups of 50 mice of each sex were fed diets containing 0, 600, 1,200, or 2,500 ppm for 104 weeks.

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female, × C3H/HeN MTV^-, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the NTP. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Animals were shipped to the study laboratory at 5 weeks of age. The animals were quarantined at the study facility for 15 days. Thereafter, a complete necropsy was performed on five rats and five mice of each sex to assess their health status. The rodents were placed on study at 7 weeks of age. The health of the animals was monitored during the course of the study according to the protocols of the NTP Sentinel Animal Program (Appendix K).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid $B6C3F_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE STUDIES OF C.I. DISPERSE BLUE 1

	Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN				
Study Laboratory	Southern Research Institute	Southern Research Institute	Southern Research Institute	Southern Research Institute
Size of Study Groups	5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses	Rats--188, 375, 750, 1,500, or 3,000 mg/kg C.I. Disperse Blue 1 in 5 ml corn oil/kg body weight by gavage (3,000 mg/kg in 10 ml/kg); mice--125, 250, 500, 1,000, or 2,000 mg/kg in 10 ml/kg corn oil by gavage (2,000 mg/kg in 20 ml/kg)	0, 3,100, 6,200, 12,500, 25,000, or 50,000 ppm C.I. Disperse Blue 1 in feed	Rats--0, 1,200, 2,500, 5,000, 10,000, or 20,000 ppm C.I. Disperse Blue 1 in feed; mice--0, 600, 1,200, 2,500, 5,000, or 10,000 ppm in feed	Rats--0, 1,250, 2,500, or 5,000 ppm C.I. Disperse Blue 1 in feed; mice--0, 600, 1,200, or 2,500 ppm in feed
Date of First Dose	12/14/78	3/14/79	5/23/79	3/19/80
Date of Last Dose	N/A	3/27/79	8/21/79	Rats--3/9/82; mice--3/16/82
Duration of Dosing	One time only	14 consecutive d	91 d	Rats--103 wk; mice--104 wk
Type and Frequency of Observation	Observed 2 × d; initial body weights taken	Observed 2 × d; weighed on d 1, 7, and 15	Observed 2 × d; feed consumption, clinical signs, and weight recorded 1 × wk	Observed 2 × d; clinical observations and weight recorded 1 × wk for 3 mo, 1 × mo thereafter
Necropsy and Histologic Examination	Necropsy performed on all animals.	Necropsy performed on all animals; no histologic examination was performed	Necropsy performed on all animals; histologic exam performed on all control and high dose animals and those that died before the end of the studies; the following tissues were examined: skin, mandibular and mesenteric lymph nodes, mammary gland, salivary gland, thigh muscle, femur (including marrow), thymus, trachea, lungs and bronchi, heart, thyroid gland, parathyroids, esophagus, stomach, small intestine, colon, liver, pancreas, brain, spleen, kidneys, adrenal glands, urinary bladder, vesicular gland/prostate/testis or ovary/uterus, and pituitary gland	Necropsy performed on all animals; histologic exam performed on all animals; tissues examined include: skin, mandibular and mesenteric lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, femur (including marrow), costochondral junction, thymus, larynx, trachea, lungs and bronchi, heart, thyroid gland, parathyroids, esophagus, stomach, duodenum, jejunum, ileum, colon, cecum, rectum, liver, pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles/prostate/testis or ovary/uterus, nasal cavity, brain, pituitary gland, spinal cord (examined selectively), and eyes (examined selectively)
ANIMALS AND ANIMAL MAINTENANCE				
Strain and Species	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE STUDIES OF C.I. DISPERSE BLUE 1 (Continued)

	Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)				
Animal Source	Charles River Breeding Laboratories (Wilmington, MA)	Charles River Breeding Laboratories (Portage, MI)	Harlan Industries (Indianapolis, IN)	Charles River Breeding Laboratories (Portage, MI)
Animal Identification	Ear punch	Ear punch	Ear punch	Ear punch
Time Held Before Study	14 d	14 d	14 d	15 d
Age When Placed on Study	Rats--43-51 d; mice--43-57 d	Rats--43-50 d; mice--43-57 d	5-6 wk	7 wk
Age When Killed	Rats--57-65 d; mice--57-71 d	Rats--57-64 d; mice--57-71 d	18-19 wk	Rats--111-112 wk; mice--112-113 wk
Necropsy Dates	12/29/78	3/29/79-3/31/79	8/23/79-8/25/79	Rats--3/17/82-3/24/82; mice--3/25/82-4/2/82
Method of Animal Distribution	Assigned to cages by a series of random numbers, then to groups by another series of random numbers	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Feed	Wayne Lab Blox® (Allied Mills, Inc., Chicago, IL); available ad libitum	Same as single-administration studies	Same as single-administration studies	NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum
Bedding	Beta Chips® (Northeastern Products Corp., Warrensburg, NY); sawdust (PWI, Inc., Loweville, NY)	Beta Chips® (Northeastern Products Corp, Warrensburg, NY)	Same as 14-d studies	Same as single-administration studies
Water	Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cages	Polycarbonate (Lab Products, Garfield, NJ)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cage Filters	Reemay spunbonded polyester (Snow Filtration, Cincinnati, OH)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Animals per Cage	5	5	5	5
Animal Room Environment	Temp--21°-23° C; humidity--30%-50%; fluorescent light 12 h/d; 15 room air changes/h	Same as single-administration studies	Same as single-administration studies	Temp--22.2°-25.0° C; humidity--19%-86%; fluorescent light 12 h/d; 15 room air changes/h
Other Chemicals on Study in Same Room	None	None	None	None

The C57BL/6 mice were homogeneous at all loci studied. Eighty-five percent of the C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of randomly bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6 colony were used as parents for the hybrid B6C3F$_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

All animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 4.

Clinical Examinations and Pathology

All animals were observed twice daily, and clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 13 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Moribund animals were killed, as were animals that survived to the end of the study. A necropsy was performed on all animals, including those found dead unless they were excessively autolyzed or cannibalized. 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 in each group.

Examinations for grossly visible lesions were performed on major tissues or organs. Urinary bladders were opened at necropsy and examined for the presence of calculi. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 4.

When the pathology examination was completed, the slides, individual animal data records, and summary tables were sent to an independent quality assurance laboratory. Individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assurance pathologist. Slides of all target tissues and those about which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative coded slides selected by the Chairperson were reviewed by PWG pathologists, who reached a consensus and compared their findings with the original and quality assurance diagnoses. When diagnostic differences were found, the PWG sent the appropriate slides and comments to the original pathologist for review. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent evaluations, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Nonneoplastic lesions are not examined by the quality assurance pathologist or the PWG. Certain nonneoplastic findings are reviewed by the quality assurance pathologist and the PWG if they are considered part of the toxic response to a chemical or if they are deemed of special interest.

Statistical Methods

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

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 dead of other than natural causes or were found to be missing; 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. 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., skin or mammary tumors) 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: Three statistical methods are used to analyze tumor incidence data. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high dose and low dose groups with controls and tests for overall dose-response trends.

For studies in which compound administration has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. All reported P values for tumor analyses are one-sided.

Life Table Analyses--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals on which a necropsy was actually performed during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

Unadjusted Analyses--Primarily, survival-adjusted methods are used to evaluate tumor incidence. In addition, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendix containing the analyses of primary tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

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

III. RESULTS

RATS

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

SINGLE-ADMINISTRATION STUDIES

All the rats survived 14 days to the end of the studies. Final mean body weights were not recorded. The urine was blue for all dosed males and females from day 1 through days 2-6. Dietary concentrations for the 14-day studies were set at the highest concentration considered not to interfere with nutrient requirements (50,000 ppm), since deaths did not occur in the single-administration gavage studies.

FOURTEEN-DAY STUDIES

Two female rats that received 50,000 ppm died (Table 5). All other animals survived to the end of the studies. Male rats that received 25,000 ppm or 50,000 ppm and female rats that received 50,000 ppm lost weight. Rats that received 6,200 ppm or 12,500 ppm gained notably less weight than did the controls. Feed consumption was not measured. All dosed rats had blue urine. Compound-related clinical signs observed in high dose animals included inactivity, hunched back, and sunken eyes. All tissues at all doses appeared blue at necropsy. Because of the deaths of two female rats in the high dose group and weight loss in the two highest dose groups of the males, the high dose for the 13-week studies was set at 20,000 ppm for both male and female rats.

TABLE 5. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY FEED STUDIES OF C.I. DISPERSE BLUE 1

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	5/5	141 ± 10	208 ± 8	+67 ± 5	--
3,100	5/5	142 ± 4	194 ± 7	+52 ± 3	93
6,200	5/5	137 ± 5	178 ± 5	+41 ± 2	86
12,500	5/5	141 ± 9	173 ± 11	+32 ± 4	83
25,000	5/5	131 ± 6	123 ± 10	− 8 ± 6	59
50,000	5/5	142 ± 10	96 ± 6	−46 ± 6	46
FEMALE					
0	5/5	99 ± 3	130 ± 2	+31 ± 2	--
3,100	5/5	98 ± 2	124 ± 3	+26 ± 1	95
6,200	5/5	94 ± 3	104 ± 7	+10 ± 6	80
12,500	5/5	101 ± 3	115 ± 6	+14 ± 4	88
25,000	5/5	97 ± 3	98 ± 6	+ 1 ± 5	75
50,000	(d) 3/5	94 ± 4	65 ± 4	−33 ± 3	50

(a) Number surviving/number in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors
(d) Day of death: 8, 9

THIRTEEN-WEEK STUDIES

The deaths of two male rats in the 10,000-ppm group were not considered to be compound related, primarily because no rats that received C.I. Disperse Blue 1 at 20,000 ppm died (Table 6) and no significant compound-related pathologic effects were observed in these two animals. Final mean body weights relative to those of the controls were 8% and 14% lower than that of the controls for male rats that received 10,000 or 20,000 ppm and 10% lower for females that received 20,000 ppm. Feed consumption by dosed and control groups was comparable. The urine of all dosed rats was blue. The extrahepatic bile ducts of 4/10 male rats in the 20,000-ppm group were distended by aggregates of dark-blue crystalline material.

Compound-related histopathologic effects in both males and females included pigmentation of the thyroid gland follicle, renal pigmentation and/or dilatation, nephrosis, chronic inflammation and/or hyperplasia of the transitional epithelium of the urinary bladder, and calculi of the urinary tract in groups receiving 2,500 ppm or higher (Table 7). No compound-related histopathologic effects were observed at 1,200 ppm.

Dose Selection Rationale: The maximum dietary concentration for the 2-year studies was set at 5,000 ppm because the effects on the kidney at 10,000 and 20,000 ppm were considered to be potentially life threatening. The choices of 2,500 and 5,000 ppm allowed further definition of the consequences of compound-induced urinary bladder hyperplasia and inflammation, and 1,250 ppm was selected as an apparent no-effect level.

TABLE 6. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF C.I. DISPERSE BLUE 1

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 4	Week 13
MALE							
0	10/10	103 ± 4	279 ± 8	+176 ± 8	--	16	14
1,200	10/10	106 ± 1	273 ± 7	+167 ± 6	98	16	14
2,500	10/10	104 ± 2	272 ± 6	+168 ± 5	97	15	14
5,000	10/10	107 ± 3	265 ± 6	+158 ± 7	95	17	15
10,000	(e) 8/10	106 ± 2	257 ± 8	+151 ± 8	92	17	15
20,000	10/10	106 ± 2	241 ± 6	+135 ± 5	86	15	15
FEMALE							
0	10/10	87 ± 2	169 ± 6	+ 82 ± 4	--	12	10
1,200	10/10	91 ± 1	177 ± 4	+ 86 ± 3	105	12	10
2,500	10/10	91 ± 2	173 ± 4	+ 82 ± 3	102	12	10
5,000	10/10	87 ± 2	173 ± 8	+ 86 ± 6	102	12	10
10,000	10/10	90 ± 2	170 ± 4	+ 80 ± 4	101	12	10
20,000	10/10	93 ± 2	152 ± 6	+ 59 ± 5	90	11	11

(a) Number surviving/number in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams of feed per animal per day
(e) Week of death: 12

TABLE 7. INCIDENCES OF COMPOUND-RELATED HISTOPATHOLOGIC EFFECTS IN RATS IN THE THIRTEEN-WEEK FEED STUDIES OF C.I. DISPERSE BLUE 1

	Control	1,200 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
MALE						
Thyroid follicle pigmentation	0/10	0/10	0/10	0/10	8/9	10/10
Urinary tract						
Renal pigmentation	0/10	0/10	0/10	0/10	9/10	10/10
Nephrosis	(a) 6/10	0/10	0/10	(b) 9/10	(c) 10/10	(d) 10/10
Hydronephrosis	0/10	0/10	0/10	0/10	0/10	5/10
Calculi	0/10	0/10	8/10	10/10	10/10	10/10
Urinary bladder chronic inflammation	0/10	0/10	(e) 3/9	4/10	10/10	10/10
Urinary bladder transitional epithelium hyperplasia	0/10	0/10	(e) 9/9	(e) 10/10	10/10	10/10
Urinary bladder squamous metaplasia	0/10	0/10	0/10	0/10	0/10	2/10
Liver pigmentation	0/10	0/10	0/10	0/10	0/10	2/10
FEMALE						
Thyroid follicle pigmentation	0/10	0/10	0/10	2/10	10/10	10/10
Urinary tract						
Renal pigmentation	0/10	0/10	0/10	9/10	10/10	10/10
Nephrosis	0/10	0/10	0/10	2/10	10/10	10/10
Hydronephrosis	0/10	0/10	0/10	0/10	0/10	1/10
Calculi	0/10	0/10	5/10	10/10	10/10	10/10
Urinary bladder chronic inflammation	0/10	0/10	(e) 4/10	(e) 2/10	(e) 9/10	7/10
Urinary bladder transitional epithelium hyperplasia	0/10	0/10	(e) 2/10	(e) 8/10	(e) 10/10	9/10
Urinary bladder squamous metaplasia	0/10	0/10	0/10	0/10	0/10	1/10
Liver pigmentation	0/10	0/10	0/10	0/10	0/10	0/10

(a) Minimal to mild
(b) Mild
(c) Moderate to severe
(d) Severe
(e) Diagnoses by Quality Assurance Pathologist; this lesion was not reported by the original pathologist but was reported during review of the slides and was confirmed by a Pathology Working Group review.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male and female rats were lower than those of the controls throughout the study (Table 8 and Figure 2). Mean body weights of mid dose male and female rats were marginally (6%) lower by the end of the study. The average daily feed consumption per rat by low dose, mid dose, or high dose rats was 101%, 104%, or 109% that of the controls for males and 105%, 102%, or 103% that of the controls for females (Appendix L, Tables L1 and L2). The average amount of C.I. Disperse Blue 1 consumed per day was approximately 45, 95, and 217 mg/kg for low dose, mid dose, and high dose male rats and 56, 111, and 240 mg/kg for low dose, mid dose, and high dose female rats. Dose-related clinical signs for male and female rats included blue urine, firmness in the area of the urinary bladder, wet fur in the pelvic area, blue fur and extremities, and feces stained blue-green. Some female high dose rats also had blue crusty material in the area of the vagina.

TABLE 8. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1

Weeks on Study	Control		1,250 ppm			2,500 ppm			5,000 ppm		
	Av Wt (grams)	No. of Survivors	Av Wt (grams)	Wt (percent of controls)	No. of Survivors	Av Wt (grams)	Wt. (percent of controls)	No. of Survivors	Av Wt (grams)	Wt (percent of controls)	No. of Survivors
MALE											
0	139	50	139	100	50	138	99	50	135	97	50
1	174	50	175	101	50	174	100	50	162	93	50
2	211	50	212	100	50	210	100	50	199	94	50
3	241	50	241	100	50	239	99	50	227	94	50
4	260	50	262	101	50	259	100	50	247	95	50
5	277	50	277	100	50	279	101	50	264	95	50
6	293	50	293	100	50	292	100	50	276	94	50
7	308	50	309	100	50	306	99	50	289	94	50
8	322	50	322	100	50	319	99	50	299	93	50
9	331	50	331	100	50	330	100	50	310	94	50
10	340	50	340	100	50	336	99	50	318	94	50
11	345	50	348	101	50	344	100	50	326	94	49
12	353	50	354	100	50	352	100	50	333	94	49
13	357	50	357	100	50	355	99	50	333	93	49
18	385	50	389	101	50	386	100	50	362	94	49
22	405	50	410	101	50	400	99	49	370	91	48
27	427	50	422	99	50	422	99	49	384	90	48
31	440	50	444	101	50	442	100	49	401	91	48
35	452	50	454	100	50	449	99	49	414	92	48
40	468	50	469	100	50	468	100	49	429	92	48
44	480	50	481	100	50	480	100	49	437	91	48
49	488	50	488	100	50	484	99	49	441	90	48
52	494	50	496	100	50	491	99	49	446	90	48
57	495	50	482	97	50	485	98	49	445	90	47
62	503	50	494	98	50	490	97	49	446	89	45
67	503	50	493	98	50	493	98	48	451	90	41
71	506	49	494	98	49	494	98	48	453	90	36
75	510	49	500	98	49	495	97	48	455	89	31
80	508	48	501	99	47	494	97	44	454	89	25
84	499	47	495	99	47	476	95	41	435	87	23
87	496	46	490	99	47	478	96	38	431	87	22
91	495	41	489	99	45	477	96	35	438	88	15
97	490	37	486	99	42	460	94	30	404	82	10
101	479	33	481	100	40	457	95	21	410	86	4
104	471	30	469	100	39	444	94	20	400	85	4
FEMALE											
0	109	50	110	101	50	108	99	50	109	100	50
1	127	50	130	102	50	128	101	50	124	98	50
2	144	50	145	101	50	144	100	50	134	93	49
3	158	50	157	99	50	157	99	50	149	94	48
4	166	50	167	101	50	166	100	50	160	96	48
5	175	50	174	99	50	174	99	50	170	97	48
6	182	50	182	100	50	180	99	50	176	97	48
7	188	50	188	100	50	186	99	50	181	96	48
8	194	50	194	100	50	191	98	50	187	96	48
9	197	50	197	100	50	194	98	50	192	97	48
10	199	50	200	101	50	198	99	50	193	97	48
11	202	50	205	101	50	201	100	50	197	98	48
12	204	50	205	100	50	203	100	50	199	98	48
13	203	50	204	100	50	202	100	50	198	98	48
18	215	50	218	101	50	217	101	49	210	98	48
22	223	50	222	100	50	221	99	49	210	94	48
27	236	49	234	99	50	228	97	49	218	92	48
31	242	49	241	100	50	239	99	49	223	92	48
35	248	49	246	99	49	246	99	49	229	92	48
40	259	49	256	99	49	250	97	48	234	90	48
44	268	49	265	99	48	261	97	47	240	90	48
49	274	49	272	99	48	265	97	46	241	88	48
52	282	49	280	99	48	271	96	46	246	87	47
57	290	49	289	100	48	277	96	46	253	87	45
62	304	49	304	100	48	287	94	45	261	86	44
67	316	49	316	100	48	301	95	44	270	85	40
71	331	47	327	99	47	314	95	44	281	85	40
75	339	47	336	99	45	318	94	44	288	85	37
80	345	46	339	98	44	322	93	44	292	85	37
84	349	46	344	99	42	321	92	42	289	83	35
87	350	45	349	100	41	324	93	42	293	84	34
91	357	44	355	99	41	332	93	40	297	83	31
97	360	41	361	100	39	336	93	38	298	83	27
101	369	38	362	98	37	341	92	36	303	82	21
104	364	36	360	99	37	343	94	33	318	87	15

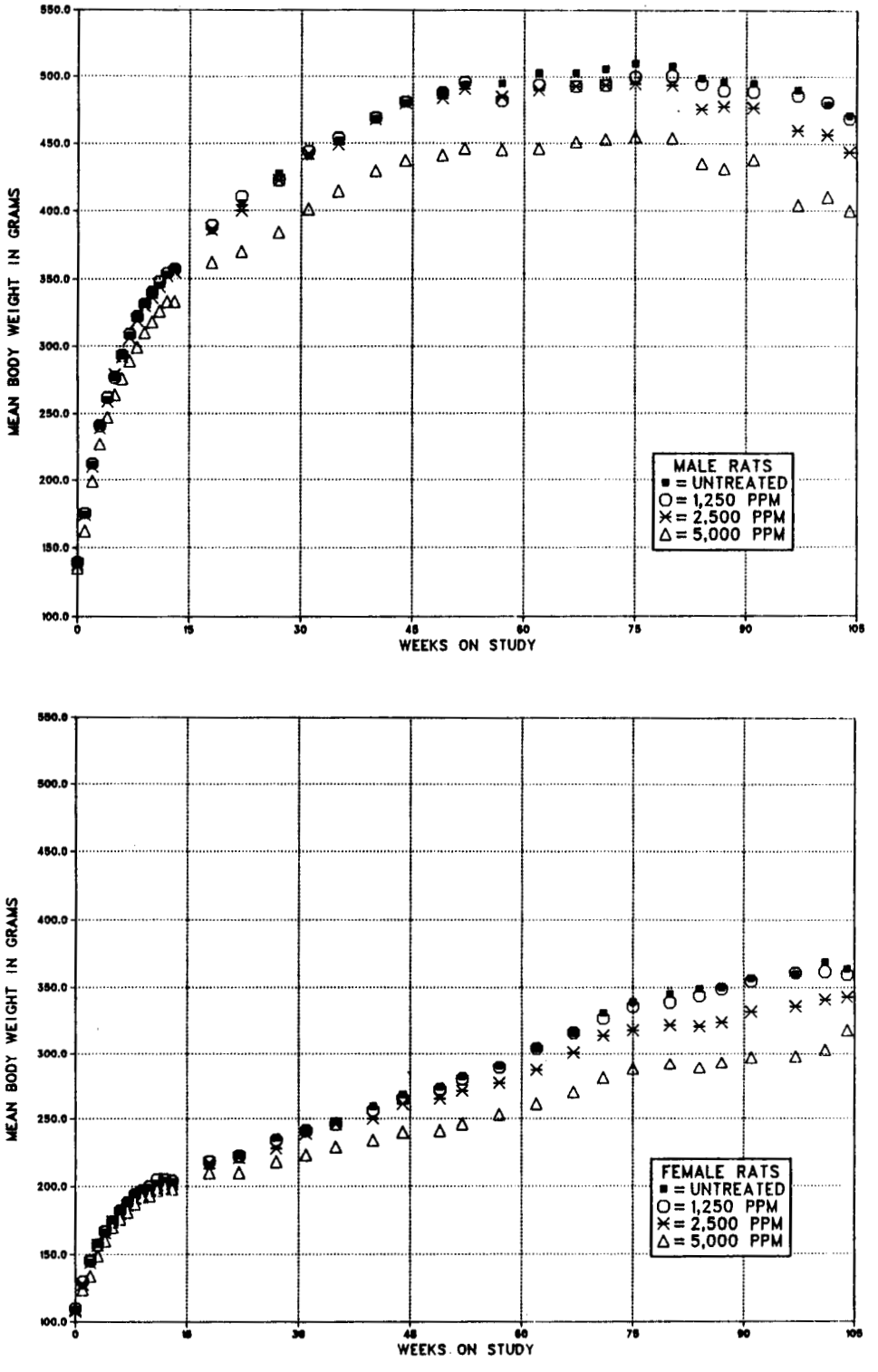


FIGURE 2. GROWTH CURVES FOR RATS FED DIETS CONTAINING C.I. DISPERSE BLUE 1 FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats fed diets containing C.I. Disperse Blue 1 at the concentrations used in these studies and for the controls are shown in the Kaplan and Meier curves in Figure 3. The survival of the male and female high dose groups was significantly reduced compared with that of the controls (Table 9). The survival (compared with the controls) was significantly reduced after week 65 for the high dose male group and after week 72 for the high dose female group. Survival of the mid dose male group was marginally reduced, the effect being significant after week 100.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the urinary system, prostate, eye, pituitary gland, thyroid gland, parathyroid, subcutaneous tissue, pancreatic islet, hematopoietic system, adrenal gland, testis, liver, mammary gland, uterus, or multiple organs. Histopathologic findings on neoplasms in rats are summarized in Appendix A (Tables A1 and A2); Appendix A (Tables A3 and A4) also gives the survival and tumor status for individual male and female rats. Findings on nonneoplastic lesions are summarized in Appendix C (Tables C1 and C2). Appendix E (Tables E1 and E2) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the four groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in control animals are listed in Appendix F.

Current NTP practice is to use life table analysis and incidental tumor tests to determine the significance of tumor occurrence; however, because of the considerable mortality in the high dose groups, the incidental tumor test lacks sensitivity for these groups. For this reason, the Fisher exact test and Cochran-Armitage trend test were also used in analyses of tumors in these studies.

TABLE 9. SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1

	Control	1,250 ppm	2,500 ppm	5,000 ppm
MALE (a)				
Animals initially in study	50	50	50	50
Nonaccidental deaths before termination (c)	20	11	30	46
Killed at termination	29	39	20	4
Died during termination period	1	0	0	0
Survival P values (c)	<0.001	0.090	0.045	<0.001
FEMALE (a)				
Animals initially in study	50	50	50	50
Nonaccidental deaths before termination (c)	13	13	16	34
Killed at termination	36	33	32	15
Died during termination period	1	4	2	1
Survival P values (c)	<0.001	0.904	0.583	<0.001

(a) Terminal kill period: weeks 104-105
(b) Includes animals killed in a moribund condition
(c) 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.

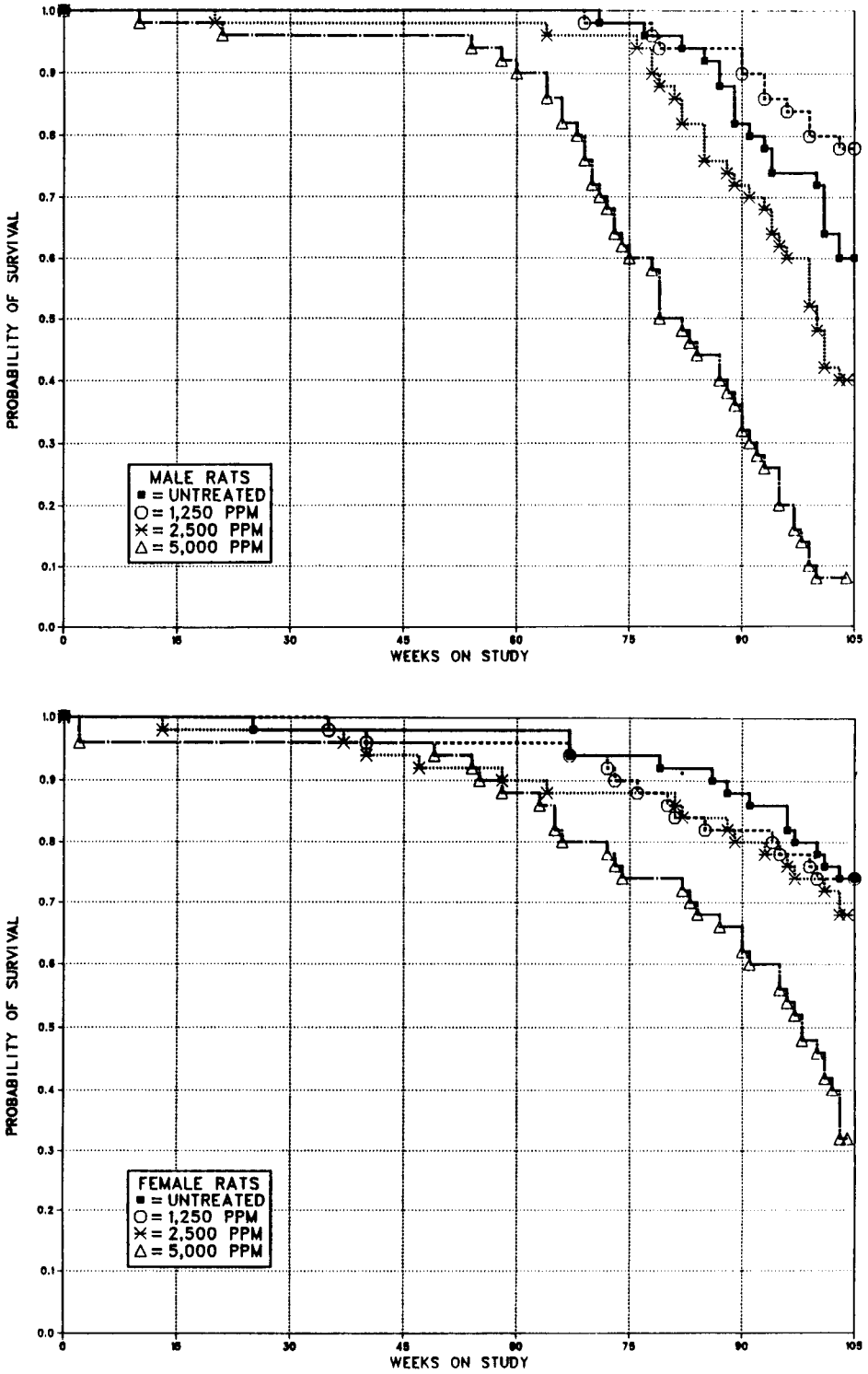


FIGURE 3. KAPLAN-MEIER SURVIVAL CURVES FOR RATS FED DIETS CONTAINING C.I. DISPERSE BLUE 1 FOR TWO YEARS

Urinary System: The incidences of nonneoplastic and neoplastic lesions in the urinary system were increased in dosed male and dosed female rats (Table 10). Nonneoplastic lesions observed at increased incidences included renal and urinary bladder calculi, renal casts, hydronephrosis and renal degeneration, renal and urinary bladder epithelial hyperplasia, urinary bladder squamous metaplasia, and pigmentation of the kidney and urinary bladder.

In addition to the lesions listed in Table 10, lipomatosis of the urinary bladder was present in nine mid dose female rats and one high dose female rat. It could not be determined if the condition was neoplastic.

TABLE 10. INCIDENCES OF URINARY SYSTEM LESIONS IN RATS IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1

Tissue/Lesion	Control	1,250 ppm	2,500 ppm	5,000 ppm
MALE				
Urinary Bladder				
Pigmentation	0/49	(a) 36/50	(a) 14/50	(a) 11/49
Calculi				
Gross	0/49	0/50	(a) 16/50	(a) 21/49
Microscopic	0/49	0/50	1/50	(a) 15/49
Epithelial hyperplasia	0/49	2/50	(a) 28/50	(a) 42/49
Squamous metaplasia	0/49	0/50	(a) 10/50	(a) 12/49
Carcinoma	0/49	0/50	1/50	0/49
Squamous cell papilloma	0/49	0/50	1/50	3/49
Squamous cell carcinoma	0/49	0/50	1/50	1/49
Transitional cell papilloma	0/49	0/50	(a) 8/50	4/49
Transitional cell carcinoma	0/49	0/50	4/50	(a) 8/49
Sarcoma	0/49	0/50	1/50	0/49
Leiomyoma	0/49	0/50	1/50	0/49
Leiomyosarcoma	0/49	0/50	(b) 6/50	(a) 41/49
Kidney				
Pigmentation	1/49	(a) 48/50	(a) 50/50	(a) 45/50
Calculi				
Gross	0/49	1/50	1/50	(a) 12/50
Microscopic	0/49	0/50	2/50	(a) 19/50
Hydronephrosis	0/49	0/50	(b) 5/50	(b) 5/50
Epithelial hyperplasia	0/49	2/50	(a) 8/50	(a) 11/50
Transitional cell carcinoma	0/49	1/50	0/50	1/50
Tubular cell adenocarcinoma	0/49	0/50	1/50	0/50
Sarcoma	0/49	1/50	0/50	0/50
Kidney/Tubule				
Cast	0/49	(a) 50/50	(a) 49/50	(a) 46/50
Degeneration	0/49	(a) 46/50	(a) 41/50	(a) 32/50
Ureter				
Transitional cell carcinoma	0/49	0/50	0/50	1/50
Transitional cell papilloma	0/49	0/50	0/50	0/50

TABLE 10. INCIDENCES OF URINARY SYSTEM LESIONS IN RATS IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1 (Continued)

Tissue/Lesion	Control	1,250 ppm	2,500 ppm	5,000 ppm
FEMALE				
Urinary Bladder				
Pigmentation	0/48	(a) 44/50	(a) 9/50	(a) 13/48
Calculi				
Gross	0/48	0/50	(a) 12/50	(a) 37/48
Microscopic	0/48	0/50	1/50	(a) 7/48
Epithelial hyperplasia	0/48	4/50	(a) 42/50	(a) 40/48
Squamous metaplasia	0/48	0/50	(a) 13/50	(a) 35/48
Carcinoma	0/48	0/50	0/50	0/48
Squamous cell papilloma	0/48	0/50	1/50	(a) 7/48
Squamous cell carcinoma	0/48	0/50	1/50	4/48
Transitional cell papilloma	0/48	0/50	(a) 9/50	(a) 15/48
Transitional cell carcinoma	0/48	0/50	(a) 10/50	(a) 13/48
Sarcoma	0/48	0/50	0/50	1/48
Leiomyoma	0/48	0/50	1/50	4/48
Leiomyosarcoma	0/48	0/50	2/50	(a) 23/48
Lipomatosis	0/48	0/50	9/50	1/48
Kidney				
Pigmentation	1/49	(a) 47/50	(a) 49/50	(a) 48/50
Calculi				
Gross	0/49	3/50	0/50	3/50
Microscopic	1/49	0/50	1/50	(a) 15/50
Hydronephrosis	0/49	0/50	1/50	(a) 15/50
Epithelial hyperplasia	0/49	2/50	(a) 12/50	(a) 15/50
Transitional cell papilloma	0/49	0/50	0/50	1/50
Kidney/Tubule				
Cast	0/49	(a) 44/50	(a) 47/50	(a) 46/50
Degeneration	0/49	(a) 19/50	(a) 37/50	(a) 26/50
Ureter				
Transitional cell papilloma	0/49	0/50	0/50	1/50

(a) $P<0.01$ vs controls
(b) $P<0.05$ vs controls

In male rats, the following tumor types occurred in the urinary bladder with significant positive trends: squamous cell papilloma, squamous cell papilloma or carcinoma (combined), transitional cell papilloma, transitional cell carcinoma, and leiomyosarcoma (Table 11). The incidences of transitional cell neoplasms and leiomyosarcomas in the mid dose and high dose groups were significantly greater than those in the controls. The incidences of squamous cell neoplasms in the high dose groups only were significantly greater than those in the controls.

In female rats, the following tumor types occurred in the urinary bladder with significant positive trends: squamous cell papilloma, squamous cell carcinoma, transitional cell papilloma, transitional cell carcinoma, leiomyoma, and leiomyosarcoma (Table 11). Incidences in mid dose and high dose groups were greater than those in the controls for transitional cell papillomas and transitional cell carcinomas. The incidences of squamous cell papilloma, squamous cell carcinoma, leiomyoma, and leiomyosarcoma in the high dose group were significantly greater than those in the controls.

The transitional cell neoplasms were either solid or papillary. Most papillomas were well differentiated and projected into the bladder lumen without invasion of the submucosa. Transitional cell carcinomas were larger and more pleomorphic and showed more mitotic activity than did the transitional cell papillomas. The carcinomas frequently projected into the bladder lumen and invaded the submucosa.

The architecture of squamous cell papillomas was similar to that of their transitional cell counterpart, except for the surface of the fibrovascular core, which was covered with hyperkeratotic squamous epithelium. Mixed papillomas containing both transitional cell and squamous cell epithelium were also observed. These mixed papillomas probably represented transitional cell papillomas with areas of squamous cell metaplasia. Squamous cell carcinomas resembled their transitional cell counterpart in structure, but the invading sheets, nests, and cords were composed of keratizing squamous cells.

The lipomatosis consisted of benign-appearing adipose tissue cells that infiltrated the submucosa and the area between smooth muscle bundles in the muscularis. A few circumscribed masses of lipocytes were encapsulated by fibrous tissue giving the appearance of a lipoma. It is not known if this condition is neoplastic.

Neoplasms diagnosed as leiomyosarcomas consisted of anastomosing bundles and bands of spindle cells. Some whorls were evident. Most cells had elongated or oval nuclei that contained reticulated chromatin. Cells were loosely arranged and had minimal stromal fibrosis. Mitotic activity was usually low. The neoplasms were well demarcated from the normal muscle and varied considerably in size. Small neoplasms caused variable elevation of the overlying mucosa, whereas larger neoplasms usually caused obliteration or reduction of the bladder lumen and extensive alteration of the mucosa, which included hyperplasia and/or squamous metaplasia.

TABLE 11. ANALYSIS OF URINARY BLADDER TUMORS IN RATS IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1 (a)

	Control	1,250 ppm	2,500 ppm	5,000 ppm
MALE (b)				
Squamous Cell Papilloma				
Overall Rates	0/49 (0%)	0/50 (0%)	1/50 (2%)	3/49 (6%)
Adjusted Rates	0.0%	0.0%	5.0%	20.6%
Terminal Rates	0/30 (0%)	0/39 (0%)	1/20 (5%)	0/4 (0%)
Life Table Tests	P<0.001	(c)	P=0.419	P=0.019
Incidental Tumor Tests	P=0.044	(c)	P=0.419	P=0.288
Cochran-Armitage Trend Test	P=0.020			
Fisher Exact Test		(c)	P=0.505	P=0.121
Squamous Cell Papilloma or Carcinoma (d)				
Overall Rates	0/49 (0%)	0/50 (0%)	2/50 (4%)	4/49 (8%)
Adjusted Rates	0.0%	0.0%	8.7%	26.7%
Terminal Rates	0/30 (0%)	0/39 (0%)	1/20 (5%)	0/4 (0%)
Life Table Tests	P<0.001	(c)	P=0.161	P=0.004
Incidental Tumor Tests	P=0.020	(c)	P=0.245	P=0.157
Cochran-Armitage Trend Test	P=0.008			
Fisher Exact Test		(c)	P=0.253	P=0.059
Transitional Cell Papilloma				
Overall Rates	0/49 (0%)	0/50 (0%)	8/50 (16%)	4/49 (8%)
Adjusted Rates	0.0%	0.0%	27.7%	35.9%
Terminal Rates	0/30 (0%)	0/39 (0%)	3/20 (15%)	0/4 (0%)
Life Table Tests	P<0.001	(c)	P=0.002	P=0.002
Incidental Tumor Tests	P=0.043	(c)	P=0.006	P=0.157
Cochran-Armitage Trend Test	P=0.021			
Fisher Exact Test		(c)	P=0.003	P=0.059
Transitional Cell Carcinoma				
Overall Rates	0/49 (0%)	0/50 (0%)	4/50 (8%)	8/49 (16%)
Adjusted Rates	0.0%	0.0%	13.2%	32.9%
Terminal Rates	0/30 (0%)	0/39 (0%)	1/20 (5%)	0/4 (0%)
Life Table Tests	P<0.001	(c)	P=0.041	P<0.001
Incidental Tumor Tests	P=0.009	(c)	P=0.090	P=0.070
Cochran-Armitage Trend Test	P<0.001			
Fisher Exact Test		(c)	P=0.061	P=0.003
Transitional Cell Papilloma or Carcinoma (e)				
Overall Rates	0/49 (0%)	0/50 (0%)	10/50 (20%)	11/49 (22%)
Adjusted Rates	0.0%	0.0%	32.1%	55.0%
Terminal Rates	0/30 (0%)	0/39 (0%)	3/20 (15%)	0/4 (0%)
Life Table Tests	P<0.001	(c)	P<0.001	P<0.001
Incidental Tumor Tests	P=0.001	(c)	P=0.002	P=0.020
Cochran-Armitage Trend Test	P<0.001			
Fisher Exact Test		(c)	P<0.001	P<0.001
Leiomyosarcoma				
Overall Rates	0/49 (0%)	0/50 (0%)	6/50 (12%)	41/49 (84%)
Adjusted Rates	0.0%	0.0%	17.9%	100.0%
Terminal Rates	0/30 (0%)	0/39 (0%)	1/20 (5%)	4/4 (100%)
Life Table Tests	P<0.001	(c)	P=0.010	P<0.001
Incidental Tumor Tests	P<0.001	(c)	P=0.030	P<0.001
Cochran-Armitage Trend Test	P<0.001			
Fisher Exact Test		(c)	P=0.014	P<0.001
Leiomyoma or Leiomyosarcoma (f)				
Overall Rates	0/49 (0%)	0/50 (0%)	7/50 (14%)	41/49 (84%)
Adjusted Rates	0.0%	0.0%	19.8%	100.0%
Terminal Rates	0/30 (0%)	0/39 (0%)	1/20 (5%)	4/4 (100%)
Life Table Tests	P<0.001	(c)	P=0.005	P<0.001
Incidental Tumor Tests	P<0.001	(c)	P=0.016	P<0.001
Cochran-Armitage Trend Test	P<0.001			
Fisher Exact Test		(c)	P=0.007	P<0.001

TABLE 11. ANALYSIS OF URINARY BLADDER TUMORS IN RATS IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1 (a) (Continued)

	Control	1,250 ppm	2,500 ppm	5,000 ppm
FEMALE				
Squamous Cell Papilloma				
Overall Rates	0/48 (0%)	0/50 (0%)	1/50 (2%)	7/48 (15%)
Adjusted Rates	0.0%	0.0%	2.7%	31.6%
Terminal Rates	0/37 (0%)	0/37 (0%)	0/34 (0%)	4/16 (25%)
Life Table Tests	P<0.001	(c)	P=0.489	P<0.001
Incidental Tumor Tests	P<0.001	(c)	P=0.500	P=0.005
Cochran-Armitage Trend Test	P<0.001			
Fisher Exact Test		(c)	P=0.510	P=0.006
Squamous Cell Carcinoma				
Overall Rates	0/48 (0%)	0/50 (0%)	1/50 (2%)	4/48 (8%)
Adjusted Rates	0.0%	0.0%	2.7%	19.3%
Terminal Rates	0/37 (0%)	0/37 (0%)	0/34 (0%)	1/16 (6%)
Life Table Tests	P<0.001	(c)	P=0.489	P=0.012
Incidental Tumor Tests	P=0.035	(c)	P=0.500	P=0.106
Cochran-Armitage Trend Test	P=0.005			
Fisher Exact Test		(c)	P=0.510	P=0.059
Squamous Cell Papilloma or Carcinoma (g)				
Overall Rates	0/48 (0%)	0/50 (0%)	1/50 (2%)	11/48 (23%)
Adjusted Rates	0.0%	0.0%	2.7%	46.0%
Terminal Rates	0/37 (0%)	0/37 (0%)	0/34 (0%)	5/16 (31%)
Life Table Tests	P<0.001	(c)	P=0.489	P<0.001
Incidental Tumor Tests	P<0.001	(c)	P=0.500	P<0.001
Cochran-Armitage Trend Test	P<0.001			
Fisher Exact Test		(c)	P=0.510	P<0.001
Transitional Cell Papilloma				
Overall Rates	0/48 (0%)	0/50 (0%)	9/50 (18%)	15/48 (31%)
Adjusted Rates	0.0%	0.0%	25.4%	53.0%
Terminal Rates	0/37 (0%)	0/37 (0%)	8/34 (24%)	6/16 (38%)
Life Table Tests	P<0.001	(c)	P=0.002	P<0.001
Incidental Tumor Tests	P<0.001	(c)	P=0.002	P<0.001
Cochran-Armitage Trend Test	P<0.001			
Fisher Exact Test		(c)	P=0.002	P<0.001
Transitional Cell Carcinoma				
Overall Rates	0/48 (0%)	0/50 (0%)	10/50 (20%)	13/48 (27%)
Adjusted Rates	0.0%	0.0%	27.6%	54.6%
Terminal Rates	0/37 (0%)	0/37 (0%)	8/34 (24%)	7/16 (44%)
Life Table Tests	P<0.001	(c)	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	(c)	P<0.001	P<0.001
Cochran-Armitage Trend Test	P<0.001			
Fisher Exact Test		(c)	P<0.001	P<0.001
Transitional Cell Papilloma or Carcinoma (h)				
Overall Rates	0/48 (0%)	0/50 (0%)	15/50 (30%)	21/48 (44%)
Adjusted Rates	0.0%	0.0%	40.2%	70.7%
Terminal Rates	0/37 (0%)	0/37 (0%)	12/34 (35%)	9/16 (56%)
Life Table Tests	P<0.001	(c)	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	(c)	P<0.001	P<0.001
Cochran-Armitage Trend Test	P<0.001			
Fisher Exact Test		(c)	P<0.001	P<0.001
Leiomyoma				
Overall Rates	0/48 (0%)	0/50 (0%)	1/50 (2%)	4/48 (8%)
Adjusted Rates	0.0%	0.0%	2.9%	19.1%
Terminal Rates	0/37 (0%)	0/37 (0%)	1/34 (3%)	2/16 (13%)
Life Table Tests	P<0.001	(c)	P=0.483	P=0.012
Incidental Tumor Tests	P=0.005	(c)	P=0.483	P=0.048
Cochran-Armitage Trend Test	P=0.005			
Fisher Exact Test		(c)	P=0.510	P=0.059

TABLE 11. ANALYSIS OF URINARY BLADDER TUMORS IN RATS IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1 (a) (Continued)

	Control	1,250 ppm	2,500 ppm	5,000 ppm
FEMALE (Continued)				
Leiomyosarcoma				
Overall Rates	0/48 (0%)	0/50 (0%)	2/50 (4%)	23/48 (48%)
Adjusted Rates	0.0%	0.0%	5.9%	80.4%
Terminal Rates	0/37 (0%)	0/37 (0%)	2/34 (6%)	11/16 (69%)
Life Table Tests	P<0.001	(c)	P=0.220	P<0.001
Incidental Tumor Tests	P<0.001	(c)	P=0.220	P<0.001
Cochran-Armitage Trend Test	P<0.001			
Fisher Exact Test		(c)	P=0.258	P<0.001
Leiomyoma or Leiomyosarcoma (i)				
Overall Rates	0/48 (0%)	0/50 (0%)	3/50 (6%)	26/48 (54%)
Adjusted Rates	0.0%	0.0%	8.8%	85.6%
Terminal Rates	0/37 (0%)	0/37 (0%)	3/34 (9%)	12/16 (75%)
Life Table Tests	P<0.001	(c)	P=0.106	P<0.001
Incidental Tumor Tests	P<0.001	(c)	P=0.106	P<0.001
Cochran-Armitage Trend Test	P<0.001			
Fisher Exact Test		(c)	P=0.129	P<0.001

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes); the estimated dose in milligrams per kilogram body weight is given in Chapter III (Body Weights and Clinical Signs) and in Appendix L (Tables L1 and L2).
(b) No urinary bladder neoplasms have been observed in 439 control male F344/N rats at the study laboratory.
(c) No P value is reported because no tumors were observed in the 1,250-ppm and control groups.
(d) Historical incidence of squamous cell papillomas or carcinomas (combined) in NTP studies: 0/2,189
(e) Historical incidence in NTP studies (mean): 5/2,189 (0.2%)
(f) Historical incidence in NTP studies (mean): 1/2,189 (<0.1%)
(g) No squamous cell tumors have been observed. Historical incidence of papilloma, NOS, in NTP studies (mean): 2/2,263 (0.1%).
(h) Historical incidence at study laboratory (mean): 1/439 (0.2%); no other urinary bladder tumors have been observed at the study laboratory. Historical incidence in NTP studies: 5/2,263 (0.2%) (includes two papillomas, NOS).
(i) Historical incidence in NTP studies: 0/2,263

Prostate: Epithelial hyperplasia was observed at increased incidence in mid dose male rats (control, 3/49, 6%; low dose, 1/50, 2%; mid dose, 12/50, 24%; high dose, 5/50, 10%).

Eye: Cataracts and retinopathy were observed at increased incidences in control male and mid dose female rats (cataracts and retinopathy--male: control, 20/49, 41%; low dose, 0/50; mid dose, 0/50; high dose, 6/50, 12%; cataracts--female: control, 1/49, 2%; low dose, 1/50, 2%; mid dose, 19/50, 38%; high dose, 1/50, 2%; retinopathy--female: control, 2/49, 4%; low dose, 1/50, 2%; mid dose, 21/50, 42%; high dose, 1/50, 2%). The groups with increased occurrences of cataracts and retinopathy were on the top racks in the animal rooms; the observed eye effects were considered to have been caused by the proximity of the animals to the room lighting.

Pituitary Gland: Adenomas and adenomas or carcinomas (combined) in female rats occurred with positive trends significant by the life table test only (Table 12). The incidences of adenomas and adenomas or carcinomas (combined) in low and mid dose female rats were significantly increased over controls. The increased occurrence of these neoplasms in high dose female rats was significant only by the life table test. The incidence of adenomas or carcinomas (combined) in control female rats was lower than that in historical controls.

TABLE 12. ANALYSIS OF PITUITARY GLAND TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	Control	1,250 ppm	2,500 ppm	5,000 ppm
Hyperplasia				
Overall Rates	5/49 (10%)	3/49 (6%)	0/50 (0%)	2/49 (4%)
Adenoma				
Overall Rates	10/49 (20%)	21/49 (43%)	20/50 (40%)	15/49 (31%)
Adjusted Rates	24.1%	48.5%	53.6%	48.1%
Terminal Rates	6/37 (16%)	15/37 (41%)	17/34 (50%)	4/16 (25%)
Life Table Tests	P=0.005	P=0.020	P=0.016	P=0.010
Incidental Tumor Tests	P=0.288	P=0.006	P=0.014	P=0.380
Cochran-Armitage Trend Test	P=0.326			
Fisher Exact Test		P=0.014	P=0.028	P=0.177
Carcinoma				
Overall Rates	2/49 (4%)	3/49 (6%)	0/50 (0%)	1/49 (2%)
Adjusted Rates	4.7%	7.1%	0.0%	6.3%
Terminal Rates	1/37 (3%)	1/37 (3%)	0/34 (0%)	1/16 (6%)
Life Table Tests	P=0.382N	P=0.486	P=0.261N	P=0.709N
Incidental Tumor Tests	P=0.146N	P=0.549	P=0.249N	P=0.541N
Cochran-Armitage Trend Test	P=0.241N			
Fisher Exact Test		P=0.500	P=0.242N	P=0.500N
Adenoma or Carcinoma (a)				
Overall Rates	12/49 (24%)	24/49 (49%)	20/50 (40%)	16/49 (33%)
Adjusted Rates	28.1%	53.1%	53.6%	52.4%
Terminal Rates	7/37 (19%)	16/37 (43%)	17/34 (50%)	5/16 (31%)
Life Table Tests	P=0.011	P=0.017	P=0.044	P=0.014
Incidental Tumor Tests	P=0.479	P=0.005	P=0.044	P=0.470
Cochran-Armitage Trend Test	P=0.464			
Fisher Exact Test		P=0.010	P=0.075	P=0.251

(a) Historical incidence at study laboratory (mean ± SD): 177/431 (41% ± 12%); historical incidence in NTP studies: 1,074/2,262 (47% ± 11%)

Thyroid Gland: The incidences of thyroid gland follicle pigmentation were increased in dosed male and dosed female rats (male: control, 0/49; low dose, 46/50, 92%; mid dose, 41/49, 84%; high dose, 42/50, 84%; female: control, 0/49; low dose, 21/50, 42%; mid dose, 31/50, 62%; high dose, 39/50, 78%). This pigmentation was characterized by the accumulation of blue granules in the cytoplasm of follicular epithelial cells.

The C-cell adenomas and C-cell adenomas or carcinomas (combined) in male rats occurred with significant positive trends by the life table test, but the incidences in the dosed groups were not significantly greater than those in the controls (Table 13). C-cell adenomas or carcinomas (combined) in female rats occurred as follows: control, 3/49 (6%); low dose, 5/50 (10%); mid dose, 3/50 (6%); high dose, 0/50. The incidence of C-cell hyperplasia was relatively constant with dose.

TABLE 13. ANALYSIS OF THYROID GLAND LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	Control	1,250 ppm	2,500 ppm	5,000 ppm
MALE				
C-Cell Hyperplasia				
Overall Rates	4/49 (8%)	7/50 (14%)	2/49 (4%)	4/50 (8%)
C-Cell Adenoma				
Overall Rates	1/49 (2%)	2/50 (4%)	4/49 (8%)	3/50 (6%)
Adjusted Rates	2.2%	5.1%	16.3%	31.8%
Terminal Rates	0/30 (0%)	2/39 (5%)	2/20 (10%)	1/4 (25%)
Life Table Tests	P=0.003	P=0.563	P=0.105	P=0.059
Incidental Tumor Tests	P=0.135	P=0.453	P=0.196	P=0.413
Cochran-Armitage Trend Test	P=0.227			
Fisher Exact Test		P=0.508	P=0.181	P=0.316
C-Cell Carcinoma				
Overall Rates	1/49 (2%)	2/50 (4%)	1/49 (2%)	0/50 (0%)
C-Cell Adenoma or Carcinoma (a)				
Overall Rates	2/49 (4%)	4/50 (8%)	5/49 (10%)	3/50 (6%)
Adjusted Rates	5.4%	9.7%	19.1%	31.8%
Terminal Rates	1/30 (3%)	3/39 (8%)	2/20 (10%)	1/4 (25%)
Life Table Tests	P=0.014	P=0.434	P=0.119	P=0.089
Incidental Tumor Tests	P=0.327	P=0.271	P=0.233	P=0.474
Cochran-Armitage Trend Test	P=0.471			
Fisher Exact Test		P=0.349	P=0.218	P=0.510

(a) Historical incidence at study laboratory (mean ± SD): 50/435 (11% ± 6%); historical incidence in NTP studies: 196/2,230 (9% ± 5%)

Parathyroid: Hyperplasia was observed at increased incidences in mid dose and high dose male rats and in high dose female rats (male: control, 0/46; low dose, 1/48, 2%; mid dose, 7/49, 14%; high dose, 7/49, 14%; female: control, 0/47; low dose, 0/48; mid dose, 1/47, 2%; high dose, 4/48, 8%).

Subcutaneous Tissue: The incidence of sarcomas in dosed male rats was significant (P=0.028) by the incidental tumor trend test, and the incidence in the high dose group (3/50, 6%) was significantly greater (P=0.012) than that in the control group (0/49) by the life table test. No significant positive or negative trend occurred when sarcomas were combined with fibromas, fibrosarcomas, or neurofibrosarcomas (combined): control, 5/49 (10%); low dose, 5/50 (10%); mid dose, 2/50 (4%); high dose, 3/50 (6%).

In female rats, the fibromas or fibrosarcomas (combined) occurred with a significant negative trend (P=0.006) by the incidental tumor test (control, 5/49, 10%; low dose, 2/50, 4%; mid dose, 1/50, 2%; high dose, 0/50).

Pancreatic Islets: Adenomas and adenomas or carcinomas (combined) in male rats occurred with significant positive trends, and the incidence of adenomas or carcinomas (combined) in high dose males was significantly greater than that in the controls (Table 14). All neoplasms were well differentiated, resembling normal islet tissue. The adenomas were solitary, circumscribed lesions often 2-3 mm in diameter. The islet cell carcinomas often elicited a scirrhous response, and acinar structures were incorporated at the margin of the lesion. In no animal did the lesion extend beyond the pancreas.

TABLE 14. ANALYSIS OF PANCREATIC ISLET CELL TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	Control	1,250 ppm	2,500 ppm	5,000 ppm
Adenoma				
Overall Rates	1/49 (2%)	0/50 (0%)	4/50 (8%)	2/50 (4%)
Adjusted Rates	3.3%	0.0%	14.9%	27.2%
Terminal Rates	1/30 (3%)	0/39 (0%)	2/20 (10%)	1/4 (25%)
Life Table Tests	P=0.011	P=0.448N	P=0.105	P=0.099
Incidental Tumor Tests	P=0.132	P=0.448N	P=0.151	P=0.251
Cochran-Armitage Trend Test	P=0.242			
Fisher Exact Test		P=0.495N	P=0.187	P=0.508
Carcinoma				
Overall Rates	0/49 (0%)	2/50 (4%)	1/50 (2%)	1/50 (2%)
Adenoma or Carcinoma (a)				
Overall Rates	1/49 (2%)	2/50 (4%)	5/50 (10%)	3/50 (6%)
Adjusted Rates	3.3%	5.1%	18.9%	51.5%
Terminal Rates	1/30 (3%)	2/39 (5%)	2/20 (10%)	2/4 (50%)
Life Table Tests	P=0.001	P=0.591	P=0.050	P=0.009
Incidental Tumor Tests	P=0.042	P=0.591	P=0.102	P=0.022
Cochran-Armitage Trend Test	P=0.222			
Fisher Exact Test		P=0.508	P=0.107	P=0.316

(a) Historical incidence at study laboratory (mean ± SD): 27/436 (6% ± 3%); historical incidence in NTP studies: 129/2,226 (6% ± 4%)

Negative trends: Some tumor types occurred with significant negative trends (Table 15). Mesotheliomas in male rats occurred with a significant negative trend, and the incidence in the mid dose animals was significantly lower than that in the controls.

Mononuclear cell leukemia occurred with a significant negative trend, and incidences in high dose males, mid dose females, and high dose females were significantly lower than those in the controls.

Adrenal gland pheochromocytomas and pheochromocytomas or malignant pheochromocytomas (combined) in male rats occurred with significant negative trends, and the incidences in the high dose group were significantly lower than those in the controls.

Testicular interstitial cell tumors in male rats occurred with a significant negative trend, and the incidence in the high dose group was significantly lower than that in the controls.

Pituitary gland adenomas or carcinomas (combined) in male rats occurred with a significant negative trend, and the incidences in the low and mid dose groups were significantly lower than those in the controls.

The incidence of neoplastic nodules of the liver in low dose male rats was significantly lower than that in the controls. The incidence of neoplastic nodules or hepatocellular carcinomas (combined) in low dose male rats was not significantly different from that in the controls.

Mammary gland fibroadenomas in female rats occurred with a significant negative trend, and the incidence in the high dose group was significantly lower than that of the controls.

Endometrial stromal polyps of the uterus occurred with a significant negative trend in female rats, and the incidence in the mid dose group was significantly lower than that in the controls.

TABLE 15. NEGATIVE TRENDS IN TUMOR INCIDENCES IN RATS IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1

	Control	1,250 ppm	2,500 ppm	5,000 ppm
MALE				
Mesothelioma (a)				
Overall Rates	4/49 (8%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
Adjusted Rates	10.8%	2.6%	0.0%	2.2%
Terminal Rates	1/30 (3%)	1/39 (3%)	0/20 (0%)	0/4 (0%)
Life Table Tests	P=0.346N	P=0.139N	P=0.119N	P=0.682N
Incidental Tumor Tests	P=0.047N	P=0.254N	P=0.039N	P=0.096N
Cochran-Armitage Trend Test	P=0.101N			
Fisher Exact Test		P=0.175N	P=0.057N	P=0.175N
Mononuclear Cell Leukemia (b)				
Overall Rates	15/49 (31%)	10/50 (20%)	13/50 (26%)	2/50 (4%)
Adjusted Rates	40.0%	22.2%	35.7%	24.4%
Terminal Rates	9/30 (30%)	5/39 (13%)	1/20 (5%)	0/4 (0%)
Life Table Tests	P=0.444N	P=0.086N	P=0.426	P=0.404N
Incidental Tumor Tests	P<0.001N	P=0.305N	P=0.263N	P=0.016N
Cochran-Armitage Trend Test	P=0.001N			
Fisher Exact Test		P=0.163N	P=0.388N	P<0.001N
Adrenal Pheochromocytoma or Malignant Pheochromocytoma (c)				
Overall Rates	20/49 (41%)	21/50 (42%)	23/50 (46%)	4/50 (8%)
Adjusted Rates	52.2%	46.2%	72.0%	54.7%
Terminal Rates	13/30 (43%)	15/39 (38%)	12/20 (60%)	2/4 (50%)
Life Table Tests	P=0.218	P=0.345N	P=0.055	P=0.563N
Incidental Tumor Tests	P=0.018N	P=0.515	P=0.265	P=0.020N
Cochran-Armitage Trend Test	P<0.001N			
Fisher Exact Test		P=0.534	P=0.375	P<0.001N
Testicular Interstitial Cell Tumor (d)				
Overall Rates	44/49 (90%)	44/50 (88%)	38/50 (76%)	16/50 (32%)
Adjusted Rates	95.6%	95.7%	97.4%	92.9%
Terminal Rates	28/30 (93%)	37/39 (95%)	19/20 (95%)	3/4 (75%)
Life Table Tests	P=0.001	P=0.048N	P=0.145	P=0.021
Incidental Tumor Tests	P=0.001N	P=0.301N	P=0.164N	P=0.001N
Cochran-Armitage Trend Test	P<0.001N			
Fisher Exact Test		P=0.515N	P=0.060N	P<0.001N

TABLE 15. NEGATIVE TRENDS IN TUMOR INCIDENCES IN RATS IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1 (Continued)

	Control	1,250 ppm	2,500 ppm	5,000 ppm
MALE (Continued)				
Pituitary Gland Adenoma or Carcinoma (e)				
Overall Rates	16/49 (33%)	6/48 (13%)	7/48 (15%)	4/48 (8%)
Adjusted Rates	41.4%	16.2%	24.8%	43.2%
Terminal Rates	9/30 (30%)	6/37 (16%)	3/19 (16%)	1/4 (25%)
Life Table Tests	P=0.523N	P=0.006N	P=0.174N	P=0.494
Incidental Tumor Tests	P=0.039N	P=0.020N	P=0.037N	P=0.066N
Cochran-Armitage Trend Test	P=0.004N			
Fisher Exact Test		P=0.016N	P=0.031N	P=0.003N
Liver Neoplastic Nodule				
Overall Rates	4/49 (8%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted Rates	13.3%	0.0%	0.0%	0.0%
Terminal Rates	4/30 (13%)	0/39 (0%)	0/20 (0%)	0/4 (0%)
Life Table Tests	P=0.051N	P=0.035N	P=0.123N	P=0.519N
Incidental Tumor Tests	P=0.051N	P=0.035N	P=0.123N	P=0.519N
Cochran-Armitage Trend Test	P=0.020N			
Fisher Exact Test		P=0.056N	P=0.056N	P=0.056N
Liver Neoplastic Nodule or Hepatocellular Carcinoma (f)				
Overall Rates	4/49 (8%)	2/50 (4%)	2/50 (4%)	0/50 (0%)
Adjusted Rates	13.3%	5.1%	5.4%	0.0%
Terminal Rates	4/30 (13%)	2/39 (5%)	0/20 (0%)	0/4 (0%)
Life Table Tests	P=0.269N	P=0.223N	P=0.486N	P=0.519N
Incidental Tumor Tests	P=0.081N	P=0.223N	P=0.368N	P=0.519N
Cochran-Armitage Trend Test	P=0.042N			
Fisher Exact Test		P=0.329N	P=0.329N	P=0.056N
FEMALE				
Mononuclear Cell Leukemia (g)				
Overall Rates	9/49 (18%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates	22.2%	7.6%	2.9%	8.7%
Terminal Rates	6/37 (16%)	2/37 (5%)	1/34 (3%)	1/16 (6%)
Life Table Tests	P=0.067N	P=0.072N	P=0.016N	P=0.209N
Incidental Tumor Tests	P=0.014N	P=0.092N	P=0.014N	P=0.042N
Cochran-Armitage Trend Test	P=0.012N			
Fisher Exact Test		P=0.056N	P=0.008N	P=0.024N
Mammary Gland Fibroadenoma (h)				
Overall Rates	24/49 (49%)	19/50 (38%)	27/50 (54%)	7/50 (14%)
Adjusted Rates	58.3%	48.6%	67.1%	37.8%
Terminal Rates	20/37 (54%)	17/37 (46%)	21/34 (62%)	5/16 (31%)
Life Table Tests	P=0.272N	P=0.221N	P=0.217	P=0.132N
Incidental Tumor Tests	P=0.030N	P=0.273N	P=0.219	P=0.017N
Cochran-Armitage Trend Test	P<0.001N			
Fisher Exact Test		P=0.185N	P=0.383	P<0.001N
Uterine Endometrial Stromal Polyps (i)				
Overall Rates	16/49 (33%)	9/50 (18%)	3/50 (6%)	5/50 (10%)
Adjusted Rates	41.9%	23.6%	8.0%	20.4%
Terminal Rates	15/37 (41%)	8/37 (22%)	2/34 (6%)	2/16 (13%)
Life Table Tests	P=0.064N	P=0.082N	P=0.002N	P=0.241N
Incidental Tumor Tests	P=0.019N	P=0.092N	P=0.002N	P=0.102N
Cochran-Armitage Trend Test	P=0.002N			
Fisher Exact Test		P=0.074N	P<0.001N	P=0.006N

(a) Historical incidence of mesothelioma at study laboratory: 1.1%; historical incidence of mesothelioma in NTP studies: 2.3%
(b) Historical incidence of leukemia at study laboratory (mean ± SD): 27% ± 9%; historical incidence of leukemia in NTP studies: 28% ± 10%
(c) Historical incidence at study laboratory (mean ± SD): 19% ± 12%; historical incidence in NTP studies: 18% ± 9%
(d) Historical incidence at study laboratory (mean ± SD): 88% ± 8%; historical incidence in NTP studies: 88% ± 9%
(e) Historical incidence at study laboratory (mean ± SD): 19% ± 11%; historical incidence in NTP studies: 24% ± 12%
(f) Historical incidence at study laboratory (mean ± SD): 3% ±2%; historical incidence in NTP studies: 4% ± 4%
(g) Historical incidence of leukemia at study laboratory (mean ± SD): 16% ± 6%; historical incidence of leukemia in NTP studies: 18% ± 7%
(h) Historical incidence at study laboratory (mean ± SD): 27% ± 6%; historical incidence in NTP studies: 23% ± 10%
(i) Historical incidence at study laboratory (mean ± SD): 15% ± 5%; historical incidence in NTP studies: 18% ± 8%

SINGLE-ADMINISTRATION STUDIES

All animals survived to the end of the studies. Final mean body weights were not recorded. The urine of all dosed male and female mice was blue from day 2 through days 3-6. Because deaths did not occur in the single-administration gavage studies, the maximum dietary concentration for the 14-day studies was set at 50,000 ppm, which is the highest concentration considered not to interfere with nutrient requirements.

FOURTEEN-DAY STUDIES

All mice that received C.I. Disperse Blue 1 at 25,000 or 50,000 ppm and 3/5 males and 2/5 females in the 12,500-ppm groups died before the end of the studies (Table 16). Surviving mice in the 12,500-ppm group lost weight. Mice that received C.I. Disperse Blue 1 at 6,200 ppm gained notably less weight than did the controls. Feed consumption was not measured.

All dosed mice had blue urine. Mice that received C.I. Disperse Blue 1 at 12,500, 25,000, or 50,000 ppm were inactive. Most organs were blue in all dosed groups at necropsy.

The maximum dietary concentrations for the 13-week studies were set at 10,000 ppm based on the deaths of animals at 12,500 ppm and higher in the 14-day studies.

TABLE 16. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY FEED STUDIES OF C.I. DISPERSE BLUE 1

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	5/5	25.8 ± 0.6	28.4 ± 0.5	+ 2.6 ± 0.5	--
3,100	5/5	27.2 ± 0.7	28.6 ± 0.6	+ 1.4 ± 0.2	101
6,200	5/5	26.0 ± 0.4	26.8 ± 0.4	+ 0.8 ± 0.2	94
12,500	(d) 2/5	25.4 ± 1.2	19.0 ± 1.0	− 6.0 ± 1.0	67
25,000	(e) 0/5	27.0 ± 0.8	(f)	(f)	--
50,000	(g) 0/5	26.0 ± 0.9	(f)	(f)	--
FEMALE					
0	5/5	19.0 ± 0.7	21.4 ± 0.6	+ 2.4 ± 0.2	--
3,100	5/5	19.8 ± 0.4	21.2 ± 0.6	+ 1.4 ± 0.2	99
6,200	5/5	18.8 ± 0.2	20.0 ± 0.0	+ 1.2 ± 0.2	93
12,500	(h) 3/5	18.8 ± 0.6	14.3 ± 0.7	− 4.7 ± 0.3	67
25,000	(i) 0/5	20.0 ± 0.6	(f)	(f)	--
50,000	(j) 0/5	19.4 ± 0.4	(f)	(f)	--

(a) Number surviving/number in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 10, 11, 15
(e) Day of death: 6, 7, 9, 10, 10
(f) No data are reported due to the 100% mortality in this group.
(g) Day of death: 6, 6, 6, 7, 7
(h) Day of death: 12, 13
(i) Day of death: 6, 6, 6, 6,7
(j) Day of death: 5, 5, 6, 6, 6

THIRTEEN-WEEK STUDIES

Seven of 10 males and 4/10 females that received C.I. Disperse Blue 1 at 10,000 ppm, 1/10 males that received 5,000 ppm, and 2/10 males that received 1,200 ppm died before the end of the studies (Table 17). Final mean body weights were 34% lower than those of the controls for male mice in the 10,000-ppm group and 7% and 17% lower for female mice in the 5,000- or 10,000-ppm groups. Feed consumption was increased in the 10,000-ppm groups by the end of the studies. The urine of dosed mice was blue in all groups.

Compound-related histopathologic effects included chronic inflammation and/or hyperplasia of the transitional epithelium of the urinary bladder, pigmentation of the thyroid gland follicles, renal pigmentation, nephrosis, pigment calculi of the urinary tract, focal myocardial necrosis in male and female mice, and mild degeneration of the germinal epithelium of the testis in males (Table 18). These lesions were present at 2,500 ppm and higher concentrations.

Dose Selection Rationale: The maximum dietary concentration for the 2-year studies was set at 2,500 ppm because of compound-related deaths at 10,000 ppm and the presence of potentially life-threatening renal lesions at 5,000 ppm in the 13-week studies. The choice of 2,500 ppm also allowed further definition of the consequences of compound-related urinary bladder hyperplasia and inflammation; 600 and 1,200 ppm were apparent no-effect levels in the 13-week studies.

TABLE 17. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF C.I. DISPERSE BLUE 1

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 4	Week 13
MALE							
0	10/10	23.4 ± 0.6	35.7 ± 0.9	+ 12.3 ± 0.9	--	6	8
600	10/10	24.4 ± 0.5	37.5 ± 0.7	+ 13.1 ± 0.6	105	6	11
1,200	(e) 8/10	24.0 ± 0.5	37.3 ± 1.0	+ 13.4 ± 0.7	104	5	11
2,500	10/10	22.9 ± 0.4	36.1 ± 0.6	+ 13.2 ± 0.4	101	7	9
5,000	(f) 9/10	24.2 ± 0.5	35.8 ± 0.6	+ 11.8 ± 0.8	100	6	10
10,000	(g) 3/10	24.7 ± 0.5	23.7 ± 1.2	+ 0.3 ± 0.7	66	5	26
FEMALE							
0	10/10	19.1 ± 0.4	26.0 ± 0.7	+ 6.9 ± 0.5	--	5	8
600	10/10	18.5 ± 0.2	26.9 ± 0.7	+ 8.4 ± 0.7	103	5	9
1,200	10/10	18.6 ± 0.2	28.4 ± 0.7	+ 9.8 ± 0.7	109	5	10
2,500	10/10	19.3 ± 0.3	25.9 ± 0.4	+ 6.6 ± 0.3	100	4	9
5,000	10/10	18.3 ± 0.2	24.3 ± 0.5	+ 6.0 ± 0.6	93	4	8
10,000	(h) 6/10	18.1 ± 0.2	21.7 ± 2.2	+ 3.7 ± 2.2	83	5	14

(a) Number surviving/number in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams of feed per animal per day
(e) Week of death: 11, 13
(f) Week of death: 10
(g) Week of death: 2, 5, 6, 8, 8, 9, 12
(h) Week of death: 6, 7, 12, 12

TABLE 18. INCIDENCES OF COMPOUND-RELATED HISTOPATHOLOGIC EFFECTS IN MICE IN THE THIRTEEN-WEEK FEED STUDIES OF C.I. DISPERSE BLUE 1

	Control	1,200 ppm	2,500 ppm	5,000 ppm	10,000 ppm
MALE					
Thyroid follicle pigmentation	0/10	2/10	7/10	10/10	5/8
Urinary tract					
Renal pigmentation	0/10	1/10	0/10	7/10	9/9
Nephrosis	0/10	1/10	0/10	4/10	8/9
Hydronephrosis	0/10	0/10	0/10	1/10	7/9
Pigment calculi	0/10	1/10	0/10	3/10	7/9
Urinary bladder chronic inflammation	0/10	1/10	(a) 3/10	(a) 10/10	6/8
Urinary bladder transitional epithelium hyperplasia	0/10	0/10	(a) 3/10	(a) 4/10	4/8
Myocardial necrosis	0/10	0/10	0/10	0/10	(a) 5/8
Testicular degeneration	0/10	0/10	0/10	0/10	(a) 4/9
FEMALE					
Thyroid follicle pigmentation	0/10	0/10	8/10	10/10	6/7
Urinary tract					
Renal pigmentation	0/10	0/10	2/10	10/10	9/9
Nephrosis	0/10	0/10	3/10	10/10	9/9
Hydronephrosis	0/10	0/10	0/10	1/10	6/9
Pigment calculi	0/10	0/10	5/10	10/10	7/9
Urinary bladder chronic inflammation	0/10	0/10	(a) 10/10	10/10	7/8
Urinary bladder transitional epithelium hyperplasia	0/10	0/10	(a) 6/10	(a) 6/10	2/8
Myocardial necrosis	0/10	0/10	0/10	0/10	2/8

(a) Diagnoses by Quality Assurance Pathologist

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed male mice were comparable to those of the controls (Table 19 and Figure 4). Mean body weights of high dose female mice were generally lower and mean body weights of low dose female mice were generally greater than those of the controls during the 2nd year of the study. The average daily feed consumption by low dose, mid dose, and high dose male mice was 90%, 92%, and 102% that of the controls and by low dose, mid dose, and high dose female mice, 103%, 104%, and 107% that of the controls (Appendix L, Tables L3 and L4). The average amount of C.I. Disperse Blue 1 consumed per day was approximately 112, 239, and 540 mg/kg for low dose, mid dose, and high dose male mice and 108, 235, and 520 mg/kg for low dose, mid dose, and high dose female mice.

During the 2-year studies, male mice in all groups had alopecia, externally cannibalized genitalia, and scratches; dosed male and female mice had blue hair, blue urine, and firmness in the area of the urinary bladder.

TABLE 19. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1

Weeks on Study	Control		600 ppm			1,200 ppm			2,500 ppm		
	Av Wt (grams)	No. of Survivors	Av Wt (grams)	Wt (percent of controls)	No. of Survivors	Av Wt (grams)	Wt. (percent of controls)	No. of Survivors	Av Wt (grams)	Wt (percent of controls)	No. of Survivors
MALE											
0	25.7	50	26.4	103	50	25.7	100	50	25.8	100	50
1	24.4	50	26.7	109	50	25.5	105	50	26.8	110	50
2	27.1	50	28.0	103	50	27.1	100	50	28.1	104	50
3	28.6	50	29.0	101	50	28.6	100	50	28.9	101	50
4	29.4	50	29.4	100	50	28.6	97	50	29.4	100	50
5	29.9	50	30.0	100	50	29.0	97	50	29.3	98	50
6	29.7	50	31.2	105	50	30.7	103	50	31.5	106	50
7	30.9	50	32.7	106	50	31.3	101	50	32.4	105	50
8	32.3	50	33.3	103	50	32.4	100	50	32.9	102	50
9	32.7	50	34.2	105	50	32.5	99	50	33.9	104	50
10	33.2	49	34.1	103	49	32.9	99	50	34.1	103	50
11	33.3	49	34.6	104	49	33.5	101	50	34.8	105	50
12	34.3	46	35.5	103	49	34.1	99	50	35.1	102	49
13	34.8	45	35.8	103	49	34.5	99	50	35.8	103	49
18	36.3	43	37.6	104	49	36.0	99	50	37.7	104	49
22	38.2	42	39.2	103	49	38.0	99	50	39.5	103	48
27	38.7	42	39.3	102	48	37.6	97	49	40.0	103	48
31	40.0	42	41.0	103	48	38.3	96	49	40.8	102	48
35	41.3	42	43.1	104	48	40.4	98	49	42.1	102	48
39	40.8	42	43.7	107	48	37.4	92	49	41.9	103	47
44	42.4	41	44.6	105	48	41.1	97	49	43.7	103	45
49	43.4	41	44.7	103	48	40.3	93	49	43.6	100	45
52	44.1	41	45.6	103	48	41.6	94	49	43.1	98	44
57	44.0	40	45.1	103	48	40.9	93	49	42.7	97	41
62	43.4	40	44.3	102	48	40.8	94	49	42.1	97	38
66	43.3	40	44.5	103	48	41.0	95	48	41.9	97	37
71	43.9	39	43.8	100	44	41.1	94	45	41.5	95	35
75	41.1	39	43.6	106	44	40.7	99	44	41.5	101	34
80	43.0	37	42.4	99	41	40.8	95	42	41.1	96	32
84	42.4	37	41.8	99	40	40.1	95	41	39.7	94	32
87	42.5	37	41.8	98	39	39.7	93	39	39.4	93	28
91	41.4	35	41.5	100	38	38.4	93	39	39.4	95	26
97	39.5	29	39.9	101	33	38.8	98	36	39.3	99	23
101	40.3	26	39.3	98	33	38.1	95	36	38.3	95	22
105	39.3	25	38.0	97	30	38.5	98	35	39.7	101	20
FEMALE											
0	19.0	50	20.0	105	50	20.2	106	50	19.6	103	50
1	18.3	50	19.6	107	50	19.8	108	50	20.0	109	50
2	19.7	50	21.0	107	50	20.9	106	50	20.8	106	50
3	21.4	50	21.8	102	50	22.0	103	50	21.8	102	50
4	21.9	50	22.4	102	50	22.1	101	50	22.0	100	50
5	21.7	50	22.8	105	50	22.9	106	50	23.1	106	50
6	22.7	50	23.5	104	50	23.9	105	50	23.6	104	50
7	23.9	50	25.1	105	50	24.3	102	50	24.6	103	50
8	24.3	50	25.0	103	50	24.8	102	50	24.8	102	50
9	24.0	50	25.3	105	50	24.8	103	50	25.1	105	50
10	24.7	50	25.7	104	50	25.3	102	50	25.9	105	50
11	25.0	50	25.7	103	50	25.3	101	50	26.1	104	50
12	26.3	50	26.3	100	50	26.1	99	50	26.1	99	50
13	26.2	50	27.0	103	50	26.1	100	50	26.3	100	50
18	28.4	50	30.1	106	50	28.2	99	50	28.6	101	50
22	30.2	50	30.7	102	50	29.7	98	50	30.4	101	50
27	31.6	50	33.2	105	50	32.1	102	50	32.2	102	50
31	33.2	50	34.7	105	50	33.1	100	50	34.2	103	50
35	35.9	50	38.5	107	50	36.2	101	50	36.3	101	50
39	37.8	50	41.4	110	50	37.9	100	50	37.7	100	50
44	39.0	50	42.9	110	50	39.4	101	50	39.4	101	50
49	42.5	50	46.1	108	50	42.4	100	50	41.1	97	50
52	43.0	50	47.1	110	50	43.5	101	50	40.8	95	50
57	41.7	50	47.0	113	50	42.7	102	50	41.0	98	50
62	42.4	50	47.0	111	50	43.8	103	50	40.4	95	50
66	43.8	50	48.1	110	49	45.0	103	49	40.7	93	50
71	44.1	50	48.9	111	48	44.8	102	48	40.7	92	48
75	44.1	50	49.3	112	48	45.8	104	48	42.2	96	48
80	43.7	49	48.4	111	44	45.5	104	48	40.8	93	47
84	44.2	47	47.4	107	41	45.1	102	48	40.3	91	47
87	45.3	46	49.2	109	37	45.4	100	46	41.3	91	45
91	44.1	44	50.1	114	35	45.6	103	44	41.9	95	41
97	44.6	40	49.2	110	30	46.5	104	38	41.1	92	36
101	45.8	34	49.8	109	29	47.3	103	36	40.7	89	31
105	44.5	33	48.9	110	27	46.2	104	35	40.5	91	26

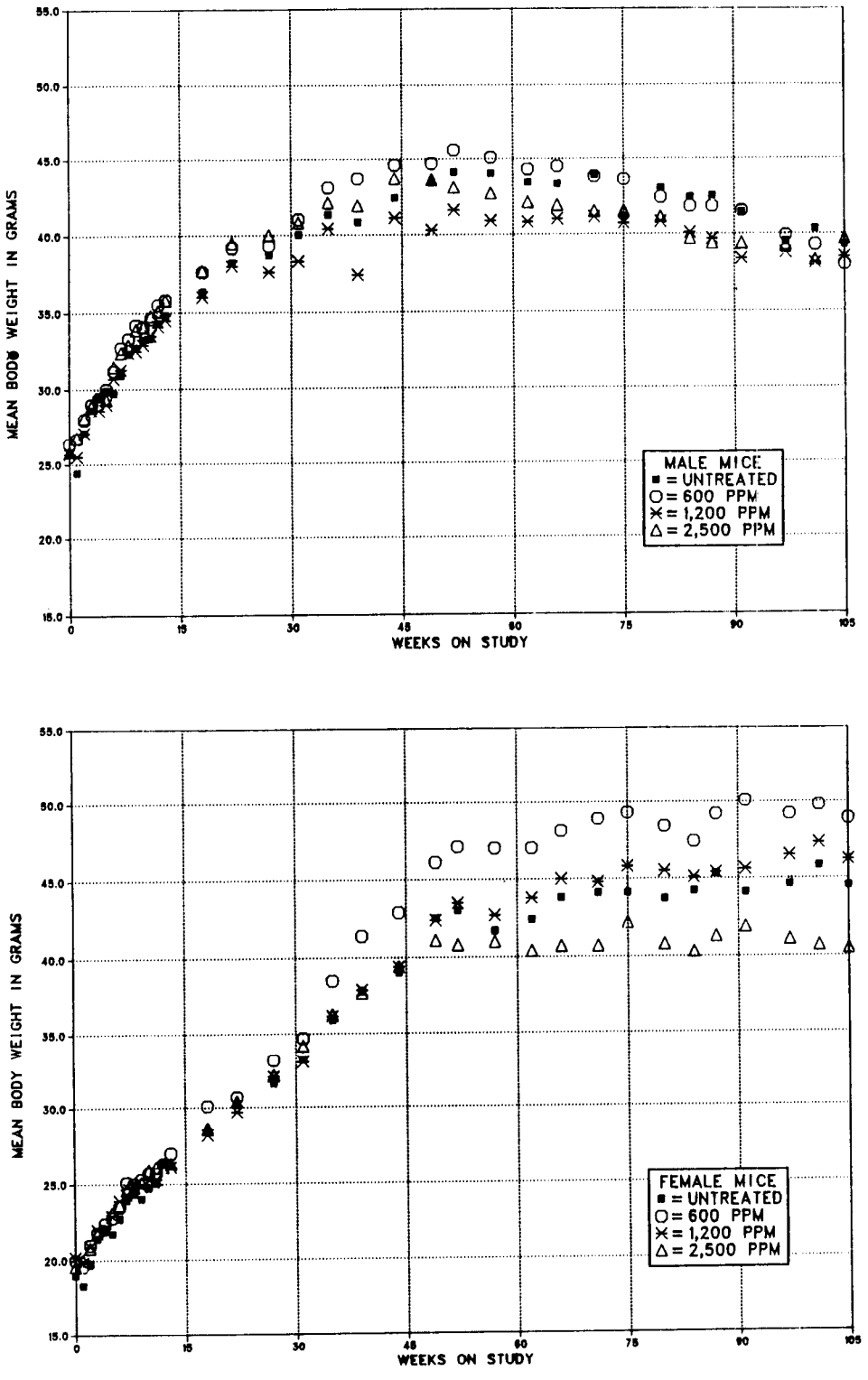


FIGURE 4. GROWTH CURVES FOR MICE FED DIETS CONTAINING C.I. DISPERSE BLUE 1 FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice fed diets containing C.I. Disperse Blue 1 at the concentrations used in these studies and for the controls are shown in the Kaplan and Meier curves in Figure 5. The survival of the male control group was significantly reduced compared with that of the mid dose group. The early deaths in the control male group were associated with external genitalia cannibalization. Survival analysis, in which early deaths in the control group are censored, indicated a significant trend (P=0.028) toward lower survival, primarily because of the decreased survival of the high dose group relative to that of the low dose and mid dose groups rather than that of the control group; none of the dosed groups showed a significant reduction in survival in pairwise comparisons with controls (Table 20). No significant differences in survival were observed between any groups of female mice.

Pathology and Statistical Analyses of Results

This section describes significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the urinary system, liver, lung, hematopoietic system, subcutaneous tissue, thyroid gland, stomach, ovary, and uterus. Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1 and B2); Appendix B (Tables B3 and B4) also gives the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D (Tables D1 and D2). Appendix E (Tables E3 and E4) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the four groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in control animals are listed in Appendix F.

TABLE 20. SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1

	Control	600 ppm	1,200 ppm	2,500 ppm
MALE (a)				
Animals initially in study	50	50	50	50
Nonaccidental deaths before termination (b)	25	19	14	29
Killed at termination	23	30	35	20
Died during termination period	2	1	1	1
Survival P values (c)	0.211	0.256	0.039	0.463
Survival P values (d)	0.028	0.964	0.412	0.076
FEMALE (a)				
Animals initially in study	50	50	50	50
Nonaccidental deaths before termination (b)	16	23	15	21
Killed at termination	32	27	34	27
Died during termination period	2	0	1	2
Survival P values (c)	0.721	0.119	0.882	0.389

(a) Terminal kill period: weeks 104-106
(b) Includes animals killed in a moribund condition
(c) 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.
(d) Results obtained if animals dying before week 19 are censored (8 control, 1 low dose, 0 mid dose, and 2 high dose)

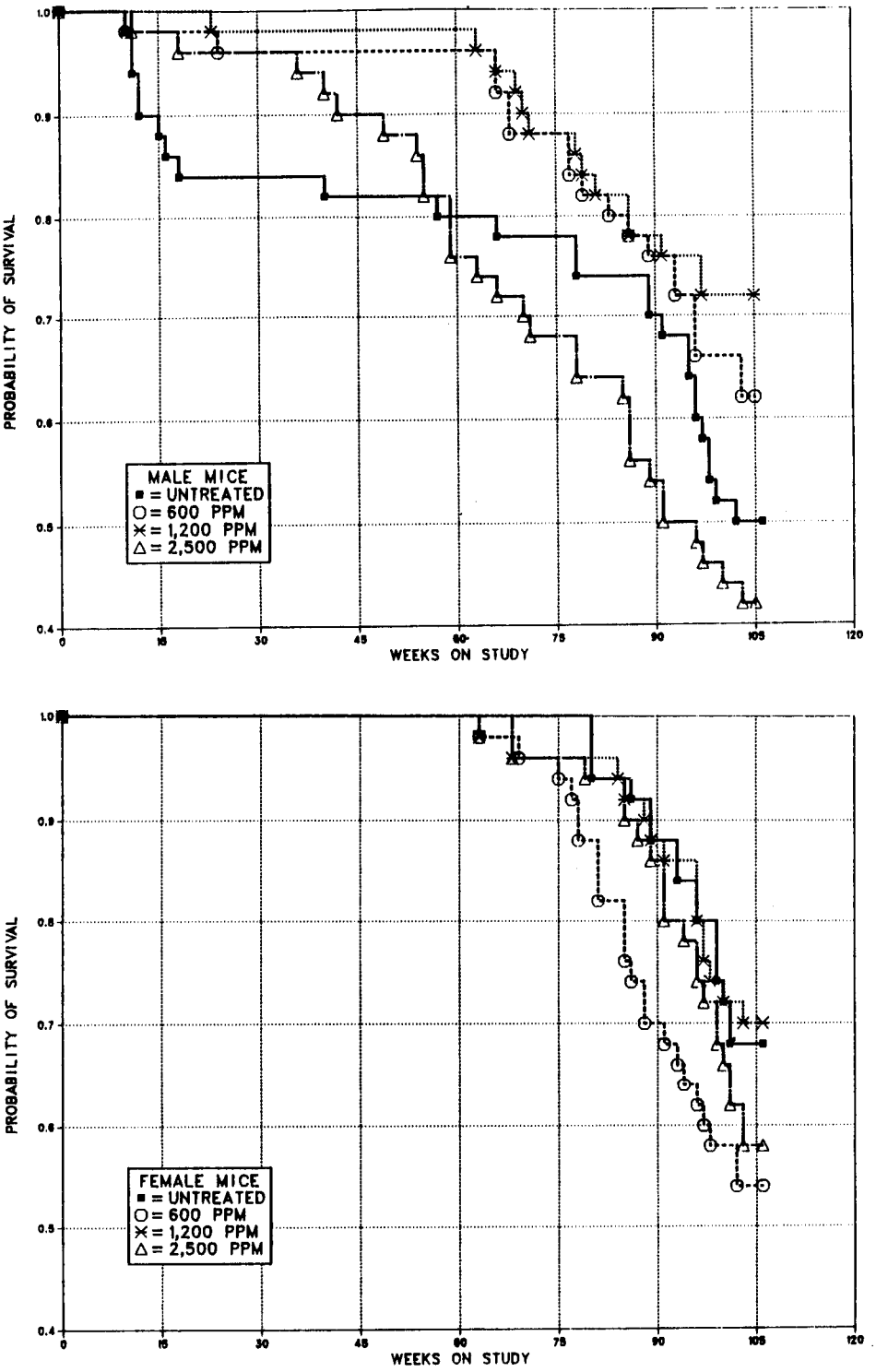


FIGURE 5. KAPLAN-MEIER SURVIVAL CURVES FOR MICE FED DIETS CONTAINING C.I. DISPERSE BLUE 1 FOR TWO YEARS

Urinary System: Blue pigmentation of the urinary bladder and kidney, inflammation and epithelial hyperplasia in the urinary bladder, calculi in the urinary bladder lumen, fibrosis of the urinary bladder, casts in the renal tubular lumina, and renal degeneration were found at significantly increased incidences at various concentrations in male and female mice (Table 21). The renal tubular degeneration was characterized by tubular dilatation and enlarged, flattened, or otherwise distorted tubular epithelial cells. The incidences of neoplastic lesions of the urinary bladder or kidney were not significantly increased in dosed male or female mice.

TABLE 21. INCIDENCES OF URINARY SYSTEM LESIONS IN MICE IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1

Tissue/Lesion	Control	600 ppm	1,200 ppm	2,500 ppm
MALE				
Urinary Bladder				
Pigmentation	0/50	(a) 27/49	(a) 11/50	0/50
Inflammation	2/50	5/49	(b) 11/50	(a) 36/50
Lymphocytic inflammatory infiltrate	6/50	(a) 21/49	(a) 30/50	(a) 20/50
Calculi				
Gross observation only	0/50	0/49	(a) 16/50	(a) 39/50
Microscopic	0/50	0/49	2/50	(a) 10/50
Epithelial hyperplasia	0/50	1/49	(a) 11/50	(a) 42/50
Fibrosis	0/50	0/49	(b) 7/50	(a) 22/50
Squamous cell carcinoma	0/50	0/49	0/50	1/50
Fibroma	0/50	0/49	0/50	1/50
Kidney				
Hydronephrosis	1/50	1/50	4/50	4/50
Pigmentation	0/50	(a) 45/50	(a) 47/50	(a) 32/50
Kidney/Tubule				
Cast	2/50	(a) 47/50	(a) 48/50	(a) 50/50
Degeneration	0/50	(a) 23/50	(a) 25/50	(a) 35/50
FEMALE				
Urinary Bladder				
Pigmentation	0/49	(a) 23/50	(a) 35/50	(a) 9/50
Inflammation	0/49	4/50	(b) 8/50	(a) 37/50
Lymphocytic inflammatory infiltrate	15/49	24/50	(a) 33/50	23/50
Calculi				
Gross observation only	0/49	0/50	0/50	(a) 30/50
Microscopic	0/49	0/50	0/50	1/50
Epithelial hyperplasia	0/49	1/50	1/50	(a) 26/50
Fibrosis	0/49	0/50	0/50	(a) 23/50
Sarcoma, NOS	0/49	0/50	0/50	1/50
Kidney				
Hydronephrosis	0/50	0/50	0/50	2/50
Pigmentation	1/50	(a) 38/50	(a) 46/50	(a) 46/50
Kidney/Tubule				
Cast	1/50	(a) 41/50	(a) 48/50	(a) 50/50
Degeneration	0/50	(a) 13/50	(a) 15/50	(a) 40/50

(a) $P<0.001$ vs controls
(b) $P<0.01$ vs controls

Liver: Hepatocellular adenomas in male mice occurred with a significant positive trend by life table analysis; however, the incidental tumor test is probably more appropriate for these generally nonfatal neoplasms (Table 22). The incidences of hepatocellular adenomas in low dose female mice and of hepatocellular adenomas or carcinomas (combined) in low dose and high dose male mice were significantly greater than those in the controls.

TABLE 22. ANALYSIS OF LIVER TUMORS IN MICE IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1 (a)

	Control	600 ppm	1,200 ppm	2,500 ppm
MALE				
Hepatocellular Adenoma				
Overall Rates	3/50 (6%)	9/50 (18%)	10/50 (20%)	9/50 (18%)
Adjusted Rates	10.4%	29.0%	24.9%	37.3%
Terminal Rates	2/25 (8%)	9/31 (29%)	7/36 (19%)	7/21 (33%)
Life Table Tests	P=0.034	P=0.114	P=0.113	P=0.032
Incidental Tumor Tests	P=0.106	P=0.124	P=0.141	P=0.078
Hepatocellular Carcinoma				
Overall Rates	6/50 (12%)	15/50 (30%)	13/50 (26%)	8/50 (16%)
Adjusted Rates	22.2%	37.3%	31.4%	28.2%
Terminal Rates	5/25 (20%)	7/31 (23%)	8/36 (22%)	3/21 (14%)
Life Table Tests	P=0.384	P=0.079	P=0.205	P=0.266
Incidental Tumor Tests	P=0.449N	P=0.057	P=0.202	P=0.502
Hepatocellular Adenoma or Carcinoma (b)				
Overall Rates	9/50 (18%)	21/50 (42%)	20/50 (40%)	16/50 (32%)
Adjusted Rates	31.7%	53.0%	47.3%	57.1%
Terminal Rates	7/25 (28%)	13/31 (42%)	14/36 (39%)	10/21 (48%)
Life Table Tests	P=0.062	P=0.044	P=0.109	P=0.032
Incidental Tumor Tests	P=0.217	P=0.032	P=0.111	P=0.116
FEMALE				
Hepatocellular Adenoma				
Overall Rates	2/50 (4%)	12/49 (24%)	3/50 (6%)	2/50 (4%)
Adjusted Rates	5.9%	36.7%	8.6%	6.9%
Terminal Rates	2/34 (6%)	8/26 (31%)	3/35 (9%)	2/29 (7%)
Life Table Tests	P=0.174N	P=0.001	P=0.513	P=0.637
Incidental Tumor Tests	P=0.161N	P=0.007	P=0.513	P=0.637
Hepatocellular Carcinoma				
Overall Rates	1/50 (2%)	2/49 (4%)	0/50 (0%)	2/50 (4%)
Hepatocellular Adenoma or Carcinoma (c)				
Overall Rates	3/50 (6%)	13/49 (27%)	3/50 (6%)	4/50 (8%)
Adjusted Rates	8.8%	40.2%	8.6%	12.4%
Terminal Rates	3/34 (9%)	9/26 (35%)	3/35 (9%)	3/29 (10%)
Life Table Tests	P=0.297N	P=0.002	P=0.651N	P=0.422
Incidental Tumor Tests	P=0.282N	P=0.008	P=0.651N	P=0.448

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes); the dose in milligrams per kilogram body weight is given in Chapter III (body weights and clinical signs) and in Appendix L.
(b) Historical incidence at study laboratory (mean ± SD): 143/446 (32% ± 5%); historical incidence in NTP studies: 725/2,334 (31% ± 7%)
(c) Historical incidence at study laboratory (mean ± SD): 30/445 (7% ± 4%); historical incidence in NTP studies: 196/2,469 (8% ± 5%)

Lung: Alveolar/bronchiolar adenomas and alveolar/bronchiolar adenomas or carcinomas (combined) in male mice occurred with significant positive trends, and the incidence of alveolar/bronchiolar adenomas or carcinomas (combined) in high dose male mice was significantly greater than that in the controls (Table 23).

Hematopoietic System: Lymphomas (all types) in male mice occurred with a significant positive trend (P=0.046, incidental tumor test), but the incidences in the dosed groups were not significantly greater than that in the controls (control, 4/50, 8%; low dose, 3/50, 6%; mid dose, 7/50, 14%; high dose, 7/50, 14%). The historical incidence of lymphoma or leukemia in male B6C3F$_1$ mice at the testing laboratory is 40/498 (8% ± 5%), and the overall historical incidence in the NTP studies is 224/1,791 (13% ± 7%). The following incidences of lymphomas (all types) were observed in female mice: control, 17/50 (34%); low dose, 15/50 (30%); mid dose, 16/50 (32%); high dose, 17/50 (34%).

TABLE 23. ANALYSIS OF LUNG LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	Control	600 ppm	1,200 ppm	2,500 ppm
Hyperplasia				
Overall Rates	2/50 (4%)	1/49 (2%)	1/50 (2%)	0/50 (0%)
Alveolar/Bronchiolar Adenoma				
Overall Rates	1/50 (2%)	3/49 (6%)	5/50 (10%)	5/50 (10%)
Adjusted Rates	4.0%	9.1%	13.9%	23.8%
Terminal Rates	1/25 (4%)	2/30 (7%)	5/36 (14%)	5/21 (24%)
Life Table Tests	P=0.033	P=0.366	P=0.203	P=0.063
Incidental Tumor Tests	P=0.028	P=0.332	P=0.203	P=0.063
Alveolar/Bronchiolar Carcinoma				
Overall Rates	3/50 (6%)	6/49 (12%)	1/50 (2%)	6/50 (12%)
Alveolar/Bronchiolar Adenoma or Carcinoma (a)				
Overall Rates	4/50 (8%)	9/49 (18%)	5/50 (10%)	11/50 (22%)
Adjusted Rates	15.0%	27.2%	13.9%	49.3%
Terminal Rates	3/25 (12%)	7/30 (23%)	5/36 (14%)	10/21 (48%)
Life Table Tests	P=0.015	P=0.192	P=0.564N	P=0.015
Incidental Tumor Tests	P=0.018	P=0.168	P=0.616	P=0.017

(a) Historical incidence at study laboratory (mean ± SD): 83/446 (19% ± 7%); historical incidence in NTP studies: 393/2,328 (17% ± 8%)

Integumentary System: Subcutaneous Tissue--Fibromas and fibromas or fibrosarcomas (combined) in male mice occurred with significant negative trends, and the incidences in the high dose group were significantly lower than those in the controls (Table 24). The incidences of fibromas or fibrosarcomas (combined) in female mice were as follows: control, 2/50 (4%); low dose, 2/50 (4%); mid dose, 1/50 (2%); high dose, 1/50 (2%).

Thyroid Gland: The incidence of pigmentation (blue pigment deposits in colloid or epithelial cells) was increased in dosed mice (male: control, 0/49; low dose, 46/50, 92%; mid dose, 45/49, 92%; high dose, 31/49, 63%; female: control, 0/48; low dose, 46/50, 92%; mid dose, 46/50, 92%; high dose, 41/46, 89%). Cystic degeneration was observed at increased incidence in dosed mice (male: control, 4/49,8%; low dose, 14/50, 28%; mid dose, 16/49, 33%; high dose, 35/49, 71%; female: control, 4/48; low dose, 17/50, 34%; mid dose, 14/50, 28%; high dose, 27/46, 59%). The cystic degeneration was characterized by irregularly shaped follicles that had flattened epithelial cells and diminished density of colloid.

Stomach: Increased incidences of cysts were observed in the glandular stomach of dosed male and female mice (male: control, 3/50, 6%; low dose, 7/49, 14%; mid dose, 12/50, 24%; high dose, 6/50, 12%; female: control, 3/49, 6%; low dose, 10/50, 20%; mid dose, 8/50, 16%; high dose, 9/49, 18%). The following incidences of squamous cell papillomas or carcinomas (combined) were observed: male--control, 1/50 (2%); low dose, 1/49 (2%); mid dose, 0/50; high dose, 2/50 (4%); female--control, 0/49; low dose, 0/50; mid dose, 0/50; high dose, 1/49 (2%).

Ovary/Uterus: Suppurative inflammation was observed in the ovary, uterus, or multiple organs of 14/50 (28%) control, 14/50 (28%) low dose, 13/50 (26%) mid dose, and 16/50 (32%) high dose female mice.

TABLE 24. ANALYSIS OF SUBCUTANEOUS TISSUE TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	Control	600 ppm	1,200 ppm	2,500 ppm
Fibroma				
Overall Rates	6/50 (12%)	7/50 (14%)	5/50 (10%)	0/50 (0%)
Adjusted Rates	22.0%	22.6%	13.9%	0.0%
Terminal Rates	4/25 (16%)	7/31 (23%)	5/36 (14%)	0/21 (0%)
Life Table Tests	P=0.014N	P=0.577N	P=0.270N	P=0.031N
Incidental Tumor Tests	P=0.020N	P=0.612	P=0.453N	P=0.045N
Fibrosarcoma				
Overall Rates	12/50 (24%)	13/50 (26%)	7/50 (14%)	5/50 (10%)
Adjusted Rates	34.5%	35.1%	18.1%	17.4%
Terminal Rates	3/25 (12%)	8/31 (26%)	5/36 (14%)	1/21 (5%)
Life Table Tests	P=0.056N	P=0.494N	P=0.061N	P=0.142N
Incidental Tumor Tests	P=0.050N	P=0.561	P=0.375N	P=0.101N
Fibroma or Fibrosarcoma (a)				
Overall Rates	16/50 (32%)	19/50 (38%)	12/50 (24%)	5/50 (10%)
Adjusted Rates	46.4%	52.0%	31.3%	17.4%
Terminal Rates	7/25 (28%)	14/31 (45%)	10/36 (28%)	1/21 (5%)
Life Table Tests	P=0.008N	P=0.566N	P=0.068N	P=0.035N
Incidental Tumor Tests	P=0.006N	P=0.472	P=0.338N	P=0.017N

(a) Historical incidence of integumentary system fibromas or fibrosarcomas at study laboratory (mean ± SD): 24/448 (5% ± 5%); historical incidence in NTP studies: 91/2,343 (4% ± 5%)

IV. DISCUSSION AND CONCLUSIONS

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C.I. Disperse Blue 1 (primarily 1,4,5,8-tetraaminoanthraquinone) was studied for potential toxicity and carcinogenicity in male and female $B6C3F_1$ mice and F344/N rats. Feed was selected as the route of administration because of the perception that a greater amount of compound can be absorbed via the gastrointestinal tract than through the skin, thus providing a more rigorous test for systemic carcinogenic potential. C.I. Disperse Blue 1 was absorbed via the gastrointestinal tract; all dosed animals in the single-administration, 14-day, and 13-week studies had blue urine, and blue pigment was found in tissues at necropsy. Similar observations were made in studies of HC Blue No. 1 (NTP, 1985a) and HC Blue No. 2 (NTP, 1985b).

In the 13-week studies, no compound-related deaths of rats occurred at dietary concentrations up to 20,000 ppm. In the studies in mice, 7/10 males and 4/10 females in the 10,000-ppm (highest dose) group and 1/10 males in the 5,000-ppm group died. The primary pathologic effect of feeding C.I. Disperse Blue 1 for 13 weeks occurred in the urinary system. Dose-related increases in the incidences of renal pigmentation, nephrosis, hydronephrosis, and calculi as well as chronic inflammation, hyperplasia of the transitional epithelium, and squamous metaplasia of the urinary bladder occurred in rats (see Table 7) and mice (see Table 18) of each sex at doses of 2,500 ppm and higher. Based on these results, dietary concentrations of 0, 1,250, 2,500, or 5,000 ppm for rats and 0, 600, 1,200, or 2,500 ppm for mice were chosen for the 2-year studies.

Rats

In the 2-year studies in rats, the reduced survival of high dose male and female rats (and to a lesser extent, mid dose male rats) was considered to have been caused by urinary bladder neoplasms. The reduced survival in these groups lowered the sensitivity of the incidental tumor test; for this reason, the Fisher exact test and Cochran-Armitage trend test were also used in evaluating the significance of tumor incidences. The most notable pathologic alterations occurred in the urinary bladder. Other than pigmentation (assumed to be a direct effect of the compound's presence in the tissues) and calculi, the most prominent nonneoplastic lesions were epithelial hyperplasia and squamous metaplasia in the mid dose and high dose groups of both male and female rats. These effects may have been secondary to the formation of urinary bladder calculi, which occurred frequently in the mid dose and high dose groups. Epithelial hyperplasia has been reported to result from irritation of the urinary bladder of rats (Chin et al., 1981; Kuhlmann and Longnecker, 1984).

Neoplastic lesions of the urinary bladder of both male and female rats were increased in the mid dose (2,500 ppm) and the high dose (5,000 ppm) groups (see Table 11). These lesions were dose related and did not occur in control or low dose animals. In male rats, transitional cell papillomas, transitional cell carcinomas, and especially leiomyosarcomas occurred at high incidences (41/49 for leiomyosarcomas in high dose males). These types of tumors are rare (historical incidence less than 0.1%) in F344/N male rats (Appendix F, Table F1). Mid and high dose female rats had highly significant increases in the incidences of transitional cell papillomas and transitional cell carcinomas of the urinary bladder. In addition, high dose female animals had significant increases in squamous cell papillomas or carcinomas (combined) and in leiomyosarcomas and leiomyomas or leiomyosarcomas (combined). These types of tumors are uncommon in F344/N female rats (Table F2) and did not occur in either control or low dose animals.

In a previous 2-year study of melamine (2,4,6-triamino-*s*-triazine), the presence of urinary bladder calculi was associated with the presence of transitional cell neoplasms in the male rat urinary bladder (NTP, 1983; Melnick et al., 1984). Furthermore, an association between calculi and bladder tumors in rats and mice has been suggested by other studies (Weil et al., 1965; Clayson, 1974; Cheng, 1980). The urinary bladder tumor type most often associated with calculi has been the transitional cell tumor (Melnick et al., 1984; Chin et al., 1981); neither urinary bladder leiomyosarcomas nor squamous cell carcinomas have been shown to be associated with calculi.

In the present study, statistical tests for association of various urinary bladder tumor types with the presence of gross calculi or with gross and

microscopic (combined) calculi were conducted. The data were divided into four time intervals, and all animals dying within each interval were placed into one of four groups: tumor only, calculi only, both, or neither. These 2 × 2 tables were pooled over the time intervals by the procedure of Mantel-Haenszel (1959).

These data for squamous cell papillomas or carcinomas (combined), transitional cell papillomas or carcinomas (combined), and leiomyomas or leiomyosarcomas (combined) in rats are given in Table 25. The results of these analyses are presented in Table 26 both for individual dose groups of animals and for tumor type, combined across doses. Combining across doses is considered appropriate because the objective is to test associations between calculi and tumors, a relationship not expected to be affected by dose.

Associations of calculi and urinary bladder neoplasms suggest that the urinary bladder calculi may have influenced the occurrence of neoplasms in rats fed C.I. Disperse Blue 1. However, as can be seen from Table 25, a number of animals had urinary bladder neoplasms without observed calculi. There was a positive ($P < 0.05$) correlation between the occurrence of squamous cell papillomas or carcinomas (combined) and the occurrence of gross calculi only for the pooled male rats. The lack of a positive association for any individual group may be due to poor sensitivity because of the relatively low number of squamous cell bladder tumors occurring in any single group. There was a positive association between transitional cell neoplasms and both gross and combined gross and microscopic calculi for all groups except the high dose males. Leiomyomas or leiomyosarcomas (combined) were associated with the presence of gross calculi for the mid dose and high dose female groups, but not for mid dose or high dose males.

Tumors of the smooth muscle layers of the bladder (leiomyomas and leiomyosarcomas) are not expected to be affected by calculi because of the intervening epithelium between this tissue and bladder calculi. However, solid particles (presumably C.I. Disperse Blue 1) were observed in the submucosa and interstitial tissues of dosed rats. Whether the presence of these "particles" contributed to the occurrence of leiomyomas and leiomyosarcomas in this study is not known. Despite the statistical associations between the presence of calculi and urinary bladder neoplasms in rats, especially in the females, mice of each sex exhibited high incidences of urinary bladder calculi but no increase in urinary bladder neoplasms. Thus, if calculi contributed to the occurrence of bladder neoplasms in rats dosed with C.I. Disperse Blue 1, a similar effect was not operative in mice. Moreover, C.I. Disperse Blue 1 was found to be mutagenic (Appendix M), and aromatic amines in general are known to cause cancer of the urinary bladder irrespective of calculi formation (Clayson and Garner, 1976).

The apparent increases in the incidences of thyroid gland C-cell adenomas in male rats and pituitary gland adenomas in female rats were not considered to be compound related. In both cases, the incidences in all dosed groups were near the means for historical control groups (Tables F5 and F8), and the incidences of these tumors were significant only by the life table test, which is not the most appropriate test for these generally nonlethal tumors.

The positive trend ($P = 0.042$ by the incidental tumor test) for the occurrence of pancreatic islet cell adenomas or carcinomas (combined) in male rats was supported by a greater incidence of these neoplasms in the high dose group ($P = 0.022$ by the incidental tumor test). However, the incidence in concurrent control males (2%) was lower than the mean of historical controls (6% ± 4%), and incidences in the dosed groups (low, 4%; mid, 10%; high, 6%) were similar to historical controls. Thus, the increase in occurrence of pancreatic islet cell neoplasms is not clearly related to the administration of C.I. Disperse Blue 1.

The increased incidences of parathyroid hyperplasia observed in mid dose and high dose male rats and high dose female rats may have been related to the deleterious effects of C.I. Disperse Blue 1 on the kidneys. If calcium resorption by the kidney is affected by C.I. Disperse Blue 1-induced nephropathy, then the parathyroids would be expected to respond by

TABLE 25. ASSOCIATION OF URINARY BLADDER TUMORS WITH CALCULI IN RATS IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1 (a)

Weeks on Test	Male Tumors/Calculi (b) +/+	+/−	−/+	−/−	Female Tumors/Calculi (b) +/+	+/−	−/+	−/−
Transitional cell papilloma or carcinoma								
High dose								
0-52	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	1 (1)
53-78	1 (2)	3 (2)	4 (11)	9 (2)	4 (4)	0 (0)	1 (2)	5 (4)
79-104	5 (6)	2 (1)	8 (13)	11 (6)	9 (9)	0 (0)	11 (12)	2 (1)
Terminal kill	0 (0)	0 (0)	3 (3)	1 (1)	8 (8)	0 (0)	4 (4)	3 (3)
Mid dose								
0-52	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	4 (4)
53-78	0 (0)	0 (0)	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	2 (2)
79-104	5 (5)	2 (2)	1 (1)	17 (17)	2 (2)	2 (2)	2 (2)	6 (6)
Terminal kill	2 (2)	1 (1)	6 (7)	11 (10)	6 (7)	5 (4)	2 (2)	19 (19)
Leiomyoma or leiomyosarcoma								
High dose								
0-52	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	1 (1)
53-78	4 (12)	12 (4)	1 (1)	0 (0)	1 (1)	0 (0)	4 (5)	5 (4)
79-104	9 (15)	12 (6)	4 (4)	1 (1)	14 (14)	0 (0)	6 (7)	2 (1)
Terminal kill	3 (3)	1 (1)	0 (0)	0 (0)	11 (11)	0 (0)	1 (1)	3 (3)
Mid dose								
0-52	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	4 (4)
53-78	0 (0)	0 (0)	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	2 (2)
79-104	2 (2)	4 (4)	4 (4)	15 (15)	1 (1)	0 (0)	3 (3)	8 (8)
Terminal kill	0 (0)	1 (1)	8 (9)	11 (10)	2 (2)	0 (0)	6 (7)	24 (23)
Squamous cell papilloma or carcinoma								
High dose								
0-52	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	1 (1)
53-78	1 (1)	0 (0)	4 (12)	12 (4)	1 (1)	1 (1)	4 (5)	4 (3)
79-104	3 (3)	0 (0)	10 (16)	13 (7)	4 (4)	0 (0)	16 (17)	2 (1)
Terminal kill	0 (0)	0 (0)	3 (3)	1 (1)	5 (5)	0 (0)	7 (7)	3 (3)
Mid dose								
0-52	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	4 (4)
53-78	0 (0)	0 (0)	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)	2 (2)
79-104	1 (1)	0 (0)	5 (5)	19 (19)	1 (1)	0 (0)	3 (3)	8 (8)
Terminal kill	1 (1)	0 (0)	7 (8)	12 (11)	0 (0)	0 (0)	8 (9)	24 (23)

(a) Analyzed by 2 × 2 contingency tables and tested for association by Mantel-Haenszel test
(b) Number of animals in which the presence or absence of calculi was observed grossly and indicated neoplasms were observed microscopically. Numbers in parentheses indicate total number of animals observed grossly or microscopically as having presence or absence of calculi and indicated neoplasms.

TABLE 26. STATISTICAL ANALYSES OF ASSOCIATIONS BETWEEN THE PRESENCE OF URINARY BLADDER CALCULI AND TUMORS IN RATS IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1

Neoplasm	P Value Calculi (observed grossly)	P Value Calculi (observed grossly or microscopically)
Squamous Cell Papillomas or Carcinomas		
High dose male	0.072	0.523
Mid dose male	0.186	0.217
Combined male	0.008	0.084
High dose female	0.449	0.653
Mid dose female	0.724	0.733
Combined female	0.215	0.326
Transitional Cell Papillomas or Carcinomas		
High dose male	0.561	0.799
Mid dose male	0.004	0.006
Combined male	0.009	0.068
High dose female	0.003	0.012
Mid dose female	0.017	0.006
Combined female	<0.001	<0.001
Leiomyoma or Leiomyosarcoma		
High dose male	0.128	0.935
Mid dose male	0.746	0.712
Combined male	0.315	0.984
High dose female	0.001	0.006
Mid dose female	0.029	0.041
Combined female	<0.001	<0.001

secreting parathormone to increase calcium resorption by the kidney and calcium intake by the gastrointestinal tract. Continued stimulation of the parathyroid could be expected to cause parathyroid hyperplasia.

The increased incidence of epithelial hyperplasia of the prostate was greater in the mid dose group than in the high dose group of male rats; this difference may have occurred because the high mortality in the latter group precluded the development of this lesion. Although no mechanism is apparent whereby C.I. Disperse Blue 1 would affect the prostate, other sites in the genito-urinary system of rats were affected by C.I. Disperse Blue 1 in these studies.

Decreases ($P<0.05$) in the occurrence of some neoplasms in male or female rats could not be attributed to the shortened survival of the high dose groups (see Table 15). These included mesotheliomas (all sites), pituitary gland adenomas or carcinomas (combined), and liver neoplastic nodules in male rats and mononuclear cell leukemia and uterine endometrial stromal polyps in female rats. Except for mononuclear cell leukemia in female rats, the incidences of these tumors in the concurrent control animals were greater than in historical controls at the laboratory or Programwide, whereas those in the low dose and mid dose groups were similar to historical controls. For mononuclear cell leukemia in female rats, the concurrent control incidence was equivalent to historical controls, whereas those in the dosed groups were lower. The cause and biologic significance of the decreased occurrences of these tumors are unknown.

Increased occurrences of several nonneoplastic changes in the kidney, including calculi, hydronephrosis, and epithelial hyperplasia, were observed in rats (see Table 10). It is not clear whether C.I. Disperse Blue 1 produced these

changes by a direct toxic chemical effect or if they occurred secondary to the compound precipitating as a solid in the kidney. Similarly, the hydronephrosis may be secondary to calculi or tumor-induced obstruction of the ureter.

The apparent decrease in urinary bladder pigmentation in the high dose animals was probably due to replacement of normal bladder tissue by tumor tissue. Pigmentation was less obvious in tumors and was not diagnosed as such.

Mice

Dietary concentrations of C.I. Disperse Blue 1 were 0, 600, 1,200, or 2,500 ppm in the 2-year studies in mice. The survival of the male control group was reduced compared with that of the mid dose group, apparently because of the death of 8/50 male control mice before week 19. The survival analysis (see Table 20), in which male mice dying before week 19 are censored, shows a positive trend ($P=0.028$) for reduced survival in dosed mice, due primarily to a marginal reduction ($P=0.076$) in the survival of the high dose group relative to that of the controls. The small decrease in body weight of the high dose female mice after week 66 and the marginally decreased survival of high dose male mice, as well as the high incidence of nonneoplastic kidney and urinary bladder effects observed in the high dose male and female mice, suggest that a marginally toxic dose was used as the high dose in these experiments (see Table 21).

The occurrences of hepatocellular adenomas or carcinomas (combined) were increased relative to controls in low dose female mice and in low dose and high dose male mice (see Table 22). The survival-adjusted trends in mice were not significant ($P>0.05$), and the group incidences did not indicate strict dose response (male: control, 9/50; low dose, 21/50; mid dose, 20/50; high dose, 16/50; female: control, 3/50; low dose, 13/49; mid dose, 3/50; high dose, 4/50). The absence of a dose-related increase in overall liver tumor incidence in the high dose group of male mice may have been due to reduced survival in that group. The incidence of hepatocellular adenomas or carcinomas (combined) in the concurrent control males (18%) was less than that in historical controls (32% ± 5% at the laboratory, 31% ± 7% Programwide).

The incidence of hepatocellular adenomas or carcinomas (combined) in concurrent control female mice (6%) was similar to that in historical controls (7% ± 4% at the laboratory, 8% ± 5% Programwide), whereas the incidence in the low dose group (27%) was greater than that ever observed in control groups (range, 0-20%; Table F18). The reason for the increased occurrence of these neoplasms in low dose, but not in mid dose or high dose, female mice is unknown; this increase is not considered to be compound related in female mice. The structurally related compounds, 2-aminoanthraquinone (NCI, 1978a) and 1-amino-2-methylanthraquinone (NCI, 1978b), caused hepatocellular tumors in mice.

In male mice, there was an increased incidence of alveolar/bronchiolar adenomas or carcinomas (combined) in the high dose group relative to controls; however, the incidence of these tumors in the control group (8%) was low compared with that in historical controls (19% ± 7% at the laboratory, 17% ± 8% Programwide), whereas the incidence in the high dose group (22%) was similar to that of historical controls. Reduced survival in the control and high dose male groups may have somewhat precluded lung tumor development in these two groups.

The marginally positive ($P=0.046$) trend for lymphomas of all types in male mice was not supported by a significantly increased incidence in any of the dosed groups, and the control incidence (8%) was low in comparison to Programwide historical controls (13%). Thus, the apparent marginal increase in lymphomas was not considered to be compound related.

The cause and biologic significance of the decreased incidences of subcutaneous tissue fibromas or fibrosarcomas (combined) in high dose male mice is unknown.

Effects on the urinary system were the most notable nonneoplastic manifestation of dietary administration of C.I. Disperse Blue 1 to mice. Compound-related effects included inflammation, calculi, epithelial hyperplasia, and fibrosis

(females only) of the urinary bladder and cast formation and tubular degeneration in the kidney (see Table 21). Of particular interest is the observation that mice had high incidences of urinary bladder calculi and the high dose groups had high incidences of epithelial hyperplasia, although an increased incidence of bladder neoplasms was not observed. The reason that rats and mice displayed different urinary system responses to C.I. Disperse Blue 1 remains unknown; however, a similar result was obtained in the 2-year studies of melamine in which both male rats and mice developed calculi, but only male rats had an increased incidence of bladder tumors (NTP, 1983).

Cystic degeneration of the thyroid gland of both male and female mice was detected at all doses. However, there is no indication that this effect contributed to the early deaths. The thyroid gland may be capable of concentrating C.I. Disperse Blue 1, since this is the primary organ in which pigmentation in the form of blue deposits in cells was noted in the 2-year studies in mice.

Conclusions: Under the conditions of these feed studies of C.I. Disperse Blue 1, there was *clear evidence of carcinogenicity** for male and female F344/N rats as shown by the increased occurrence of transitional cell papillomas and carcinomas, of leiomyomas and leiomyosarcomas, and of squamous cell papillomas and carcinomas of the urinary bladder. Urinary bladder calculi were observed in the groups of rats in which urinary bladder neoplasms were increased. Positive associations existed between the presence of calculi and transitional cell neoplasms in male and female rats, leiomyomas or leiomyosarcomas (combined) in female rats, and squamous cell neoplasms in male rats. A marginally increased occurrence of pancreatic islet cell adenomas or carcinomas (combined) was observed in male rats exposed to C.I. Disperse Blue 1. There was *equivocal evidence of carcinogenicity* of C.I. Disperse Blue 1 in male $B6C3F_1$ mice as shown by marginally increased incidences of hepatocellular adenomas or carcinomas (combined) in dosed male mice and a marginally increased occurrence of alveolar/bronchiolar adenomas or carcinomas (combined) in high dose male mice. There was *no evidence of carcinogenicity* of C.I. Disperse Blue 1 in female $B6C3F_1$ mice.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.

V. REFERENCES

V. REFERENCES

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	49	50	50	50
ANIMALS EXAMINED HISTOPATH	49	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)	5 (10%)	2 (4%)	
SQUAMOUS CELL CARCINOMA	1 (2%)			
BASAL-CELL CARCINOMA	1 (2%)			
ADNEXAL ADENOMA	1 (2%)			
SEBACEOUS ADENOMA	1 (2%)			
KERATOACANTHOMA	7 (14%)	2 (4%)	4 (8%)	1 (2%)
*SUBCUT TISSUE	(49)	(50)	(50)	(50)
KERATOACANTHOMA			1 (2%)	
SARCOMA, NOS				3 (6%)
FIBROMA	4 (8%)	4 (8%)	2 (4%)	
FIBROSARCOMA	1 (2%)			
LIPOMA	1 (2%)	2 (4%)		
NEUROFIBROSARCOMA		1 (2%)		
RESPIRATORY SYSTEM				
#LUNG	(49)	(50)	(49)	(50)
TRANSITIONAL-CELL CARCINOMA, MET				1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	1 (2%)	3 (6%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)		
SARCOMA, NOS, METASTATIC				1 (2%)
LIPOSARCOMA, METASTATIC	1 (2%)			
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
LEUKEMIA, MONONUCLEAR CELL	15 (31%)	10 (20%)	13 (26%)	2 (4%)
#SPLEEN	(49)	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)			
#MANDIBULAR L. NODE	(49)	(50)	(50)	(50)
CARCINOMA, NOS, METASTATIC		1 (2%)		
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
*TONGUE	(49)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)	
#LIVER	(49)	(50)	(50)	(50)
NEOPLASTIC NODULE	4 (8%)			
HEPATOCELLULAR CARCINOMA		2 (4%)	2 (4%)	
SARCOMA, NOS, METASTATIC		1 (2%)		1 (2%)
#HEPATIC CAPSULE	(49)	(50)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA, MET				1 (2%)
#FORESTOMACH	(49)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)		
#JEJUNUM	(49)	(50)	(47)	(50)
ADENOCARCINOMA, NOS			1 (2%)	
#ILEUM	(49)	(50)	(47)	(50)
SARCOMA, NOS			1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
URINARY SYSTEM				
#KIDNEY	(49)	(50)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA				1 (2%)
TUBULAR-CELL ADENOCARCINOMA			1 (2%)	
SARCOMA, NOS		1 (2%)		
#KIDNEY/PELVIS	(49)	(50)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA		1 (2%)		
*URETER	(49)	(50)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA				1 (2%)
#URINARY BLADDER	(49)	(50)	(50)	(49)
CARCINOMA, NOS			1 (2%)	
SQUAMOUS CELL PAPILLOMA			1 (2%)	3 (6%)
SQUAMOUS CELL CARCINOMA			1 (2%)	1 (2%)
TRANSITIONAL-CELL PAPILLOMA			8 (16%)	4 (8%)
TRANSITIONAL-CELL CARCINOMA			4 (8%)	8 (16%)
SARCOMA, NOS			1 (2%)	
LEIOMYOMA			1 (2%)	
LEIOMYOSARCOMA			6 (12%)	41 (84%)
ENDOCRINE SYSTEM				
#PITUITARY	(49)	(48)	(48)	(48)
CARCINOMA, NOS	3 (6%)	1 (2%)	1 (2%)	1 (2%)
ADENOMA, NOS	13 (27%)	5 (10%)	6 (13%)	3 (6%)
#ADRENAL	(49)	(50)	(50)	(50)
CORTICAL ADENOMA		1 (2%)		
#ADRENAL MEDULLA	(49)	(50)	(50)	(50)
PHEOCHROMOCYTOMA	19 (39%)	20 (40%)	23 (46%)	3 (6%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)	1 (2%)		1 (2%)
#THYROID	(49)	(50)	(49)	(50)
FOLLICULAR-CELL ADENOMA		1 (2%)		
FOLLICULAR-CELL CARCINOMA	1 (2%)	1 (2%)		1 (2%)
C-CELL ADENOMA	1 (2%)	2 (4%)	4 (8%)	3 (6%)
C-CELL CARCINOMA	1 (2%)	2 (4%)	1 (2%)	
#PANCREATIC ISLETS	(49)	(50)	(50)	(50)
ISLET-CELL ADENOMA	1 (2%)		4 (8%)	2 (4%)
ISLET-CELL CARCINOMA		2 (4%)	1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(50)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)		
FIBROADENOMA	6 (12%)	3 (6%)	1 (2%)	1 (2%)
*PREPUTIAL GLAND	(49)	(50)	(50)	(50)
CARCINOMA, NOS	4 (8%)	2 (4%)		1 (2%)
#PROSTATE	(49)	(50)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA, INV				1 (2%)
ADENOMA, NOS				1 (2%)
#TESTIS	(49)	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR	44 (90%)	44 (88%)	38 (76%)	16 (32%)
NERVOUS SYSTEM				
*CHOROID PLEXUS	(49)	(50)	(50)	(50)
PAPILLOMA, NOS		1 (2%)		
#BRAIN	(49)	(50)	(50)	(50)
GRANULAR-CELL TUMOR, MALIGNANT	1 (2%)			
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(49)	(50)	(50)	(50)
CARCINOMA, NOS		1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
SPECIAL SENSE ORGANS (Continued)				
*ZYMBAL GLAND	(49)	(50)	(50)	(50)
CARCINOMA, NOS				1 (2%)
MUSCULOSKELETAL SYSTEM				
*MUSCLE OF LEG	(49)	(50)	(50)	(50)
LIPOSARCOMA	1 (2%)			
BODY CAVITIES				
*TUNICA VAGINALIS	(49)	(50)	(50)	(50)
MESOTHELIOMA, NOS	1 (2%)			1 (2%)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
CARCINOMA, NOS			1 (2%)	
SARCOMA, NOS	1 (2%)	1 (2%)		
SARCOMA, NOS, METASTATIC		1 (2%)		
LEIOMYOSARCOMA, INVASIVE				1 (2%)
MESOTHELIOMA, NOS	2 (4%)	1 (2%)		
MESOTHELIOMA, MALIGNANT	1 (2%)			
HEAD				
SARCOMA, NOS			1	
TAIL				
SQUAMOUS CELL CARCINOMA	1			
ADIPOSE TISSUE				
LIPOMA				1
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH	8	5	12	12
MORIBUND SACRIFICE	13	6	18	34
TERMINAL SACRIFICE	29	39	20	4
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS**	49	49	47	46
TOTAL PRIMARY TUMORS	142	121	135	102
TOTAL ANIMALS WITH BENIGN TUMORS	48	48	45	24
TOTAL BENIGN TUMORS	100	92	99	38
TOTAL ANIMALS WITH MALIGNANT TUM	26	21	28	45
TOTAL MALIGNANT TUMORS	35	28	36	63
TOTAL ANIMALS WITH SECONDARY TUM##	1	3		4
TOTAL SECONDARY TUMORS	1	3		6
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT	7	1		1
TOTAL UNCERTAIN TUMORS	7	1		1

* NUMBER OF ANIMALS NECROPSIED
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	49	50	50	50
ANIMALS EXAMINED HISTOPATH	49	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)	
BASAL-CELL CARCINOMA			1 (2%)	
*SUBCUT TISSUE	(49)	(50)	(50)	(50)
SARCOMA, NOS				1 (2%)
FIBROMA	3 (6%)	2 (4%)		
FIBROSARCOMA	2 (4%)		1 (2%)	
OSTEOSARCOMA			1 (2%)	
NEUROFIBROSARCOMA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(49)	(50)	(49)	(50)
SQUAMOUS CELL CARCINOMA, METASTA				1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (2%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA				1 (2%)
OSTEOSARCOMA, METASTATIC			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)	
MALIG. LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
LEUKEMIA, MONONUCLEAR CELL	9 (18%)	3 (6%)	1 (2%)	2 (4%)
CIRCULATORY SYSTEM				
*PELVIS	(49)	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)			
DIGESTIVE SYSTEM				
#LIVER	(49)	(50)	(50)	(50)
NEOPLASTIC NODULE	1 (2%)		2 (4%)	
#PANCREAS	(49)	(50)	(50)	(49)
ACINAR-CELL ADENOMA	1 (2%)			
URINARY SYSTEM				
#KIDNEY	(49)	(50)	(50)	(50)
TRANSITIONAL-CELL PAPILLOMA				1 (2%)
*URETER	(49)	(50)	(50)	(50)
TRANSITIONAL-CELL PAPILLOMA				1 (2%)
#URINARY BLADDER	(48)	(50)	(50)	(48)
SQUAMOUS CELL PAPILLOMA			1 (2%)	7 (15%)
SQUAMOUS CELL CARCINOMA			1 (2%)	4 (8%)
TRANSITIONAL-CELL PAPILLOMA			9 (18%)	15 (31%)
TRANSITIONAL-CELL CARCINOMA			10 (20%)	13 (27%)
ADENOMATOUS POLYP, NOS		1 (2%)		
SARCOMA, NOS				1 (2%)
LEIOMYOMA			1 (2%)	4 (8%)
LEIOMYOSARCOMA			2 (4%)	23 (48%)

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#PITUITARY	(49)	(49)	(50)	(49)
CARCINOMA, NOS	2 (4%)	3 (6%)		1 (2%)
ADENOMA, NOS	10 (20%)	21 (43%)	20 (40%)	15 (31%)
#ADRENAL	(48)	(50)	(50)	(50)
CORTICAL ADENOMA	1 (2%)			
CORTICAL CARCINOMA				1 (2%)
GANGLIONEUROMA				1 (2%)
#ADRENAL MEDULLA	(48)	(50)	(50)	(50)
PHEOCHROMOCYTOMA	5 (10%)	5 (10%)	10 (20%)	3 (6%)
#THYROID	(49)	(50)	(50)	(50)
FOLLICULAR-CELL ADENOMA		2 (4%)		
C-CELL ADENOMA	2 (4%)	5 (10%)	2 (4%)	
C-CELL CARCINOMA	1 (2%)	1 (2%)	1 (2%)	
#PANCREATIC ISLETS	(49)	(50)	(50)	(49)
ISLET-CELL ADENOMA	1 (2%)			
ISLET-CELL CARCINOMA		1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(50)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	1 (2%)	1 (2%)
FIBROADENOMA	24 (49%)	19 (38%)	27 (54%)	7 (14%)
*CLITORAL GLAND	(49)	(50)	(50)	(50)
CARCINOMA, NOS	2 (4%)	3 (6%)	6 (12%)	1 (2%)
ADENOMA, NOS	1 (2%)			
#UTERUS	(49)	(50)	(50)	(50)
LEIOMYOSARCOMA		1 (2%)		
ENDOMETRIAL STROMAL POLYP	16 (33%)	9 (18%)	3 (6%)	5 (10%)
ENDOMETRIAL STROMAL SARCOMA	1 (2%)	2 (4%)	1 (2%)	1 (2%)
#CERVIX UTERI	(49)	(50)	(50)	(50)
ENDOMETRIAL STROMAL POLYP		1 (2%)		
NERVOUS SYSTEM				
#BRAIN	(49)	(50)	(50)	(50)
CARCINOMA, NOS, INVASIVE	1 (2%)			1 (2%)
OLIGODENDROGLIOMA			1 (2%)	
SPECIAL SENSE ORGANS				
*EYELID	(49)	(50)	(50)	(50)
NEUROFIBROSARCOMA	1 (2%)			
MUSCULOSKELETAL SYSTEM				
*MUSCLE OF BACK	(49)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, META				1 (2%)
*MUSCLE OF THORAX	(49)	(50)	(50)	(50)
LIPOMA		1 (2%)		
BODY CAVITIES				
*MESENTERY	(49)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, META				1 (2%)

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA				1 (2%)
FIBROSARCOMA, INVASIVE	1 (2%)			
LEIOMYOSARCOMA, METASTATIC				1 (2%)
MESOTHELIOMA, MALIGNANT			1 (2%)	
MESOTHELIOMA, METASTATIC			1 (2%)	
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH	5	5	7	14
MORIBUND SACRIFICE	9	12	11	21
TERMINAL SACRIFICE	36	33	32	15
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS**	44	41	45	43
TOTAL PRIMARY TUMORS	84	81	109	110
TOTAL ANIMALS WITH BENIGN TUMORS	38	37	40	36
TOTAL BENIGN TUMORS	64	66	75	59
TOTAL ANIMALS WITH MALIG TUMORS	18	15	26	34
TOTAL MALIGNANT TUMORS	19	15	32	51
TOTAL ANIMALS WITH SEC TUMORS##	2		2	4
TOTAL SECONDARY TUMORS	2		2	5
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1		2	
TOTAL UNCERTAIN TUMORS	1		2	

* NUMBER OF ANIMALS NECROPSIED
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1: UNTREATED CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	087	105	071	101	103	105	104	105	105	103	077	100	105	105	105	105	105	105	105	105	105	105	091	089	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								X	
Squamous cell carcinoma										X															
Basal-cell carcinoma																						X			
Adnexal adenoma							X																		
Sebaceous adenoma																	X								
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																						X			
Fibrosarcoma																							X		
Lipoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X																				
Alveolar/bronchiolar carcinoma				X																					
Liposarcoma, metastatic																		X							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS											X														
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																					X	X			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS				X	X				X			X	X	X							X				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma	X			X		X	X	X	X			X	X						X	X			X		
Pheochromocytoma, malignant											X														
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell carcinoma	X																								
C-cell adenoma	X																								
C-cell carcinoma																				X					
Parathyroid	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma				X		X		X															X		
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial-cell tumor	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS														X											
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular-cell tumor, malignant																									
MUSCULOSKELETAL SYSTEM																									
Muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma											X														
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS				X																					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS																									
Mesothelioma, NOS														X											
Mesothelioma, malignant																									
Leukemia, mononuclear cell	X						X		X					X	X	X						X	X	X	
Tail																									
Squamous cell carcinoma		X																							

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed
: : No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	085	105	105	093	105	105	089	082	094	094	105	105	105	105	105	105	104	087	101	105	101	089	101	105	105	ISSUES UMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
Squamous cell papilloma																										1
Squamous cell carcinoma																										1
Basal-cell carcinoma																										1
Adnexal adenoma																										1
Sebaceous adenoma																										1
Keratoacanthoma	X	X	X						X							X		X	X							7
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
Fibroma											X							X							X	4
Fibrosarcoma																										1
Lipoma								X																		1
RESPIRATORY SYSTEM																										
an ai	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																										1
Liposarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule					X															X						4
Bile duct	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
Pancreas	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS				X								X										X				3
Adenoma, NOS	X				X	X		X					X		X											13
Adrenal	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma	X				X		X		X		X				X		X			X						19
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular-cell carcinoma																										1
C-cell adenoma																										1
C-cell carcinoma																										1
Parathyroid	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pancreatic islets	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet-cell adenoma																	X									1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
Fibroadenoma				X																X						6
Testis	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial-cell tumor		X	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X		X		X	X	X	44
Prostate	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
Carcinoma, NOS															X			X	X							4
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granular-cell tumor, malignant																		X								1
MUSCULOSKELETAL SYSTEM																										
Muscle	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
Liposarcoma																										1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
Mesothelioma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
Sarcoma, NOS									X																	1
Mesothelioma, NOS																					X					2
Mesothelioma, malignant							X																			1
Leukemia, mononuclear cell					X				X											X	X			X		15
Tail										A																
Squamous cell carcinoma																										1

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1: LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	104	104	078	093	096	104	104	093	104	099	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma										X			X												
Keratoacanthoma														X	X										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma		X				X																			
Lipoma																									
Neurofibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Alveolar/bronchiolar carcinoma																					X				
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																									
Thymus	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma															X										
Sarcoma, NOS, metastatic									X																
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS									X																
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional-cell carcinoma							X																		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Carcinoma, NOS																					X				
Adenoma, NOS							X					X													
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma		X			X	X								X	X	X			X	X	X	X			
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma																								X	
Follicular-cell carcinoma		X																							
C-cell adenoma												X													
C-cell carcinoma																									
Parathyroid	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell carcinoma										X											X				
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma																					X				
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial-cell tumor	X	X	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS		X																							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Choroid plexus																									
Papilloma, NOS										X															
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS																									
Sarcoma, NOS, metastatic																									
Mesothelioma, NOS													X												
Leukemia, mononuclear cell	X					X							X		X										

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	104	105	103	105	105	105	105	105	105	105	105	090	105	105	069	105	105	105	105	079	105	090	099	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Squamous cell papilloma									X							X			X							5
Keratoacanthoma																										2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Fibroma							X										X									4
Lipoma								X			X															2
Neurofibrosarcoma																								X		1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic																								X		1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																									X	2
Sarcoma, NOS, metastatic																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																									X	1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional-cell carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS																										1
Adenoma, NOS					X									X			X									5
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																									X	1
Pheochromocytoma			X			X		X	X	X	X			X	X					X		X				20
Pheochromocytoma, malignant																			X							1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular-cell adenoma																										1
Follicular-cell carcinoma																										1
C-cell adenoma									X																	2
C-cell carcinoma																					X	X				2
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet-cell carcinoma																										2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Adenocarcinoma, NOS																					X					1
Fibroadenoma											X					X										3
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial-cell tumor	X	X	X	X	X	X		X	X	X	X		X	X		X	X	X	X		X	X	X	X	X	44
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Carcinoma, NOS																			X							2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Choroid plexus																										*
Papilloma, NOS																										1
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Carcinoma, NOS																								X		1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Sarcoma, NOS															X											1
Sarcoma, NOS, metastatic															X											1
Mesothelioma, NOS																										1
Leukemia, mononuclear cell			X									X				X				X		X			X	10

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1: MID DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	094	104	099	064	104	088	104	104	082	104	099	104	091	104	104	096	104	078	081	101	078	104	104	082	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma														X											
Keratoacanthoma							X			X					X										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma											X														
Fibroma				X																					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X																							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																		X							
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																						X			
Sarcoma, NOS												X													
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular-cell adenocarcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																							X		
Squamous cell papilloma																									
Squamous cell carcinoma																									
Transitional-cell papilloma		X											X		X										
Transitional-cell carcinoma															X										
Sarcoma, NOS																									X
Leiomyoma																								X	
Leiomyosarcoma						X				X															
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																X									
Adenoma, NOS					X				X										X				X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Pheochromocytoma	X	X			X		X	X			X	X			X	X	X	X	X			X	X		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma	X						X					X													
C-cell carcinoma			X																						
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma																X			X						X
Islet-cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma															X										
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Interstitial-cell tumor	X	X	X		X	X	X	X		X		X	X	X	X	X	X			X	X	X	X		X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																								X	
Leukemia, mononuclear cell	X		X				X									X		X	X	X					
Head, NOS																									
Sarcoma, NOS									X																

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: MID DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	085	104	099	104	099	079	104	104	104	100	085	085	101	103	089	093	101	104	120	094	076	104	095	104	100	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	50*
Squamous cell papilloma																										2
Keratoacanthoma																		X								4
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Keratoacanthoma																										1
Fibroma														X												2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	49
Alveolar/bronchiolar adenoma			X																				X			3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Squamous cell papilloma																	X									1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			X																							2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	47
Adenocarcinoma, NOS																										1
Sarcoma, NOS																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular-cell adenocarcinoma																		X								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										1
Squamous cell papilloma									X																	1
Squamous cell carcinoma										X																1
Transitional-cell papilloma								X		X			X		X											8
Transitional-cell carcinoma			X											X	X											4
Sarcoma, NOS																										1
Leiomyoma																										1
Leiomyosarcoma						X					X					X	X									6
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
Carcinoma, NOS																										1
Adenoma, NOS					X																			X		6
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X		X		X		X		X				X				X	X		X						23
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	49
C-cell adenoma													X													4
C-cell carcinoma																										1
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	49
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet-cell adenoma		X																								4
Islet-cell carcinoma														X												1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Fibroadenoma																										1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial-cell tumor	X	X	X		X		X	X	X	X			X	X	X	X	X	X		X		X	X	X	X	38
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Carcinoma, NOS																										1
Leukemia, mononuclear cell			X		X					X		X	X		X											13
Head, NOS																										
Sarcoma, NOS																										1

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1: HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	082	104	069	099	083	087	010	073	104	069	088	079	072	098	084	090	060	044	100	087	044	066	079	066	075
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																X									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS											X														
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional-cell carcinoma, metastatic																									
Sarcoma, NOS, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional-cell carcinoma, metastatic																									
Sarcoma, NOS, metastatic																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional-cell carcinoma																									
Ureter	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Transitional-cell carcinoma																				X					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma				X		X		X																	
Squamous cell carcinoma																									
Transitional-cell papilloma				X		X													X						
Transitional-cell carcinoma						X					X		X												
Leiomyosarcoma		X	X	X	X			X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS				X																					
Adenoma, NOS									X						X										
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma		X							X																
Pheochromocytoma, malignant								X																	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell carcinoma																									
C-cell adenoma																		X							
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma								X	X																
Islet-cell carcinoma		X																							
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+
Fibroadenoma															X										
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial-cell tumor		X	X	X					X			X		X		X			X		X				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional-cell carcinoma, invasive																									
Adenoma, NOS																									
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																						X			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	+	+	N	N	N	N	N	N	N	N	N	+	N	N	N	+	N	+	N	N	N	N	N
Carcinoma, NOS				X																					
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leiomyosarcoma, invasive																X			X						
Leukemia, mononuclear cell																									
Adipose tissue																									
Lipoma																									

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	0262	0272	0282	0293	0303	0311	0323	0333	0343	0355	0363	0373	0383	0393	0401	0411	0422	0433	0441	0445	0456	0467	0478	0489	0497	0500	TOTAL
WEEKS ON STUDY	0997	0990	0700	0995	0992	0991	0558	0778	0779	0773	0779	0795	0898	0700	0995	0664	0993	0719	0999	0774	0664	0668	0554	0997	0521		TISSUES TUMORS
INTEGUMENTARY SYSTEM																											
Skin	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Keratoacanthoma																											1
Subcutaneous tissue	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Sarcoma, NOS				X																					X		3
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional-cell carcinoma, metastatic										X																	1
Sarcoma, NOS, metastatic				X																							1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	44
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																											
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional-cell carcinoma, metastatic										X																	1
Sarcoma, NOS, metastatic																									X		1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional-cell carcinoma																									X		1
Ureter	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Transitional-cell carcinoma																											1
Urinary bladder	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																											3
Squamous cell carcinoma												X															1
Transitional-cell papilloma																								X			4
Transitional-cell carcinoma	X					X				X								X									8
Leiomyosarcoma		X	X	X	X			X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		41
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS																											1
Adenoma, NOS												X															3
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma					X																						3
Pheochromocytoma, malignant																											1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular-cell carcinoma										X																	1
C-cell adenoma						X				X																	3
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet-cell adenoma																											2
Islet-cell carcinoma																											1
REPRODUCTIVE SYSTEM																											
Mammary gland	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Fibroadenoma																											1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial-cell tumor		X			X	X									X		X		X						X		16
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional-cell carcinoma, invasive										X																	1
Adenoma, NOS															X												1
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Carcinoma, NOS																											1
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																											
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	50*
Carcinoma, NOS																											1
BODY CAVITIES																											
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Mesothelioma, NOS																	X										1
ALL OTHER SYSTEMS																											
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Leiomyosarcoma, invasive																		X									1
Leukemia, mononuclear cell																											2
Adipose tissue																											
Lipoma																		X									1

*Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1: UNTREATED CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	103	105	105	105	105	091	105	079	105	105	105	105	105	096	105	025	067	105	105	097	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Fibroma														X									X		
Fibrosarcoma											X														
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	A	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Neoplastic nodule																									X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Acinar-cell adenoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Carcinoma, NOS														X						X					
Adenoma, NOS																	X								
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	–	+	+	+
Cortical adenoma																									
Pheochromocytoma																									X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
C-cell adenoma																					X				
C-cell carcinoma													X												
Parathyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	A	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Islet-cell adenoma																					X				
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Fibroadenoma	X	X	X				X		X			X	X		X		X			X	X		X		
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N
Carcinoma, NOS								X										X							
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Endometrial stromal polyp					X		X					X					X	X			X	X			
Endometrial stromal sarcoma										X															
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Carcinoma, NOS, invasive													X												
SPECIAL SENSE ORGANS																									
Eye appendages	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N
Neurofibrosarcoma																									
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N
Hemangiosarcoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N
Fibrosarcoma, invasive											X														
Leukemia, mononuclear cell	X			X					X														X		

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed
: : No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: UNTREATED CONTROL (*Continued*)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	101	105	104	105	105	104	067	098	105	105	105	105	105	105	105	100	086	105	105	105	088	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
Fibroma							X																			3
Fibrosarcoma								X																		2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar-cell adenoma				X																						1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																										2
Adenoma, NOS		X			X	X			X		X			X		X	X			X						10
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cortical adenoma						X																				1
Pheochromocytoma			X							X						X								X		5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell adenoma				X																						2
C-cell carcinoma																										1
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet-cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49*
Fibroadenoma	X	X		X	X	X	X						X		X		X		X		X		X			24
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
Carcinoma, NOS																										2
Adenoma, NOS							X																			1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp	X		X	X							X	X	X	X	X	X										16
Endometrial stromal sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS, invasive																										1
SPECIAL SENSE ORGANS																										
Eye appendages	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
Neurofibrosarcoma																				X						1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
Hemangiosarcoma									X																	1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49*
Osteosarcoma, invasive																										1
Leukemia, mononuclear cell	X						X				X								X		X					9

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1: LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	105	105	104	105	105	094	104	085	105	105	080	105	105	035	105	105	105	105	105	104	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma									X							X									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																									X
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS	X	X		X		X			X	X	X	X	X		X				X		X			X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma										X		X							X					X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma		X											X												
C-cell adenoma				X																				X	
C-cell carcinoma																								X	
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma				X		X	X		X	X		X			X			X	X		X			X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																						X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma				X																					
Endometrial stromal polyp	X															X						X	X		X
Endometrial stromal sarcoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma												X													
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell										X				X											

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	105	072	067	076	105	105	081	105	104	040	105	100	099	095	104	105	105	105	105	105	105	105	105	073	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Fibroma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenomatous polyp, NOS																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS					X			X									X									3
Adenoma, NOS			X										X		X	X				X				X	X	21
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma												X														5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular-cell adenoma																										2
C-cell adenoma			X			X																			X	5
C-cell carcinoma																										1
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet-cell carcinoma	X																									1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Adenocarcinoma, NOS													X													1
Fibroadenoma	X						X		X	X				X			X				X		X			19
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Carcinoma, NOS						X															X					3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Endometrial stromal polyp							X								X				X	X	X					10
Endometrial stromal sarcoma															X			X								2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Lipoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Leukemia, mononuclear cell							X																			3

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1: MID DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	093	104	104	104	104	047	058	088	040	013	104	104	082	064	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
Squamous cell papilloma						X																			
Basal cell carcinoma																					X				
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
Fibrosarcoma																									
Osteosarcoma																									
Neurofibrosarcoma								X																	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											
Osteosarcoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule	X																								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma																									
Transitional cell papilloma			X	X						X		X			X			X						
Transitional cell carcinoma				X						X		X			X						X			
Leiomyoma					X																				
Leiomyosarcoma										X															
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X	X		X		X	X		X			X			X			X	X			X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma				X			X																	X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																									
C-cell carcinoma									X																
Parathyroid	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma	X	X	X	X		X	X	X		X	X							X				X	X		X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS							X								X										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp									X																
Endometrial stromal sarcoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma																			X						
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, malignant																				X					
Mesothelioma, metastatic																				X					
Malig. lymphoma, lymphocytic type																									
Malig. lymphoma, histiocytic type																									
Leukemia, mononuclear cell										X															

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: MID DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	037	103	089	097	081	104	104	104	101	104	104	104	104	104	104	096	104	104	104	104	104	104	103	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
Basal cell carcinoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																X										1
Osteosarcoma				X																						1
Neurofibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																										1
Osteosarcoma, metastatic					X																					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																					X					2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma										X																1
Squamous cell carcinoma										X																1
Transitional cell papilloma								X	X							X										9
Transitional cell carcinoma			X		X								X										X	X		10
Leiomyoma																										1
Leiomyosarcoma								X																		2
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS				X							X		X		X		X		X	X		X			X	20
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma													X				X	X	X		X		X	X	X	10
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma									X															X		2
C-cell carcinoma																										1
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell carcinoma																								X		1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																			X							1
Fibroadenoma				X			X		X		X	X	X	X	X		X		X	X		X		X	X	27
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS												X			X	X	X									6
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp						X		X																		3
Endometrial stromal sarcoma																				X						1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oligodendroglioma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, malignant																										1
Mesothelioma, metastatic																										1
Malig. lymphoma, lymphocytic type														X												1
Malig. lymphoma, histiocytic type				X																						1
Leukemia, mononuclear cell																										1

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1: HIGH DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	055	104	073	054	066	049	104	063	103	090	084	082	101	095	104	104	072	095	090	065	097	103	104	091	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastat																						X			
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional-cell papilloma			X																						
Ureter	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Transitional-cell papilloma									X																
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																	X						X		X
Squamous cell carcinoma		X																				X			
Transitional-cell papilloma			X			X	X	X	X	X		X	X	X		X							X		X
Transitional-cell carcinoma		X	X					X		X				X				X					X		
Sarcoma, NOS																			X						
Leiomyoma														X	X										
Leiomyosarcoma		X				X					X	X		X			X			X	X	X	X	X	X
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS															X										
Adenoma, NOS											X			X				X		X			X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical carcinoma																									
Pheochromocytoma		X																						X	
Ganglioneuroma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma							X																		X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp												X													
Endometrial stromal sarcoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive															X										
MUSCULOSKELETAL SYSTEM																									
Muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastat																									
BODY CAVITIES																									
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, metastat																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma																									
Leiomyosarcoma, metastatic																		X							
Leukemia, mononuclear cell																									

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	065	104	100	104	104	096	002	104	083	103	087	074	104	103	104	104	058	104	002	102	104	098	098	101	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Sarcoma, NOS										X																1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastat																										1
Alveolar/bronchiolar carcinoma										X																1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Pancreas	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional-cell papilloma																										1
Ureter	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Transitional-cell papilloma																										1
Urinary bladder	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
Squamous cell papilloma	X	X	X												X											7
Squamous cell carcinoma										X														X		4
Transitional-cell papilloma					X			X				X														15
Transitional-cell carcinoma			X		X	X		X							X		X									13
Sarcoma, NOS																										1
Leiomyoma								X																X		4
Leiomyosarcoma					X						X	X	X	X		X		X		X	X	X	X		X	23
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																										1
Adenoma, NOS	X	X	X			X	X				X		X							X				X	X	15
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical carcinoma															X											1
Pheochromocytoma													X													3
Ganglioneuroma												X														1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	48
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Adenocarcinoma, NOS																									X	1
Fibroadenoma										X			X			X		X		X					7
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Carcinoma, NOS										X																1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp					X				X						X						X					5
Endometrial stromal sarcoma														X												1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										1
MUSCULOSKELETAL SYSTEM																										
Muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Squamous cell carcinoma, metastat										X																1
BODY CAVITIES																										
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Squamous cell carcinoma, metastat										X																1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Squamous cell carcinoma	X																									1
Leiomyosarcoma, metastatic																										1
Leukemia, mononuclear cell					X							X														2

*Animals necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATH	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)			
BASAL-CELL TUMOR				1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
SARCOMA, NOS	3 (6%)	2 (4%)	2 (4%)	3 (6%)
SARCOMA, NOS, METASTATIC			1 (2%)	
FIBROMA	†6 (12%)	7 (14%)	5 (10%)	
FIBROSARCOMA	†12 (24%)	†13 (26%)	†7 (14%)	5 (10%)
RESPIRATORY SYSTEM				
#LUNG	(50)	(49)	(50)	(50)
SQUAMOUS CELL CARCINOMA, MET	1 (2%)			
HEPATOCELLULAR CARCINOMA, MET	2 (4%)	4 (8%)	6 (12%)	2 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	3 (6%)	5 (10%)	5 (10%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	3 (6%)	6 (12%)	1 (2%)	6 (12%)
SARCOMA, NOS, METASTATIC			1 (2%)	
FIBROSARCOMA, METASTATIC	1 (2%)	3 (6%)		
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MALIG. LYMPHOMA, UNDIFFER-TYPE	1 (2%)			
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	1 (2%)	1 (2%)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		1 (2%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)	1 (2%)	5 (10%)	2 (4%)
#SPLEEN	(50)	(49)	(50)	(50)
MALIGNANT LYMPHOMA, MIXED TYPE				1 (2%)
#MEDIASTINAL L. NODE	(50)	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, MET				1 (2%)
#MESENTERIC L. NODE	(50)	(50)	(50)	(50)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)		1 (2%)
#AXILLARY LYMPH NODE	(50)	(50)	(50)	(50)
SARCOMA, NOS, METASTATIC		1 (2%)		
FIBROSARCOMA, METASTATIC	1 (2%)			
#PEYERS PATCH	(48)	(48)	(49)	(50)
MALIGNANT LYMPHOMA, MIXED TYPE				1 (2%)
#THYMUS	(47)	(48)	(46)	(45)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)			
CIRCULATORY SYSTEM				
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
HEMANGIOMA		1 (2%)		1 (2%)
#BONE MARROW	(46)	(50)	(49)	(49)
HEMANGIOSARCOMA				1 (2%)
#SPLEEN	(50)	(49)	(50)	(50)
HEMANGIOMA	1 (2%)			
HEMANGIOSARCOMA	2 (4%)			2 (4%)
#LIVER	(50)	(50)	(50)	(50)
HEMANGIOMA		1 (2%)		
HEMANGIOSARCOMA	2 (4%)			2 (4%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
#LIVER	(50)	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA	3 (6%)	9 (18%)	10 (20%)	9 (18%)
HEPATOCELLULAR CARCINOMA	6 (12%)	15 (30%)	13 (26%)	8 (16%)
#PANCREAS	(49)	(49)	(50)	(49)
ALVEOLAR/BRONCHIOLAR CA, MET		1 (2%)		
#FORESTOMACH	(50)	(49)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)		2 (4%)
SQUAMOUS CELL CARCINOMA	1 (2%)			
*RECTUM	(50)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)			
URINARY SYSTEM				
#KIDNEY	(50)	(50)	(50)	(50)
HEPATOCELLULAR CARCINOMA, MET			1 (2%)	
#URINARY BLADDER	(50)	(49)	(50)	(50)
SQUAMOUS CELL CARCINOMA				1 (2%)
FIBROMA				1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY INTERMEDIARY	(44)	(44)	(47)	(50)
ADENOMA, NOS				1 (2%)
#ADRENAL	(49)	(48)	(49)	(50)
CORTICAL ADENOMA			1 (2%)	1 (2%)
#ADRENAL MEDULLA	(49)	(48)	(49)	(50)
PHEOCHROMOCYTOMA	1 (2%)			
#THYROID	(49)	(50)	(49)	(49)
FOLLICULAR-CELL ADENOMA	2 (4%)	4 (8%)	5 (10%)	2 (4%)
C-CELL ADENOMA				1 (2%)
#PARATHYROID	(33)	(41)	(32)	(31)
ADENOMA, NOS	1 (3%)			
#PANCREATIC ISLETS	(49)	(49)	(50)	(49)
ISLET-CELL ADENOMA		1 (2%)		
REPRODUCTIVE SYSTEM				
*PREPUTIAL GLAND	(50)	(50)	(50)	(50)
CARCINOMA, NOS				1 (2%)
#PROSTATE	(50)	(49)	(50)	(49)
SQUAMOUS CELL CARCINOMA, MET				1 (2%)
*SEMINAL VESICLE	(50)	(50)	(50)	(50)
CARCINOSARCOMA	1 (2%)			
#TESTIS	(50)	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR				1 (2%)
NERVOUS SYSTEM				
#BRAIN	(49)	(50)	(50)	(50)
CARCINOMA, NOS, INVASIVE	1 (2%)			
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(50)	(50)	(50)	(50)
CARCINOMA, NOS	1 (2%)			
ADENOMA, NOS	2 (4%)	3 (6%)	1 (2%)	2 (4%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM				
*MUSCLE OF THORAX	(50)	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, MET	1 (2%)			
BODY CAVITIES				
*MEDIASTINUM	(50)	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, META				1 (2%)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, METASTA				1 (2%)
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH	13	9	3	11
MORIBUND SACRIFICE	14	11	12	19
TERMINAL SACRIFICE	23	30	35	20
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS**	35	44	34	34
TOTAL PRIMARY TUMORS	56	70	59	63
TOTAL ANIMALS WITH BENIGN TUMORS	15	21	22	17
TOTAL BENIGN TUMORS	18	30	27	27
TOTAL ANIMALS WITH MALIGNANT TUM	28	36	23	26
TOTAL MALIGNANT TUMORS	38	40	32	36
TOTAL ANIMALS WITH SECONDARY TUM##	6	9	9	5
TOTAL SECONDARY TUMORS	7	9	9	6

* NUMBER OF ANIMALS NECROPSIED
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN
† MULTIPLE OCCURRENCE OF MORPHOLOGY IN THE SAME ORGAN; TISSUE IS COUNTED ONCE ONLY.

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATH	50	50	50	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
SARCOMA, NOS				1 (2%)
FIBROMA			1 (2%)	
FIBROSARCOMA	2 (4%)	†2 (4%)		1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(49)	(50)	(50)	(50)
CARCINOMA, NOS, METASTATIC			1 (2%)	
HEPATOCELLULAR CARCINOMA, MET		1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA		4 (8%)	1 (2%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS		1 (2%)		
MALIG. LYMPHOMA, LYMPHO TYPE	1 (2%)	3 (6%)	2 (4%)	5 (10%)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)		1 (2%)	1 (2%)
MALIGNANT LYMPHOMA, MIXED TYPE	13 (26%)	10 (20%)	11 (22%)	10 (20%)
#SPLEEN	(50)	(49)	(50)	(49)
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)	1 (2%)		
#MESENTERIC L. NODE	(50)	(50)	(50)	(50)
MALIG. LYMPHOMA, LYMPHO TYPE				1 (2%)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
#LUNG	(49)	(50)	(50)	(50)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
CIRCULATORY SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)			
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)			
*MUSCLE OF BACK	(50)	(50)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)		
DIGESTIVE SYSTEM				
#LIVER	(50)	(49)	(50)	(50)
HEPATOCELLULAR ADENOMA	2 (4%)	12 (24%)	3 (6%)	2 (4%)
HEPATOCELLULAR CARCINOMA	1 (2%)	2 (4%)		2 (4%)
#FORESTOMACH	(49)	(50)	(50)	(49)
SQUAMOUS CELL PAPILLOMA				1 (2%)
#DUODENUM	(50)	(49)	(48)	(48)
ADENOMATOUS POLYP, NOS	1 (2%)	2 (4%)	2 (4%)	
#JEJUNUM	(50)	(49)	(48)	(48)
ADENOMATOUS POLYP, NOS		1 (2%)		
URINARY SYSTEM				
#URINARY BLADDER	(49)	(50)	(50)	(50)
SARCOMA, NOS				1 (2%)

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#PITUITARY	(48)	(45)	(48)	(45)
ADENOMA, NOS	7 (15%)	4 (9%)	8 (17%)	8 (18%)
#ADRENAL	(48)	(48)	(50)	(49)
PHEOCHROMOCYTOMA		1 (2%)		1 (2%)
#THYROID	(48)	(50)	(50)	(46)
FOLLICULAR-CELL ADENOMA	4 (8%)	1 (2%)	4 (8%)	1 (2%)
FOLLICULAR-CELL CARCINOMA		1 (2%)	1 (2%)	
#PANCREATIC ISLETS	(50)	(50)	(49)	(46)
ISLET-CELL ADENOMA	1 (2%)	1 (2%)		
ISLET-CELL CARCINOMA			1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
CARCINOMA, NOS			1 (2%)	
ADENOCARCINOMA, NOS	2 (4%)	3 (6%)	1 (2%)	
ADENOCA/SQUAMOUS METAPLASIA	1 (2%)			
#UTERUS	(50)	(50)	(50)	(50)
ADENOCARCINOMA, NOS			1 (2%)	
LEIOMYOMA		1 (2%)	1 (2%)	1 (2%)
ENDOMETRIAL STROMAL POLYP	3 (6%)	2 (4%)	1 (2%)	1 (2%)
#OVARY	(49)	(47)	(49)	(41)
GRANULOSA-CELL TUMOR	2 (4%)			
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*HARDERIAN GLAND	(50)	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)	1 (2%)	3 (6%)	
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
NONE				
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
FIBROSARCOMA, METASTATIC	2 (4%)			
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	50	50	50	50
NATURAL DEATH	13	14	10	18
MORIBUND SACRIFICE	5	9	6	5
TERMINAL SACRIFICE	32	27	34	27

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS**	29	33	33	30
TOTAL PRIMARY TUMORS	47	56	46	40
TOTAL ANIMALS WITH BENIGN TUMORS	14	24	20	14
TOTAL BENIGN TUMORS	19	30	24	17
TOTAL ANIMALS WITH MALIGNANT TUM	25	23	22	21
TOTAL MALIGNANT TUMORS	26	26	22	23
TOTAL ANIMALS WITH SECONDARY TUM##	2	1	1	
TOTAL SECONDARY TUMORS	2	1	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2			
TOTAL UNCERTAIN TUMORS	2			

* NUMBER OF ANIMALS NECROPSIED
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN
† MULTIPLE OCCURRENCE OF MORPHOLOGY IN THE SAME ORGAN; TISSUE IS COUNTED ONCE ONLY.

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1: UNTREATED CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	015	040	091	105	105	105	097	011	106	057	106	106	106	106	089	105	106	106	066	012	106	106	106	096	078
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																X									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																								X	X
Fibroma																									
Fibrosarcoma			X			X													X						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastat																X									
Hepatocellular carcinoma, metasta						X																			
Alveolar/bronchiolar adenoma										X															
Alveolar/bronchiolar carcinoma						X																			
Fibrosarcoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma						X																			
Hemangiosarcoma																	X							X	
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																							X		
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma													X										X		
Hepatocellular carcinoma						X									X		X				X				
Hemangiosarcoma																								X	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	+	+	+	+	+	+	+	+	+	N	N	N	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma							X																		
Small intestine	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Rectum	N	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
Squamous cell carcinoma										X															
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	–	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma														X											
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma												X													
Parathyroid	+	+	+	+	+	+	+	–	+	+	–	–	–	+	+	–	+	+	+	+	+	+	+	–	+
Adenoma, NOS																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinosarcoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																									
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS																							X		
MUSCULOSKELETAL SYSTEM																									
Muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+
Squamous cell carcinoma, metastat																X									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, undiffer-type																									
Malig. lymphoma, histiocytic type							X																		
Malignant lymphoma, mixed type																									

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed
: No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	106	105	016	106	078	096	106	095	106	106	012	110	106	111	106	098	102	106	105	118	089	099	098	095	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Squamous cell carcinoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Sarcoma, NOS																					X					3
Fibroma				X					X@X								X		X				X			6
Fibrosarcoma	X					X@X	X									X	X					X	X	X		12
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic																										1
Hepatocellular carcinoma, metastatic																									X	2
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																X		X								3
Fibrosarcoma, metastatic																								X		1
Trachea	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hemangiosarcoma																										2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic																	X									1
Thymus	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	47
Malignant lymphoma, mixed type																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma					X																					3
Hepatocellular carcinoma							X																		X	6
Hemangiosarcoma					A																					2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	N	+	N	N	+	+	+	+	+	50*
Pancreas	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Small intestine	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Rectum	+	+	N	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	N	+	+	+	+	+	50*
Squamous cell carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	44
Adrenal	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular-cell adenoma								X																		2
Parathyroid	+	–	–	+	+	+	–	–	–	+	–	–	–	+	+	–	+	+	+	+	–	+	+	–	+	33
Adenoma, NOS																		X								1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Carcinosarcoma	X																									1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	49
Carcinoma, NOS, invasive		X																								1
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Carcinoma, NOS		X																								1
Adenoma, NOS	X																									2
MUSCULOSKELETAL SYSTEM																										
Muscle	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	50*
Squamous cell carcinoma, metastat																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Malig. lymphoma, undiffer-type															X											1
Malig. lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type																			X							1

* Animals necropsied
@ Multiple occurrence of morphology

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1: LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	010	105	105	068	105	105	105	103	079	105	105	105	024	105	105	093	105	105	089	093	104	096	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS									X																
Fibroma		X			X													X						X	X
Fibrosarcoma						X						X		X			X		X		X	X@	X		
Hemangioma							X																		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metasta								X								X									
Alveolar/bronchiolar adenoma																X									
Alveolar/bronchiolar carcinoma		X	X															X							
Fibrosarcoma, metastatic																			X		X				
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic																									
Malignant lymphoma, mixed type																									
Thymus	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma					X																		X		X
Hepatocellular carcinoma								X		X						X	X	X		X			X		X
Hemangioma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	N	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+
Pancreas	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar ca, metastat																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																				X					
Small intestine	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Adrenal	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma		X								X		X													
Parathyroid	–	+	+	+	+	–	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma		X																							
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	+	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																				X					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, lymphocytic type																									
Malignant lymphoma, mixed type															X										

@ Multiple occurrence of morphology

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	096	105	066	096	105	105	105	105	066	105	086	105	105	103	105	068	105	105	083	105	105	077	105	077	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Sarcoma, NOS																							X			2
Fibroma									X							X										7
Fibrosarcoma	X	X	X		X					X																13
Hemangioma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	49
Hepatocellular carcinoma, metasta												X			X											4
Alveolar/bronchiolar adenoma								X						X												3
Alveolar/bronchiolar carcinoma						X							X							X						6
Fibrosarcoma, metastatic		X																								3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, metastatic																							X			1
Malignant lymphoma, mixed type											X															1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	48
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																X		X	X		X	X		X		9
Hepatocellular carcinoma				X								X		X	X			X		X					X	15
Hemangioma	X																									1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	N	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	50*
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar ca, metastat																				X						1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	–	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adrenal	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular-cell adenoma																				X						4
Parathyroid	+	–	+	+	–	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	41
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet-cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Adenoma, NOS																X		X								3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Malig. lymphoma, lymphocytic type																								X		1
Malignant lymphoma, mixed type																										1

* Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1: MID DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	105	070	097	105	105	091	023	105	105	105	069	105	105	105	105	071	066	097	105	105	086	105	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																	X								
Sarcoma, NOS, metastatic																	X								
Fibroma																			X	X			X		
Fibrosarcoma			X									X										X@			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic						X				X		X		X							X				
Alveolar/bronchiolar adenoma																						X			
Alveolar/bronchiolar carcinoma																									
Sarcoma, NOS, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma				X		X					X				X										X
Hepatocellular carcinoma						X				X		X		X				X	X		X	X			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	+	+	+	N	+	N	+	+	N	N	+	+	N	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastat																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Follicular-cell adenoma										X															
Parathyroid	–	–	+	–	+	–	+	+	–	–	+	+	–	–	+	+	+	+	–	–	–	–	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, lymphocytic type																									
Malig. lymphoma, histiocytic type																									
Malignant lymphoma, mixed type										X		X			X			X							

@ Multiple occurrence of morphology

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: MID DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	105	105	105	105	105	105	105	086	105	063	105	105	079	105	105	105	105	105	105	105	105	078	081		TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	-	+	+	+		50*
Sarcoma, NOS																									X	2
Sarcoma, NOS, metastatic																										1
Fibroma															X					X						5
Fibrosarcoma				X			X@							X									X			7
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hepatocellular carcinoma, metastatic									X																	6
Alveolar/bronchiolar adenoma						X	X								X			X								5
Alveolar/bronchiolar carcinoma							X																			1
Sarcoma, NOS, metastatic																									X	1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Thymus	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+		46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hepatocellular adenoma	X				X	X													X					X		10
Hepatocellular carcinoma	X						X	X	X															X		13
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50*
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hepatocellular carcinoma, metastat	X																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Adrenal	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Cortical adenoma																			X							1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Follicular-cell adenoma		X				X		X				X														5
Parathyroid	-	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		32
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		50*
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		50*
Adenoma, NOS						X																				1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		50*
Malig. lymphoma, lymphocytic type					X																					1
Malig. lymphoma, histiocytic type		X																								1
Malignant lymphoma, mixed type																					X					5

*Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1: HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	089	086	105	096	105	059	105	086	078	040	105	063	105	054	059	105	105	118	104	105	059	011	105	085	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
Basal-cell tumor							X																		
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibrosarcoma											X														
Hemangioma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metasta																									
Alveolar/bronchiolar adenoma							X										X								
Alveolar/bronchiolar carcinoma		X														X									X
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								X	
Malignant lymphoma, mixed type																									X
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar ca, metastat																									
Malignant lymphoma, mixed type																	X								
Thymus	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	–	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma			X				X				X		X				X								
Hepatocellular carcinoma																								X	X
Hemangiosarcoma									X															X	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	N	N	+	+	+	N	+	+	+	+	N	+	+	+	N	N	+	N	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type			X																						
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Fibroma																				X					
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS							X																		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma													X												
C-cell adenoma																									
Parathyroid	–	–	+	+	+	–	+	–	+	–	+	+	+	–	–	+	+	+	+	+	–	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	+	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial-cell tumor																									
Prostate	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastat																									
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS											X														
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS								X								X								
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar ca, metastat																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar ca, metastat		X																							
Malig. lymphoma, lymphocytic type												X													
Malig. lymphoma, histiocytic type																									
Malignant lymphoma, mixed type																							X		

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	091	105	105	071	042	097	100	091	105	055	049	105	055	036	105	086	103	105	105	073	070	066	105		TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Basal-cell tumor																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Sarcoma, NOS													X									X	X			3
Fibrosarcoma		X					X		X			X														5
Hemangioma							X																			1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic									X									X								2
Alveolar/bronchiolar adenoma			X																	X					X	5
Alveolar/bronchiolar carcinoma										X			X								X					6
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																			X							1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																				X						2
Malignant lymphoma, mixed type																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar ca, metastatic																					X					1
Malignant lymphoma, mixed type																										1
Thymus	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X						X		X									X						9
Hepatocellular carcinoma				X					X								X	X			X		X			8
Hemangiosarcoma																										2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	50*
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma	X																								X	2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																	X									1
Fibroma																										1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma													X													1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular-cell adenoma																									X	2
C-cell adenoma			X																							1
Parathyroid	+	–	+	–	–	–	–	–	+	+	–	–	+	+	–	–	+	+	+	+	–	+	+	+	+	31
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	+	N	N	N	N	+	N	N	N	50*	
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial-cell tumor				X																						1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, metastat																	X									1
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Carcinoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Adenoma, NOS																										2
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Alveolar/bronchiolar ca, metastat																					X					1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Alveolar/bronchiolar ca, metastat																										1
Malig. lymphoma, lymphocytic type																										1
Malig. lymphoma, histiocytic type									X																	1
Malignant lymphoma, mixed type																				X						2

*Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1: *UNTREATED CONTROL*

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	096	099	106	106	105	106	105	106	106	105	106	106	106	100	106	089	105	106	106	105	105	106	106	106
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																						X			
Hemangiosarcoma													X												
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma				X										X											
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, *NOS*																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS					X				X					X						X				X	
Adrenal	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma		X			X																			X	
Parathyroid	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	–	+	+	–	–	–	–	–	–
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma																				X					
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																								X	
Adenoca/squamous metaplasia																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																		X							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Granulosa-cell tumor											X														
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS											X														
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, metastatic																						X			
Hemangiosarcoma																									
Malig. lymphoma, lymphocytic type																									
Malig. lymphoma, histiocytic type															X		X								
Malignant lymphoma, mixed type	X	X		X	X	X			X	X	X	X		X				X							

\+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed
: No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	106	080	106	080	101	086	089	105	106	096	106	093	105	105	096	099	093	106	105	106	080	099	106	105	101	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	50*
Fibrosarcoma					X																					2
Hemangiosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma																						X				1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type																			X							1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	48
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										2
Hepatocellular carcinoma																								X		1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	50*
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenomatous polyp, NOS									X																	1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS										X	X															7
Adrenal	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	48
Follicular-cell adenoma																									X	4
Parathyroid	–	+	–	+	–	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	–	+	+	+	–	34
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet-cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	50*
Adenocarcinoma, NOS																						X				2
Adenoca/squamous metaplasia													X													1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp										X															X	3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa-cell tumor																			X							2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Adenoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Fibrosarcoma, metastatic					X																					2
Hemangiosarcoma				X																						1
Malig. lymphoma, lymphocytic type																									X	1
Malig. lymphoma, histiocytic type																										2
Malignant lymphoma, mixed type		X					X																			13

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1: LOW DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0201	0202	0203	0204	0205
WEEKS ON STUDY	0939	1006	1006	1006	0996	1006	1006	1006	1006	0997	1006	0991	1002	1006	1006	0816	1006	0888	1006	1006	0886	1006	1006	0881
INTEGUMENTARY SYSTEM																								
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
Fibrosarcoma										X@		X												
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metasta																								
Alveolar/bronchiolar adenoma								X							X								
Alveolar/bronchiolar carcinoma																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																								
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+
CIRCULATORY SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma				X					X							X			X			X		
Hepatocellular carcinoma							X																	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS									X															
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+
Adenoma, NOS						X			X											X				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Pheochromocytoma																				X				
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma																								
Follicular-cell carcinoma																								
Parathyroid	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma														X										
REPRODUCTIVE SYSTEM																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																X				X				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																								
Endometrial stromal polyp											X	X												
Ovary	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																								
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																								
MUSCULOSKELETAL SYSTEM																								
Muscle	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
ALL OTHER SYSTEMS																								
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS																X								
Malig. lymphoma, lymphocytic type													X		X									
Malignant lymphoma, mixed type	X							X				X		X								X		

@ Multiple occurrence of morphology

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035	0036	0037	0038	0039	0040	0041	0042	0043	0044	0045	0046	0047	0048	0049	0050	TOTAL
WEEKS ON STUDY	1006	0755	1006	1006	0998	0778	1006	1006	1006	0881	0669	1006	0776	1006	1006	1006	0885	1002	1006	0663	0885	0885	0994	0778	0886	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Fibrosarcoma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metasta								X																		1
Alveolar/bronchiolar adenoma								X															X			4
Alveolar/bronchiolar carcinoma																			X							1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type														X												1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma			X				X	X		X			X	X										X		12
Hepatocellular carcinoma								X																		2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	50*
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenomatous polyp, NOS	X			X																						3
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	45
Adenoma, NOS								X																		4
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular-cell adenoma																									X	1
Follicular-cell carcinoma			X																							1
Parathyroid	+	+	+	+	–	+	+	–	+	+	–	+	+	–	+	+	+	+	+	–	+	+	+	+	+	43
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet-cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	50*
Adenocarcinoma, NOS																		X								3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma								X																		1
Endometrial stromal polyp																										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Adenoma, NOS																			X							1
MUSCULOSKELETAL SYSTEM																										
Muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Hemangiosarcoma											X															1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Malignant lymphoma, NOS																										1
Malig. lymphoma, lymphocytic type					X																					3
Malignant lymphoma, mixed type	X								X			X												X	X	10

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1: MID DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	096	106	106	105	106	106	106	106	096	098	106	106	106	106	084	106	106	097	106	106	106	106	106	096	091
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																							X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																									
Alveolar/bronchiolar adenoma																				X					
Alveolar/bronchiolar carcinoma				X																					
Malig. lymphoma, histiocytic type																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malig. lymphoma, histiocytic type																X									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma		X																		X					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS							X				X					X									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma						X					X							X							
Follicular-cell carcinoma																									
Parathyroid	–	+	+	+	+	+	+	–	–	+	+	+	–	+	–	+	+	–	–	+	+	+	+	–	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenocarcinoma, NOS																	X								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																		X							
Leiomyoma														X											
Endometrial stromal polyp																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS						X																		X	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, lymphocytic type		X			X																				
Malig. lymphoma, histiocytic type																									
Malignant lymphoma, mixed type	X		X			X				X	X		X										X		

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: MID DOSE (Continued)

ANIMAL NUMBER	0262	0267	0282	0289	0330	0331	0332	0333	0334	0335	0336	0337	0338	0339	0340	0341	0342	0343	0344	0345	0346	0347	0348	0349	0350	TOTAL
WEEKS ON STUDY	1006	1006	1006	0633	1006	1006	1006	1006	0668	0997	1006	1006	1006	0885	1006	1008	1008	1006	1006	1006	1003	1006	1006	1006	0889	1006	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic																								X		1
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																										1
Malig. lymphoma, histiocytic type														X												1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malig. lymphoma, histiocytic type																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma					X																					3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	50*
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	–	-	+	+	+	+	+	+	+	+	+	+	48
Adenomatous polyp, NOS											X	X														2
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	48
Adenoma, NOS								X					X		X			X	X							8
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular-cell adenoma																			X							4
Follicular-cell carcinoma													X													1
Parathyroid	+	+	+	+	+	+	+	–	–	+	+	+	+	–	–	+	–	+	–	+	+	+	+	+	+	36
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet-cell carcinoma																									X	1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Carcinoma, NOS																								X		1
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
Leiomyoma																										1
Endometrial stromal polyp										X																1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Adenoma, NOS					X																					3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
Malig. lymphoma, lymphocytic type																										2
Malig. lymphoma, histiocytic type		X																								1
Malignant lymphoma, mixed type											X						X	X		X						11

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1: HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	106	106	089	091	106	068	106	106	106	068	106	106	106	106	094	091	106	106	091	087	106	099	106	106	106
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS						X																			
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma	X																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malig. lymphoma, lymphocytic type							X																		
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																		X							
Hepatocellular carcinoma			X																						
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	–	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma							X																		
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Adenoma, NOS	X						X										X				X				X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Follicular-cell adenoma																					X				
Parathyroid	–	+	–	–	+	+	+	+	+	+	+	+	–	–	–	–	+	+	–	–	+	–	+	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Endometrial stromal polyp																									
Ovary	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, lymphocytic type											X	X							X			X			
Malig. lymphoma, histiocytic type																									
Malignant lymphoma, mixed type	X	X											X	X			X							X	

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	104	099	106	085	103	097	106	105	106	096	079	106	106	104	101	106	101	106	106	106	103	085	106	096	100	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50*
Sarcoma, NOS																										1
Fibrosarcoma																								X		1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X														X		2
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		49
Spleen	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Malig. lymphoma, lymphocytic type																										1
Thymus	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+		45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	–		45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hepatocellular adenoma											X															2
Hepatocellular carcinoma																X										2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+		50*
Pancreas	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		46
Esophagus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+		47
Stomach	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+		48
Large intestine	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Sarcoma, NOS							X																			1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	–	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+		45
Adenoma, NOS			X															X					X			8
Adrenal	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Pheochromocytoma									X																	1
Thyroid	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+		46
Follicular-cell adenoma																										1
Parathyroid	–	–	+	+	–	+	+	–	+	+	–	+	–	+	–	–	–	–	+	+	+	+	+	–		27
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50*
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leiomyoma	X																									1
Endometrial stromal polyp															X											1
Ovary	+	+	+	+	+	+	–	–	+	+	–	+	–	+	–	+	+	+	–	+	+	–	+	+		41
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		50*
Malig. lymphoma, lymphocytic type				X																						5
Malig. lymphoma, histiocytic type			X																							1
Malignant lymphoma, mixed type	X						X				X			X												10

* Animals necropsied

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	49	50	50	50
ANIMALS EXAMINED HISTOPATH	49	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(50)	(50)	(50)
ABSCESS, CHRONIC				1 (2%)
FIBROSIS				1 (2%)
NECROSIS, NOS				1 (2%)
HYPERPLASIA, NOS	1 (2%)			
HYPERKERATOSIS	1 (2%)			
*SUBCUT TISSUE	(49)	(50)	(50)	(50)
CYST, NOS				1 (2%)
EDEMA, NOS			1 (2%)	
INFLAMMATION, NOS				1 (2%)
INFLAMMATION, CHRONIC SUPPURATIVE	1 (2%)			
ABSCESS, CHRONIC				1 (2%)
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(49)	(50)	(49)	(50)
LYMPHOCYTIC INFLAM INFILTR	1 (2%)			
#LUNG/BRONCHIOLE	(49)	(50)	(49)	(50)
FIBROSIS				1 (2%)
#LUNG	(49)	(50)	(49)	(50)
CONGESTION, NOS	1 (2%)		1 (2%)	
INFLAMMATION, INTERSTITIAL	1 (2%)		2 (4%)	
BRONCHOPNEUMONIA, ACUTE			1 (2%)	
INFLAMMATION, ACUTE NECROTIZING		1 (2%)		
#LUNG/ALVEOLI	(49)	(50)	(49)	(50)
EDEMA, NOS				1 (2%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(49)	(50)	(50)	(49)
HYPERPLASIA, HEMATOPOIETIC				1 (2%)
#SPLEEN	(49)	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)		1 (2%)	
INFLAMMATION, FIBRINOUS		1 (2%)		
FIBROSIS	1 (2%)	2 (4%)		
FIBROSIS, FOCAL		1 (2%)	1 (2%)	
PIGMENTATION, NOS				1 (2%)
HEMOSIDEROSIS				1 (2%)
ATROPHY, NOS				1 (2%)
HISTIOCYTOSIS				1 (2%)
HEMATOPOIESIS	2 (4%)	2 (4%)		1 (2%)
#MANDIBULAR L. NODE	(49)	(50)	(50)	(50)
CYST, NOS			1 (2%)	
ATROPHY, NOS				1 (2%)
PLASMACYTOSIS			1 (2%)	
#BRONCHIAL LYMPH NODE	(49)	(50)	(50)	(50)
DEPLETION, LYMPHOID		1 (2%)		
#MESENTERIC L. NODE	(49)	(50)	(50)	(50)
CYST, NOS			1 (2%)	
ATROPHY, NOS			1 (2%)	
DEPLETION, LYMPHOID			1 (2%)	
ANGIECTASIS		1 (2%)		
#RENAL LYMPH NODE	(49)	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	1 (2%)	
PIGMENTATION, NOS		2 (4%)		
DEPLETION, LYMPHOID			1 (2%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)				
#ILIAC LYMPH NODE	(49)	(50)	(50)	(50)
CYST, NOS				1 (2%)
#AXILLARY LYMPH NODE	(49)	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)			
#INGUINAL LYMPH NODE	(49)	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID				1 (2%)
#LUNG	(49)	(50)	(49)	(50)
LEUKOCYTOSIS, NOS	2 (4%)			
#LIVER	(49)	(50)	(50)	(50)
LEUKOCYTOSIS, NOS	2 (4%)		2 (4%)	
HEMATOPOIESIS	1 (2%)			1 (2%)
#PEYERS PATCH	(49)	(50)	(47)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)		
#THYROID	(49)	(50)	(49)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)			
CIRCULATORY SYSTEM				
#MANDIBULAR L. NODE	(49)	(50)	(50)	(50)
LYMPHANGIECTASIS		3 (6%)		
#MESENTERIC L. NODE	(49)	(50)	(50)	(50)
LYMPHANGIECTASIS				1 (2%)
#RENAL LYMPH NODE	(49)	(50)	(50)	(50)
LYMPHANGIECTASIS		1 (2%)		
#HEART	(49)	(50)	(50)	(50)
INFLAMMATION, INTERSTITIAL	2 (4%)	2 (4%)	4 (8%)	16 (32%)
INFLAMMATION, CHRONIC			2 (4%)	
HEMOSIDEROSIS				1 (2%)
#HEART/ATRIUM	(49)	(50)	(50)	(50)
THROMBOSIS, NOS		1 (2%)		
#MYOCARDIUM	(49)	(50)	(50)	(50)
MINERALIZATION			3 (6%)	1 (2%)
INFLAMMATION, CHRONIC	42 (86%)	43 (86%)	37 (74%)	23 (46%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
DEGENERATION, NOS			1 (2%)	
#ENDOCARDIUM	(49)	(50)	(50)	(50)
INFLAMMATION, FIBRINOUS				1 (2%)
*AORTA	(49)	(50)	(50)	(50)
MINERALIZATION			1 (2%)	
*CORONARY ARTERY	(49)	(50)	(50)	(50)
MINERALIZATION				1 (2%)
*SUP. PANC-DUOD. ARTERY	(49)	(50)	(50)	(50)
HYPERTROPHY, NOS		1 (2%)		
*MESENTERIC ARTERY	(49)	(50)	(50)	(50)
PERIARTERITIS				1 (2%)
*HEPATIC VEIN	(49)	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)	1 (2%)
#LIVER	(49)	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		1 (2%)	
#PANCREAS	(49)	(50)	(50)	(50)
PERIARTERITIS	1 (2%)	1 (2%)	2 (4%)	1 (2%)
*MESENTERY	(49)	(50)	(50)	(50)
PERIARTERITIS		1 (2%)		
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(49)	(50)	(49)	(48)
INFLAMMATION, CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC FOCAL				2 (4%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)				
#LIVER	(49)	(50)	(50)	(50)
DEFORMITY, NOS		1 (2%)		
CYST, NOS		1 (2%)		
CONGESTION, CHRONIC PASSIVE	1 (2%)			
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)			
INFLAMMATION, GRANULOMA FOCAL		4 (8%)		
DEGENERATION, NOS	1 (2%)			
DEGENERATION, CYSTIC	4 (8%)	7 (14%)		1 (2%)
NECROSIS, FOCAL		1 (2%)		
NECROSIS, COAGULATIVE	1 (2%)		2 (4%)	
PIGMENTATION, NOS		1 (2%)		
CYTOPLASMIC VACUOLIZATION	6 (12%)	7 (14%)	5 (10%)	1 (2%)
FOCAL CELLULAR CHANGE	1 (2%)			
CLEAR-CELL CHANGE		1 (2%)		
CYTOLOGIC ALTERATION, NOS	1 (2%)		2 (4%)	
ANGIECTASIS	2 (4%)		1 (2%)	1 (2%)
#LIVER/CENTRILOBULAR	(49)	(50)	(50)	(50)
DEGENERATION, NOS	3 (6%)		1 (2%)	
ATROPHY, NOS				1 (2%)
#BILE DUCT	(49)	(50)	(50)	(50)
HYPERPLASIA, NOS	19 (39%)	21 (42%)	20 (40%)	8 (16%)
#PANCREAS	(49)	(50)	(50)	(50)
HEMORRHAGE				1 (2%)
HEMORRHAGIC CYST			1 (2%)	
INFLAMMATION, INTERSTITIAL				1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
ATROPHY, FOCAL		1 (2%)	1 (2%)	2 (4%)
#PANCREATIC ACINUS	(49)	(50)	(50)	(50)
ATROPHY, NOS	3 (6%)	2 (4%)	8 (16%)	
ATROPHY, FOCAL			1 (2%)	
HYPERPLASIA, NOS				1 (2%)
HYPERPLASIA, FOCAL	1 (2%)			
#STOMACH	(49)	(50)	(50)	(50)
MINERALIZATION			2 (4%)	
#GASTRIC MUCOSA	(49)	(50)	(50)	(50)
MINERALIZATION			1 (2%)	
NECROSIS, FOCAL	1 (2%)			
#GLANDULAR STOMACH	(49)	(50)	(50)	(50)
MINERALIZATION				1 (2%)
INFLAMMATION, NECROTIZING				1 (2%)
FIBROSIS				1 (2%)
#GASTRIC SUBMUCOSA	(49)	(50)	(50)	(50)
EDEMA, NOS	1 (2%)			
#GASTRIC MUSCULARIS	(49)	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL			1 (2%)	
#FORESTOMACH	(49)	(50)	(50)	(50)
EDEMA, NOS	1 (2%)			1 (2%)
ULCER, NOS	1 (2%)			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)			
HYPERPLASIA, NOS				1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)			1 (2%)
HYPERKERATOSIS	1 (2%)		1 (2%)	
#JEJUNUM	(49)	(50)	(47)	(50)
INFLAMMATION, CHRON SUPPURATIVE		1 (2%)		
HYPERPLASIA, EPITHELIAL		1 (2%)		
#JEJUNAL MUCOSA	(49)	(50)	(47)	(50)
ULCER, NOS		1 (2%)		
#COLON	(49)	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)		2 (4%)
INFLAMMATION, CHRONIC FOCAL				1 (2%)
PARASITISM	1 (2%)		2 (4%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
URINARY SYSTEM				
#KIDNEY	(49)	(50)	(50)	(50)
HYDRONEPHROSIS			5 (10%)	5 (10%)
PYELONEPHRITIS, FOCAL		1 (2%)		
INFLAMMATION, INTERSTITIAL			1 (2%)	
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		4 (8%)	6 (12%)
FIBROSIS, DIFFUSE		4 (8%)	5 (10%)	4 (8%)
NEPHROPATHY	46 (94%)	45 (90%)	41 (82%)	42 (84%)
DEGENERATION, NOS			2 (4%)	2 (4%)
NEPHROSIS, NOS	2 (4%)	3 (6%)	5 (10%)	3 (6%)
PIGMENTATION, NOS	1 (2%)	48 (96%)	50 (100%)	45 (90%)
#KIDNEY/CORTEX	(49)	(50)	(50)	(50)
CYST, NOS		3 (6%)	3 (6%)	2 (4%)
MULTIPLE CYSTS			2 (4%)	
#KIDNEY/MEDULLA	(49)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)	
#RENAL PAPILLA	(49)	(50)	(50)	(50)
INFLAMMATION, ACUTE SUPPURATIVE				1 (2%)
NECROSIS, NOS			1 (2%)	
#PERIRENAL TISSUE	(49)	(50)	(50)	(50)
HEMORRHAGE		1 (2%)		
#KIDNEY/TUBULE	(49)	(50)	(50)	(50)
CALCULUS, MICROSCOPIC EXAMINATION				1 (2%)
CAST, NOS		50 (100%)	49 (98%)	46 (92%)
DEGENERATION, NOS		46 (92%)	41 (82%)	32 (64%)
#KIDNEY/PELVIS	(49)	(50)	(50)	(50)
CALCULUS, UNKN GROSS OR MICRO		1 (2%)	1 (2%)	12 (24%)
CALCULUS, MICROSCOPIC EXAMINATION			2 (4%)	18 (36%)
HEMORRHAGE			1 (2%)	
ULCER, NOS				1 (2%)
NECROSIS, NOS				1 (2%)
HYPERPLASIA, EPITHELIAL		2 (4%)	8 (16%)	11 (22%)
*URETER	(49)	(50)	(50)	(50)
CALCULUS, UNKN GROSS OR MICRO			1 (2%)	
CALCULUS, GROSS OBSERVATION ONLY				1 (2%)
HYPERPLASIA, EPITHELIAL				1 (2%)
#URINARY BLADDER	(49)	(50)	(50)	(49)
CALCULUS, GROSS OBSERVATION ONLY			16 (32%)	21 (43%)
CALCULUS, MICROSCOPIC EXAMINATION			1 (2%)	15 (31%)
CYST, NOS			1 (2%)	
CONGESTION, NOS			1 (2%)	
HEMORRHAGE		1 (2%)	2 (4%)	3 (6%)
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, ACUTE			1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE				1 (2%)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	4 (8%)	2 (4%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
INFLAMMATION, CHRONIC SUPPURATIVE			1 (2%)	
DEGENERATION, MUCOID				1 (2%)
PIGMENTATION, NOS		36 (72%)	14 (28%)	11 (22%)
HYPERPLASIA, EPITHELIAL		2 (4%)	28 (56%)	42 (86%)
HYPERPLASIA, PAPILLARY				1 (2%)
HYPERKERATOSIS				1 (2%)
METAPLASIA, SQUAMOUS			10 (20%)	12 (24%)
#U. BLADDER/SUBMUCOSA	(49)	(50)	(50)	(49)
HEMORRHAGE	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
*URETHRA	(49)	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL				1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#PITUITARY	(49)	(48)	(48)	(48)
CYST, NOS	2 (4%)	1 (2%)	2 (4%)	1 (2%)
CRYSTALS, NOS		1 (2%)		
PIGMENTATION, NOS				1 (2%)
HYPERPLASIA, FOCAL	2 (4%)	6 (13%)	1 (2%)	1 (2%)
ANGIECTASIS	15 (31%)	8 (17%)	7 (15%)	2 (4%)
#ADRENAL	(49)	(50)	(50)	(50)
ACCESSORY STRUCTURE			1 (2%)	
#ADRENAL CORTEX	(49)	(50)	(50)	(50)
ACCESSORY STRUCTURE	1 (2%)		1 (2%)	
DEGENERATION, NOS	1 (2%)			
DEGENERATION, LIPOID		7 (14%)	5 (10%)	1 (2%)
CYTOPLSMIC VACUOLIZATION	4 (8%)	3 (6%)	5 (10%)	7 (14%)
CYTOLOGIC ALTERATION, NOS	1 (2%)	1 (2%)		
HYPERPLASIA, FOCAL	2 (4%)	3 (6%)	5 (10%)	
#ADRENAL MEDULLA	(49)	(50)	(50)	(50)
MINERALIZATION		1 (2%)		
HYPERPLASIA, FOCAL	10 (20%)	8 (16%)	4 (8%)	1 (2%)
ANGIECTASIS			2 (4%)	
#THYROID	(49)	(50)	(49)	(50)
EMBRYONAL DUCT CYST	1 (2%)			1 (2%)
THYROGLOSSAL DUCT CYST	1 (2%)		1 (2%)	
CYSTIC FOLLICLES	1 (2%)	1 (2%)		2 (4%)
FOLLICULAR CYST, NOS				1 (2%)
DEGENERATION, CYSTIC	1 (2%)			
PIGMENTATION, NOS		1 (2%)	1 (2%)	
HYPERPLASIA, CYSTIC	3 (6%)		1 (2%)	1 (2%)
HYPERPLASIA, C-CELL	4 (8%)	7 (14%)	2 (4%)	4 (8%)
#THYROID FOLLICLE	(49)	(50)	(49)	(50)
PIGMENTATION, NOS		46 (92%)	41 (84%)	42 (84%)
#PARATHYROID	(46)	(48)	(49)	(49)
HYPERPLASIA, NOS		1 (2%)	7 (14%)	7 (14%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(50)	(50)	(50)
CYSTIC DUCTS	10 (20%)	4 (8%)	5 (10%)	2 (4%)
PIGMENTATION, NOS	1 (2%)			
HYPERPLASIA, FOCAL				1 (2%)
HYPERPLASIA, CYSTIC				2 (4%)
ADENOSIS	1 (2%)	3 (6%)	2 (4%)	1 (2%)
*MAMMARY LOBULE	(49)	(50)	(50)	(50)
HYPERPLASIA, NOS	1 (2%)		2 (4%)	
*BULBOURETHRAL GLAND	(49)	(50)	(50)	(50)
DILATATION, NOS		1 (2%)		
*PREPUTIAL GLAND	(49)	(50)	(50)	(50)
CYST, NOS			1 (2%)	
CYSTIC DUCTS	2 (4%)	2 (4%)	3 (6%)	
ULCER, NOS				1 (2%)
INFLAMMATION, SUPPURATIVE	3 (6%)			2 (4%)
INFLAMMATION, ACUTE			1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)		1 (2%)	
HYPERPLASIA, CYSTIC			1 (2%)	
#PROSTATE	(49)	(50)	(50)	(50)
CYSTIC DUCTS				1 (2%)
HEMORRHAGE			1 (2%)	
INFLAMMATION, SUPPURATIVE	10 (20%)	7 (14%)	10 (20%)	7 (14%)
INFLAMMATION, ACUTE			1 (2%)	
ABSCESS, NOS			1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		1 (2%)
INFLAMMATION, CHRONIC	1 (2%)	2 (4%)		5 (10%)
INFLAMMATION, CHRONIC SUPPURA	3 (6%)	1 (2%)		3 (6%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM				
#PROSTATE (Continued)	(49)	(50)	(50)	(50)
FIBROSIS				1 (2%)
PIGMENTATION, NOS		1 (2%)		
HYPERPLASIA, EPITHELIAL	3 (6%)	1 (2%)	12 (24%)	5 (10%)
HYPERPLASIA, CYSTIC				1 (2%)
*SEMINAL VESICLE	(49)	(50)	(50)	(50)
ATROPHY, NOS	1 (2%)		1 (2%)	
HYPERPLASIA, NOS				1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)			
*COAGULATING GLAND	(49)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE				1 (2%)
#TESTIS	(49)	(50)	(50)	(50)
ATROPHY, NOS	9 (18%)	14 (28%)	6 (12%)	3 (6%)
HYPERPLASIA, INTERSTITIAL CELL	2 (4%)	1 (2%)	2 (4%)	5 (10%)
*SPERMATIC CORD	(49)	(50)	(50)	(50)
STEATITIS	1 (2%)	1 (2%)		1 (2%)
INFLAMMATION, HEMORRHAGIC				1 (2%)
PIGMENTATION, NOS				1 (2%)
NERVOUS SYSTEM				
#BRAIN	(49)	(50)	(50)	(50)
HEMORRHAGE	1 (2%)	1 (2%)		1 (2%)
#CEREBELLUM	(49)	(50)	(50)	(50)
HEMORRHAGE			2 (4%)	
*SPINAL CORD	(49)	(50)	(50)	(50)
HEMORRHAGE		1 (2%)		
SPECIAL SENSE ORGANS				
*EYE	(49)	(50)	(50)	(50)
HEMORRHAGE	1 (2%)	1 (2%)		
INFLAMMATION, SUPPURATIVE		1 (2%)		
FIBROSIS			1 (2%)	
RETINOPATHY	20 (41%)			6 (12%)
CATARACT	20 (41%)			6 (12%)
PHTHISIS BULBI			1 (2%)	
*EYE/CORNEA	(49)	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)	
*EYE/RETINA	(49)	(50)	(50)	(50)
ATROPHY, NOS	1 (2%)			
*MIDDLE EAR	(49)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)	
MUSCULOSKELETAL SYSTEM				
*BONE	(49)	(50)	(50)	(50)
FIBROUS OSTEODYSTROPHY		1 (2%)	5 (10%)	2 (4%)
*SKULL	(49)	(50)	(50)	(50)
FIBROUS OSTEODYSTROPHY				1 (2%)
HYPEROSTOSIS			2 (4%)	
*FEMUR	(49)	(50)	(50)	(50)
OSTEOPOROSIS				1 (2%)
FIBROUS OSTEODYSTROPHY			1 (2%)	1 (2%)
*CREMASTER MUSCLE	(49)	(50)	(50)	(50)
STEATITIS	1 (2%)			

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
BODY CAVITIES				
*MESENTERY	(49)	(50)	(50)	(50)
EDEMA, NOS		1 (2%)		
HEMORRHAGE			1 (2%)	
STEATITIS			1 (2%)	
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
MINERALIZATION				1 (2%)
PIGMENTATION, NOS				1 (2%)
SPECIAL MORPHOLOGY SUMMARY				
AUTOLYSIS/NO NECROPSY	1			

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

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	49	50	50	50
ANIMALS EXAMINED HISTOPATH	49	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(49)	(50)	(50)	(50)
CYST, NOS				1 (2%)
ULCER, NOS		1 (2%)		
INFLAMMATION, CHRONIC	2 (4%)	1 (2%)		
HYPERKERATOSIS	3 (6%)	5 (10%)	1 (2%)	
*SUBCUT TISSUE	(49)	(50)	(50)	(50)
INFLAMMATION, CHRONIC	2 (4%)			
RESPIRATORY SYSTEM				
#LUNG	(49)	(50)	(49)	(50)
CONGESTION, NOS		1 (2%)		
INFLAMMATION, INTERSTITIAL		1 (2%)		
INFLAMMATION, SUPPURATIVE			1 (2%)	1 (2%)
ABSCESS, NOS			1 (2%)	
HYPERPLASIA, ADENOMATOUS		1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)		
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(49)	(50)	(50)	(50)
DEPLETION, LYMPHOID				1 (2%)
#BONE MARROW	(49)	(50)	(50)	(50)
OSTEOSCLEROSIS				1 (2%)
HYPERPLASIA, RETICULUM CELL			1 (2%)	
#SPLEEN	(49)	(50)	(50)	(49)
CONGESTION, NOS		1 (2%)		
NECROSIS, FOCAL	1 (2%)			
HEMOSIDEROSIS	1 (2%)	1 (2%)	1 (2%)	6 (12%)
HYPERPLASIA, LYMPHOID				1 (2%)
HEMATOPOIESIS	1 (2%)	1 (2%)	3 (6%)	2 (4%)
#MANDIBULAR L. NODE	(49)	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID		2 (4%)	1 (2%)	1 (2%)
#MESENTERIC L. NODE	(49)	(50)	(50)	(50)
DEPLETION, LYMPHOID			1 (2%)	
ANGIECTASIS		1 (2%)	1 (2%)	
#RENAL LYMPH NODE	(49)	(50)	(50)	(50)
CYST, NOS				1 (2%)
#LIVER	(49)	(50)	(50)	(50)
LEUKOCYTOSIS, NOS		1 (2%)		
HEMATOPOIESIS			2 (4%)	
CIRCULATORY SYSTEM				
#LYMPH NODE	(49)	(50)	(50)	(50)
LYMPHANGIECTASIS				1 (2%)
#MANDIBULAR L. NODE	(49)	(50)	(50)	(50)
LYMPHANGIECTASIS	1 (2%)			
#MEDIASTINAL L. NODE	(49)	(50)	(50)	(50)
LYMPHANGIECTASIS		1 (2%)		
#MESENTERIC L. NODE	(49)	(50)	(50)	(50)
LYMPHANGIECTASIS				1 (2%)
#ILIAC LYMPH NODE	(49)	(50)	(50)	(50)
LYMPHANGIECTASIS				1 (2%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)				
#HEART	(49)	(50)	(50)	(50)
MINERALIZATION			2 (4%)	
INFLAMMATION, INTERSTITIAL	2 (4%)	3 (6%)	1 (2%)	1 (2%)
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, ACUTE FOCAL		1 (2%)		
INFLAMMATION, CHRONIC			1 (2%)	
FIBROSIS, FOCAL			1 (2%)	
PERIARTERITIS			1 (2%)	
#MYOCARDIUM	(49)	(50)	(50)	(50)
THROMBUS, MURAL				1 (2%)
INFLAMMATION, CHRONIC	32 (65%)	28 (56%)	36 (72%)	31 (62%)
*CORONARY ARTERY	(49)	(50)	(50)	(50)
PERIARTERITIS				1 (2%)
#PANCREAS	(49)	(50)	(50)	(49)
PERIARTERITIS			1 (2%)	
#STOMACH	(49)	(50)	(50)	(49)
PERIARTERITIS			1 (2%)	
*MESENTERY	(49)	(50)	(50)	(50)
PERIARTERITIS			1 (2%)	
#ADRENAL CORTEX	(48)	(50)	(50)	(50)
THROMBOSIS, NOS		1 (2%)		
DIGESTIVE SYSTEM				
#LIVER	(49)	(50)	(50)	(50)
DEFORMITY, NOS	5 (10%)	1 (2%)	2 (4%)	
CONGESTION, NOS		1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	3 (6%)	1 (2%)	1 (2%)
INFLAMMATION, FIBRINOUS		1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)			1 (2%)
INFLAMMA, GRANULOMATOUS FOCAL	11 (22%)	13 (26%)	10 (20%)	1 (2%)
NECROSIS, FOCAL			1 (2%)	
NECROSIS, COAGULATIVE	2 (4%)			1 (2%)
CYTOPLASMIC VACUOLIZATION	4 (8%)	2 (4%)	5 (10%)	2 (4%)
BASOPHILIC CYTO CHANGE	2 (4%)	3 (6%)		
FOCAL CELLULAR CHANGE	1 (2%)			
CYTOLOGIC ALTERATION, NOS	2 (4%)	3 (6%)	2 (4%)	
ANGIECTASIS		1 (2%)	1 (2%)	
#LIVER/HEPATOCYTES	(49)	(50)	(50)	(50)
CYTOPLASMIC VACUOLIZATION	2 (4%)	1 (2%)		2 (4%)
#BILE DUCT	(49)	(50)	(50)	(50)
HYPERPLASIA, NOS	7 (14%)	2 (4%)	2 (4%)	2 (4%)
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)		1 (2%)
#PANCREAS	(49)	(50)	(50)	(49)
LYMPHOCYTIC INFLAMM INFILTR		1 (2%)		
ATROPHY, FOCAL		2 (4%)		
#PANCREATIC ACINUS	(49)	(50)	(50)	(49)
ATROPHY, NOS			2 (4%)	2 (4%)
ATROPHY, FOCAL		1 (2%)	1 (2%)	
#GASTRIC MUCOSA	(49)	(50)	(50)	(49)
MINERALIZATION				2 (4%)
#GLANDULAR STOMACH	(49)	(50)	(50)	(49)
CYST, NOS		1 (2%)		
#GASTRIC SUBMUCOSA	(49)	(50)	(50)	(49)
EDEMA, NOS	2 (4%)	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)			

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)				
#FORESTOMACH	(49)	(50)	(50)	(49)
EDEMA, NOS	2 (4%)			
ULCER, NOS	3 (6%)	1 (2%)		2 (4%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)			3 (6%)
NECROSIS, FOCAL				1 (2%)
HYPERPLASIA, EPITHELIAL				1 (2%)
HYPERPLASIA, FOCAL		1 (2%)		
URINARY SYSTEM				
#KIDNEY	(49)	(50)	(50)	(50)
MINERALIZATION	1 (2%)			
HYDRONEPHROSIS				15 (30%)
PYELONEPHRITIS, NOS			1 (2%)	1 (2%)
PYELONEPHRITIS, FOCAL	1 (2%)	2 (4%)		
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)		
INFLAMMATION, INTERSTITIAL				1 (2%)
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, ACUTE FOCAL				1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE				1 (2%)
INFLAMMATION, CHRONIC			2 (4%)	2 (4%)
INFLAMMATION, CHRONIC FOCAL				2 (4%)
INFLAMMATION, CHRONIC DIFFUSE			1 (2%)	
FIBROSIS				1 (2%)
SCAR			2 (4%)	
FIBROSIS, DIFFUSE				6 (12%)
NEPHROPATHY	25 (51%)	22 (44%)	33 (66%)	30 (60%)
DEGENERATION, NOS			4 (8%)	4 (8%)
NEPHROSIS, NOS	2 (4%)	3 (6%)	2 (4%)	9 (18%)
INFARCT, HEALED			1 (2%)	
PIGMENTATION, NOS		47 (94%)	49 (98%)	48 (96%)
ATROPHY, NOS			1 (2%)	4 (8%)
#KIDNEY/CORTEX	(49)	(50)	(50)	(50)
CYST, NOS	1 (2%)			
ABSCESS, CHRONIC			1 (2%)	
SCAR			1 (2%)	
#RENAL PAPILLA	(49)	(50)	(50)	(50)
NECROSIS, NOS				1 (2%)
NECROSIS, COAGULATIVE			1 (2%)	
#KIDNEY/TUBULE	(49)	(50)	(50)	(50)
CALCULUS, UNKN GROSS OR MICRO				1 (2%)
CALCULUS, MICROSCOPIC EXAMIN	1 (2%)			
CAST, NOS		44 (88%)	47 (94%)	46 (92%)
CYST, NOS				1 (2%)
DEGENERATION, NOS		19 (38%)	37 (74%)	26 (52%)
PIGMENTATION, NOS	1 (2%)			
#KIDNEY/PELVIS	(49)	(50)	(50)	(50)
CALCULUS, UNKN GROSS OR MICRO		3 (6%)		1 (2%)
CALCULUS, GROSS OBSERVATION ONLY				1 (2%)
CALCULUS, MICROSCOPIC EXAMIN			1 (2%)	15 (30%)
MINERALIZATION	1 (2%)			
HYDRONEPHROSIS			1 (2%)	
HEMORRHAGE				1 (2%)
ULCER, NOS				1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)	4 (8%)
INFLAMMATION, CHRONIC				2 (4%)
NECROSIS, NOS			1 (2%)	3 (6%)
HYPERPLASIA, EPITHELIAL		2 (4%)	12 (24%)	15 (30%)
METAPLASIA, SQUAMOUS				1 (2%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
URINARY SYSTEM (Continued)				
*URETER	(49)	(50)	(50)	(50)
CALCULUS, UNKN GROSS OR MICRO				1 (2%)
CALCULUS,GROSS OBSERVATION ONLY				1 (2%)
CALCULUS, MICROSCOPIC EXAMINATION				1 (2%)
DILATATION, NOS			1 (2%)	3 (6%)
ULCER, NOS				1 (2%)
HYPERPLASIA, NOS				1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	1 (2%)	3 (6%)
#URINARY BLADDER	(48)	(50)	(50)	(48)
CALCULUS, GROSS OBSERVATION ONLY			12 (24%)	37 (77%)
CALCULUS, MICROSCOPIC EXAMINATION			1 (2%)	7 (15%)
HEMORRHAGE	1 (2%)		1 (2%)	
ULCER, NOS				1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)			1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	3 (6%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)	
INFLAMMATION, CHRONIC SUPPURATIVE				2 (4%)
FIBROSIS				3 (6%)
DEGENERATION, MUCOID			1 (2%)	
PIGMENTATION, NOS		44 (88%)	9 (18%)	13 (27%)
HYPERPLASIA, EPITHELIAL		4 (8%)	42 (84%)	40 (83%)
HYPERPLASIA, PAPILLARY			2 (4%)	1 (2%)
HYPERKERATOSIS				1 (2%)
METAPLASIA, SQUAMOUS			13 (26%)	35 (73%)
#U. BLADDER/MUCOSA	(48)	(50)	(50)	(48)
HEMORRHAGE				1 (2%)
ULCER, NOS				1 (2%)
METAPLASIA, SQUAMOUS				1 (2%)
#U. BLADDER/SUBMUCOSA	(48)	(50)	(50)	(48)
INFLAMMATION, CHRONIC			1 (2%)	
#U. BLADDER/MUSCULARIS	(48)	(50)	(50)	(48)
METAMORPHOSIS, FATTY			1 (2%)	
LIPOMATOSIS			9 (18%)	1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(49)	(49)	(50)	(49)
CYST, NOS	8 (16%)	7 (14%)	3 (6%)	6 (12%)
MULTIPLE CYSTS	2 (4%)	11 (22%)		2 (4%)
HEMORRHAGIC CYST	2 (4%)			
PIGMENTATION, NOS				1 (2%)
HYPERPLASIA, NOS				1 (2%)
HYPERPLASIA, FOCAL	4 (8%)	3 (6%)		1 (2%)
HYPERPLASIA, CYSTIC	1 (2%)			
ANGIECTASIS	15 (31%)	25 (51%)	18 (36%)	15 (31%)
#ADRENAL	(48)	(50)	(50)	(50)
DEGENERATION, LIPOID				1 (2%)
ANGIECTASIS	2 (4%)			
#ADRENAL CORTEX	(48)	(50)	(50)	(50)
ACCESSORY STRUCTURE	1 (2%)			
CYST, NOS	1 (2%)	1 (2%)		
HEMORRHAGE				1 (2%)
HEMORRHAGIC CYST		1 (2%)		
DEGENERATION, NOS				1 (2%)
DEGENERATION, LIPOID	2 (4%)	9 (18%)	1 (2%)	4 (8%)
NECROSIS, NOS				1 (2%)
NECROSIS, FOCAL		1 (2%)		1 (2%)
CYTOPLASMIC VACUOLIZATION	5 (10%)			4 (8%)
CYTOLOGIC ALTERATION, NOS		1 (2%)	1 (2%)	
HYPERPLASIA, NODULAR	1 (2%)			
HYPERPLASIA, FOCAL	1 (2%)	2 (4%)		1 (2%)
ANGIECTASIS		2 (4%)		

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)				
#ADRENAL MEDULLA	(48)	(50)	(50)	(50)
PIGMENTATION, NOS				1 (2%)
HYPERPLASIA, NOS				1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)	4 (8%)	3 (6%)	2 (4%)
#THYROID	(49)	(50)	(50)	(50)
EMBRYONAL DUCT CYST		1 (2%)	1 (2%)	
CYSTIC FOLLICLES				1 (2%)
HYPERPLASIA, C-CELL	8 (16%)	7 (14%)	10 (20%)	4 (8%)
#THYROID FOLLICLE	(49)	(50)	(50)	(50)
PIGMENTATION, NOS		21 (42%)	31 (62%)	39 (78%)
METAPLASIA, SQUAMOUS		1 (2%)		
#PARATHYROID	(47)	(48)	(47)	(48)
HYPERPLASIA, NOS			1 (2%)	4 (8%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(49)	(50)	(50)	(50)
CYST, NOS	1 (2%)	1 (2%)		2 (4%)
CYSTIC DUCTS	23 (47%)	21 (42%)	20 (40%)	17 (34%)
HYPERPLASIA, CYSTIC	5 (10%)	4 (8%)	2 (4%)	
ADENOSIS	1 (2%)	2 (4%)	2 (4%)	
*MAMMARY LOBULE	(49)	(50)	(50)	(50)
HYPERPLASIA, NOS	5 (10%)	1 (2%)	4 (8%)	11 (22%)
*PREPUTIAL GLAND	(49)	(50)	(50)	(50)
ABSCESS, CHRONIC			1 (2%)	
*CLITORAL GLAND	(49)	(50)	(50)	(50)
CYSTIC DUCTS	1 (2%)		4 (8%)	2 (4%)
INFLAMMATION, SUPPURATIVE	1 (2%)		1 (2%)	
INFLAMMATION, CHRONIC SUP	1 (2%)			
HYPERPLASIA, NOS				1 (2%)
#UTERUS	(49)	(50)	(50)	(50)
HYDROMETRA		2 (4%)	1 (2%)	
HEMORRHAGE	1 (2%)			
HEMORRHAGE, CHRONIC			1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)		
POLYP, INFLAMMATORY		1 (2%)		
#CERVIX UTERI	(49)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE		2 (4%)		
#UTERUS/ENDOMETRIUM	(49)	(50)	(50)	(50)
CYST, NOS	2 (4%)	6 (12%)	3 (6%)	2 (4%)
HEMORRHAGE		1 (2%)		
INFLAMMATION, SUPPURATIVE			1 (2%)	
HYPERPLASIA, CYSTIC	4 (8%)	2 (4%)	5 (10%)	3 (6%)
HYPERPLASIA, ADENOMATOUS		1 (2%)		
#OVARY	(49)	(50)	(50)	(50)
CYST, NOS	1 (2%)			
CYSTIC FOLLICLES		5 (10%)	2 (4%)	1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)		
NERVOUS SYSTEM				
*PERIPHERAL NERVE	(49)	(50)	(50)	(50)
HEMORRHAGE		1 (2%)		
#BRAIN	(49)	(50)	(50)	(50)
HEMORRHAGE		1 (2%)		
HEMORRHAGIC CYST		1 (2%)		
#OLFACTORY BULB	(49)	(50)	(50)	(50)
HEMORRHAGE	1 (2%)			
*SPINAL CORD	(49)	(50)	(50)	(50)
HEMORRHAGE		1 (2%)		

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
SPECIAL SENSE ORGANS				
*EYE	(49)	(50)	(50)	(50)
RETINOPATHY	2 (4%)	1 (2%)	21 (42%)	1 (2%)
CATARACT	1 (2%)	1 (2%)	19 (38%)	1 (2%)
*VITREOUS BODY	(49)	(50)	(50)	(50)
HEMORRHAGE			1 (2%)	
*EYE/CORNEA	(49)	(50)	(50)	(50)
ULCER, NOS				1 (2%)
*MIDDLE EAR	(49)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)	
MUSCULOSKELETAL SYSTEM				
*BONE	(49)	(50)	(50)	(50)
FIBROUS OSTEODYSTROPHY			1 (2%)	1 (2%)
*SKULL	(49)	(50)	(50)	(50)
HYPEROSTOSIS	6 (12%)	10 (20%)	3 (6%)	4 (8%)
BODY CAVITIES				
*MESENTERY	(49)	(50)	(50)	(50)
STEATITIS	2 (4%)	8 (16%)	1 (2%)	3 (6%)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)		
NECROSIS, FAT				1 (2%)
PIGMENTATION, NOS				2 (4%)
ALL OTHER SYSTEMS				
TAIL				
INFLAMMATION, SUPPURATIVE			1	
HYPERKERATOSIS	1			
OMENTUM				
STEATITIS			1	
PIGMENTATION, NOS			1	
BROAD LIGAMENT				
STEATITIS	4	3	1	1
PIGMENTATION, NOS				1
SPECIAL MORPHOLOGY SUMMARY				
AUTOLYSIS/NO NECROPSY	1			

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
FOREIGN BODY, NOS				1 (2%)
CYST, NOS	1 (2%)			
HEMORRHAGE		1 (2%)		
ULCER, NOS	1 (2%)			
INFLAMMATION, ACUTE SUPPURATIVE	2 (4%)		3 (6%)	
INFLAMMATION, ACUTE/CHRONIC	2 (4%)	13 (26%)	14 (28%)	13 (26%)
INFLAMMATION, CHRONIC	8 (16%)	3 (6%)	3 (6%)	2 (4%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		2 (4%)
EROSION			1 (2%)	
FIBROSIS	7 (14%)	10 (20%)	†17 (34%)	†9 (18%)
FIBROSIS, FOCAL	1 (2%)	1 (2%)		
ALOPECIA	†1 (62%)	†34 (68%)	†40 (80%)	†35 (70%)
HYPERPLASIA, NOS		6 (12%)		1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
CYST, NOS				1 (2%)
EDEMA, NOS			1 (2%)	
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	
INFLAMMATION, GRANULOMATOUS			1 (2%)	
INFLAMMATION, GRANULOMATOUS FOCAL			1 (2%)	
INFECTION, FUNGAL			2 (4%)	
RESPIRATORY SYSTEM				
#LUNG	(50)	(49)	(50)	(50)
CONGESTION, NOS	2 (4%)			2 (4%)
LYMPHOCYTIC INFLAMMATORY INFILTR	14 (28%)	4 (8%)	13 (26%)	11 (22%)
PNEUMONIA, INTERSTITIAL CHRONIC	1 (2%)			1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)			
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)	1 (2%)	1 (2%)	
HISTIOCYTOSIS	1 (2%)	2 (4%)		1 (2%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(46)	(50)	(49)	(49)
HYPERPLASIA, NOS				1 (2%)
#SPLEEN	(50)	(49)	(50)	(50)
NECROSIS, FOCAL	1 (2%)			
HEMOSIDEROSIS				1 (2%)
ATROPHY, NOS		1 (2%)	1 (2%)	2 (4%)
ANGIECTASIS	1 (2%)			
HYPERPLASIA, LYMPHOID			2 (4%)	
HEMATOPOIESIS	12 (24%)	14 (29%)	11 (22%)	7 (14%)
#MANDIBULAR L. NODE	(50)	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)			
#LUMBAR LYMPH NODE	(50)	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)			

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)				
#MESENTERIC L. NODE	(50)	(50)	(50)	(50)
CONGESTION, NOS			1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE			1 (2%)	
CHOLESTEROL DEPOSIT	1 (2%)			
HYPERPLASIA, NOS	1 (2%)			
ANGIECTASIS	9 (18%)	10 (20%)	9 (18%)	6 (12%)
HYPERPLASIA, LYMPHOID	2 (4%)	1 (2%)	2 (4%)	1 (2%)
HEMATOPOIESIS	1 (2%)			
#RENAL LYMPH NODE	(50)	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID				1 (2%)
#ILIAC LYMPH NODE	(50)	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID				2 (4%)
#AXILLARY LYMPH NODE	(50)	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)		
#INGUINAL LYMPH NODE	(50)	(50)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)		
ANGIECTASIS		1 (2%)		
HYPERPLASIA, LYMPHOID	2 (4%)	4 (8%)	5 (10%)	2 (4%)
#LIVER	(50)	(50)	(50)	(50)
HEMATOPOIESIS		1 (2%)		1 (2%)
#THYMUS	(47)	(48)	(46)	(45)
CYST, NOS			1 (2%)	
CIRCULATORY SYSTEM				
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
LYMPHANGIECTASIS			1 (2%)	
#MESENTERIC L. NODE	(50)	(50)	(50)	(50)
LYMPHANGIECTASIS	1 (2%)		1 (2%)	
#ILIAC LYMPH NODE	(50)	(50)	(50)	(50)
LYMPHANGIECTASIS				1 (2%)
#INGUINAL LYMPH NODE	(50)	(50)	(50)	(50)
LYMPHANGIECTASIS			1 (2%)	1 (2%)
#HEART	(50)	(50)	(49)	(50)
ENDOCARDITIS, BACTERIAL		1 (2%)		
FIBROSIS		1 (2%)		
DEGENERATION, NOS				1 (2%)
*PULMONARY ARTERY	(50)	(50)	(50)	(50)
THROMBUS, ORGANIZED		1 (2%)		
#PANCREAS	(49)	(49)	(50)	(49)
PERIARTERITIS			1 (2%)	
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(50)	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	3 (6%)	2 (4%)	
#LIVER	(50)	(50)	(50)	(50)
CYST, NOS	1 (2%)			1 (2%)
HEMORRHAGE		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)	2 (4%)		
FIBROSIS, FOCAL				2 (4%)
NECROSIS, NOS	1 (2%)		2 (4%)	1 (2%)
NECROSIS, FOCAL	4 (8%)	2 (4%)	4 (8%)	
NECROSIS, COAGULATIVE		1 (2%)		
PIGMENTATION, NOS				4 (8%)
CYTOPLASMIC VACUOLIZATION		2 (4%)		
CYTOLOGIC ALTERATION, NOS	2 (4%)			4 (8%)
ATROPHY, NOS		1 (2%)		
ANGIECTASIS				1 (2%)
HISTIOCYTOSIS				1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)				
*GALLBLADDER	(50)	(50)	(50)	(50)
RETENTION OF CONTENT				1 (2%)
HEMORRHAGE			1 (2%)	
PIGMENTATION, NOS				1 (2%)
#BILE DUCT	(50)	(50)	(50)	(50)
HYPERPLASIA, FOCAL				1 (2%)
#PANCREAS	(49)	(49)	(50)	(49)
DILATATION/DUCTS	1 (2%)			
HEMORRHAGE			1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)	
NECROSIS, FOCAL			1 (2%)	
ATROPHY, FOCAL	1 (2%)			1 (2%)
#STOMACH	(50)	(49)	(50)	(50)
ULCER, ACUTE				1 (2%)
#GASTRIC MUCOSA	(50)	(49)	(50)	(50)
INFLAMMATION, ACUTE FOCAL			1 (2%)	
PIGMENTATION, NOS				1 (2%)
HYPERPLASIA, EPITHELIAL				1 (2%)
#GLANDULAR STOMACH	(50)	(49)	(50)	(50)
CYST, NOS	3 (6%)	7 (14%)	12 (24%)	6 (12%)
#FORESTOMACH	(50)	(49)	(50)	(50)
FOREIGN BODY, NOS				1 (2%)
CYST, NOS	1 (2%)			
ULCER, NOS			1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE				1 (2%)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)	1 (2%)
HYPERKERATOSIS			1 (2%)	1 (2%)
#DUODENUM	(48)	(48)	(49)	(50)
PIGMENTATION, NOS			1 (2%)	
HYPERPLASIA, ADENOMATOUS			1 (2%)	
*RECTUM	(50)	(50)	(50)	(50)
PROLAPSE		1 (2%)		
URINARY SYSTEM				
#KIDNEY	(50)	(50)	(50)	(50)
CALCULUS, GROSS OBSERVATION ONLY			1 (2%)	
CAST, NOS	2 (4%)	1 (2%)		1 (2%)
HYDRONEPHROSIS	1 (2%)	1 (2%)	4 (8%)	4 (8%)
CYST, NOS	2 (4%)	1 (2%)		
LYMPHOCYTIC INFLAM INFILTR	32 (64%)	36 (72%)	39 (78%)	28 (56%)
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, CHRONIC			1 (2%)	
FIBROSIS	1 (2%)			1 (2%)
SCAR		2 (4%)		1 (2%)
NEPHROPATHY	1 (2%)			
PIGMENTATION, NOS		45 (90%)	47 (94%)	32 (64%)
METAPLASIA, OSSEOUS				1 (2%)
#KIDNEY/CORTEX	(50)	(50)	(50)	(50)
CYST, NOS				1 (2%)
#RENAL PAPILLA	(50)	(50)	(50)	(50)
NECROSIS, NOS				1 (2%)
#KIDNEY/TUBULE	(50)	(50)	(50)	(50)
CAST, NOS		46 (92%)	48 (96%)	49 (98%)
DEGENERATION, NOS		23 (46%)	25 (50%)	35 (70%)
#KIDNEY/PELVIS	(50)	(50)	(50)	(50)
CALCULUS, MICROSCOPIC EXAMINATION				4 (8%)
DILATATION, NOS				1 (2%)
NECROSIS, NOS				1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	2 (4%)	2 (4%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
URINARY SYSTEM (Continued)				
*URETER	(50)	(50)	(50)	(50)
CALCULUS, MICROSCOPIC EXAMIN				1 (2%)
DILATATION, NOS		1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
FIBROSIS, FOCAL				1 (2%)
HYPERPLASIA, EPITHELIAL				2 (4%)
#URINARY BLADDER	(50)	(49)	(50)	(50)
CALCULUS, GROSS OBSERVATION ONLY			16 (32%)	39 (78%)
CALCULUS, MICROSCOPIC EXAMINATION			2 (4%)	10 (20%)
CONGESTION, NOS			1 (2%)	
HEMORRHAGE	1 (2%)			
LYMPHOCYTIC INFLAMMATORY INFILTR	6 (12%)	21 (43%)	30 (60%)	20 (40%)
INFLAMMATION, ACUTE		1 (2%)		1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE	2 (4%)			1 (2%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	10 (20%)
INFLAMMATION, CHRONIC		3 (6%)	10 (20%)	24 (48%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
FIBROSIS			7 (14%)	21 (42%)
FIBROSIS, FOCAL				1 (2%)
PIGMENTATION, NOS		27 (55%)	11 (22%)	
HYPERPLASIA, EPITHELIAL		1 (2%)	11 (22%)	42 (84%)
HYPERPLASIA, CYSTIC				1 (2%)
*URETHRA	(50)	(50)	(50)	(50)
DILATATION, NOS				1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)		2 (4%)
INFLAMMATION, CHRONIC			1 (2%)	
HYPERPLASIA, EPITHELIAL				2 (4%)
ENDOCRINE SYSTEM				
#PITUITARY	(44)	(44)	(47)	(50)
CYST, NOS		3 (7%)		
#ADRENAL CORTEX	(49)	(48)	(49)	(50)
CYST, NOS			1 (2%)	
HYPERTROPHY, FOCAL			1 (2%)	
HYPERPLASIA, FOCAL	2 (4%)			
#ADRENAL MEDULLA	(49)	(48)	(49)	(50)
HYPERPLASIA, FOCAL	1 (2%)			
#THYROID	(49)	(50)	(49)	(49)
CYSTIC FOLLICLES	3 (6%)	2 (4%)	2 (4%)	5 (10%)
DEGENERATION, CYSTIC	4 (8%)	14 (28%)	16 (33%)	35 (71%)
PIGMENTATION, NOS		45 (90%)	45 (92%)	31 (63%)
HYPERPLASIA, FOLLICULAR-CELL	3 (6%)	11 (22%)	16 (33%)	16 (33%)
#THYROID FOLLICLE	(49)	(50)	(49)	(49)
PIGMENTATION, NOS		1 (2%)		
#PANCREATIC ISLETS	(49)	(49)	(50)	(49)
HYPERPLASIA, NOS	4 (8%)			2 (4%)
REPRODUCTIVE SYSTEM				
*BULBOURETHRAL GLAND	(50)	(50)	(50)	(50)
HYPERPLASIA, CYSTIC			1 (2%)	
*PENIS	(50)	(50)	(50)	(50)
CALCULUS, GROSS OBSERVATION ONLY				1 (2%)
PROLAPSE	1 (2%)		1 (2%)	1 (2%)
*PREPUCE	(50)	(50)	(50)	(50)
FOREIGN BODY, NOS				1 (2%)
INFLAMMATION, SUPPURATIVE				1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)				
*PREPUTIAL GLAND	(50)	(50)	(50)	(50)
CYST, NOS				1 (2%)
CYSTIC DUCTS	12 (24%)	7 (14%)	5 (10%)	3 (6%)
INFLAMMATION, ACUTE			1 (2%)	
INFLAMMATION, ACUTE SUPPURATIVE	2 (4%)	6 (12%)	5 (10%)	1 (2%)
INFLAMMATION, ACUTE/CHRONIC	3 (6%)	2 (4%)	3 (6%)	1 (2%)
INFLAMMATION, CHRONIC	4 (8%)	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, NOS			1 (2%)	
HYPERPLASIA, EPITHELIAL	1 (2%)			
#PROSTATE	(50)	(49)	(50)	(49)
INFLAMMATION, ACUTE				1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE	3 (6%)	2 (4%)		2 (4%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	2 (4%)
INFLAMMATION, CHRONIC	1 (2%)		1 (2%)	2 (4%)
HYPERPLASIA, EPITHELIAL		1 (2%)		1 (2%)
*SEMINAL VESICLE	(50)	(50)	(50)	(50)
DILATATION, NOS	1 (2%)			1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC			1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	3 (6%)			1 (2%)
FIBROSIS	1 (2%)			1 (2%)
HYPERPLASIA, EPITHELIAL	1 (2%)			
*EPIDIDYMIS	(50)	(50)	(50)	(50)
DILATATION, NOS		1 (2%)		
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)		
INFLAMMATION, CHRONIC FOCAL		1 (2%)		
FIBROSIS, FOCAL				1 (2%)
*SCROTUM	(50)	(50)	(50)	(50)
PIGMENTATION, NOS				1 (2%)
NERVOUS SYSTEM				
#BRAIN/MENINGES	(49)	(50)	(50)	(50)
PERIVASCULAR CUFFING		2 (4%)		
#BRAIN	(49)	(50)	(50)	(50)
CORPORA AMYLACEA		1 (2%)		
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*BONE	(50)	(50)	(50)	(50)
FRACTURE, NOS	1 (2%)			
*SKULL	(50)	(50)	(50)	(50)
HYPEROSTOSIS	1 (2%)			
*SKELETAL MUSCLE	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)		
INFECTION, FUNGAL		1 (2%)		
BODY CAVITIES				
*MESENTERY	(50)	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)	
NECROSIS, NOS	1 (2%)			
NECROSIS, FAT		2 (4%)	1 (2%)	2 (4%)
PIGMENTATION, NOS				3 (6%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)	5 (10%)	1 (2%)	3 (6%)
INFLAMMATION, ACUTE SUPPURATIVE				1 (2%)
PIGMENTATION, NOS		2 (4%)	3 (6%)	18 (36%)
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED	1	1		

* NUMBER OF ANIMALS NECROPSIED
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
† MULTIPLE OCCURRENCE OF MORPHOLOGY IN THE SAME ORGAN; TISSUE IS COUNTED ONCE ONLY.

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATH	50	50	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(50)	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
FIBROSIS	1 (2%)			2 (4%)
ALOPECIA	†28 (56%)	†20 (40%)	†43 (86%)	26 (52%)
*SUBCUT TISSUE	(50)	(50)	(50)	(50)
EDEMA, NOS			2 (4%)	
NECROSIS, FAT				1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(49)	(50)	(50)	(50)
CONGESTION, NOS				1 (2%)
HEMORRHAGE		1 (2%)		
LYMPHOCYTIC INFLAMM INFILTR	14 (29%)	10 (20%)	13 (26%)	6 (12%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
LEUKOCYTOSIS, NOS		1 (2%)		
HEMATOPOIESIS	1 (2%)	1 (2%)		
#BONE MARROW	(48)	(49)	(49)	(49)
HYPERPLASIA, NOS				1 (2%)
#SPLEEN	(50)	(49)	(50)	(49)
FIBROSIS			1 (2%)	
NECROSIS, FOCAL				1 (2%)
ATROPHY, NOS			1 (2%)	
ANGIECTASIS		1 (2%)		
HYPERPLASIA, LYMPHOID	1 (2%)	7 (14%)		4 (8%)
HEMATOPOIESIS	13 (26%)	14 (29%)	7 (14%)	18 (37%)
#LYMPH NODE	(50)	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)		
#MANDIBULAR L. NODE	(50)	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)			
#MEDIASTINAL L. NODE	(50)	(50)	(50)	(50)
HYPERPLASIA, NOS	2 (4%)	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, LYMPHOID	1 (2%)	2 (4%)		
#LUMBAR LYMPH NODE	(50)	(50)	(50)	(50)
ANGIECTASIS	1 (2%)			
#MESENTERIC L. NODE	(50)	(50)	(50)	(50)
HEMORRHAGE				1 (2%)
HYPERPLASIA, NOS				2 (4%)
ANGIECTASIS	4 (8%)	3 (6%)		1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)		
HEMATOPOIESIS		1 (2%)		
#RENAL LYMPH NODE	(50)	(50)	(50)	(50)
HYPERPLASIA, NOS	2 (4%)			1 (2%)
HYPERPLASIA, LYMPHOID	1 (2%)			2 (4%)
#ILIAC LYMPH NODE	(50)	(50)	(50)	(50)
CONGESTION, NOS				1 (2%)
HYPERPLASIA, NOS	1 (2%)			1 (2%)
ANGIECTASIS				1 (2%)
HYPERPLASIA, LYMPHOID				2 (4%)
#LUNG	(49)	(50)	(50)	(50)
LEUKOCYTOSIS, NOS				1 (2%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)				
#LIVER	(50)	(49)	(50)	(50)
LEUKOCYTOSIS, NOS	7 (14%)	7 (14%)	4 (8%)	8 (16%)
HEMATOPOIESIS		1 (2%)	2 (4%)	3 (6%)
#ADRENAL	(48)	(48)	(50)	(49)
HEMATOPOIESIS	1 (2%)			
CIRCULATORY SYSTEM				
#HEART	(50)	(50)	(49)	(50)
THROMBUS, MURAL				1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
FIBROSIS, FOCAL				1 (2%)
#LIVER	(50)	(49)	(50)	(50)
THROMBOSIS, NOS		1 (2%)		
#UTERUS	(50)	(50)	(50)	(50)
THROMBOSIS, NOS				1 (2%)
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(46)	(49)	(49)	(45)
LYMPHOCYTIC INFLAM INFILTR		2 (4%)	5 (10%)	2 (4%)
FIBROSIS		1 (2%)		
#LIVER	(50)	(49)	(50)	(50)
CONGENITAL MALFORMATION, NOS		1 (2%)		
MULTIPLE CYSTS		1 (2%)		
LYMPHOCYTIC INFLAM INFILTR	1 (2%)	1 (2%)		
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)			
INFLAMMATION, ACUTE/CHRONIC				1 (2%)
INFLAMMATION, CHRONIC		1 (2%)		
GRANULOMA, NOS				1 (2%)
FIBROSIS		1 (2%)		
NECROSIS, FOCAL	2 (4%)	2 (4%)	2 (4%)	3 (6%)
CYTOPLASMIC VACUOLIZATION	1 (2%)	2 (4%)		1 (2%)
CYTOLOGIC ALTERATION, NOS		2 (4%)	1 (2%)	
ANGIECTASIS				2 (4%)
HISTIOCYTOSIS		1 (2%)		
#PANCREAS	(50)	(50)	(49)	(46)
DILATATION/DUCTS			2 (4%)	1 (2%)
LYMPHOCYTIC INFLAM INFILTR				1 (2%)
ATROPHY, NOS			4 (8%)	1 (2%)
ATROPHY, FOCAL				1 (2%)
#PANCREATIC DUCT	(50)	(50)	(49)	(46)
FIBROSIS			1 (2%)	
HYPERPLASIA, NOS			2 (4%)	
#ESOPHAGUS	(48)	(50)	(50)	(47)
CYSTIC DUCTS				1 (2%)
#STOMACH	(49)	(50)	(50)	(49)
LYMPHOCYTIC INFLAM INFILTR	1 (2%)			
#GASTRIC MUCOSA	(49)	(50)	(50)	(49)
EROSION	1 (2%)			
#GLANDULAR STOMACH	(49)	(50)	(50)	(49)
CYST, NOS	3 (6%)	10 (20%)	8 (16%)	9 (18%)
CYSTIC DUCTS			1 (2%)	
#FORESTOMACH	(49)	(50)	(50)	(49)
EDEMA, NOS				1 (2%)
LYMPHOCYTIC INFLAM INFILTR				1 (2%)
INFLAMMATION, ACUTE FOCAL				1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE	2 (4%)			
INFLAMMATION, ACUTE/CHRONIC	1 (2%)			
INFLAMMATION, CHRONIC FOCAL				1 (2%)
HYPERPLASIA, EPITHELIAL	3 (6%)			3 (6%)
HYPERKERATOSIS			1 (2%)	3 (6%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)				
#DUODENUM	(50)	(49)	(48)	(48)
HYPERPLASIA, ADENOMATOUS	1 (2%)			
#ILEUM	(50)	(49)	(48)	(48)
AMYLOIDOSIS	1 (2%)			1 (2%)
#COLON	(50)	(50)	(48)	(48)
AMYLOIDOSIS			1 (2%)	
URINARY SYSTEM				
#KIDNEY	(50)	(50)	(50)	(50)
CAST, NOS	1 (2%)	3 (6%)	1 (2%)	
HYDRONEPHROSIS				2 (4%)
CYST, NOS	1 (2%)			1 (2%)
LYMPHOCYTIC INFLAM INFILTR	28 (56%)	36 (72%)	33 (66%)	37 (74%)
SCAR		1 (2%)		
NEPHROPATHY	1 (2%)			
DEGENERATION, NOS				1 (2%)
PIGMENTATION, NOS	1 (2%)	38 (76%)	46 (92%)	46 (92%)
METAPLASIA, OSSEOUS		2 (4%)		
#RENAL PAPILLA	(50)	(50)	(50)	(50)
NECROSIS, NOS				1 (2%)
#KIDNEY/TUBULE	(50)	(50)	(50)	(50)
DILATATION, NOS				5 (10%)
CAST, NOS		38 (76%)	47 (94%)	50 (100%)
DEGENERATION, NOS		13 (26%)	15 (30%)	39 (78%)
NECROSIS, NOS				1 (2%)
#KIDNEY/PELVIS	(50)	(50)	(50)	(50)
CALCULUS, GROSS OBSERV ONLY				1 (2%)
CALCULUS, MICROSCOPIC EXAMIN				1 (2%)
CAST, NOS				1 (2%)
*URETER	(50)	(50)	(50)	(50)
CALCULUS, MICROSCOPIC EXAMIN				1 (2%)
LYMPHOCYTIC INFLAM INFILTR				1 (2%)
INFLAMMATION, CHRONIC				2 (4%)
FIBROSIS				1 (2%)
HYPERPLASIA, EPITHELIAL				4 (8%)
#URINARY BLADDER	(49)	(50)	(50)	(50)
CALCULUS, GROSS OBSERV ONLY				30 (60%)
CALCULUS, MICROSCOPIC EXAMI				1 (2%)
LYMPHOCYTIC INFLAM INFILTR	15 (31%)	24 (48%)	33 (66%)	23 (46%)
INFLAMMATION, ACUTE/CHRONIC				2 (4%)
INFLAMMATION, CHRONIC		4 (8%)	7 (14%)	36 (72%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)	1 (2%)
FIBROSIS				23 (46%)
PIGMENTATION, NOS		23 (46%)	35 (70%)	9 (18%)
HYPERPLASIA, EPITHELIAL		1 (2%)	1 (2%)	26 (52%)
ENDOCRINE SYSTEM				
#PITUITARY	(48)	(45)	(48)	(45)
HEMOSIDEROSIS		3 (7%)		2 (4%)
HYPERPLASIA, NOS	1 (2%)			
HYPERPLASIA, FOCAL	2 (4%)		2 (4%)	2 (4%)
ANGIECTASIS	7 (15%)	4 (9%)	7 (15%)	5 (11%)
#ADRENAL	(48)	(48)	(50)	(49)
ECTOPIA	1 (2%)			
#ADRENAL/CAPSULE	(48)	(48)	(50)	(49)
HYPERPLASIA, FOCAL			1 (2%)	
#ADRENAL CORTEX	(48)	(48)	(50)	(49)
CYST, NOS		1 (2%)	1 (2%)	
CYTOPLASMIC VACUOLIZATION	1 (2%)	2 (4%)		

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)				
#ADRENAL MEDULLA	(48)	(48)	(50)	(49)
HYPERPLASIA, NOS			1 (2%)	1 (2%)
HYPERPLASIA, FOCAL			1 (2%)	1 (2%)
#THYROID	(48)	(50)	(50)	(46)
EMBRYONAL DUCT CYST				1 (2%)
CYSTIC FOLLICLES	4 (8%)	1 (2%)	3 (6%)	2 (4%)
DEGENERATION, CYSTIC	4 (8%)	17 (34%)	14 (28%)	27 (59%)
PIGMENTATION, NOS		46 (92%)	46 (92%)	41 (89%)
HYPERPLASIA, C-CELL	1 (2%)			
HYPERPLASIA, FOLLICULAR-CELL	6 (13%)	4 (8%)	7 (14%)	13
#PANCREATIC ISLETS	(50)	(50)	(49)	(46)
HYPERPLASIA, NOS				2 (4%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(50)	(50)	(50)	(50)
CYSTIC DUCTS	10 (20%)	5 (10%)	7 (14%)	8 (16%)
HYPERPLASIA, NOS				1 (2%)
#UTERUS	(50)	(50)	(50)	(50)
HYDROMETRA	1 (2%)			
CYST, NOS			1 (2%)	
HEMORRHAGE		1 (2%)		
INFLAMMATION, ACUTE SUPPURATIVE	5 (10%)	2 (4%)	7 (14%)	5 (10%)
CHOLESTEROL DEPOSIT				1 (2%)
HEMOSIDEROSIS				1 (2%)
ANGIECTASIS				1 (2%)
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)	(50)
HEMORRHAGE	1 (2%)			
INFLAMMATION, ACUTE SUPPURATIVE	1 (2%)			
HYPERPLASIA, NOS			1 (2%)	1 (2%)
HYPERPLASIA, CYSTIC	47 (94%)	46 (92%)	47 (94%)	48 (96%)
#OVARY/PAROVARIAN	(49)	(47)	(49)	(41)
MULTIPLE CYSTS		1 (2%)		
#OVARY	(49)	(47)	(49)	(41)
MINERALIZATION		1 (2%)		
CYST, NOS	10 (20%)	6 (13%)	11 (22%)	3 (7%)
FOLLICULAR CYST, NOS		1 (2%)		
MULTIPLE CYSTS		2 (4%)		
PAROVARIAN CYST		2 (4%)	1 (2%)	2 (5%)
HEMORRHAGE			1 (2%)	
HEMATOMA, NOS				1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE	4 (8%)			2 (5%)
INFLAMMATION, CHRONIC		1 (2%)		
ABSCESS, CHRONIC			1 (2%)	
FIBROSIS			1 (2%)	
NECROSIS, NOS			1 (2%)	
CALCIFICATION, NOS			1 (2%)	
NERVOUS SYSTEM				
#BRAIN/MENINGES	(50)	(50)	(50)	(50)
LYMPHOCYTIC INFLAM INFILTR	1 (2%)	1 (2%)	1 (2%)	
PERIVASCULAR CUFFING	1 (2%)	1 (2%)	1 (2%)	
#BRAIN	(50)	(50)	(50)	(50)
COMPRESSION, NOS	1 (2%)	1 (2%)	1 (2%)	2 (4%)
HEMORRHAGE				1 (2%)
PERIVASCULAR CUFFING		1 (2%)		1 (2%)
SPECIAL SENSE ORGANS				
NONE				

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	CONTROL (UNTR)	LOW DOSE	MID DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM				
*BONE	(50)	(50)	(50)	(50)
HYPEROSTOSIS	1 (2%)			
*SKULL	(50)	(50)	(50)	(50)
HYPEROSTOSIS	1 (2%)			
*FEMUR	(50)	(50)	(50)	(50)
FRACTURE, NOS		1 (2%)		
*MUSCLE HIP/THIGH	(50)	(50)	(50)	(50)
LYMPHOCYTIC INFLAM INFILTR				1 (2%)
BODY CAVITIES				
*MEDIASTINUM	(50)	(50)	(50)	(50)
LYMPHOCYTIC INFLAM INFILTR			1 (2%)	
ANGIECTASIS				1 (2%)
*MESENTERY	(50)	(50)	(50)	(50)
HEMORRHAGE			1 (2%)	1 (2%)
NECROSIS, FAT	2 (4%)	4 (8%)	4 (8%)	5 (10%)
PIGMENTATION, NOS				1 (2%)
ANGIECTASIS				1 (2%)
ALL OTHER SYSTEMS				
*MULTIPLE ORGANS	(50)	(50)	(50)	(50)
LYMPHOCYTIC INFLAM INFILTR	1 (2%)	2 (4%)	2 (4%)	4 (8%)
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE	7 (14%)	12 (24%)	6 (12%)	10 (20%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)		
NECROSIS, FAT		1 (2%)		
PIGMENTATION, NOS		4 (8%)	3 (6%)	5 (10%)
FOOT				
INFLAMMATION, ACUTE/CHRONIC			1	
SPECIAL MORPHOLOGY SUMMARY				
NONE				

* NUMBER OF ANIMALS NECROPSIED
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
† MULTIPLE OCCURRENCE OF MORPHOLOGY IN THE SAME ORGAN; TISSUE IS COUNTED ONCE ONLY.

APPENDIX E

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	Control	1,250 ppm	2,500 ppm	5,000 ppm
Skin: Squamous Cell Papilloma				
Overall Rates (a)	1/49 (2%)	5/50 (10%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	2.3%	12.8%	10.0%	0.0%
Terminal Rates (c)	0/30 (0%)	5/39 (13%)	2/20 (10%)	0/4 (0%)
Life Table Tests (d)	P=0.570	P=0.165	P=0.387	P=0.667N
Incidental Tumor Tests (d)	P=0.574N	P=0.114	P=0.432	P=0.375N
Cochran-Armitage Trend Test (d)	P=0.160N			
Fisher Exact Test		P=0.107	P=0.508	P=0.495N
Skin: Squamous Cell Papilloma or Carcinoma				
Overall Rates (a)	2/49 (4%)	5/50 (10%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	5.3%	12.8%	10.0%	0.0%
Terminal Rates (c)	0/30 (0%)	5/39 (13%)	2/20 (10%)	0/4 (0%)
Life Table Tests (d)	P=0.568N	P=0.320	P=0.562	P=0.562N
Incidental Tumor Tests (d)	P=0.339N	P=0.214	P=0.689	P=0.163N
Cochran-Armitage Trend Test (d)	P=0.089N			
Fisher Exact Test		P=0.226	P=0.684N	P=0.242N
Skin: Keratoacanthoma				
Overall Rates (a)	7/49 (14%)	2/50 (4%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	18.4%	5.1%	20.0%	5.6%
Terminal Rates (c)	3/30 (10%)	2/39 (5%)	4/20 (20%)	0/4 (0%)
Life Table Tests (d)	P=0.441N	P=0.052N	P=0.477N	P=0.444N
Incidental Tumor Tests (d)	P=0.129N	P=0.116N	P=0.334N	P=0.057N
Cochran-Armitage Trend Test (d)	P=0.036N			
Fisher Exact Test		P=0.075N	P=0.251N	P=0.028N
Integumentary System: Keratoacanthoma				
Overall Rates (a)	7/49 (14%)	2/50 (4%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	18.4%	5.1%	22.7%	5.6%
Terminal Rates (c)	3/30 (10%)	2/39 (5%)	4/20 (20%)	0/4 (0%)
Life Table Tests (d)	P=0.531N	P=0.052N	P=0.610N	P=0.444N
Incidental Tumor Tests (d)	P=0.145N	P=0.116N	P=0.429N	P=0.057N
Cochran-Armitage Trend Test (d)	P=0.044N			
Fisher Exact Test		P=0.075N	P=0.365N	P=0.028N
Subcutaneous Tissue: Fibroma				
Overall Rates (a)	4/49 (8%)	4/50 (8%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	13.3%	9.8%	6.7%	0.0%
Terminal Rates (c)	4/30 (13%)	3/39 (8%)	0/20 (0%)	0/4 (0%)
Life Table Tests (d)	P=0.262N	P=0.502N	P=0.503N	P=0.519N
Incidental Tumor Tests (d)	P=0.067N	P=0.542N	P=0.368N	P=0.519N
Cochran-Armitage Trend Test (d)	P=0.030N			
Fisher Exact Test		P=0.631N	P=0.329N	P=0.056N
Subcutaneous Tissue: Fibroma or Fibrosarcoma				
Overall Rates (a)	5/49 (10%)	4/50 (8%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	15.4%	9.8%	6.7%	0.0%
Terminal Rates (c)	4/30 (13%)	3/39 (8%)	0/20 (0%)	0/4 (0%)
Life Table Tests (d)	P=0.164N	P=0.359N	P=0.360N	P=0.371N
Incidental Tumor Tests (d)	P=0.025N	P=0.464N	P=0.227N	P=0.212N
Cochran-Armitage Trend Test (d)	P=0.015N			
Fisher Exact Test		P=0.487N	P=0.210N	P=0.027N
Subcutaneous Tissue: Fibroma, Fibrosarcoma, or Neurofibrosarcoma				
Overall Rates (a)	5/49 (10%)	5/50 (10%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	15.4%	12.3%	6.7%	0.0%
Terminal Rates (c)	4/30 (13%)	4/39 (10%)	0/20 (0%)	0/4 (0%)
Life Table Tests (d)	P=0.171N	P=0.478N	P=0.360N	P=0.371N
Incidental Tumor Tests (d)	P=0.028N	P=0.582N	P=0.227N	P=0.212N
Cochran-Armitage Trend Test (d)	P=0.013N			
Fisher Exact Test		P=0.617N	P=0.210N	P=0.027N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	Control	1,250 ppm	2,500 ppm	5,000 ppm
Subcutaneous Tissue: Sarcoma				
Overall Rates (a)	0/49 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	0.0%	0.0%	21.1%
Terminal Rates (c)	0/30 (0%)	0/39 (0%)	0/20 (0%)	0/4 (0%)
Life Table Tests (d)	P<0.001	(e)	(e)	P=0.012
Incidental Tumor Tests (d)	P=0.028	(e)	(e)	P=0.171
Cochran-Armitage Trend Test (d)	P=0.012			
Fisher Exact Test		(e)	(e)	P=0.125
Subcutaneous Tissue: Sarcoma, Fibrosarcoma, or Neurofibrosarcoma				
Overall Rates (a)	1/49 (2%)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	2.4%	2.6%	0.0%	21.1%
Terminal Rates (c)	0/30 (0%)	1/39 (3%)	0/20 (0%)	0/4 (0%)
Life Table Tests (d)	P=0.012	P=0.721N	P=0.526N	P=0.052
Incidental Tumor Tests (d)	P=0.207	P=0.694	P=0.455N	P=0.440
Cochran-Armitage Trend Test (d)	P=0.163			
Fisher Exact Test		P=0.747N	P=0.495N	P=0.316
Subcutaneous Tissue: Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma				
Overall Rates (a)	5/49 (10%)	5/50 (10%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	15.4%	12.3%	9.8%	21.1%
Terminal Rates (c)	4/30 (13%)	4/39 (10%)	0/20 (0%)	0/4 (0%)
Life Table Tests (d)	P=0.194	P=0.478N	P=0.527N	P=0.185
Incidental Tumor Tests (d)	P=0.379N	P=0.582N	P=0.336N	P=0.614
Cochran-Armitage Trend Test (d)	P=0.233N			
Fisher Exact Test		P=0.617N	P=0.346N	P=0.346N
Lung: Alveolar/Bronchiolar Adenoma				
Overall Rates (a)	1/49 (2%)	1/50 (2%)	3/49 (6%)	0/50 (0%)
Adjusted Rates (b)	3.1%	2.6%	13.0%	0.0%
Terminal Rates (c)	0/30 (0%)	1/39 (3%)	2/20 (10%)	0/4 (0%)
Life Table Tests (d)	P=0.356	P=0.706N	P=0.191	P=0.892N
Incidental Tumor Tests (d)	P=0.629	P=0.748	P=0.308	P=0.479N
Cochran-Armitage Trend Test (d)	P=0.405N			
Fisher Exact Test		P=0.747N	P=0.309	P=0.495N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma				
Overall Rates (a)	2/49 (4%)	1/50 (2%)	3/49 (6%)	0/50 (0%)
Adjusted Rates (b)	5.8%	2.6%	13.0%	0.0%
Terminal Rates (c)	0/30 (0%)	1/39 (3%)	2/20 (10%)	0/4 (0%)
Life Table Tests (d)	P=0.533	P=0.432N	P=0.338	P=0.747N
Incidental Tumor Tests (d)	P=0.399N	P=0.564N	P=0.547	P=0.210N
Cochran-Armitage Trend Test (d)	P=0.238N			
Fisher Exact Test		P=0.492N	P=0.500	P=0.242N
Hematopoietic System: Mononuclear Cell Leukemia				
Overall Rates (a)	15/49 (31%)	10/50 (20%)	13/50 (26%)	2/50 (4%)
Adjusted Rates (b)	40.0%	22.2%	35.7%	24.4%
Terminal Rates (c)	9/30 (30%)	5/39 (13%)	1/20 (5%)	0/4 (0%)
Life Table Tests (d)	P=0.444N	P=0.086N	P=0.426	P=0.404N
Incidental Tumor Tests (d)	P<0.001N	P=0.305N	P=0.263N	P=0.016N
Cochran-Armitage Trend Test (d)	P=0.001N			
Fisher Exact Test		P=0.163N	P=0.388N	P<0.001N
Liver: Neoplastic Nodule				
Overall Rates (a)	4/49 (8%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	13.3%	0.0%	0.0%	0.0%
Terminal Rates (c)	4/30 (13%)	0/39 (0%)	0/20 (0%)	0/4 (0%)
Life Table Tests (d)	P=0.051N	P=0.035N	P=0.123N	P=0.519N
Incidental Tumor Tests (d)	P=0.051N	P=0.035N	P=0.123N	P=0.519N
Cochran-Armitage Trend Test (d)	P=0.020N			
Fisher Exact Test		P=0.056N	P=0.056N	P=0.056N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	Control	1,250 ppm	2,500 ppm	5,000 ppm
Liver: Neoplastic Nodule or Hepatocellular Carcinoma				
Overall Rates (a)	4/49 (8%)	2/50 (4%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	13.3%	5.1%	5.4%	0.0%
Terminal Rates (c)	4/30 (13%)	2/39 (5%)	0/20 (0%)	0/4 (0%)
Life Table Tests (d)	P=0.269N	P=0.223N	P=0.486N	P=0.519N
Incidental Tumor Tests (d)	P=0.081N	P=0.223N	P=0.368N	P=0.519N
Cochran-Armitage Trend Test (d)	P=0.042N			
Fisher Exact Test		P=0.329N	P=0.329N	P=0.056N
Urinary Bladder: Squamous Cell Papilloma				
Overall Rates (a)	0/49 (0%)	0/50 (0%)	1/50 (2%)	3/49 (6%)
Adjusted Rates (b)	0.0%	0.0%	5.0%	20.6%
Terminal Rates (c)	0/30 (0%)	0/39 (0%)	1/20 (5%)	0/4 (0%)
Life Table Tests (d)	P<0.001	(e)	P=0.419	P=0.019
Incidental Tumor Tests (d)	P=0.044	(e)	P=0.419	P=0.288
Cochran-Armitage Trend Test (d)	P=0.020			
Fisher Exact Test		(e)	P=0.505	P=0.121
Urinary Bladder: Squamous Cell Papilloma or Carcinoma				
Overall Rates (a)	0/49 (0%)	0/50 (0%)	2/50 (4%)	4/49 (8%)
Adjusted Rates (b)	0.0%	0.0%	8.7%	26.7%
Terminal Rates (c)	0/30 (0%)	0/39 (0%)	1/20 (5%)	0/4 (0%)
Life Table Tests (d)	P<0.001	(e)	P=0.161	P=0.004
Incidental Tumor Tests (d)	P=0.020	(e)	P=0.245	P=0.157
Cochran-Armitage Trend Test (d)	P=0.008			
Fisher Exact Test		(e)	P=0.253	P=0.059
Urinary Bladder: Transitional Cell Papilloma				
Overall Rates (a)	0/49 (0%)	0/50 (0%)	8/50 (16%)	4/49 (8%)
Adjusted Rates (b)	0.0%	0.0%	27.7%	35.9%
Terminal Rates (c)	0/30 (0%)	0/39 (0%)	3/20 (15%)	0/4 (0%)
Life Table Tests (d)	P<0.001	(e)	P=0.002	P=0.002
Incidental Tumor Tests (d)	P=0.043	(e)	P=0.006	P=0.157
Cochran-Armitage Trend Test (d)	P=0.021			
Fisher Exact Test		(e)	P=0.003	P=0.059
Urinary Bladder: Transitional Cell Carcinoma				
Overall Rates (a)	0/49 (0%)	0/50 (0%)	4/50 (8%)	8/49 (16%)
Adjusted Rates (b)	0.0%	0.0%	13.2%	32.9%
Terminal Rates (c)	0/30 (0%)	0/39 (0%)	1/20 (5%)	0/4 (0%)
Life Table Tests (d)	P<0.001	(e)	P=0.041	P<0.001
Incidental Tumor Tests (d)	P=0.009	(e)	P=0.090	P=0.070
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test		(e)	P=0.061	P=0.003
Urinary Bladder: Transitional Cell Papilloma or Carcinoma				
Overall Rates (a)	0/49 (0%)	0/50 (0%)	10/50 (20%)	11/49 (22%)
Adjusted Rates (b)	0.0%	0.0%	32.1%	55.0%
Terminal Rates (c)	0/30 (0%)	0/39 (0%)	3/20 (15%)	0/4 (0%)
Life Table Tests (d)	P<0.001	(e)	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.001	(e)	P=0.002	P=0.020
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test		(e)	P<0.001	P<0.001
Urinary Bladder: Leiomyosarcoma				
Overall Rates (a)	0/49 (0%)	0/50 (0%)	6/50 (12%)	41/49 (84%)
Adjusted Rates (b)	0.0%	0.0%	17.9%	100.0%
Terminal Rates (c)	0/30 (0%)	0/39 (0%)	1/20 (5%)	4/4 (100%)
Life Table Tests (d)	P<0.001	(e)	P=0.010	P<0.001
Incidental Tumor Tests (d)	P<0.001	(e)	P=0.030	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test		(e)	P=0.014	P<0.001

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	Control	1,250 ppm	2,500 ppm	5,000 ppm
Urinary Bladder: Leiomyoma or Leiomyosarcoma				
Overall Rates (a)	0/49 (0%)	0/50 (0%)	7/50 (14%)	41/49 (84%)
Adjusted Rates (b)	0.0%	0.0%	19.8%	100.0%
Terminal Rates (c)	0/30 (0%)	0/39 (0%)	1/20 (5%)	4/4 (100%)
Life Table Tests (d)	P<0.001	(e)	P=0.005	P<0.001
Incidental Tumor Tests (d)	P<0.001	(e)	P=0.016	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test		(e)	P=0.007	P<0.001
Pituitary: Adenoma				
Overall Rates (a)	13/49 (27%)	5/48 (10%)	6/48 (13%)	3/48 (6%)
Adjusted Rates (b)	35.6%	13.5%	22.3%	33.8%
Terminal Rates (c)	8/30 (27%)	5/37 (14%)	3/19 (16%)	1/4 (25%)
Life Table Tests (d)	P=0.523N	P=0.015N	P=0.257N	P=0.541
Incidental Tumor Tests (d)	P=0.078N	P=0.036N	P=0.098N	P=0.135N
Cochran-Armitage Trend Test (d)	P=0.009N			
Fisher Exact Test		P=0.036N	P=0.068N	P=0.007N
Pituitary: Carcinoma				
Overall Rates (a)	3/49 (6%)	1/48 (2%)	1/48 (2%)	1/48 (2%)
Adjusted Rates (b)	7.9%	2.7%	3.2%	14.3%
Terminal Rates (c)	1/30 (3%)	1/37 (3%)	0/19 (0%)	0/4 (0%)
Life Table Tests (d)	P=0.639	P=0.256N	P=0.394N	P=0.663
Incidental Tumor Tests (d)	P=0.263N	P=0.387N	P=0.236N	P=0.359N
Cochran-Armitage Trend Test (d)	P=0.247N			
Fisher Exact Test		P=0.316N	P=0.316N	P=0.316N
Pituitary: Adenoma or Carcinoma				
Overall Rates (a)	16/49 (33%)	6/48 (13%)	7/48 (15%)	4/48 (8%)
Adjusted Rates (b)	41.4%	16.2%	24.8%	43.2%
Terminal Rates (c)	9/30 (30%)	6/37 (16%)	3/19 (16%)	1/4 (25%)
Life Table Tests (d)	P=0.523N	P=0.006N	P=0.174N	P=0.494
Incidental Tumor Tests (d)	P=0.039N	P=0.020N	P=0.037N	P=0.066N
Cochran-Armitage Trend Test (d)	P=0.004N			
Fisher Exact Test		P=0.016N	P=0.031N	P=0.003N
Adrenal: Pheochromocytoma				
Overall Rates (a)	19/49 (39%)	20/50 (40%)	23/50 (46%)	3/50 (6%)
Adjusted Rates (b)	51.2%	43.9%	72.0%	53.3%
Terminal Rates (c)	13/30 (43%)	14/39 (36%)	12/20 (60%)	2/4 (50%)
Life Table Tests (d)	P=0.248	P=0.351N	P=0.035	P=0.512N
Incidental Tumor Tests (d)	P=0.033N	P=0.504	P=0.180	P=0.055N
Cochran-Armitage Trend Test (d)	P<0.001N			
Fisher Exact Test		P=0.532	P=0.300	P<0.001N
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant				
Overall Rates (a)	20/49 (41%)	21/50 (42%)	23/50 (46%)	4/50 (8%)
Adjusted Rates (b)	52.2%	46.2%	72.0%	54.7%
Terminal Rates (c)	13/30 (43%)	15/39 (38%)	12/20 (60%)	2/4 (50%)
Life Table Tests (d)	P=0.218	P=0.345N	P=0.055	P=0.563N
Incidental Tumor Tests (d)	P=0.018N	P=0.515	P=0.265	P=0.020N
Cochran-Armitage Trend Test (d)	P<0.001N			
Fisher Exact Test		P=0.534	P=0.375	P<0.001N
Thyroid: C-Cell Adenoma				
Overall Rates (a)	1/49 (2%)	2/50 (4%)	4/49 (8%)	3/50 (6%)
Adjusted Rates (b)	2.2%	5.1%	16.3%	31.8%
Terminal Rates (c)	0/30 (0%)	2/39 (5%)	2/20 (10%)	1/4 (25%)
Life Table Tests (d)	P=0.003	P=0.563	P=0.105	P=0.059
Incidental Tumor Tests (d)	P=0.135	P=0.453	P=0.196	P=0.413
Cochran-Armitage Trend Test (d)	P=0.227			
Fisher Exact Test		P=0.508	P=0.181	P=0.316

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	Control	1,250 ppm	2,500 ppm	5,000 ppm
Thyroid: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	2/49 (4%)	4/50 (8%)	5/49 (10%)	3/50 (6%)
Adjusted Rates (b)	5.4%	9.7%	19.1%	31.8%
Terminal Rates (c)	1/30 (3%)	3/39 (8%)	2/20 (10%)	1/4 (25%)
Life Table Tests (d)	P=0.014	P=0.434	P=0.119	P=0.089
Incidental Tumor Tests (d)	P=0.327	P=0.271	P=0.233	P=0.474
Cochran-Armitage Trend Test (d)	P=0.471			
Fisher Exact Test		P=0.349	P=0.218	P=0.510
Pancreatic Islets: Islet Cell Adenoma				
Overall Rates (a)	1/49 (2%)	0/50 (0%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	3.3%	0.0%	14.9%	27.2%
Terminal Rates (c)	1/30 (3%)	0/39 (0%)	2/20 (10%)	1/4 (25%)
Life Table Tests (d)	P=0.011	P=0.448N	P=0.105	P=0.099
Incidental Tumor Tests (d)	P=0.132	P=0.448N	P=0.151	P=0.251
Cochran-Armitage Trend Test (d)	P=0.242			
Fisher Exact Test		P=0.495N	P=0.187	P=0.508
Pancreatic Islets: Islet Cell Adenoma or Carcinoma				
Overall Rates (a)	1/49 (2%)	2/50 (4%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	3.3%	5.1%	18.9%	51.5%
Terminal Rates (c)	1/30 (3%)	2/39 (5%)	2/20 (10%)	2/4 (50%)
Life Table Tests (d)	P=0.001	P=0.591	P=0.050	P=0.009
Incidental Tumor Tests (d)	P=0.042	P=0.591	P=0.102	P=0.022
Cochran-Armitage Trend Test (d)	P=0.222			
Fisher Exact Test		P=0.508	P=0.107	P=0.316
Mammary Gland: Fibroadenoma				
Overall Rates (a)	6/49 (12%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	16.8%	7.7%	5.0%	4.3%
Terminal Rates (c)	3/30 (10%)	3/39 (8%)	1/20 (5%)	0/4 (0%)
Life Table Tests (d)	P=0.265N	P=0.156N	P=0.131N	P=0.571N
Incidental Tumor Tests (d)	P=0.075N	P=0.248N	P=0.066N	P=0.134N
Cochran-Armitage Trend Test (d)	P=0.025N			
Fisher Exact Test		P=0.233N	P=0.053N	P=0.053N
Preputial Gland: Carcinoma				
Overall Rates (a)	4/49 (8%)	2/50 (4%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	11.2%	5.1%	0.0%	2.3%
Terminal Rates (c)	2/30 (7%)	2/39 (5%)	0/20 (0%)	0/4 (0%)
Life Table Tests (d)	P=0.347N	P=0.254N	P=0.120N	P=0.668N
Incidental Tumor Tests (d)	P=0.078N	P=0.356N	P=0.065N	P=0.174N
Cochran-Armitage Trend Test (d)	P=0.083N			
Fisher Exact Test		P=0.329N	P=0.056N	P=0.175N
Testis: Interstitial Cell Tumor				
Overall Rates (a)	44/49 (90%)	44/50 (88%)	38/50 (76%)	16/50 (32%)
Adjusted Rates (b)	95.6%	95.7%	97.4%	92.9%
Terminal Rates (c)	28/30 (93%)	37/39 (95%)	19/20 (95%)	3/4 (75%)
Life Table Tests (d)	P=0.001	P=0.048N	P=0.145	P=0.021
Incidental Tumor Tests (d)	P=0.001N	P=0.301N	P=0.164N	P=0.001N
Cochran-Armitage Trend Test (d)	P<0.001N			
Fisher Exact Test		P=0.515N	P=0.060N	P<0.001N
All Sites: Mesothelioma				
Overall Rates (a)	4/49 (8%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	10.8%	2.6%	0.0%	2.2%
Terminal Rates (c)	1/30 (3%)	1/39 (3%)	0/20 (0%)	0/4 (0%)
Life Table Tests (d)	P=0.346N	P=0.139N	P=0.119N	P=0.682N
Incidental Tumor Tests (d)	P=0.047N	P=0.254N	P=0.039N	P=0.096N
Cochran-Armitage Trend Test (d)	P=0.101N			
Fisher Exact Test		P=0.175N	P=0.057N	P=0.175N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(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 overall incidence. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the dosed and control groups.

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	Control	1,250 ppm	2,500 ppm	5,000 ppm
Subcutaneous Tissue: Fibroma				
Overall Rates (a)	3/49 (6%)	2/50 (4%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	7.7%	5.1%	0.0%	0.0%
Terminal Rates (c)	2/37 (5%)	1/37 (3%)	0/34 (0%)	0/16 (0%)
Life Table Tests (d)	P=0.077N	P=0.509N	P=0.138N	P=0.268N
Incidental Tumor Tests (d)	P=0.030N	P=0.574N	P=0.133N	P=0.154N
Cochran-Armitage Trend Test (d)	P=0.038N			
Fisher Exact Test		P=0.490N	P=0.117N	P=0.117N
Subcutaneous Tissue: Fibroma or Fibrosarcoma				
Overall Rates (a)	5/49 (10%)	2/50 (4%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	11.5%	5.1%	2.9%	0.0%
Terminal Rates (c)	2/37 (5%)	1/37 (3%)	1/34 (3%)	0/16 (0%)
Life Table Tests (d)	P=0.036N	P=0.234N	P=0.129N	P=0.097N
Incidental Tumor Tests (d)	P=0.006N	P=0.241N	P=0.119N	P=0.011N
Cochran-Armitage Trend Test (d)	P=0.013N			
Fisher Exact Test		P=0.210N	P=0.098N	P=0.027N
Subcutaneous Tissue: Fibroma, Fibrosarcoma, or Neurofibrosarcoma				
Overall Rates (a)	5/49 (10%)	2/50 (4%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	11.5%	5.1%	5.9%	0.0%
Terminal Rates (c)	2/37 (5%)	1/37 (3%)	2/34 (6%)	0/16 (0%)
Life Table Tests (d)	P=0.060N	P=0.234N	P=0.257N	P=0.097N
Incidental Tumor Tests (d)	P=0.013N	P=0.241N	P=0.242N	P=0.011N
Cochran-Armitage Trend Test (d)	P=0.021N			
Fisher Exact Test		P=0.210N	P=0.210N	P=0.027N
Hematopoietic System: Mononuclear Cell Leukemia				
Overall Rates (a)	9/49 (18%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	22.2%	7.6%	2.9%	8.7%
Terminal Rates (c)	6/37 (16%)	2/37 (5%)	1/34 (3%)	1/16 (6%)
Life Table Tests (d)	P=0.067N	P=0.072N	P=0.016N	P=0.209N
Incidental Tumor Tests (d)	P=0.014N	P=0.092N	P=0.014N	P=0.042N
Cochran-Armitage Trend Test (d)	P=0.012N			
Fisher Exact Test		P=0.056N	P=0.008N	P=0.024N
Urinary Bladder: Squamous Cell Papilloma				
Overall Rates (a)	0/48 (0%)	0/50 (0%)	1/50 (2%)	7/48 (15%)
Adjusted Rates (b)	0.0%	0.0%	2.7%	31.6%
Terminal Rates (c)	0/37 (0%)	0/37 (0%)	0/34 (0%)	4/16 (25%)
Life Table Tests (d)	P<0.001	(e)	P=0.489	P<0.001
Incidental Tumor Tests (d)	P<0.001	(e)	P=0.500	P=0.005
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test		(e)	P=0.510	P=0.006
Urinary Bladder: Squamous Cell Carcinoma				
Overall Rates (a)	0/48 (0%)	0/50 (0%)	1/50 (2%)	4/48 (8%)
Adjusted Rates (b)	0.0%	0.0%	2.7%	19.3%
Terminal Rates (c)	0/37 (0%)	0/37 (0%)	0/34 (0%)	1/16 (6%)
Life Table Tests (d)	P<0.001	(e)	P=0.489	P=0.012
Incidental Tumor Tests (d)	P=0.035	(e)	P=0.500	P=0.106
Cochran-Armitage Trend Test (d)	P=0.005			
Fisher Exact Test		(e)	P=0.510	P=0.059
Urinary Bladder: Squamous Cell Papilloma or Carcinoma				
Overall Rates (a)	0/48 (0%)	0/50 (0%)	1/50 (2%)	11/48 (23%)
Adjusted Rates (b)	0.0%	0.0%	2.7%	46.0%
Terminal Rates (c)	0/37 (0%)	0/37 (0%)	0/34 (0%)	5/16 (31%)
Life Table Tests (d)	P<0.001	(e)	P=0.489	P<0.001
Incidental Tumor Tests (d)	P<0.001	(e)	P=0.500	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test		(e)	P=0.510	P<0.001

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	Control	1,250 ppm	2,500 ppm	5,000 ppm
Urinary Bladder: Transitional Cell Papilloma				
Overall Rates (a)	0/48 (0%)	0/50 (0%)	9/50 (18%)	15/48 (31%)
Adjusted Rates (b)	0.0%	0.0%	25.4%	53.0%
Terminal Rates (c)	0/37 (0%)	0/37 (0%)	8/34 (24%)	6/16 (38%)
Life Table Tests (d)	P<0.001	(e)	P=0.002	P<0.001
Incidental Tumor Tests (d)	P<0.001	(e)	P=0.002	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test		(e)	P=0.002	P<0.001
Urinary Bladder: Transitional Cell Carcinoma				
Overall Rates (a)	0/48 (0%)	0/50 (0%)	10/50 (20%)	13/48 (27%)
Adjusted Rates (b)	0.0%	0.0%	27.6%	54.6%
Terminal Rates (c)	0/37 (0%)	0/37 (0%)	8/34 (24%)	7/16 (44%)
Life Table Tests (d)	P<0.001	(e)	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	(e)	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test		(e)	P<0.001	P<0.001
Urinary Bladder: Transitional Cell Papilloma or Carcinoma				
Overall Rates (a)	0/48 (0%)	0/50 (0%)	15/50 (30%)	21/48 (44%)
Adjusted Rates (b)	0.0%	0.0%	40.2%	70.7%
Terminal Rates (c)	0/37 (0%)	0/37 (0%)	12/34 (35%)	9/16 (56%)
Life Table Tests (d)	P<0.001	(e)	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	(e)	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test		(e)	P<0.001	P<0.001
Urinary Bladder: Leiomyoma				
Overall Rates (a)	0/48 (0%)	0/50 (0%)	1/50 (2%)	4/48 (8%)
Adjusted Rates (b)	0.0%	0.0%	2.9%	19.1%
Terminal Rates (c)	0/37 (0%)	0/37 (0%)	1/34 (3%)	2/16 (13%)
Life Table Tests (d)	P<0.001	(e)	P=0.483	P=0.012
Incidental Tumor Tests (d)	P=0.005	(e)	P=0.483	P=0.048
Cochran-Armitage Trend Test (d)	P=0.005			
Fisher Exact Test		(e)	P=0.510	P=0.059
Urinary Bladder: Leiomyosarcoma				
Overall Rates (a)	0/48 (0%)	0/50 (0%)	2/50 (4%)	23/48 (48%)
Adjusted Rates (b)	0.0%	0.0%	5.9%	80.4%
Terminal Rates (c)	0/37 (0%)	0/37 (0%)	2/34 (6%)	11/16 (69%)
Life Table Tests (d)	P<0.001	(e)	P=0.220	P<0.001
Incidental Tumor Tests (d)	P<0.001	(e)	P=0.220	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test		(e)	P=0.258	P<0.001
Urinary Bladder: Leiomyoma or Leiomyosarcoma				
Overall Rates (a)	0/48 (0%)	0/50 (0%)	3/50 (6%)	26/48 (54%)
Adjusted Rates (b)	0.0%	0.0%	8.8%	85.6%
Terminal Rates (c)	0/37 (0%)	0/37 (0%)	3/34 (9%)	12/16 (75%)
Life Table Tests (d)	P<0.001	(e)	P=0.106	P<0.001
Incidental Tumor Tests (d)	P<0.001	(e)	P=0.106	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test		(e)	P=0.129	P<0.001
Pituitary: Adenoma				
Overall Rates (a)	10/49 (20%)	21/49 (43%)	20/50 (40%)	15/49 (31%)
Adjusted Rates (b)	24.1%	48.5%	53.6%	48.1%
Terminal Rates (c)	6/37 (16%)	15/37 (41%)	17/34 (50%)	4/16 (25%)
Life Table Tests (d)	P=0.005	P=0.020	P=0.016	P=0.010
Incidental Tumor Tests (d)	P=0.288	P=0.006	P=0.014	P=0.380
Cochran-Armitage Trend Test (d)	P=0.326			
Fisher Exact Test		P=0.014	P=0.028	P=0.177

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	Control	1,250 ppm	2,500 ppm	5,000 ppm
Pituitary: Carcinoma				
Overall Rates (a)	2/49 (4%)	3/49 (6%)	0/50 (0%)	1/49 (2%)
Adjusted Rates (b)	4.7%	7.1%	0.0%	6.3%
Terminal Rates (c)	1/37 (3%)	1/37 (3%)	0/34 (0%)	1/16 (6%)
Life Table Tests (d)	P=0.382N	P=0.486	P=0.261N	P=0.709N
Incidental Tumor Tests (d)	P=0.146N	P=0.549	P=0.249N	P=0.541N
Cochran-Armitage Trend Test (d)	P=0.241N			
Fisher Exact Test		P=0.500	P=0.242N	P=0.500N
Pituitary: Adenoma or Carcinoma				
Overall Rates (a)	12/49 (24%)	24/49 (49%)	20/50 (40%)	16/49 (33%)
Adjusted Rates (b)	28.1%	53.1%	53.6%	52.4%
Terminal Rates (c)	7/37 (19%)	16/37 (43%)	17/34 (50%)	5/16 (31%)
Life Table Tests (d)	P=0.011	P=0.017	P=0.044	P=0.014
Incidental Tumor Tests (d)	P=0.479	P=0.005	P=0.044	P=0.470
Cochran-Armitage Trend Test (d)	P=0.464			
Fisher Exact Test		P=0.010	P=0.075	P=0.251
Adrenal: Pheochromocytoma				
Overall Rates (a)	5/48 (10%)	5/50 (10%)	10/50 (20%)	3/50 (6%)
Adjusted Rates (b)	13.9%	13.5%	26.4%	15.3%
Terminal Rates (c)	5/36 (14%)	5/37 (14%)	7/34 (21%)	2/16 (13%)
Life Table Tests (d)	P=0.264	P=0.615N	P=0.109	P=0.521
Incidental Tumor Tests (d)	P=0.483	P=0.615N	P=0.113	P=0.592
Cochran-Armitage Trend Test (d)	P=0.345N			
Fisher Exact Test		P=0.603N	P=0.150	P=0.335N
Thyroid: C-Cell Adenoma				
Overall Rates (a)	2/49 (4%)	5/50 (10%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	5.4%	12.0%	5.6%	0.0%
Terminal Rates (c)	2/37 (5%)	3/37 (8%)	1/34 (3%)	0/16 (0%)
Life Table Tests (d)	P=0.226N	P=0.219	P=0.666	P=0.436N
Incidental Tumor Tests (d)	P=0.073N	P=0.295	P=0.671	P=0.436N
Cochran-Armitage Trend Test (d)	P=0.089N			
Fisher Exact Test		P=0.226	P=0.684N	P=0.242N
Thyroid: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	3/49 (6%)	5/50 (10%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	8.1%	12.0%	8.5%	0.0%
Terminal Rates (c)	3/37 (8%)	3/37 (8%)	2/34 (6%)	0/16 (0%)
Life Table Tests (d)	P=0.195N	P=0.357	P=0.625	P=0.301N
Incidental Tumor Tests (d)	P=0.066N	P=0.450	P=0.629	P=0.301N
Cochran-Armitage Trend Test (d)	P=0.061N			
Fisher Exact Test		P=0.369	P=0.651N	P=0.117N
Mammary Gland: Fibroadenoma				
Overall Rates (a)	24/49 (49%)	19/50 (38%)	27/50 (54%)	7/50 (14%)
Adjusted Rates (b)	58.3%	48.6%	67.1%	37.8%
Terminal Rates (c)	20/37 (54%)	17/37 (46%)	21/34 (62%)	5/16 (31%)
Life Table Tests (d)	P=0.272N	P=0.221N	P=0.217	P=0.132N
Incidental Tumor Tests (d)	P=0.030N	P=0.273N	P=0.219	P=0.017N
Cochran-Armitage Trend Test (d)	P<0.001N			
Fisher Exact Test		P=0.185N	P=0.383	P<0.001N
Clitoral Gland: Carcinoma				
Overall Rates (a)	2/49 (4%)	3/50 (6%)	6/50 (12%)	1/50 (2%)
Adjusted Rates (b)	5.4%	8.1%	16.9%	5.0%
Terminal Rates (c)	2/37 (5%)	3/37 (8%)	5/34 (15%)	0/16 (0%)
Life Table Tests (d)	P=0.373	P=0.500	P=0.109	P=0.713
Incidental Tumor Tests (d)	P=0.538	P=0.500	P=0.113	P=0.598N
Cochran-Armitage Trend Test (d)	P=0.412N			
Fisher Exact Test		P=0.510	P=0.141	P=0.492N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	Control	1,250 ppm	2,500 ppm	5,000 ppm
Clitoral Gland: Adenoma or Carcinoma				
Overall Rates (a)	3/49 (6%)	3/50 (6%)	6/50 (12%)	1/50 (2%)
Adjusted Rates (b)	8.1%	8.1%	16.9%	5.0%
Terminal Rates (c)	3/37 (8%)	3/37 (8%)	5/34 (15%)	0/16 (0%)
Life Table Tests (d)	P=0.497	P=0.664	P=0.202	P=0.608N
Incidental Tumor Tests (d)	P=0.518N	P=0.664	P=0.207	P=0.453N
Cochran-Armitage Trend Test (d)	P=0.289N			
Fisher Exact Test		P=0.651N	P=0.254	P=0.301N
Uterus: Endometrial Stromal Polyp				
Overall Rates (a)	16/49 (33%)	9/50 (18%)	3/50 (6%)	5/50 (10%)
Adjusted Rates (b)	41.9%	23.6%	8.0%	20.4%
Terminal Rates (c)	15/37 (41%)	8/37 (22%)	2/34 (6%)	2/16 (13%)
Life Table Tests (d)	P=0.064N	P=0.082N	P=0.002N	P=0.241N
Incidental Tumor Tests (d)	P=0.019N	P=0.092N	P=0.002N	P=0.102N
Cochran-Armitage Trend Test (d)	P=0.002N			
Fisher Exact Test		P=0.074N	P<0.001N	P=0.006N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(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 overall incidence. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 1,250-ppm and control groups.

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	Control	600 ppm	1,200 ppm	2,500 ppm
Subcutaneous Tissue: Fibroma				
Overall Rates (a)	6/50 (12%)	7/50 (14%)	5/50 (10%)	0/50 (0%)
Adjusted Rates (b)	22.0%	22.6%	13.9%	0.0%
Terminal Rates (c)	4/25 (16%)	7/31 (23%)	5/36 (14%)	0/21 (0%)
Life Table Tests (d)	P=0.014N	P=0.577N	P=0.270N	P=0.031N
Incidental Tumor Tests (d)	P=0.020N	P=0.612	P=0.453N	P=0.045N
Cochran-Armitage Trend Test (d)	P=0.012N			
Fisher Exact Test		P=0.500	P=0.500N	P=0.013N
Subcutaneous Tissue: Fibrosarcoma				
Overall Rates (a)	12/50 (24%)	13/50 (26%)	7/50 (14%)	5/50 (10%)
Adjusted Rates (b)	34.5%	35.1%	18.1%	17.4%
Terminal Rates (c)	3/25 (12%)	8/31 (26%)	5/36 (14%)	1/21 (5%)
Life Table Tests (d)	P=0.056N	P=0.494N	P=0.061N	P=0.142N
Incidental Tumor Tests (d)	P=0.050N	P=0.561	P=0.375N	P=0.101N
Cochran-Armitage Trend Test (d)	P=0.020N			
Fisher Exact Test		P=0.500	P=0.154N	P=0.054N
Subcutaneous Tissue: Fibroma or Fibrosarcoma				
Overall Rates (a)	16/50 (32%)	19/50 (38%)	12/50 (24%)	5/50 (10%)
Adjusted Rates (b)	46.4%	52.0%	31.3%	17.4%
Terminal Rates (c)	7/25 (28%)	14/31 (45%)	10/36 (28%)	1/21 (5%)
Life Table Tests (d)	P=0.008N	P=0.566N	P=0.068N	P=0.035N
Incidental Tumor Tests (d)	P=0.006N	P=0.472	P=0.338N	P=0.017N
Cochran-Armitage Trend Test (d)	P=0.002N			
Fisher Exact Test		P=0.338	P=0.252N	P=0.006N
Subcutaneous Tissue: Sarcoma				
Overall Rates (a)	3/50 (6%)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	8.2%	4.6%	4.4%	7.8%
Terminal Rates (c)	0/25 (0%)	0/31 (0%)	0/36 (0%)	0/21 (0%)
Life Table Tests (d)	P=0.468	P=0.456N	P=0.442N	P=0.595
Incidental Tumor Tests (d)	P=0.256N	P=0.394N	P=0.447N	P=0.308N
Cochran-Armitage Trend Test (d)	P=0.542			
Fisher Exact Test		P=0.500N	P=0.500N	P=0.661N
Lung: Alveolar/Bronchiolar Adenoma				
Overall Rates (a)	1/50 (2%)	3/49 (6%)	5/50 (10%)	5/50 (10%)
Adjusted Rates (b)	4.0%	9.1%	13.9%	23.8%
Terminal Rates (c)	1/25 (4%)	2/30 (7%)	5/36 (14%)	5/21 (24%)
Life Table Tests (d)	P=0.033	P=0.366	P=0.203	P=0.063
Incidental Tumor Tests (d)	P=0.028	P=0.332	P=0.203	P=0.063
Cochran-Armitage Trend Test (d)	P=0.086			
Fisher Exact Test		P=0.301	P=0.102	P=0.102
Lung: Alveolar/Bronchiolar Carcinoma				
Overall Rates (a)	3/50 (6%)	6/49 (12%)	1/50 (2%)	6/50 (12%)
Adjusted Rates (b)	11.2%	18.7%	2.8%	26.3%
Terminal Rates (c)	2/25 (8%)	5/30 (17%)	1/36 (3%)	5/21 (24%)
Life Table Tests (d)	P=0.182	P=0.331	P=0.199N	P=0.160
Incidental Tumor Tests (d)	P=0.224	P=0.319	P=0.312N	P=0.175
Cochran-Armitage Trend Test (d)	P=0.295			
Fisher Exact Test		P=0.233	P=0.309N	P=0.243
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma				
Overall Rates (a)	4/50 (8%)	9/49 (18%)	5/50 (10%)	11/50 (22%)
Adjusted Rates (b)	15.0%	27.2%	13.9%	49.3%
Terminal Rates (c)	3/25 (12%)	7/30 (23%)	5/36 (14%)	10/21 (48%)
Life Table Tests (d)	P=0.015	P=0.192	P=0.564N	P=0.015
Incidental Tumor Tests (d)	P=0.018	P=0.168	P=0.616	P=0.017
Cochran-Armitage Trend Test (d)	P=0.065			
Fisher Exact Test		P=0.109	P=0.500	P=0.045

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	Control	600 ppm	1,200 ppm	2,500 ppm
Hematopoietic System: Malignant Lymphoma, Mixed Type				
Overall Rates (a)	2/50 (4%)	2/50 (4%)	5/50 (10%)	5/50 (10%)
Adjusted Rates (b)	8.0%	6.5%	13.5%	23.8%
Terminal Rates (c)	2/25 (8%)	2/31 (6%)	4/36 (11%)	5/21 (24%)
Life Table Tests (d)	P=0.049	P=0.616N	P=0.375	P=0.144
Incidental Tumor Tests (d)	P=0.042	P=0.616N	P=0.261	P=0.144
Cochran-Armitage Trend Test (d)	P=0.116			
Fisher Exact Test		P=0.691N	P=0.218	P=0.218
Hematopoietic System: Lymphoma, All Malignant				
Overall Rates (a)	4/50 (8%)	3/50 (6%)	7/50 (14%)	7/50 (14%)
Adjusted Rates (b)	14.9%	9.7%	18.9%	29.0%
Terminal Rates (c)	3/25 (12%)	3/31 (10%)	6/36 (17%)	5/21 (24%)
Life Table Tests (d)	P=0.055	P=0.392N	P=0.482	P=0.176
Incidental Tumor Tests (d)	P=0.046	P=0.419N	P=0.287	P=0.162
Cochran-Armitage Trend Test (d)	P=0.132			
Fisher Exact Test		P=0.500N	P=0.262	P=0.262
Circulatory System: Hemangiosarcoma				
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	9.4%	0.0%	0.0%	14.9%
Terminal Rates (c)	1/25 (4%)	0/31 (0%)	0/36 (0%)	2/21 (10%)
Life Table Tests (d)	P=0.159	P=0.101N	P=0.088N	P=0.410
Incidental Tumor Tests (d)	P=0.293	P=0.101N	P=0.136N	P=0.622
Cochran-Armitage Trend Test (d)	P=0.224			
Fisher Exact Test		P=0.121N	P=0.121N	P=0.500
Circulatory System: Hemangioma or Hemangiosarcoma				
Overall Rates (a)	4/50 (8%)	2/50 (4%)	0/50 (0%)	5/50 (10%)
Adjusted Rates (b)	13.2%	6.5%	0.0%	18.5%
Terminal Rates (c)	2/25 (8%)	2/31 (6%)	0/36 (0%)	2/21 (10%)
Life Table Tests (d)	P=0.246	P=0.262N	P=0.038N	P=0.394
Incidental Tumor Tests (d)	P=0.339	P=0.264N	P=0.058N	P=0.541
Cochran-Armitage Trend Test (d)	P=0.341			
Fisher Exact Test		P=0.339N	P=0.059N	P=0.500
Liver: Hepatocellular Adenoma				
Overall Rates (a)	3/50 (6%)	9/50 (18%)	10/50 (20%)	9/50 (18%)
Adjusted Rates (b)	10.4%	29.0%	24.9%	37.3%
Terminal Rates (c)	2/25 (8%)	9/31 (29%)	7/36 (19%)	7/21 (33%)
Life Table Tests (d)	P=0.034	P=0.114	P=0.113	P=0.032
Incidental Tumor Tests (d)	P=0.106	P=0.124	P=0.141	P=0.078
Cochran-Armitage Trend Test (d)	P=0.106			
Fisher Exact Test		P=0.061	P=0.036	P=0.061
Liver: Hepatocellular Carcinoma				
Overall Rates (a)	6/50 (12%)	15/50 (30%)	13/50 (26%)	8/50 (16%)
Adjusted Rates (b)	22.2%	37.3%	31.4%	28.2%
Terminal Rates (c)	5/25 (20%)	7/31 (23%)	8/36 (22%)	3/21 (14%)
Life Table Tests (d)	P=0.384	P=0.079	P=0.205	P=0.266
Incidental Tumor Tests (d)	P=0.449N	P=0.057	P=0.202	P=0.502
Cochran-Armitage Trend Test (d)	P=0.507N			
Fisher Exact Test		P=0.024	P=0.062	P=0.387
Liver: Hepatocellular Adenoma or Carcinoma				
Overall Rates (a)	9/50 (18%)	21/50 (42%)	20/50 (40%)	16/50 (32%)
Adjusted Rates (b)	31.7%	53.0%	47.3%	57.1%
Terminal Rates (c)	7/25 (28%)	13/31 (42%)	14/36 (39%)	10/21 (48%)
Life Table Tests (d)	P=0.062	P=0.044	P=0.109	P=0.032
Incidental Tumor Tests (d)	P=0.217	P=0.032	P=0.111	P=0.116
Cochran-Armitage Trend Test (d)	P=0.208			
Fisher Exact Test		P=0.008	P=0.013	P=0.083

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	Control	600 ppm	1,200 ppm	2,500 ppm
Thyroid: Follicular Cell Adenoma				
Overall Rates (a)	2/49 (4%)	4/50 (8%)	5/49 (10%)	2/49 (4%)
Adjusted Rates (b)	8.3%	12.9%	14.3%	9.5%
Terminal Rates (c)	2/24 (8%)	4/31 (13%)	5/35 (14%)	2/21 (10%)
Life Table Tests (d)	P=0.569	P=0.459	P=0.389	P=0.648
Incidental Tumor Tests (d)	P=0.569	P=0.459	P=0.389	P=0.648
Cochran-Armitage Trend Test (d)	P=0.513N			
Fisher Exact Test		P=0.349	P=0.218	P=0.691
Harderian Gland: Adenoma				
Overall Rates (a)	2/50 (4%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	8.0%	8.9%	2.8%	7.8%
Terminal Rates (c)	2/25 (8%)	2/31 (6%)	1/36 (3%)	1/21 (5%)
Life Table Tests (d)	P=0.601N	P=0.588	P=0.373N	P=0.630
Incidental Tumor Tests (d)	P=0.577N	P=0.556	P=0.373N	P=0.673N
Cochran-Armitage Trend Test (d)	P=0.508N			
Fisher Exact Test		P=0.500	P=0.500N	P=0.691
Harderian Gland: Adenoma or Carcinoma				
Overall Rates (a)	3/50 (6%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	12.0%	8.9%	2.8%	7.8%
Terminal Rates (c)	3/25 (12%)	2/31 (6%)	1/36 (3%)	1/21 (5%)
Life Table Tests (d)	P=0.434N	P=0.569N	P=0.185N	P=0.580N
Incidental Tumor Tests (d)	P=0.414N	P=0.599N	P=0.185N	P=0.490N
Cochran-Armitage Trend Test (d)	P=0.353N			
Fisher Exact Test		P=0.661	P=0.309N	P=0.500N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(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 overall incidence. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	Control	600 ppm	1,200 ppm	2,500 ppm
Lung: Alveolar/Bronchiolar Adenoma				
Overall Rates (a)	0/49 (0%)	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	0.0%	13.8%	2.9%	5.9%
Terminal Rates (c)	0/33 (0%)	3/27 (11%)	1/35 (3%)	1/29 (3%)
Life Table Tests (d)	P=0.415	P=0.041	P=0.512	P=0.218
Incidental Tumor Tests (d)	P=0.437	P=0.038	P=0.512	P=0.236
Cochran-Armitage Trend Test (d)	P=0.436			
Fisher Exact Test		P=0.061	P=0.505	P=0.253
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma				
Overall Rates (a)	1/49 (2%)	5/50 (10%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	2.5%	17.4%	5.7%	9.3%
Terminal Rates (c)	0/33 (0%)	4/27 (15%)	2/35 (6%)	2/29 (7%)
Life Table Tests (d)	P=0.422	P=0.062	P=0.505	P=0.270
Incidental Tumor Tests (d)	P=0.450	P=0.056	P=0.488	P=0.299
Cochran-Armitage Trend Test (d)	P=0.451			
Fisher Exact Test		P=0.107	P=0.508	P=0.316
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type				
Overall Rates (a)	1/50 (2%)	3/50 (6%)	2/50 (4%)	6/50 (12%)
Adjusted Rates (b)	2.8%	10.1%	5.7%	17.6%
Terminal Rates (c)	0/34 (0%)	1/27 (4%)	2/35 (6%)	4/29 (14%)
Life Table Tests (d)	P=0.032	P=0.234	P=0.507	P=0.047
Incidental Tumor Tests (d)	P=0.039	P=0.191	P=0.481	P=0.060
Cochran-Armitage Trend Test (d)	P=0.035			
Fisher Exact Test		P=0.309	P=0.500	P=0.056
Hematopoietic System: Malignant Lymphoma, Histiocytic Type				
Overall Rates (a)	2/50 (4%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	4.8%	0.0%	7.7%	3.4%
Terminal Rates (c)	0/34 (0%)	0/27 (0%)	2/35 (6%)	1/29 (3%)
Life Table Tests (d)	P=0.564N	P=0.298N	P=0.503	P=0.533N
Incidental Tumor Tests (d)	P=0.545N	P=0.218N	P=0.452	P=0.474N
Cochran-Armitage Trend Test (d)	P=0.553N			
Fisher Exact Test		P=0.248N	P=0.500	P=0.500N
Hematopoietic System: Malignant Lymphoma, Mixed Type				
Overall Rates (a)	14/50 (28%)	11/50 (22%)	11/50 (22%)	10/50 (20%)
Adjusted Rates (b)	36.7%	33.5%	28.2%	32.5%
Terminal Rates (c)	11/34 (32%)	7/27 (26%)	8/35 (23%)	9/29 (31%)
Life Table Tests (d)	P=0.295N	P=0.571N	P=0.308N	P=0.379N
Incidental Tumor Tests (d)	P=0.263N	P=0.353N	P=0.351N	P=0.325N
Cochran-Armitage Trend Test (d)	P=0.234N			
Fisher Exact Test		P=0.323N	P=0.323N	P=0.242N
Hematopoietic System: Lymphoma, All Malignant				
Overall Rates (a)	17/50 (34%)	15/50 (30%)	16/50 (32%)	17/50 (34%)
Adjusted Rates (b)	41.4%	42.4%	40.2%	51.6%
Terminal Rates (c)	11/34 (32%)	8/27 (30%)	12/35 (34%)	14/29 (48%)
Life Table Tests (d)	P=0.412	P=0.459	P=0.477N	P=0.403
Incidental Tumor Tests (d)	P=0.462	P=0.477N	P=0.557N	P=0.501
Cochran-Armitage Trend Test (d)	P=0.489			
Fisher Exact Test		P=0.415N	P=0.500N	P=0.584N
Liver: Hepatocellular Adenoma				
Overall Rates (a)	2/50 (4%)	12/49 (24%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	5.9%	36.7%	8.6%	6.9%
Terminal Rates (c)	2/34 (6%)	8/26 (31%)	3/35 (9%)	2/29 (7%)
Life Table Tests (d)	P=0.174N	P=0.001	P=0.513	P=0.637
Incidental Tumor Tests (d)	P=0.161N	P=0.007	P=0.513	P=0.637
Cochran-Armitage Trend Test (d)	P=0.148N			
Fisher Exact Test		P=0.003	P=0.500	P=0.691

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	Control	600 ppm	1,200 ppm	2,500 ppm
Liver: Hepatocellular Adenoma or Carcinoma				
Overall Rates (a)	3/50 (6%)	13/49 (27%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	8.8%	40.2%	8.6%	12.4%
Terminal Rates (c)	3/34 (9%)	9/26 (35%)	3/35 (9%)	3/29 (10%)
Life Table Tests (d)	P=0.297N	P=0.002	P=0.651N	P=0.422
Incidental Tumor Tests (d)	P=0.282N	P=0.008	P=0.651N	P=0.448
Cochran-Armitage Trend Test (d)	P=0.257N			
Fisher Exact Test		P=0.005	P=0.661	P=0.500
Small Intestine: Adenomatous Polyp				
Overall Rates (a)	1/50 (2%)	3/49 (6%)	2/48 (4%)	0/48 (0%)
Adjusted Rates (b)	2.9%	11.1%	5.9%	0.0%
Terminal Rates (c)	1/34 (3%)	3/27 (11%)	2/34 (6%)	0/28 (0%)
Life Table Tests (d)	P=0.270N	P=0.226	P=0.500	P=0.539N
Incidental Tumor Tests (d)	P=0.270N	P=0.226	P=0.500	P=0.539N
Cochran-Armitage Trend Test (d)	P=0.248N			
Fisher Exact Test		P=0.301	P=0.485	P=0.510N
Pituitary: Adenoma				
Overall Rates (a)	7/48 (15%)	4/45 (9%)	8/48 (17%)	8/45 (18%)
Adjusted Rates (b)	19.6%	16.7%	24.2%	30.8%
Terminal Rates (c)	6/34 (18%)	4/24 (17%)	8/33 (24%)	8/26 (31%)
Life Table Tests (d)	P=0.183	P=0.481N	P=0.478	P=0.289
Incidental Tumor Tests (d)	P=0.184	P=0.480N	P=0.469	P=0.293
Cochran-Armitage Trend Test (d)	P=0.268			
Fisher Exact Test		P=0.300N	P=0.500	P=0.445
Thyroid: Follicular Cell Adenoma				
Overall Rates (a)	4/48 (8%)	1/50 (2%)	4/50 (8%)	1/46 (2%)
Adjusted Rates (b)	11.0%	2.6%	10.9%	3.6%
Terminal Rates (c)	2/32 (6%)	0/27 (0%)	3/35 (9%)	1/28 (4%)
Life Table Tests (d)	P=0.237N	P=0.252N	P=0.609N	P=0.220N
Incidental Tumor Tests (d)	P=0.241N	P=0.213N	P=0.629	P=0.219N
Cochran-Armitage Trend Test (d)	P=0.236N			
Fisher Exact Test		P=0.168N	P=0.619N	P=0.194N
Thyroid: Follicular Cell Adenoma or Carcinoma				
Overall Rates (a)	4/48 (8%)	2/50 (4%)	5/50 (10%)	1/46 (2%)
Adjusted Rates (b)	11.0%	6.2%	13.6%	3.6%
Terminal Rates (c)	2/32 (6%)	1/27 (4%)	4/35 (11%)	1/28 (4%)
Life Table Tests (d)	P=0.225N	P=0.435N	P=0.538	P=0.220N
Incidental Tumor Tests (d)	P=0.228N	P=0.393N	P=0.491	P=0.219N
Cochran-Armitage Trend Test (d)	P=0.223N			
Fisher Exact Test		P=0.319N	P=0.526	P=0.194N
Mammary Gland: Adenocarcinoma				
Overall Rates (a)	2/50 (4%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	5.4%	9.1%	2.9%	0.0%
Terminal Rates (c)	1/34 (3%)	1/27 (4%)	1/35 (3%)	0/29 (0%)
Life Table Tests (d)	P=0.115N	P=0.410	P=0.502N	P=0.269N
Incidental Tumor Tests (d)	P=0.104N	P=0.439	P=0.519N	P=0.246N
Cochran-Armitage Trend Test (d)	P=0.105N			
Fisher Exact Test		P=0.500	P=0.500N	P=0.247N
Mammary Gland: Adenocarcinoma, Carcinoma, or Adenocarcinoma/Squamous Metaplasia				
Overall Rates (a)	3/50 (6%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	8.2%	9.1%	5.0%	0.0%
Terminal Rates (c)	2/34 (6%)	1/27 (4%)	1/35 (3%)	0/29 (0%)
Life Table Tests (d)	P=0.081N	P=0.563	P=0.501N	P=0.149N
Incidental Tumor Tests (d)	P=0.072N	P=0.592	P=0.529N	P=0.136N
Cochran-Armitage Trend Test (d)	P=0.072N			
Fisher Exact Test		P=0.661	P=0.500N	P=0.121N

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1 (Continued)

	Control	600 ppm	1,200 ppm	2,500 ppm
Uterus: Endometrial Stromal Polyp				
Overall Rates (a)	3/50 (6%)	2/50 (4%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	7.9%	6.5%	2.5%	3.0%
Terminal Rates (c)	1/34 (3%)	1/27 (4%)	0/35 (0%)	0/29 (0%)
Life Table Tests (d)	P=0.216N	P=0.604N	P=0.304N	P=0.344N
Incidental Tumor Tests (d)	P=0.184N	P=0.561N	P=0.360N	P=0.290N
Cochran-Armitage Trend Test (d)	P=0.206N			
Fisher Exact Test		P=0.500N	P=0.309N	P=0.309N
Harderian Gland: Adenoma				
Overall Rates (a)	1/50 (2%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	2.9%	3.7%	7.9%	0.0%
Terminal Rates (c)	1/34 (3%)	1/27 (4%)	2/35 (6%)	0/29 (0%)
Life Table Tests (d)	P=0.420N	P=0.710	P=0.316	P=0.532N
Incidental Tumor Tests (d)	P=0.408N	P=0.710	P=0.294	P=0.532N
Cochran-Armitage Trend Test (d)	P=0.399N			
Fisher Exact Test		P=0.753	P=0.309	P=0.500N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(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 overall incidence. A negative trend or lower incidence in a dosed group is indicated by (N).

APPENDIX F

HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE RECEIVING NO TREATMENT

TABLE F1. HISTORICAL INCIDENCE OF URINARY BLADDER TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

	No. of Animals Examined	No. of Tumors	Diagnosis
Historical Incidence at Southern Research Institute			
	439	0	
Overall Historical Incidence			
	2,189	4	Transitional cell papilloma
		1	Leiomyoma
		1	Transitional cell carcinoma
TOTAL		(b) 6 (0.3%)	

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) The leiomyoma occurred in the same group as one of the transitional cell papillomas. No other control group had more than one of these tumors.

TABLE F2. HISTORICAL INCIDENCE OF URINARY BLADDER TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

	No. of Animals Examined	No. of Tumors	Diagnosis
Historical Incidence at Southern Research Institute			
Eugenol	40	1	Transitional cell papilloma
All others	399	0	
TOTAL	439	1 (0.2%)	
Overall Historical Incidence			
	2,263	2	Papilloma, NOS
		2	Transitional cell papilloma
		1	Transitional cell carcinoma
TOTAL		(b) 5 (0.2%)	

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) No more than one tumor was observed in any control group.

TABLE F3. HISTORICAL INCIDENCE OF LEUKEMIA IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Reserpine	18/49
Cytembena	20/50
Eugenol	13/40
Stannous chloride	6/50
Mannitol	14/50
Ziram	10/50
Propyl gallate	16/50
Zearalenone	9/50
HC Blue No. 1	13/50
TOTAL	119/439 (27.1%)
SD (b)	9.19%
Range (c)	
High	20/50
Low	6/50
Overall Historical Incidence	
TOTAL	648/2,320 (27.9%)
SD (b)	10.18%
Range (c)	
High	23/50
Low	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F4. HISTORICAL INCIDENCE OF LEUKEMIA IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Reserpine	14/50
Cytembena	10/49
Eugenol	7/40
Stannous chloride	6/50
Mannitol	10/50
Ziram	4/50
Propyl gallate	8/50
Zearalenone	7/50
HC Blue No. 1	4/50
TOTAL	70/439 (15.9%)
SD (b)	6.42%
Range (c)	
High	14/50
Low	4/50
Overall Historical Incidence	
TOTAL	414/2,370 (17.5%)
SD (b)	7.38%
Range (c)	
High	19/50
Low	(d) 0/48

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) This group had five diagnoses of lymphoma, which may represent a difference in nomenclature. The second lowest incidence was 3/50.

TABLE F5. HISTORICAL INCIDENCE OF THYROID GLAND C-CELL TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Reserpine	2/49	1/49	3/49
Cytembena	3/48	2/48	4/48
Eugenol	4/40	3/40	7/40
Stannous chloride	2/50	0/50	2/50
Mannitol	8/49	2/49	10/49
Ziram	4/50	0/50	4/50
Propyl gallate	4/50	3/50	7/50
Zearalenone	3/49	0/49	3/49
HC Blue No. 1	9/50	1/50	10/50
TOTAL	39/435 (9.0%)	12/435 (2.8%)	50/435 (11.5%)
SD (b)	5.03%	2.75%	6.42%
Range (c)			
High	9/50	3/40	10/49
Low	2/50	0/50	2/50
Overall Historical Incidence			
TOTAL	114/2,230 (5.1%)	84/2,230 (3.8%)	196/2,230 (8.8%)
SD (b)	4.38%	3.30%	5.00%
Range (c)			
High	9/50	6/49	10/49
Low	0/89	0/50	0/47

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F6. HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Pheochromocytoma	Malignant Pheochromocytoma	Pheochromocytoma or Malignant Pheochromocytoma
Historical Incidence at Southern Research Institute			
Reserpine	3/48	1/48	3/48
Cytembena	11/48	0/48	11/48
Eugenol	9/40	0/40	9/40
Stannous chloride	4/50	1/50	5/50
Mannitol	14/50	0/50	14/50
Ziram	7/50	0/50	7/50
Propyl gallate	4/50	0/50	4/50
Zearalenone	5/50	2/50	7/50
HC Blue No. 1	20/49	1/49	21/49
TOTAL	77/435 (17.7%)	5/435 (1.1%)	81/435 (18.6%)
SD (b)	11.63%	1.46%	11.68%
Range (c)			
High	20/49	2/50	21/49
Low	3/48	0/50	3/48
Overall Historical Incidence			
TOTAL	(d) 388/2,280 (17.0%)	23/2,280 (1.0%)	409/2,280 (17.9%)
SD (b)	9.20%	1.44%	9.03%
Range (c)			
High	20/49	3/48	21/49
Low	2/50	0/50	3/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes eight diagnoses of pheochromocytoma of the adrenal medulla

TABLE F7. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	All Adenoma	All Carcinoma	All Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Reserpine	14/49	4/49	18/49
Cytembena	3/50	0/50	3/50
Eugenol	2/39	0/39	2/39
Stannous chloride	11/50	1/50	12/50
Mannitol	9/46	0/46	9/46
Ziram	13/50	2/50	15/50
Propyl gallate	5/49	0/49	5/49
Zearalenone	5/46	1/46	6/46
HC Blue No. 1	9/49	2/49	11/49
TOTAL	71/428 (16.6%)	10/428 (2.3%)	81/428 (18.9%)
SD (b)	8.59%	2.78%	10.87%
Range (c)			
High	14/49	4/49	18/49
Low	2/39	0/50	2/39
Overall Historical Incidence			
TOTAL	(d) 468/2,158 (21.7%)	(e) 51/2,158 (2.4%)	519/2,158 (24.1%)
SD (b)	11.80%	2.99%	11.94%
Range (c)			
High	24/46	5/45	25/46
Low	1/47	0/50	1/47

(a) Data as of March 16, 1983, for studies of at least 104 weeks. Includes all tumors diagnosed as NOS, chromophobe, acidophil, or basophil.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes two adenomas, NOS, of the anterior pituitary
(e) Includes one carcinoma, NOS, of the anterior pituitary

TABLE F8. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Reserpine	21/46	0/46	21/46
Cytembena	18/47	3/47	21/47
Eugenol	7/39	2/39	9/39
Stannous chloride	17/50	0/50	17/50
Mannitol	24/50	1/50	25/50
Ziram	19/50	3/50	22/50
Propyl gallate	16/50	1/50	17/50
Zearalenone	13/49	1/49	14/49
HC Blue No. 1	25/50	6/50	31/50
TOTAL	160/431 (37.1%)	17/431 (3.9%)	177/431 (41.1%)
SD (b)	10.45%	3.85%	11.93%
Range (c)			
High	25/50	6/50	31/50
Low	7/39	0/50	9/39
Overall Historical Incidence			
TOTAL	995/2,262 (44.0%)	80/2,262 (3.5%)	1,074/2,262 (47.5%)
SD (b)	11.34%	4.69%	10.59%
Range (c)			
High	33/47	9/47	35/48
Low	7/39	0/50	9/39

(a) Data as of March 16, 1983, for studies of at least 104 weeks. Includes all tumors diagnosed as NOS, chromophobe, acidophil, or basophil.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F9. HISTORICAL INCIDENCE OF PANCREATIC ISLET CELL TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma (b)	Carcinoma (c)	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Reserpine	2/49	2/49	4/49
Cytembena	1/49	1/49	2/49
Eugenol	0/40	1/40	1/40
Stannous chloride	2/50	3/50	5/50
Mannitol	3/50	0/50	3/50
Ziram	2/50	1/50	2/50
Propyl gallate	0/50	2/50	2/50
Zearalenone	2/49	1/49	3/49
HC Blue No. 1	5/49	0/49	5/49
TOTAL	17/436 (3.9%)	11/436 (2.5%)	27/436 (6.2%)
SD (b)	3.12%	1.94%	2.79%
Range (c)			
High	5/49	3/50	5/49
Low	0/50	0/50	1/40
Overall Historical Incidence			
TOTAL	84/2,226 (3.8%)	46/2,226 (2.1%)	129/2,226 (5.8%)
SD (b)	3.63%	2.28%	3.70%
Range (c)			
High	6/48	4/47	7/48
Low	0/88	0/50	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F10. HISTORICAL INCIDENCE OF MESOTHELIOMAS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	No. of Animals Examined	No. of Tumors	Site	Diagnosis
Historical Incidence at Southern Research Institute				
Reserpine	49	1	Tunica vaginalis	NOS
Cytembena	50	1	Tunica vaginalis	NOS
Stannous chloride	50	1	Tunica vaginalis	NOS
Zearalenone	50	1	Tunica vaginalis	Benign
		1	Abdominal cavity	Benign
All others	240	0		
TOTAL	439	5 (1.1%)		
Overall Historical Incidence				
	2,320	1	Body cavities, NOS	NOS
		1	Abdominal cavity	Benign
		1	Abdominal cavity	NOS
		2	Peritoneum	NOS
		2	Peritoneum	Malignant
		1	Peritoneal cavity	NOS
		1	Tunica vaginalis	Benign
		24	Tunica vaginalis	NOS
		5	Tunica vaginalis	Malignant
		6	Multiple organs	NOS
		8	Multiple organs	Malignant
		1	Omentum	NOS
TOTAL		53 (2.3%)		

(a) Data as of March 16, 1983, for studies of at least 104 weeks. The greatest incidence observed in any control group is 6/50.

TABLE F11. HISTORICAL INCIDENCE OF TESTICULAR TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Interstitial Cell Tumors in Controls
Historical Incidence at Southern Research Institute	
Reserpine	43/49
Cytembena	47/50
Eugenol	38/40
Stannous chloride	34/50
Mannitol	45/50
Ziram	41/50
Propyl gallate	47/50
Zearalenone	45/50
HC Blue No. 1	45/50
TOTAL	385/439 (87.7%)
SD (b)	8.43%
Range (c)	
High	38/40
Low	34/50
Overall Historical Incidence	
TOTAL	(d) 2,002/2,285 (87.6%)
SD (b)	8.85%
Range (c)	
High	49/50
Low	29/49

(a) Data as of March 16, 1983, for studies of at least 104 weeks.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Total includes 46 diagnoses of interstitial cell tumor, malignant, 44 of which were in one control group.

TABLE F12. HISTORICAL INCIDENCE OF LIVER TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Neoplastic Nodule	Hepatocellular Carcinoma	Neoplastic Nodule or Hepatocellular Carcinoma
Historical Incidence at Southern Research Institute			
Reserpine	0/49	0/49	0/49
Cytembena	0/50	1/50	1/50
Eugenol	2/40	0/40	2/40
Stannous chloride	2/50	0/50	2/50
Mannitol	0/50	0/50	0/50
Ziram	2/50	0/50	2/50
Propyl gallate	2/50	0/50	2/50
Zearalenone	2/50	0/50	2/50
HC Blue No. 1	0/49	1/49	1/49
TOTAL	10/438 (2.3%)	2/438 (0.5%)	12/438 (2.7%)
SD (b)	2.24%	0.89%	1.85%
Range (c)			
High	2/40	1/49	2/40
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	78/2,306 (3.4%)	18/2,306 (0.8%)	96/2,306 (4.2%)
SD (b)	3.46%	1.09%	3.86%
Range (c)			
High	6/49	2/49	7/49
Low	0/50	0/90	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F13. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Fibroadenomas in Controls
Historical Incidence at Southern Research Institute	
Reserpine	14/50
Cytembena	17/49
Eugenol	14/40
Stannous chloride	16/50
Mannitol	10/50
Ziram	16/50
Propyl gallate	11/50
Zearalenone	9/50
HC Blue No. 1	13/50
TOTAL	120/439 (27.3%)
SD (b)	6.40%
Range (c)	
High	14/40
Low	9/50
Overall Historical Incidence	
TOTAL	(d) 543/2,370 (22.9%)
SD (b)	10.41%
Range (c)	
High	22/50
Low	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes four animals in one group diagnosed with cystfibroadenoma. Two fibroadenocarcinomas also have been observed.

TABLE F14. HISTORICAL INCIDENCE OF UTERINE ENDOMETRIAL TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Endometrial Stromal Polyps in Controls
Historical Incidence at Southern Research Institute	
Reserpine	10/50
Cytembena	9/48
Eusenol	6/40
Stannous chloride	11/50
Mannitol	10/50
Ziram	5/50
Propyl sallate	6/50
Zearalenone	4/50
HC Blue No. 1	5/50
TOTAL	66/438 (15.1%)
SD (b)	5.26%
Range (c)	
High	11/50
Low	4/50
Overall Historical Incidence	
TOTAL	424/2,318 (18.3%)
SD (b)	8.09%
Range (c)	
High	18/49
Low	2/47

(a) Data as of March 16, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F15. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Reserpine	7/50	6/50	12/50
Cytembena	4/47	13/47	17/47
Mannitol	3/50	11/50	14/50
Ziram	6/49	13/49	19/49
Eugenol	4/50	10/50	14/50
Propyl gallate	3/50	14/50	17/50
Zearalenone	4/50	15/50	19/50
HC Blue No. 1	4/50	11/50	15/50
Stannous chloride	7/50	10/50	16/50
TOTAL	42/446 (9.4%)	103/446 (23.1%)	143/446 (32.1%)
SD (b)	3.17%	5.58%	5.04%
Range (c)			
High	7/50	15/50	19/49
Low	3/50	6/50	12/50
Overall Historical Incidence			
TOTAL	240/2,334 (10.3%)	498/2,334 (21.3%)	725/2,334 (31.1%)
SD (b)	4.98%	6.95%	7.47%
Range (c)			
High	11/50	18/50	29/50
Low	0/49	4/50	7/44

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F16. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Reserpine	4/50	5/50	9/50
Cytembena	6/48	8/48	14/48
Mannitol	6/50	3/50	9/50
Ziram	6/49	3/49	8/49
Eugenol	9/49	5/49	13/49
Propyl gallate	3/50	1/50	4/50
Zearalenone	7/50	4/50	11/50
HC Blue No. 1	3/50	3/50	5/50
Stannous chloride	7/50	3/50	10/50
TOTAL	51/446 (11.4%)	35/446 (7.8%)	83/446 (18.6%)
SD (b)	4.10%	4.11%	6.89%
Range (c)			
High	9/49	8/48	14/48
Low	3/50	1/50	4/50
Overall Historical Incidence			
TOTAL	282/2,328 (12.1%)	119/2,328 (5.1%)	393/2,328 (16.9%)
SD (b)	6.73%	4.41%	8.32%
Range (c)			
High	14/50	9/50	17/50
Low	0/47	0/50	1/49

(a) Data as of March 16, 1983, for studies of at least 104 weeks.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F17. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Fibroma	Fibrosarcoma	Fibroma or Fibromasarcoma
Historical Incidence at Southern Research Institute			
Reserpine	0/50	0/50	0/50
Cytembena	0/49	0/49	0/49
Mannitol	2/50	3/50	4/50
Ziram	0/49	0/49	0/49
Eugenol	2/50	0/50	4/50
Propyl gallate	5/50	2/50	7/50
Zearalenone	0/50	0/50	0/50
HC Blue No. 1	3/50	1/50	5/50
Stannous chloride	0/50	3/50	4/50
TOTAL	12/448 (2.7%)	9/448 (2.0%)	24/448 (5.4%)
SD (b)	3.61%	2.65%	5.39%
Range (c)			
High	5/50	3/50	7/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	28/2,343 (1.2%)	66/2,343 (2.8%)	91/2,343 (3.9%)
SD (b)	2.02%	4.01%	4.81%
Range (c)			
High	5/50	9/48	11/48
Low	0/50	0/50	0/50

(a) Data as of March 16, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F18. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Reserpine	2/50	0/50	2/50
Cytembena	0/48	2/48	2/48
Mannitol	0/48	3/48	3/48
Ziram	7/50	2/50	9/50
Eugenol	0/50	2/50	2/50
Propyl gallate	0/50	3/50	3/50
Zearalenone	0/50	3/50	3/50
HC Blue No. 1	2/50	1/50	3/50
Stannous chloride	3/49	0/49	3/49
TOTAL	14/445 (3.1%)	16/445 (3.6%)	30/445 (6.7%)
SD (b)	4.71%	2.44%	4.34%
Range (c)			
High	7/50	3/48	9/50
Low	0/50	0/50	2/50
Overall Historical Incidence			
TOTAL	98/2,469 (4.0%)	(d) 101/2,469 (4.1%)	196/2,469 (7.9%)
SD (b)	3.90%	3.01%	4.58%
Range (c)			
High	9/49	7/48	10/49
Low	0/50	0/50	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) One hepatoblastoma was also observed.

TABLE F19. HISTORICAL INCIDENCE OF SMALL INTESTINE TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	No. of Animals Examined	No. of Tumors	Diagnosis
Historical Incidence at Southern Research Institute			
Cytembena	44	1	Adenocarcinoma, NOS
Ziram	46	1	Mucinous adenocarcinoma
HC Blue No. 1	49	1	Adenomatous polyp, NOS
Stannous chloride	48	1	Adenomatous polyp, NOS
All others	242	0	
TOTAL	429	4 (0.9%)	
Overall Historical Incidence			
	2,234	3	Adenomatous polyp, NOS
		1	Adenocarcinoma, NOS
		1	Mucinous adenocarcinoma
TOTAL		(b) 5 (0.2%)	

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) No more than one tumor was observed in any control group.

APPENDIX G

CHEMICAL CHARACTERIZATION OF

C.I. DISPERSE BLUE 1

APPENDIX G. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of C.I. Disperse Blue 1 Performed by the Analytical Chemistry Laboratory

A. Lot No. 3460777

1. Physical Properties

a. Appearance: Blue-black microcrystalline powder

b. Melting Point:	**Determined**	**Literature Values**
	Sample decomposed without melting at 335° C (visual melting point, capillary). Two overlapping exotherms from 225°-321° C, smaller exotherm from 335°-338° C (Dupont 900 DTA)	No literature value found. Manufacturer's data: m.p. 332° C (Clairol Research Laboratories)

2. Spectral Data

a. Infrared	**Determined**	**Literature Values**
(1) Instrument:	Beckman IR-12	
(2) Phase:	1.5% Potassium bromide pellet	
(3) Results:	See Figure 6	No literature reference found. Spectrum consistent with structure and with spectum of purified dye

b. Ultraviolet/Visible	**Determined**	**Literature Values**
(1) Instrument:	Cary 118	
(2) Solvent:	Methanol	Methanol

(3) Results:

Determined		Literature Values	
λ_{max} (nm)	ε	λ_{max} (nm)	ε[a]
630	6,325 ± 66 (8)	628	12,880
594	5,957 ± 93 (8)		
320 (shoulder)	2,061 ± 29 (8)		
271	6,540 ± 44 (8)		
237	18,010 ± 690 (8)		

(a) Clairol quotes 51.2% as the purity of commercial dyes. It does not state what method was used to determine purity; however, from data provided for the absorbance of the purified dye and MRI measured data, the purity of lot no. 3460777 was calculated to be 49.1%.

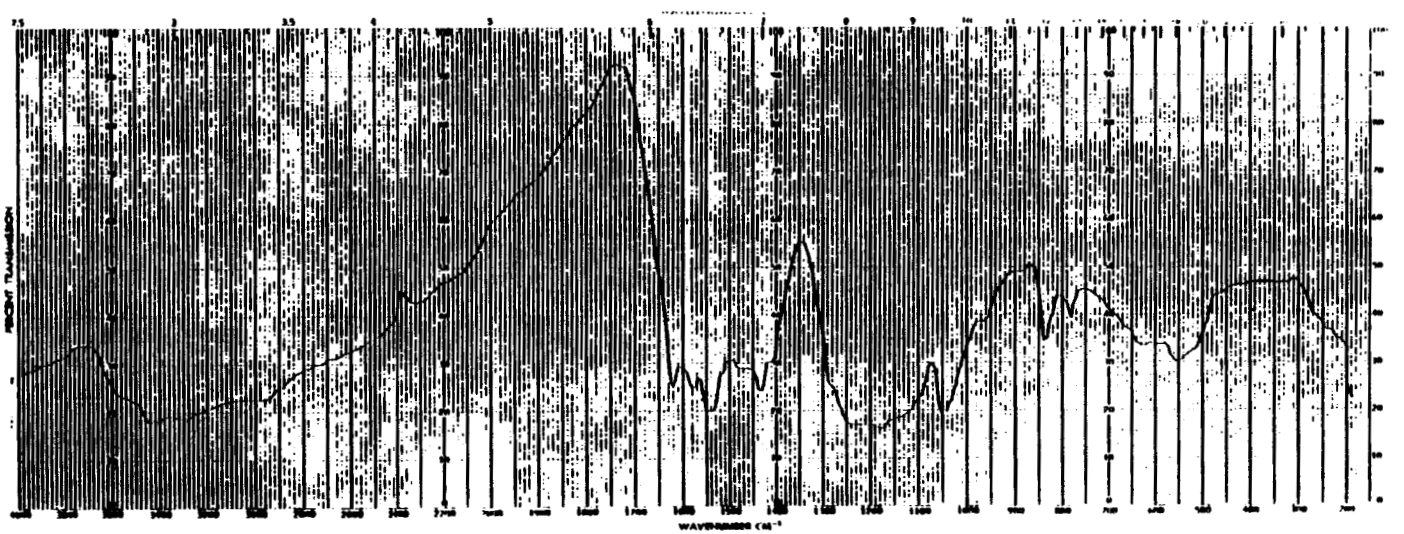


FIGURE 6. INFRARED ABSORPTION SPECTRUM OF C.I. DISPERSE BLUE 1 (LOT NO. 3460777)

c. Nuclear Magnetic Resonance

	Determined	Literature Values
(1) Instrument:	Varian EM-360A	
(2) Solvent:	Dimethylsulfoxide-d_6 with tetramethylsilane added	
(3) Assignments:	See Figure 7	No literature reference found. In structural agreement with spectrum received from Clairol for purified dye.
(4) Chemical Shift (δ):	a s 7.00 ppm b s 7.63 ppm c 0.67-1.50 ppm d 3.00-4.33 ppm (water--usually observed as a sharp singlet) e 6.33-6.93 ppm Peaks c and e are unresolved impurity peaks; peaks a, b, and d are unusually broadened and therefore may also contain unresolved impurity peaks. Integration ratios not reported because of unresolved nature of spectra. Conforms to the structure; however, broadened unresolved peaks indicative of impurities present in the sample.	

3. Titration: Titration of the amine groups with perchloric acid was unsuccessful because the compound was not sufficiently soluble in nonaqueous solvents.

4. Water Analysis (Karl Fischer): 9.74% ± 0.25(δ)%

5. Elemental Analysis

Element	C	H	N	S	Cl	Na	P
Theory (T)	62.68	4.51	20.88	0	0	0	0
Determined (D)	47.85 48.01	4.37 4.26	7.01 6.97 7.09 7.06	5.45	Not measurable	7.21 7.26	<0.01% <0.01%
Percent D/T	76	96	34				

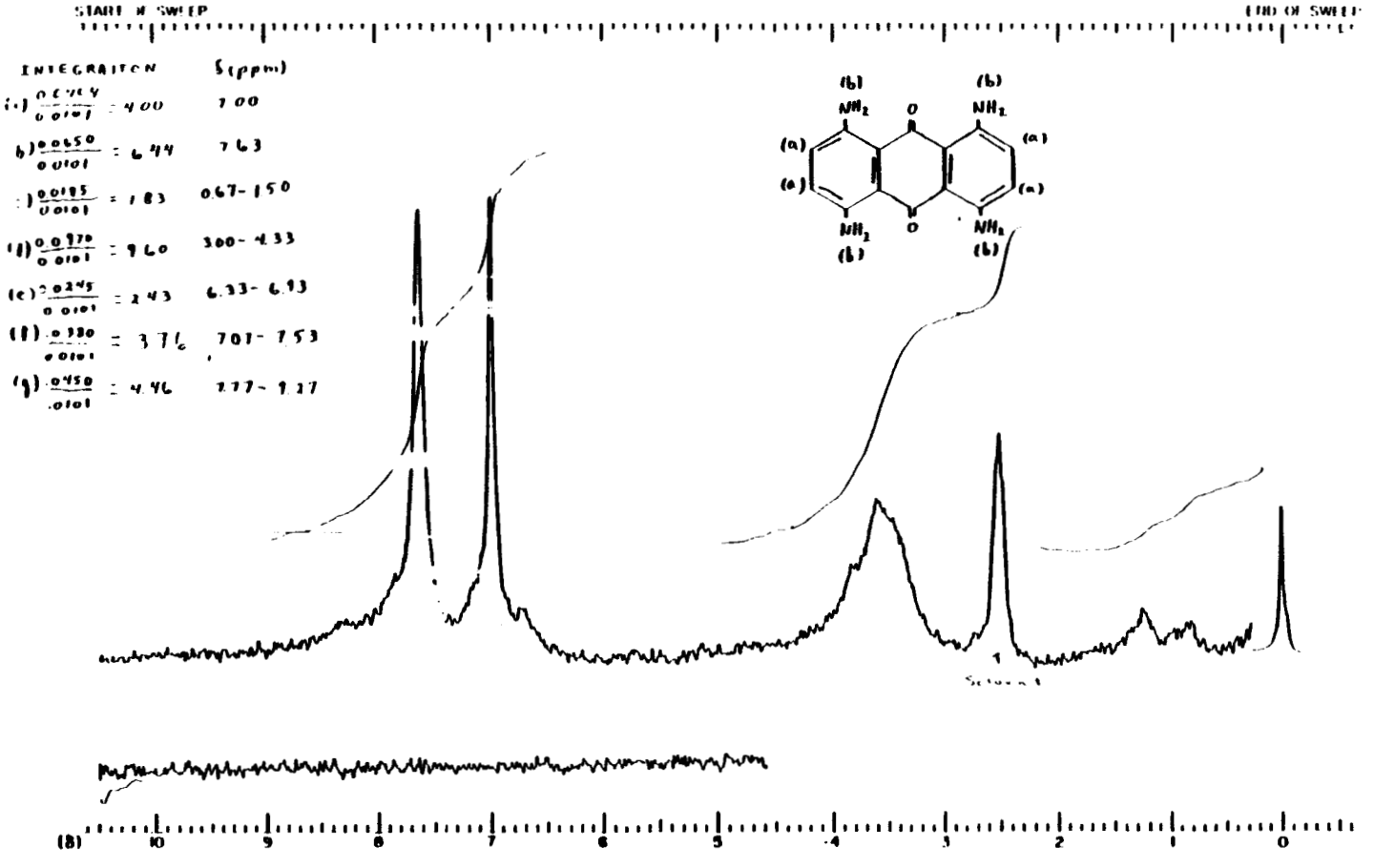


FIGURE 7. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF C.I. DISPERSE BLUE 1 (LOT NO. 3460777)

6. Chromatographic Analysis

a. Thin-Layer Chromatography

(1) Plates: Silica Gel 60 F254; 0.25 mm layer
(2) Reference standard: *p*-Aminoacetophenone
(3) Amount spotted: 5 and 30 µg; 0.1 and 3 µg/µl in water:methanol (1:9)
(4) Visualization: Ultraviolet (254 and 366 nm), furfural reagent

System 1: *n*-Butanol:ethanol:water:concentrated ammonium hydroxide (40:20:20:20)

Spot Intensity	R_f	R_{st}
Major	0.73	0.94
Trace	0.48	0.62
Slight trace	0.43	0.56
Trace	0.41	0.53
Slight trace	0.33	0.43
Slight trace	0.30	0.39
Slight trace	0.24	0.31
Trace	origin	origin

System 2: Chloroform:acetone (50:50)

Spot Intensity	R_f	R_{st}
Trace	0.55	0.90
Major	0.48	0.79
Minor	origin	origin

b. High-Performance Liquid Chromatography

(1) Instrument: Waters programmable component system
(2) Column: µBondapak C_{18}, 30 cm × 4 mm ID
(3) Detector: Ultraviolet, 280 nm
(4) Flow rate: 1.0 ml/min
(5) Solvent program: 70% (A):30% (B)
(A) Water with 5mM tetrabutylammonium hydroxide (adjusted to pH 7.4 with 1% phosphoric acid
(B) Methanol with 5mM tetrabutylammonium hydroxide and an equal amount of 1% phosphoric acid as in the water

(6) Results: Major peak and 16 impurities. Three unresolved impurity peaks had combined areas of 4.1% of the major peak area. Two other unresolved impurity peaks had a combined area of 11% of the major peak area. Three other impurities had areas of 6.6%, 4.1%, 3.4% of the major peak area. The areas of the remaining eight impurities totaled $<5.5\%$ of the major peak area.

Peak No.	Retention Time (min)	Retention Time Relative to Largest Peak		Area (percent of largest peak)
1	2.4	0.07	unresolved	4.1
2	3.0	0.09		
3	3.1	0.09		
4	4.5	0.14	unresolved	1.5
5	5.3	0.16		
6	6.6	0.20		0.94
7	7.9	0.24	unresolved	1.4
8	8.5	0.26		
9	13.0	0.39		0.30
10	19.5	0.59		0.70
11	31.1	0.94		6.6
12	33.1	1.00		100
13	41.8	1.26	unresolved	11
14	48.1	1.45		
15	64.6	1.95		4.1
16	80.0	2.42		0.45
17	107	3.24		3.4

7. Conclusions: The results of the elemental analysis for carbon and nitrogen were low; analysis for hydrogen was in agreement with the theoretical value. Elemental analysis also indicated 5.45% sulfur and 7.24% sodium. Titration with Karl Fischer reagent indicated 9.74% ± 0.25% water. The infrared spectrum was consistent with the structure and the spectrum of the purified dye provided by the manufacturer. The ultraviolet spectrum indicated absorbances at 630 nm, 594 nm, 320 nm, 271 nm, and 237nm with ε_{max} of 6,325, 5,957, 2,061, 6,540, and 18,010. Data from the manufacturer indicated an absorbance at 628 nm with an ε_{max} of 12,882. The sample ε_{max} at 630 nm is 49.1% of the corresponding ε_{max} given for the purified dye. However, nitrogen analysis indicated a maximum possible purity of 34%. The nuclear magnetic resonance spectrum was consistent with the structure, but the peaks were so broadened and unresolved that integration data were meaningless.

Thin-layer chromatography on one system indicated one major spot, three trace impurity spots, and four slight trace impurity spots. Another thin-layer chromatographic system indicated one major spot, one minor spot, and one trace impurity spot. High-performance liquid chromatography indicated one major peak and 16 impurity peaks. Three unresolved impurity peaks had combined areas of 4.1% of the major peak, and two unresolved impurity peaks had areas of 11% of the major peak. Other large impurities had areas 6.4%, 4.1%, and 3.5% of the major peak area. The areas of the other eight impurities totaled less than 6% of the major peak area.

B. Lot No. 4351828

1. Physical Properties

a. Appearance: Blue-black microcrystalline powder

b. Melting Point:	**Determined**	**Literature Values**
	No melting point seen to 290° C (visual capillary Büchi 510 mp apparatus). 35°-84° C (broad endotherm) 325°-333° C (exotherm) (Dupont 900 DTA)	No literature value found. Manufacturer's data m.p. 332° C (Clairol Research Laboratories)

2. Spectral Data

a. Infrared	**Determined**	**Literature Values**
(1) Instrument:	Beckman IR-12	
(2) Phase:	1.4% in potassium bromide pellet	
(3) Results:	See Figure 8	No literature reference found. Consistent with spectrum of purified dye (Clairol Research Laboratories)

b. Ultraviolet/Visible	**Determined**	**Literature Values**
(1) Instrument:	Cary 118	
(2) Solvent:	Acetonitrile	Methanol

(3). Results:

Determined λ_{max} (nm)	Determined ε	Literature Values λ_{max} (nm)	Literature Values ε
237	33,616 ± 646(δ)	628	12,880
271	12,564 ± 363(δ)		
323 (shoulder)	3,759 ± 252(δ)		
319 (shoulder)	4,940 ± 288(δ)		
594	14,698 ± 416(δ)		
635	15,854 ± 454(δ)		

(Clairol provided ultraviolet-visible data indicating a λ_{max} of 628 nm and an ε_{max} of 12,880 in methanol. Acetonitrile was used as the solvent for the sample spectrum because of better solubility and reproducibility. When run in methanol, a λ_{max} of 630 was observed with an ε_{max} of 14,556 ± 968.)

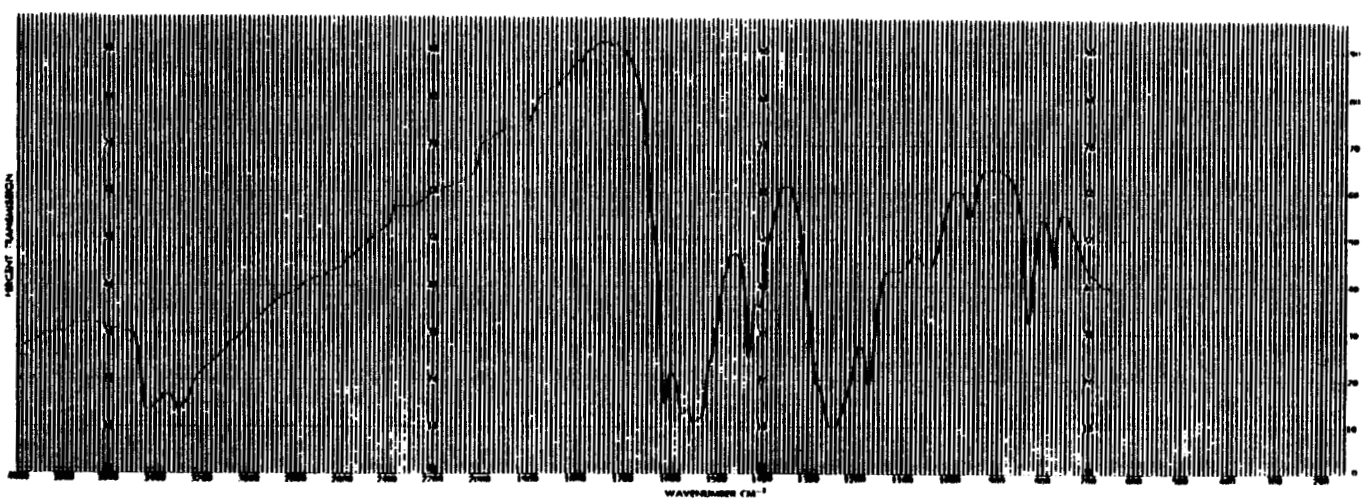


FIGURE 8. INFRARED ABSORPTION SPECTRUM OF C.I. DISPERSE BLUE 1 (LOT NO. 4351828)

c. Nuclear Magnetic Resonance	Determined	Literature Values
(1) Instrument:	Varian EM-360A	
(2) Solvent:	Dimethylsulfoxide-d_6 with internal tetramethylsilane	
(3) Assignments:	See Figure 9	Spectrum consistent with structure
(4) Chemical Shift (δ):	a s, 7.00 ppm b s, 7.63 ppm	
(5) Integration Ratios:	a 4.04 b 7.96	

3. Titration: Nonaqueous titration of two amine groups with perchloric acid--62.9% ± 0.2% (sample weights corrected for 19.47% water)

4. Water Analysis (Karl Fischer): 19.47% ± 0.58(δ)%

5. Elemental Analysis

Element	C	H	N	S
Theory (T) (a)	50.48	5.79	16.81	0
Determined (D)	49.01 48.87	5.45 5.61	15.95 15.84	0.28 0.26
Percent D/T	96.95	95.51	94.56	--

(a) Based on 19.47% water and 80.53% C.I. Disperse Blue 1 by difference

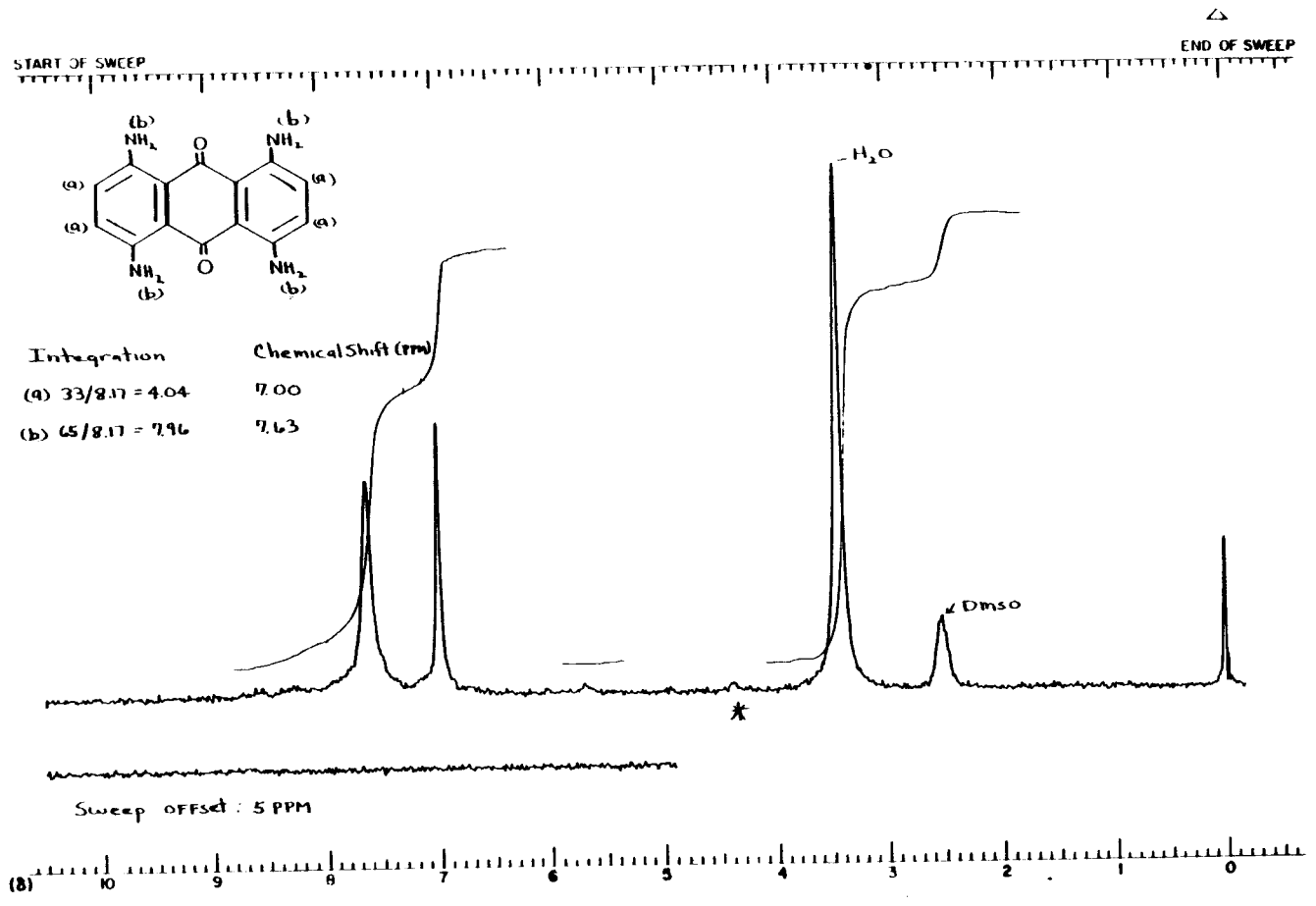


FIGURE 9. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF C.I. DISPERSE BLUE 1 (LOT NO. 4351828)

6. Chromatographic Analysis

a. Thin-Layer Chromatography

(1) **Plates:** Silica Gel 60, F 254; 0.25 mm layer
(2) **Reference standard:** α-Aminoacetophenone (2 µl of a 5 µg/µl solution in methanol)
(3) **Amount spotted:** 15 µg and 50 µg; 3 and 10 µl of a 5 µg/µl solution in methanol:water (9:1)
(4) **Visualization:** Ultraviolet light (254 nm), furfural in glacial acetic acid (10 drops:10 ml)

System 1: *n*-Butanol:ethanol:water:ammonium hydroxide (40:20:20:20)

Spot Intensity	R_f	R_{st}
Major	0.82	0.93
Minor	0.61	0.70
Trace	origin	origin

System 2: Chloroform:acetone (50:50)

Spot Intensity	R_f	R_{st}
Major	0.72	12.34
Minor	0.63	10.87
Slight trace	0.14	2.50
Trace	origin	origin

b. High-Performance Liquid Chromatography

Pump(s): Waters 6000A
Programmer: Waters 660
Detector: Waters 440
Injector: U6K
Detection: Ultraviolet, 254 nm
Flow rate: 1 ml/min
Solvent system:
(A) 5 mM Heptane sulfonic acid, sodium salt in water with 1% acetic acid
(B) 5 mM Heptane sulfonic acid, sodium salt in acetonitrile:water (90:10) with 1% acetic acid

(1) System 1

Column: μBondapak CN, 300 mm × 3.9 mm ID
Solvent program: 80% (A):20% (B), isocratic
Samples injected: 10 μl solution of 0.9 μg/μl C.I. Disperse Blue 1 in acetonitrile, filtered

Results: Major peak and three impurities, one before and two after the major peak. One impurity after the major peak had an area of 6.4% of the major peak area. The other two impurities were 1.2% and 1.3% of the major peak.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	3.2	0.40	1.2
2	8.0	1.00	100
3	13.5	1.69	1.3
4	20.8	2.60	6.4

(2) System 2

Column: μBondapak C_{18}, 300 mm × 3.9 mm ID
Solvent program: 75% (A):25% (B)
Samples injected: 10 μl solution of 0.0644 mg/ml C.I. Disperse Blue 1 in acetonitrile, filtered

Results: Major peak and seven impurities, five before and two after the major peak. Two impurities before the major peak had areas of 28.1% and 15.0% of the major peak area. Four other impurities totaled 6.2% of the major peak. One other small impurity appeared as a shoulder on the major peak and was not integrated separately.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	13.7	0.90	0.34
2	15.2	1.00	28.1
3	19.5	1.28	2.3
4	21.5	1.41	15.0
5	28.7	1.89 (shoulder)	100
6	33.5	2.20	
7	36.8	2.42	2.0
8	45.5	2.99	1.6

7. Conclusions: The results of elemental analysis for carbon and nitrogen were low and outside the variation expected for the determinations; theoretical values were corrected for the water content (19.47%) determined by Karl Fischer analysis. Sulfur analysis indicated 0.27%; the theoretical value is 0%. Titration of the amine functions, assuming two groups per molecule titrate, indicated a purity of 62.9%; this value was corrected for analyzed water.

Thin-layer chromatography indicated a minor, a trace, and a slight trace impurity. High-performance liquid chromatography (HPLC) with a µBondapak CN column indicated a major peak and three impurities, one before and two after the major peak. One impurity after the major peak had a relative area of 6.4%; the other two impurities were 1.2% and 1.3% of the major peak area. A second HPLC system with a µBondapak C_{18} column indicated a major peak and seven impurities, five before and two after the major peak. Two impurities before the major peak had 28.1% and 15.0% of the major peak area. The other impurities totaled 6.2% of the major peak. However, the developed HPLC systems were not entirely satisfactory. Filtering before HPLC analysis left a residue that was only slightly soluble in acetonitrile. The best system for the soluble components appeared to be with the CN column. The major peak on the CN column was a well-shaped peak that remained a single peak under different isocratic conditions. The major peak on the C_{18} column was a broad irregularly shaped peak that is most probably indicative of solubility problems.

The molar absorptivity measurements at 630 nm indicated that lot no. 4351828 had more dye content than the purified dye (14,560/12,880; lot no. 4351828/purified dye, both in methanol). Infrared and nuclear magnetic resonance spectra were in agreement with the data supplied by the manufacturer.

The absorbance frequencies obtained by visible, ultraviolet, infrared and nuclear magnetic resonance spectroscopy were in agreement with those obtained by the manufacturer and with the structure stated for C.I. Disperse Blue 1.

Visible spectroscopy purity indicated that C.I. Disperse Blue 1, lot no. 4351828, was purer than the manufacturer's pure dye sample (ratio of 1.13 to 1).

Considering water content (19.47%), amine titration (62.9% of the remaining 80.53%), and chromatography (indicative of a minimum of four impurities), the compound is a complex mixture of components resembling C.I. Disperse Blue 1 in structure (approximately 50% C.I. Disperse Blue 1, 19.5% water, and 30% other impurities).

II. Chemical Stability Study Performed by the Analytical Chemistry Laboratory

A. Sample Preparation and Storage: Samples were stored at −20° C, 5° C, 25° C, and 60° C for 2 weeks in glass tubes with Teflon®-lined caps.

B. Analytical Method: Samples were analyzed by the following high-performance liquid chromatography system:

Instrument System
Pump(s): Waters 6000A
Programmer: Waters 660
Detector: Waters 440
Injector: U6K
Column: μBondapak CN, 300 mm × 3.9 mm ID
Detection: Ultraviolet, 254 nm
Solvent system:
(A) 5 mM Heptanesulfonic acid, sodium salt in water with 1% acetic acid
(B) 5 mM Heptanesulfonic acid, sodium salt in acetonitrile:water (90:10) with 1% acetic acid
Solvent program: 80% (A):20% (B), isocratic
Flow rate: 1 ml/min
Samples injected: 10 μl solution of 1 mg/ml C.I. Disperse Blue 1 in acetonitrile from each storage temperature, filtered.

C. Results

Storage Temperature	Area of Major Peak (a) (percent of −20° C major peak area)
−20°	99.8 ± 9.6(δ)
5°	91.3 ± 9.6(δ)
25°	87.4 ± 9.6(δ)
60°	83.9 ± 9.6(δ)

(a) There were also two minor peaks that were observed but not quantitated. They did not appear to change throughout the analysis.

D. Conclusion: A trend indicates a decrease in the major component with increasing temperature. However, there is a fairly large experimental error that causes the values from the different storage temperatures to overlap.

III. Chemical Stability at the Study Laboratory

A. Storage Conditions: −20° C

B. Analytical Method

1. Purity Determination: The ultraviolet/visible absorption spectra of C.I. Disperse Blue 1 were measured under the following conditions:

Instrument: Cary 117
Solvent: Acetonitrile
Concentration: 10 mg/liter

2. Identity Determination: The infrared spectra of C.I. Disperse Blue 1 were run as potassium bromide disks (1.30 mg sample/600 mg potassium bromide) with a Perkin-Elmer 621.

C. Results

1. Purity

Date of Analysis	Lot No.	$\bar{\varepsilon} \times 10^{-4}$ (a)
12/22/78	4351828	1.763
03/15/79	4351828	1.721
07/25/79	4351828	1.655
11/11/79	4351828	1.253
03/05/80	4351828	1.549
07/15/80	4351828	1.533
11/13/80	4351828	1.416
03/04/81	4351828	1.704
07/15/81	4351828	1.489
11/11/81	4351828	1.460
03/09/82	4351828	1.684
04/06/82	4351828	1.466

(a) Measured at 630 ± 3 nm in acetonitrile for the bulk material

2. Identity: All infrared spectra were consistent with those supplied by the analytical chemistry laboratory.

D. Conclusion: No notable degradation occurred during the studies.

IV. Identification and Quantitation of Impurities (Analysis performed by Thermo-Electron Corporation, 125 Second Avenue, P.O. Box 459, Waltham, MA 02254.)

A. Experimental Methods

1. Rationale: The impurity profile was determined by high-performance liquid chromatography (HPLC) with an organic amine compound in the mobile phase to obtain reproducible retention times and peak shapes. This amine compound was not used in the mobile phase when the impurity peak fractions were collected. Only the major component and the two largest impurity peaks were collected and identified.

2. Impurity Profile

a. Instrumental System
Solvent delivery system: Varian 5020 HPLC
Detector: Waters 440
Injector: Waters WISP 710B
Electronic integration: Nelson 4400 Data System
Detection: Ultraviolet, 254 nm
Column: Waters μBondapak Phenyl (10 μm), 300 × 3.9 mm ID
Guard column: Waters Bondapak Phenyl/Corasil, 23 × 3.9 mm ID
Solvent system:
A: 5 mM triethanolamine in water adjusted to pH 6.7 with 10% (v/v) phosphoric acid
B: 5 mM triethanolamine in acetonitrile:water (9:1)
Solvent program: 28% B for 55 minutes, then a linear gradient from 28% B to 100% B in 20 minutes
Flow rate: 1.0 ml/minute
Samples injected: 20 μl of solutions of 0.94 mg/ml C.I. Disperse Blue 1 in dimethyl sulfoxide, filtered

b. Results: A major peak and 14 impurity peaks with areas greater than 0.1% relative to the major peak were observed (Figure 10).

Peak No.	Retention Time (min)	Retention Time (relative to major peak)	Area (a) (percent of major peak)
1	1.6	0.08	5.3
2	2.0	0.10	3.9
3	7.8	0.39	0.2
4	9.4	0.47	0.8
5	10.2	0.52	1.2
6	12.2	0.62	25.3
7	13.7	0.69	0.8
8	14.6	0.74	1.8
9	16.4	0.83	0.3
10	19.8	1.00	100
11	23.8	1.20	1.5
12	26.2	1.32	1.7
13	37.1	1.87	1.3
14	46.6	2.35	6.4
15	71.1	3.59	2.9

(a) Detector response is very dependent on the absorbance of a substance at the detection wavelength used. The values reported are absolute areas expressed as percentages of the area of the major peak and do not take into account the different molar absorptivity (ε) values of the compound and its impurities. Therefore, the areas reported do not necessarily reflect the actual weight percentages of the impurities in the sample.

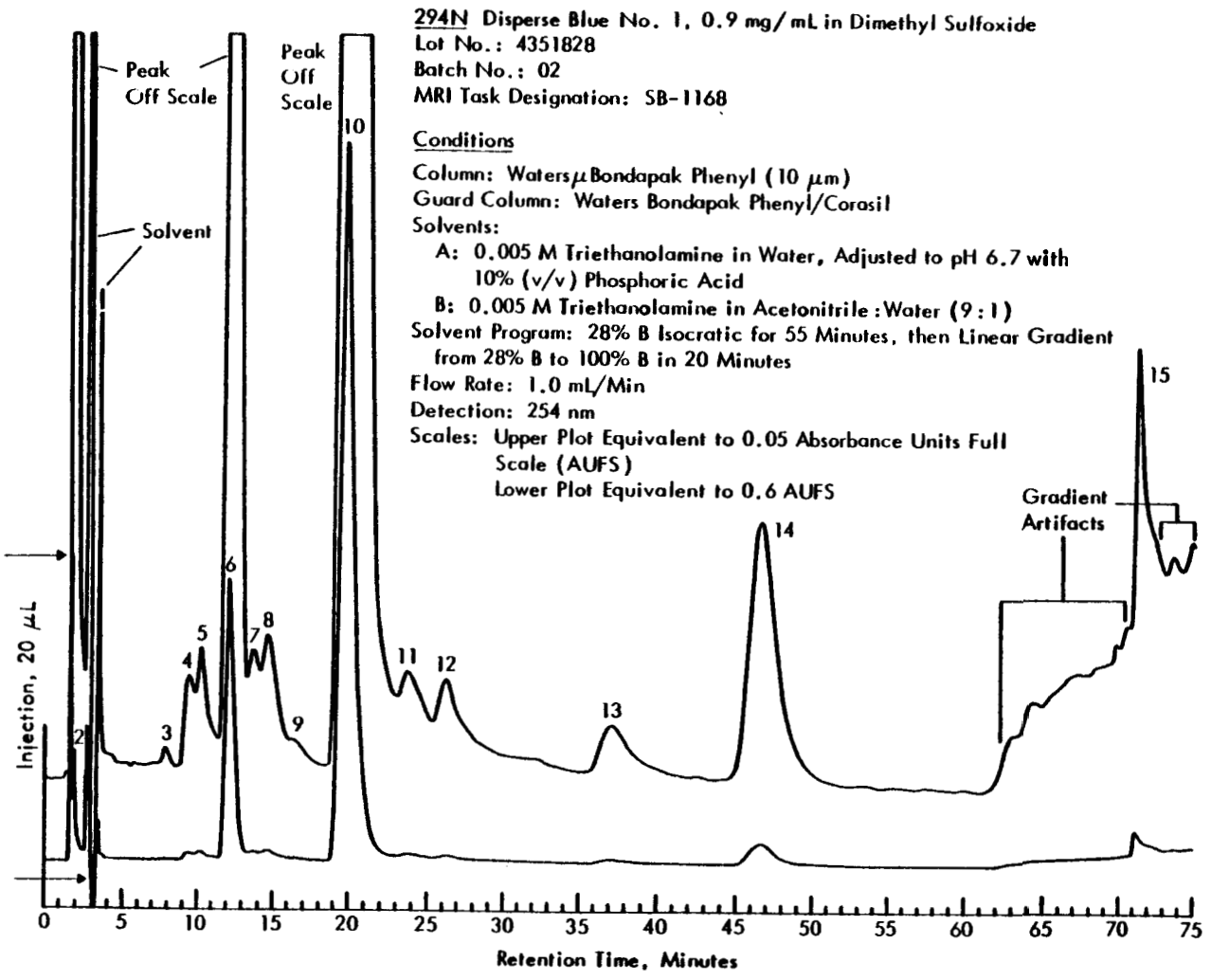


FIGURE 10. HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY IMPURITY PROFILE OF C.I. DISPERSE BLUE 1 (LOT NO. 4351828)

3. Isolation of the Major Component and Major Impurities

a. Procedure: A concentrated solution of C.I. Disperse Blue 1 was prepared in dimethyl sulfoxide and repeatedly injected into the high-performance liquid chromatographic system described below. The major peak (peak no. 10) and the two major impurity peaks (peak nos. 6 and 14) were collected as they eluted from the analytical column. The fractions were immersed in a 40° C water bath and evaporated to dryness under a stream of purified nitrogen. The samples were reconstituted in a small volume of dichloromethane and analyzed by direct inlet mass spectrometry.

b. High-Performance Liquid Chromatographic Conditions

Instrument system

Pumps: Waters 6000A
Programmer: Waters 660
Detector: Waters 440
Injector: Rheodyne 7125

Detection: Ultraviolet, 254 nm
Column: Waters μBondapak Phenyl (10 μm), 300 × 3.9 mm ID
Solvent system: Water:acetonitrile (70:30)
Flow rate: 1.0 ml/minute
Samples injected: 20 μl of solutions of 4 mg/ml C.I. Disperse Blue 1 in dimethyl sulfoxide, filtered

4. Ultraviolet/Visible Spectrophotometry of the Major Component and Major Impurities

a. Procedure: Ultraviolet/visible spectra of the major peak and the two major impurity peaks were obtained with a Hewlett-Packard 1040A high speed spectrophotometric HPLC detector. HPLC conditions were identical to those described in the impurity profile (Section IV.A.2.a). The following 1040A detector parameters were used:

Monitoring wavelength: 254 nm
Lamp current: Low
Scanning range: 210-600 nm
Scanning step: 2 nm
Samples injected:

4.0 mg/ml of C.I. Disperse Blue 1 in dimethyl sulfoxide (filtered) to obtain spectra of impurities
0.95 mg/ml of C.I. Disperse Blue 1 in dimethyl sulfoxide (filtered) to obtain spectrum of major component

b. Results: The spectrum of peak no. 14 has an absorbance maximum at a wavelength very close to the wavelength of the absorbance maximum of the major component. The spectrum of peak no. 6 is significantly different from the spectra of both the major component and peak no. 14. The spectrum of the major peak (peak no. 10) is illustrated in Figure 11. The spectra of peak nos. 6 and 14 are shown in Figures 12 and 13, respectively. All three spectra indicate some absorbance at 254 nm, the detection wavelength used for the impurity profile.

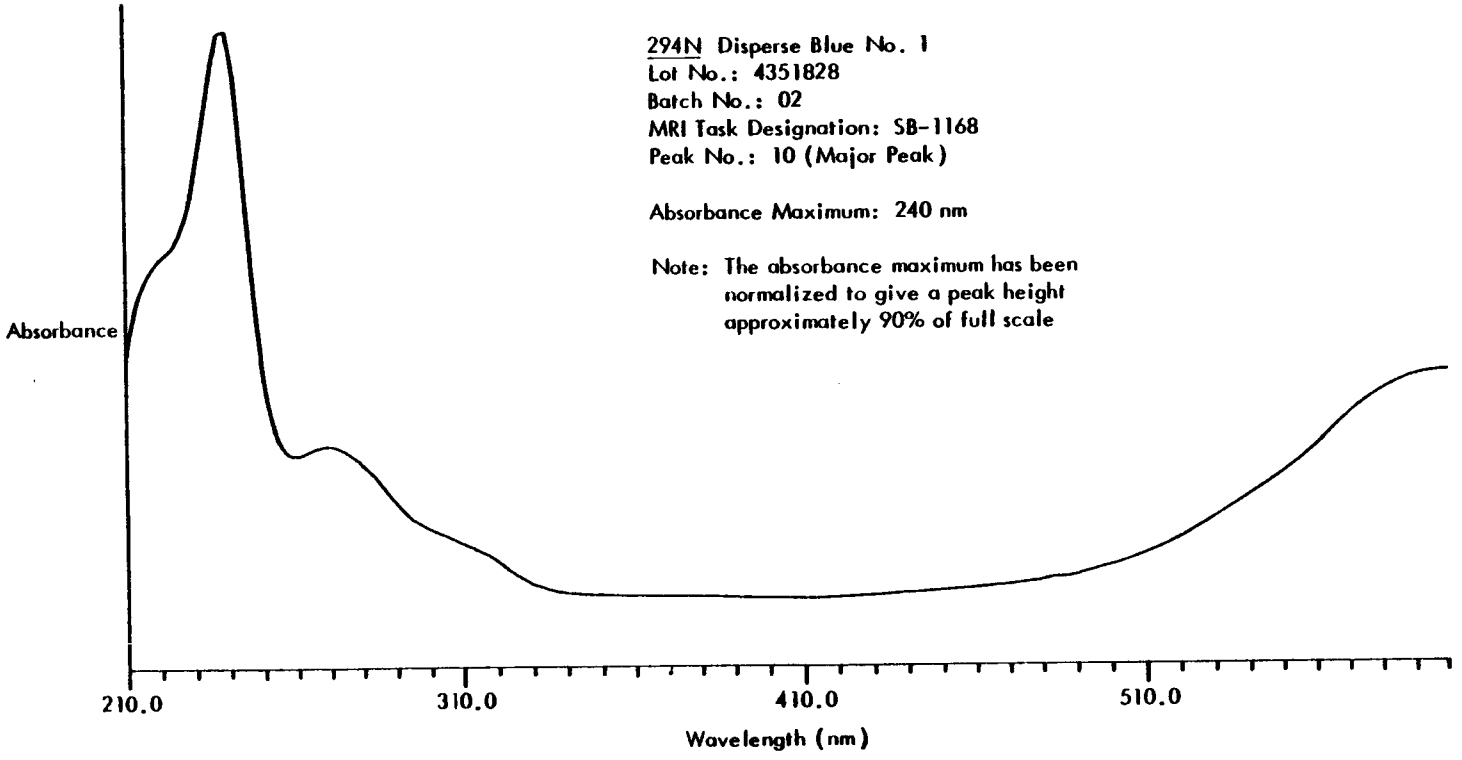


FIGURE 11. ULTRAVIOLET/VISIBLE SPECTRUM OF THE MAJOR COMPONENT OF C.I. DISPERSE BLUE 1 (LOT NO. 4351828)

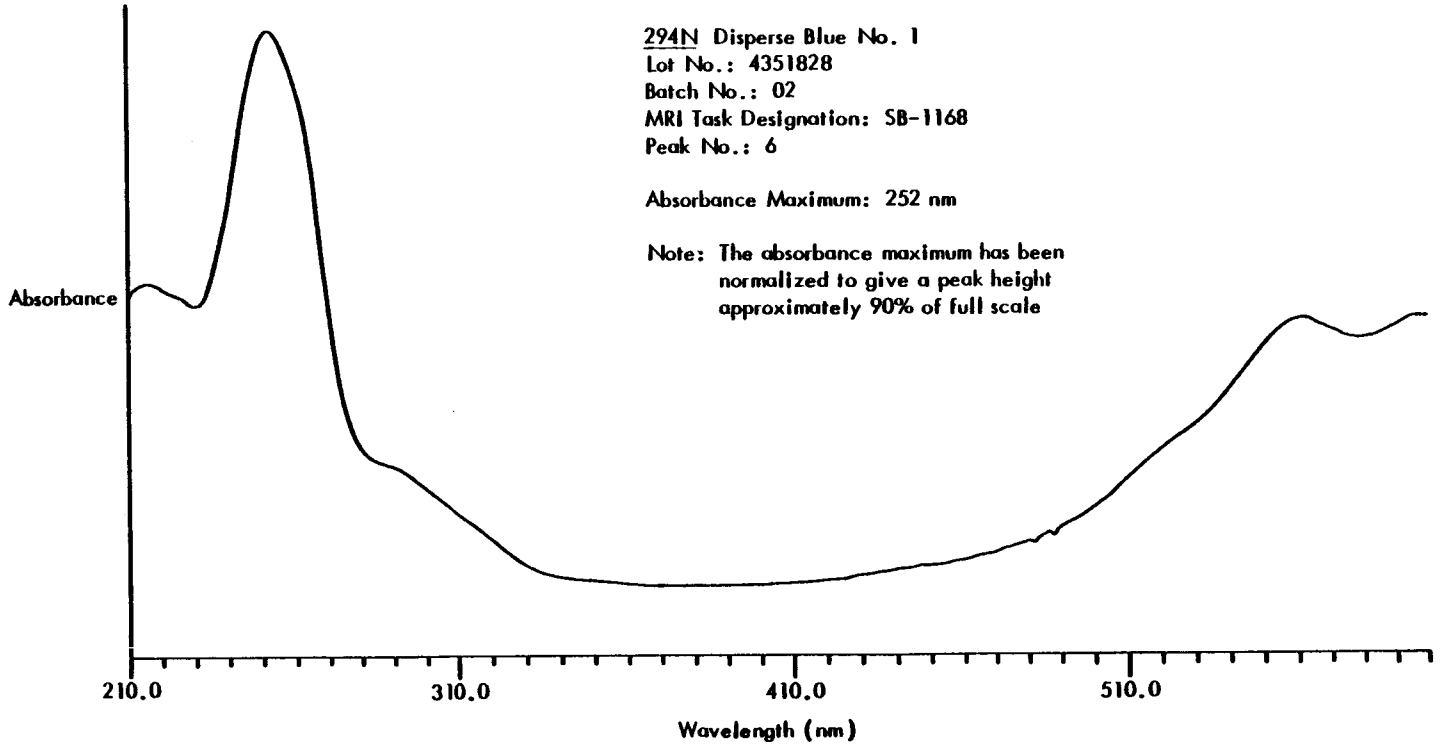


FIGURE 12. ULTRAVIOLET/VISIBLE SPECTRUM OF PEAK NO. 6 OF C.I. DISPERSE BLUE 1 (LOT NO. 4351828)

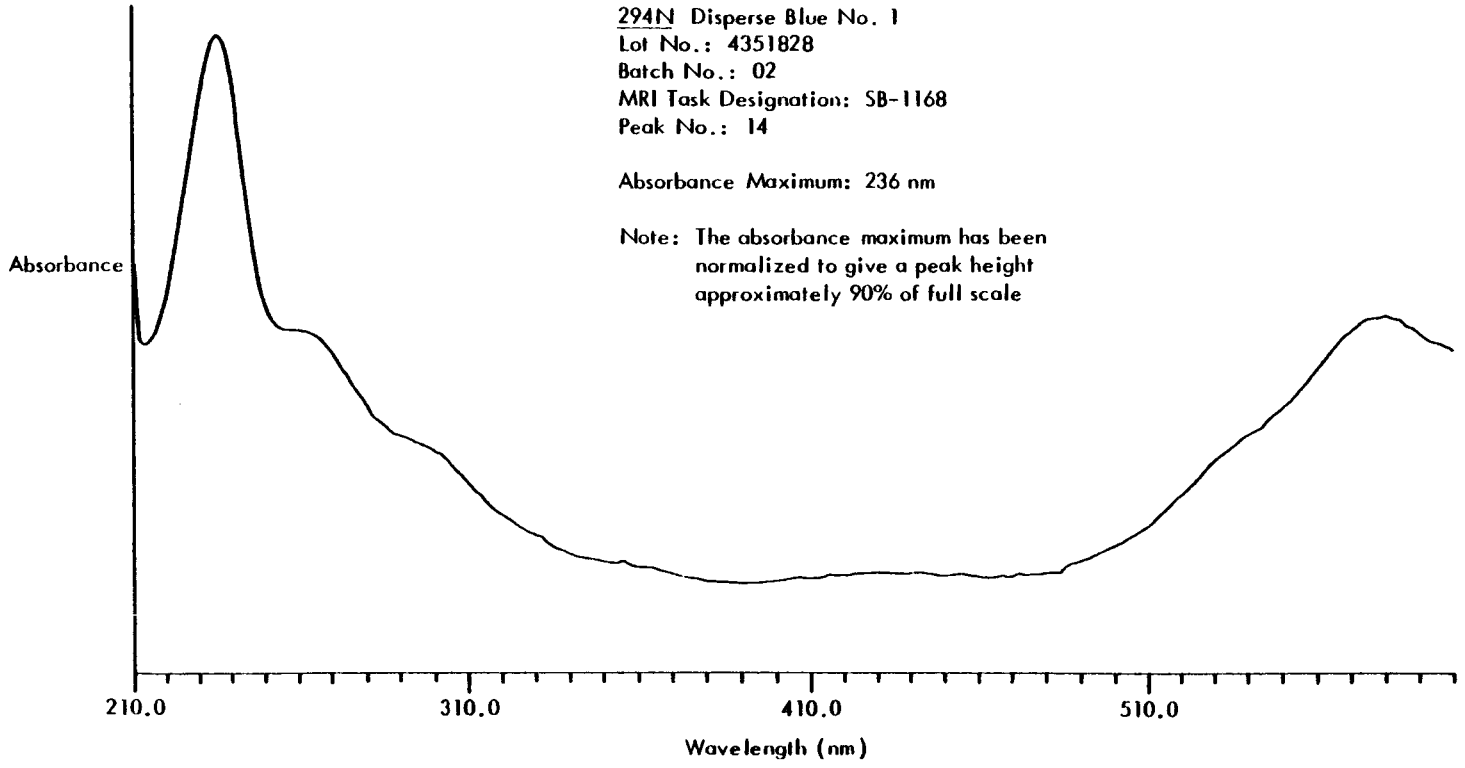


FIGURE 13. ULTRAVIOLET/VISIBLE SPECTRUM OF PEAK NO. 14 OF C.I. DISPERSE BLUE 1 (LOT NO. 4351828)

5. **Mass Spectrometric Analysis**

a. Instrument system

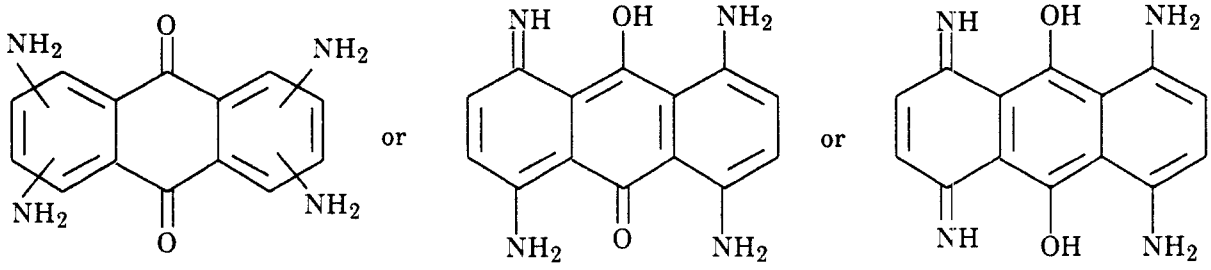
Instrument: Varian MAT 311-A mass spectrometer with an Incos 2300 data system
Electron energy: 70 eV
Scan range: 1-850 amu
Scan times (seconds): Up - 450; top - 0.00
Down - 0.00; bottom - 0.50
Electron multiplier voltage: −2,400 V
Emission current: 1 mA
Resolution: 1,000
Accelerator voltage: 3,000 V
Sample introduction: Direct inlet probe (gold cup)
Temperature program: 30°-500° C in 1,000 seconds

b. Samples: Aliquots (15 µl) of the reconstituted samples prepared as described in Section IV.A.3.a were evaporated in a gold cup for direct inlet mass spectrometric analysis.

c. Results

1. Peak no. 6: Isomer of C.I. Disperse Blue 1

The mass list obtained from peak no. 6 is given below. Ions with relative abundances less than 4.5% are not reported. The spectrum is consistent with the fragmentation expected of an isomer of C.I. Disperse Blue 1; either a positional isomer or enolic isomers are possible. This spectrum is essentially identical to that obtained from the major component. Although the exact isomeric configuration could not be deduced from the spectrum, the ion observed at m/z 134 indicates the presence of two amino groups on each phenyl ring, as is the case for C.I. Disperse Blue 1. The observed fragmentation is discussed in Section 2.

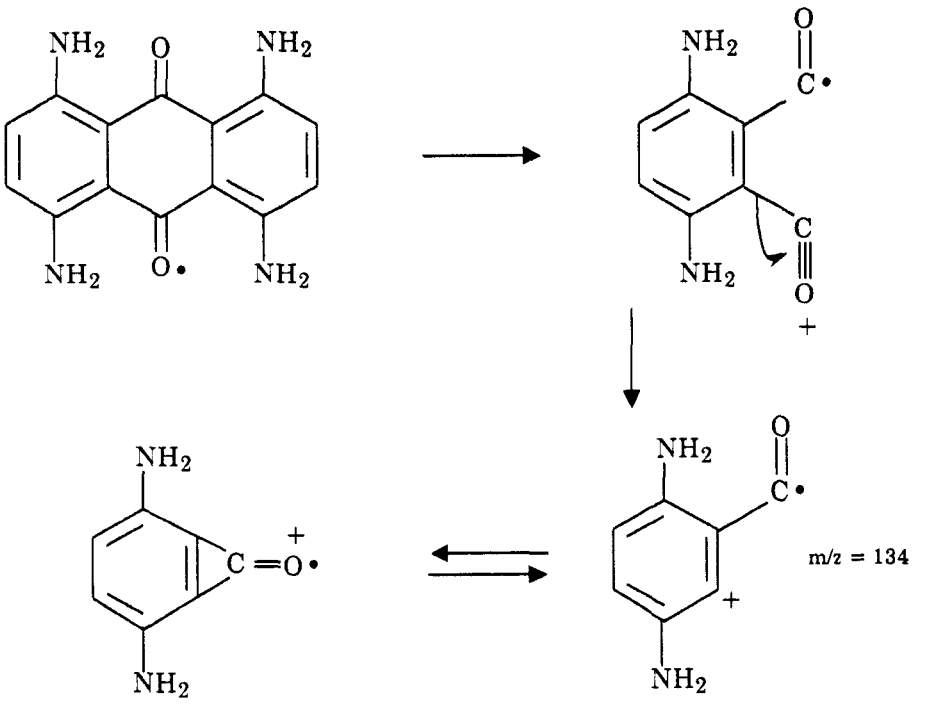


m/z	Relative Abundance (percent of m/z 268)	m/z	Relative Abundance (percent of m/z 268)
268	100.0	92	11.8
134	52.3	140	9.9
269	51.6	78	9.5
267	36.4	195	9.5
239	24.6	194	9.4
120	24.4	222	9.4
107	24.1	168	9.2
240	21.4	196	8.5
106	20.8	167	7.0
135	20.1	241	6.7
252	19.5	71	6.5
98	19.1	169	6.2
212	18.6	121	6.2
112	16.0	197	6.0
93	14.0	85	6.0
84	13.2	184	5.4
223	12.9	213	5.2
224	12.3	126	5.0
270	12.0	80	4.9
79	12.0	211	4.6

2. Peak no. 10: C.I. Disperse Blue 1

The mass list obtained from peak no. 10 is given below. Ions with relative abundances less than 4.5% are not reported. The spectrum was consistent with the fragmentation expected from C.I. Disperse Blue 1. The molecular ion (m/z 268) was the most abundant ion observed. High mass range ions observed represented the losses of an amino group (m/z 252) and a formyl group (m/z 239) from the molecular ion. The loss of both of these groups produced the ion observed at m/z 223. An important diagnostic

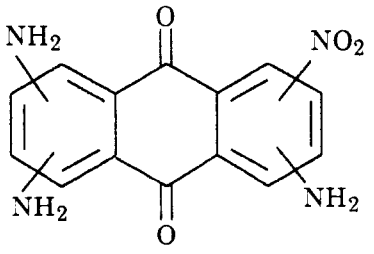
ion (m/z 134) was produced by a fragmentation typical of quinones and demonstrates the presence of two amino groups on each phenyl ring. A postulated mechanism for the production of this ion is given below.



m/z	Relative Abundance (percent of m/z 268)	m/z	Relative Abundance (percent of m/z 268)
268	100.0	252	11.1
134	69.5	140	11.0
269	52.8	222	10.4
239	35.2	126	9.8
135	32.5	194	9.5
112	27.6	197	9.3
106	25.3	212	9.3
98	22.5	168	9.0
240	21.2	196	9.0
84	19.6	195	8.0
267	19.6	167	7.4
107	19.3	169	7.3
120	18.7	121	7.1
92	17.7	241	6.5
79	17.2	89	6.0
93	15.7	65	5.8
223	13.6	80	5.7
78	12.3	225	5.6
99	12.0	141	5.6
85	11.9	66	5.2
71	11.8	105	5.1
270	11.4	113	4.8
224	11.4		

3. Peak no. 14: Triaminonitroanthraquinone

The mass list obtained from peak no. 14 is considered below. Ions with a relative abundance less than 4.5% are not reported. The spectrum is consistent with the fragmentation expected from an isomer of triaminonitroanthraquinone. An abundant molecular ion (m/z 298) was observed. Losses of hydroxyl (m/z 281), nitrous oxide (m/z 268), and nitrogen dioxide (m/z 252) from the molecuar ion indicate the presence of the nitro group. Loss of carbon monoxide followed by loss of nitrous oxide or nitrogen dioxide are observed at m/z 240 and m/z 224, respectively. Although the exact isomeric configuration could not be determined from the spectrum, the ion observed at m/z 134 indicates the presence of two amino groups on one of the phenyl rings. This suggests the presence of one amino and one nitro group on the other phenyl ring. The production of this ion is discussed in Section c.1 (peak no. 6).



m/z	Relative Abundance (percent of m/z 268)	m/z	Relative Abundance (percent of m/z 268)
298	100.0	194	8.0
252	76.6	281	8.0
268	60.8	89	7.8
224	58.9	90	7.7
299	52.7	198	7.3
269	36.5	167	7.2
85	36.1	121	7.1
197	29.2	300	7.1
253	27.7	116	6.9
134	27.6	239	6.9
112	26.6	254	6.9
120	25.3	270	6.7
240	25.2	77	6.4
169	22.4	63	6.3
98	22.1	250	6.1
225	21.9	65	6.0
71	20.8	143	6.0
99	18.9	241	6.0
84	17.5	149	5.9
196	16.9	125	5.8
126	16.5	104	5.7
107	16.2	97	5.5
135	15.4	151	5.5
140	14.9	297	5.4
106	14.8	76	5.4
223	14.1	207	5.4
168	12.7	18	5.4
114	12.2	52	5.3
113	11.8	91	5.2
115	11.8	128	5.2
170	11.4	180	5.0
127	11.4	123	4.9
222	11.4	212	4.9
179	11.2	155	4.8
251	10.9	178	4.8
79	10.6	109	4.8
92	10.6	105	4.8
141	10.6	100	4.8
142	9.8	72	4.7
152	9.4	153	4.7
195	8.9	58	4.6
78	8.8	171	4.5
93	8.5		

B. Conclusions: The two major impurities in C.I. Disperse Blue 1 were identified by mass spectrometry. Estimation of the amount of these impurities was based upon HPLC peak areas even though the spectra for the two impurities were not identical to the major component because standards were not available commercially.

One of the impurities (peak no. 6), was identified as an isomer of C.I. Disperse Blue 1 (see structure). The concentration of this impurity was estimated at approximately 25%. The second major impurity (peak no. 14) was identified as a triaminonitroanthraquinone (see structure). The concentration of this impurity was estimated to be approximately 6%.

No nitrosamine impurities were identified in this material.

APPENDIX H

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

I. Studies Conducted at the Analytical Chemistry Laboratory

A. Preparation Procedure

1. Premix: A 1.802-g sample of C.I. Disperse Blue 1 was added to 100 g of feed in a 250-ml beaker and blended with a stainless steel spatula for approximately 3 minutes.

2. Bulk Mixing: A 700-g portion of undosed rodent feed was added evenly to the bottom of a Patterson-Kelly® blender; then 100 g of premix was added in roughly equal portions to both sides of the blender. One hundred grams of undosed feed was stirred in the beaker for a few seconds to take up the fine residue adhering to the beaker walls and then added to the mix in the blender. An additional 60 g of feed was then layered over the premix before the mixture was blended.

After 10 minutes of blending, about 50 g of mix was removed from the upper left and right hand shells and from the bottom discharge port. Blending was resumed for an additional 5 minutes; then samples were again taken as before.

Duplicate 20 g ± 0.01 g weighings of each sample were transferred to 200-ml centrifuge bottles for analysis. The target concentration of C.I. Disperse Blue 1 in the blend was 1,201 ppm.

3. Extraction and Analysis: Twenty-gram samples were extracted with 150 ml of acetonitrile:acetic acid solution (95:5, v/v) by being shaken for 1 hour on a New Brunswick® gyrotory shaker set at 300 rpm. Bottles were then sonicated for 2 minutes with frequent swirling, followed by an additional hour of shaking as before.

After the extracts were clarified by being centrifuged at 2,000 rpm for 10 minutes, 2-ml aliquots of each extract were pipetted into individual 25-ml volumetric flasks and diluted to volume with extracting solvent. Absorbance of the solutions was measured in 1-cm cells at 635 nm on a Cary 118 spectrophotometer.

4. Quality Control : Duplicate analyses were run on all analytical samples. Absorbance readings of sample extracts were corrected for feed blank contribution (0.012 AU) by treating undosed feed in the same manner that samples were treated and subtracting the absorbance of the undosed feed extract from the sample absorbance. Zero-time recovery yield was determined from spiked feed samples assayed in the same time schedule as samples. Spectrophotometric linearity was determined with C.I. Disperse Blue 1 solutions at concentrations of 17.3, 13.0, and 8.7 mg/ml. The linear correlation coefficient was > 0.999.

B. Homogeneity

1. Results

Blending Time and Sampling Location	Average Concentration Found in Chemical/Vehicle Mixture (ppm) (a)
10 Right	(b) 1,120 ± 60
10 Left	1,070 ± 10
10 Bottom	1,160 ± 20
15 Right	1,110 ± 30
15 Left	1,140 ± 10
15 Bottom	1,160 ± 30

(a) Corrected for a spiked recovery yield of 92.3%. The target concentration of chemical in feed was 1,201 ppm.
(b) Error values are standard deviations.

2. Conclusion: C.I. Disperse Blue 1 was blended into feed at a concentration of 1,200 ppm with acceptable uniformity after 15 minutes' mixing by the described procedure.

C. Stability

1. Sample Preparation and Storage: Approximate 25-mg quantities of C.I. Disperse Blue 1 were weighed to the nearest 0.00001 g and carefully transferred to 200-ml centrifuge bottles containing 20.0 g of undosed rodent feed. After the chemical was thoroughly mixed with the feed, duplicate bottles were stored at −20° C, 5° C, 25° C, and 45° C storage for 2 weeks' stability testing.

2. Extraction and Analysis: Stored samples and freshly prepared spiked feeds for zero-time recovery determinations were extracted with 150 ml of acetonitrile:acetic acid solutions (95:5, v/v). Bottles were shaken for 1 hour on a New Brunswick® gyrotory shaker at 300 rpm. They were then sonicated for 2 minutes with frequent swirling, followed by an additional 1 hour of shaking as before.

The extracts were clarified by being centrifuged at 2,000 rpm for 10 minutes. A few milliliters of each clarified extract was filtered through a 0.5-µ Millipore filter and analyzed directly by the following high-performance liquid chromatographic system:

a. Instrument: Waters ALC 202 Liquid Chromatograph equipped with programmable pumps
b. Column: µBondapak C_{18}, 300 mm × 4 mm ID
c. Detector: Ultraviolet, 254 nm
d. Solvent: 55% (A):45% (B)
(A) 5.5 mM 1-Heptane sulfonic acid in aqueous 1% acetic acid
(B) 5.5 mM 1-Heptane sulfonic acid in a solution composed of acetic acid:water:acetonitrile (1:10:89, v/v/v)
e. Solvent Flow Rate: 1.0 ml/min

3. Quality Control: All analyses were run by making duplicate injections of duplicate extracts. Recovery of chemical was determined in duplicate with freshly spiked feed at the same level as was used for samples and assayed with the samples. Linearity of detector response was evaluated with standard solutions at concentrations of 192.5, 160.5, and 128.4 µg/ml. The linear correlation coefficient was 0.986.

4. Results

Storage Temperature	Parts per Million Chemical Found in Formulated Diet (a)	Target Parts per Million in Formulated Diet (b)	Percent Recovery (c,d)
−20° C	1,294	1,203	110.4 ± 3.2
	1,397	1,234	
5° C	1,212	1,217	100.0 ± 0.5
	1,258	1,252	
25° C	1,271	1,248	99.0 ± 2.9
	1,200	1,249	
45° C	1,121	1,285	87.4 ± 0.2
	1,053	1,202	

(a) Corrected for a zero-time spiked recovery yield of 81.4% ± 2.8%
(b) Calculated from individual weights of dry compound added to 20 g of undosed feed
(c) Calculated from the assay data corrected for 81.4% recovery yield.
(d) Although the duplicate analyses had a relatively small error, the loss in absorbance observed with time was probably approximately ± 5%.

5. Conclusions: The determination of C.I. Disperse Blue 1 in rodent feed presented several analytical problems. The very limited solubility of the chemical in appropriate solvents made it necessary to shake samples for 2 hours to effectively extract it from feed mixtures.

Of greater significance, however, was a problem observed during the development of the spectrophotometric method described above. Absorbance readings of C.I Disperse Blue 1 solutions in extracting solvent decreased at a rate of 7%-8% per hour at both 635 nm and 596 nm peaks. This loss occurred both with pure standard solutions and with feed extracts containing the chemical and was possibly related to an oxidation-reduction reaction. These problems are believed to be the major contributing factors to the relatively large test error, estimated at ± 5%.

Within the limits of the test error, C.I. Disperse Blue 1 exhibited no measurable loss in stability in feed after storage for 2 weeks at temperatures up to 25° C. Results at 45° C were lower than those at 25° C and 5° C by an amount greater than the overall test errors and may reflect some instability.

APPENDIX I

METHODS OF ANALYSIS OF FORMULATED DIETS

APPENDIX I. METHODS OF ANALYSIS

I. Study Laboratory

Procedure: During this study, more extraction steps were added to the analytical procedure to enhance the recovery of C.I. Disperse Blue 1 from the feed. The final procedure is outlined below.

Five-gram samples of the chemical/feed mixtures and plain feeds were weighed into large test tubes. Approximately 50 ml of acetonitrile:acetic acid (95:5) mixture was added to each sample. These mixtures were triturated for 2 minutes with the Polytron® High-Speed Blender, the mixtures allowed to settle, and the liquid supernatant decanted and filtered with a Millipore Filtering apparatus. An additional 50 ml was added to the feed residue in the test tube; the mixture was triturated for 90 seconds and the supernatant again decanted and filtered. This process was repeated two more times, each with 50-ml portions of acetonitrile-acetic acid mixture; the first was triturated for 90 seconds and the supernatant was decanted and filtered. The feed residue was triturated for 60 seconds a final time with 50 ml of mixture; this time the supernatant and the feed residue were filtered. The extract was diluted to a 250-ml volume.

The solutions of C.I. Disperse Blue 1 were at all times protected from the light with glassware wrapped in aluminum foil.

Aliquots of the extracts were diluted to a working range. The absorbance of these solutions was measured from 600 nm to 650 nm with a Cary 17 Spectrophotometer. These absorbances were then compared with a standard curve for C.I. Disperse Blue 1.

II. Analytical Chemistry Laboratory

Procedure

A. Preparation of spiked feed standards: Two working standard solutions of C.I. Disperse Blue 1 in extracting solution[a] were prepared independently and diluted with extracting solution to concentrations bracketing the desired analytical range. Aliquots (60 or 150 ml) of the standard solutions were pipetted into individual 200-ml centrifuge bottles containing 2-10 g of undosed feed to make spiked feed standards. One 200-ml centrifuge bottle containing 3 g of undosed feed was treated with extracting solution for use as a blank. The spiked feeds and the feed blank were sealed and allowed to remain overnight at room temperature before analysis.

B. Preparation of dosed feed sample: Triplicate weights of the referee feed sample (2-10 g weighed to the nearest 0.001 g) were transferred to individual 200-ml centrifuge bottles. Extracting solution (60-150 ml) was pipetted into each sample; then the bottles were sealed and allowed to stand overnight at room temperature with the standards and feed blank before analysis.

(a) Extracting solution was prepared by diluting 50 ml of concentrated acetic acid to 1,000 ml with acetonitrile.

C. Analysis: The bottles were placed on a Burrell Model 75 Wrist-Action® shaker and shaken at maximum stroke for 1 hour. The samples were placed in an ultrasonic vibratory bath for 2 minutes, with frequent swirling; then they were shaken as before for an additional hour. After the extraction mixtures were centrifuged for 10 minutes, a 4- or 6-ml aliquot of the supernatant solution from each sample bottle was diluted to 25 ml with extracting solution. The solutions were thoroughly mixed, and the absorbance of each solution was measured versus extracting solution in 1-cm quartz cells at 635 nm on a Cary 118 spectrophotometer.

The total amount of C.I. Disperse Blue 1 in the referee feed samples were determined by a linear regression equation calculated from the standard curve data, relating the absorbance of each spiked feed and blank sample to the amount of chemical in the respective spiked feed and blank sample.

D. Quality Assurance: The referee feed sample was analyzed in triplicate, and the undosed feed blank sample was analyzed once. Individually spiked portions of undosed feed (six levels) prepared from two independently weighed standards were treated like the referee feed samples for obtaining standard curve data.

APPENDIX J

RESULTS OF ANALYSIS OF FORMULATED DIETS

TABLE J1. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE THIRTEEN-WEEK FEED STUDIES OF C.I. DISPERSE BLUE 1 (a)

Date Mixed	Concentration of C.I. Disperse Blue 1 in Feed (ppm)		Determined as a Percent of Target
	Target	Determined	
06/21/79	600	450	75
	1,200	980	81.7
	2,500	2,600	104
	5,000	4,700	95.2
	10,000	10,900	109
	20,000	19,300	96.5
08/02/79	600	560	93.3
	1,200	1,160	96.7

(a) Results of duplicate analysis

TABLE J2. CONCENTRATIONS OF C.I. DISPERSE BLUE 1 IN FEED IN THE TWO-YEAR STUDIES (a)

Date Mixed	Determined Concentration for Target Concentration of				
	600 ppm	1,200 ppm	1,250 ppm	2,500 ppm	5,000 ppm
04/17/80	580		1,140	(b) 2,220	4,710
05/15/80		(b) 940	1,150	(b) 2,220	(b) 4,400
05/22/80		(c) 1,100		(c) 2,410	(c) 4,860
06/12/80	540		1,150	2,320	4,640
07/10/80		1,080	1,160	(b) 2,100	4,760
07/14/80				(c) 2,610	
08/07/80	538		1,200	2,430	4,960
09/04/80		1,120	1,280	2,300	4,710
10/02/80	553		1,160	2,300	5,010
10/30/80		1,090	1,180	2,290	4,960
11/20/80	(b) 462		1,330	2,640	4,520
11/20/80	(c) 628				
12/18/80		1,210	1,200	2,450	4,960
01/22/81	627		1,200	2,380	4,540
02/19/81		1,240	1,230	2,600	5,060
03/19/81	538		1,200	2,320	4,670
04/16/81		(b) 920	1,200	2,250	4,990
04/20/81		(c) 1,110			
05/14/81	587		1,130	2,300	4,840
06/11/81		(b) 1,010	1,340	2,400	4,780
06/15/81		(c) 1,013			
06/17/81		(c) 1,160			
07/09/81	(b) 504		1,200	2,560	4,880
07/15/81	(c) 545				
08/13/81		(b) 1,010	(b) 1,400	2,550	4,820
08/19/81		(c) 1,130	(c) 1,200		
09/03/81	(b) 518		(b) 1,040	2,320	4,560
09/09/81	(c) 561		(c) 1,110		
10/01/81		1,250	(b) 1,410	2,510	4,990
10/06/81			(c) 1,195		
10/29/81	594		1,160	2,360	4,910
11/19/81		1,080	1,180	2,440	4,580
11/26/81					4,470
					4,540
12/17/81	610		1,120	2,430	4,930
02/18/82	(d) 490	1,120	(d) 1,090	(d) 2,140	5,030
02/18/82			1,220	2,350	(d) 4,460
Mean (ppm)	549	1,089	1,203	2,367	4,766
Standard deviation	48.8	108.2	89.3	136.6	204.2
Coefficient of variation (percent)	8.9	9.9	7.4	5.8	4.3
Range (ppm)	462-627	920-1,250	1,040-1,410	2,100-2,640	4,400-5,060
Number of samples	13	12	25	25	27

(a) Results of duplicate analysis
(b) Out of specifications. Not used in the study.
(c) Remix. Not included in the mean.
(d) Out of specifications. Used in study.

TABLE J3. RESULTS OF REFEREE ANALYSIS IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1

Date Mixed	Target Concentration (ppm)	Determined Concentration	
		Study Laboratory	Analytical Laboratory (a)
05/15/80	1,250	1,150	1,170
11/20/80	2,500	2,640	2,220
05/14/81	600	587	573
12/17/81	5,000	4,930	5,000

(a) Results of the means of triplicate analysis

APPENDIX K

SENTINEL ANIMAL PROGRAM

APPENDIX K. SENTINEL ANIMAL PROGRAM

I. 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 in the program is monitored via viral serology on sera from extra (sentinel) animals in the study rooms. These animals are untreated, and they and the study animals are both subject to identical environmental con-ditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Fifteen B6C3F$_1$ mice and 15 F344/N rats of each sex are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected control animals of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests are performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai (12, 18, or 24 mo)	M.Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) Sendai (6 mo) MHV (6, 12, or 18 mo)	MHV (mouse hepatitis virus) (24 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (12, 18, or 24 mo)	RCV (rat coronavirus) Sendai (6 mo) MHV (6, 12, or 18 mo)	

II. Results

No positive serologic reactions were observed at any of the intervals tested.

APPENDIX L

FEED AND COMPOUND CONSUMPTION BY RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF C.I. DISPERSE BLUE 1

TABLE L1. FEED AND COMPOUND CONSUMPTION BY MALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

Week	Control Grams Feed/ Day (a)	Control Body Wt (g)	1,250 ppm Grams Feed/ Day (a)	1,250 ppm Body Wt (g)	1,250 ppm Low/ Cont (b)	1,250 ppm Dose/ Day (c)	2,500 ppm Grams Feed/ Day (a)	2,500 ppm Body Wt (g)	2,500 ppm Mid/ Cont (b)	2,500 ppm Dose/ Day (c)	5,000 ppm Grams Feed/ Day (a)	5,000 ppm Body Wt (g)	5,000 ppm High/ Cont (b)	5,000 ppm Dose/ Day (c)
5	17	277	17	277	1.0	77	17	279	1.0	152	18	264	1.1	341
9	16	331	16	331	1.0	60	16	330	1.0	121	15	310	0.9	242
13	17	357	17	357	1.0	60	18	355	1.1	127	16	333	0.9	240
19	16	385	13	389	0.8	42	16	386	1.0	104	16	362	1.0	221
23	14	405	15	410	1.1	46	16	400	1.1	100	15	370	1.1	203
28	17	427	17	422	1.0	50	17	422	1.0	101	16	384	0.9	208
32	16	440	16	444	1.0	45	17	442	1.1	96	17	401	1.1	212
36	16	452	14	454	0.9	39	17	449	1.1	95	17	414	1.1	205
39	16	468	17	469	1.1	45	17	468	1.1	91	17	429	1.1	198
45	15	480	16	481	1.1	42	16	480	1.1	83	16	437	1.1	183
49	17	488	17	488	1.0	44	17	484	1.0	88	18	441	1.1	204
54	16	494	16	496	1.0	40	17	491	1.1	87	18	446	1.1	202
58	17	495	17	482	1.0	44	18	485	1.1	93	17	445	1.0	191
61	16	503	17	494	1.1	43	16	490	1.0	82	17	446	1.1	191
66	18	503	17	493	0.9	43	18	493	1.0	91	19	451	1.1	211
69	17	506	17	494	1.0	43	17	494	1.0	86	17	453	1.0	188
73	16	510	16	500	1.0	40	16	495	1.0	81	17	455	1.1	187
78	15	508	16	501	1.1	40	16	494	1.1	81	18	454	1.2	198
83	14	499	15	495	1.1	38	16	476	1.1	84	16	435	1.1	184
87	15	496	16	490	1.1	41	17	478	1.1	89	17	431	1.1	197
91	15	495	16	489	1.1	41	16	477	1.1	84	22	438	1.5	251
96	16	490	16	486	1.0	41	18	460	1.1	98	18	404	1.1	223
100	15	479	16	481	1.1	42	15	457	1.0	82	25	410	1.7	305
Mean	16.0	456	16.1	453	1.0	45	16.7	447	1.0	95	17.5	409	1.1	217
SD (d)	1.0		1.0		0.1	9	0.8		0.1	17	2.2		0.2	39
CV (e)	6.3		6.2		10.0	20.0	4.8		10.0	17.9	12.6		18.2	18.0

(a) Grams of feed removed from the feeder per day. Not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of C.I. Disperse Blue 1 consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE L2. FEED AND COMPOUND CONSUMPTION BY FEMALE RATS IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	Control		1,250 ppm				2,500 ppm				5,000 ppm			
Week	Grams Feed/ Day (a)	Body Wt (g)	Grams Feed/ Day (a)	Body Wt (g)	Low/ Cont (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Wt (g)	Mid/ Cont (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Wt (g)	High/ Cont (b)	Dose/ Day (c)
5	12	175	12	174	1.0	86	12	174	1.0	172	12	170	1.0	353
9	11	197	12	197	1.1	76	11	194	1.0	142	11	192	1.0	286
13	11	203	11	204	1.0	67	11	202	1.0	136	11	198	1.0	278
19	11	215	11	218	1.0	63	11	217	1.0	127	10	210	0.9	238
23	9	223	10	222	1.1	56	10	221	1.1	113	9	210	1.0	214
28	11	236	11	234	1.0	59	11	228	1.0	121	10	218	0.9	229
32	11	242	11	241	1.0	57	11	239	1.0	115	11	223	1.0	247
36	11	248	11	246	1.0	56	9	246	0.8	91	11	229	1.0	240
39	11	259	12	256	1.1	59	11	250	1.0	110	10	234	0.9	214
45	10	268	11	265	1.1	52	10	261	1.0	96	10	240	1.0	208
49	12	274	12	272	1.0	55	11	265	0.9	104	11	241	0.9	228
54	12	282	13	280	1.1	58	13	271	1.1	120	12	246	1.0	244
58	11	290	13	289	1.2	56	12	277	1.1	108	11	253	1.0	217
61	12	304	13	304	1.1	53	12	287	1.0	105	12	261	1.0	230
66	13	316	13	316	1.0	51	13	301	1.0	108	19	270	1.5	352
69	13	331	13	327	1.0	50	13	314	1.0	104	13	281	1.0	231
73	12	339	12	336	1.0	45	12	318	1.0	94	12	288	1.0	208
78	12	345	13	339	1.1	48	13	322	1.1	101	13	292	1.1	223
83	12	349	12	344	1.0	44	12	321	1.0	93	12	289	1.0	208
87	12	350	13	349	1.1	47	13	324	1.1	100	12	293	1.0	205
91	12	357	14	355	1.2	49	13	332	1.1	98	13	297	1.1	219
96	12	360	13	361	1.1	45	13	336	1.1	97	13	298	1.1	218
100	12	369	13	362	1.1	45	13	341	1.1	95	14	303	1.2	231
Mean	11.5	284	12.1	282	1.1	56	11.7	271	1.0	111	11.8	249	1.0	240
SD (d)	0.9		1.0		0.1	10	1.2		0.1	19.1	2.0		0.1	41
CV (e)	7.8		8.3		9.1	17.9	10.3		10.0	17.2	16.9		10.0	17.1

(a) Grams of feed removed from feeder per day. Not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of C.I. Disperse Blue 1 consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE L3. FEED AND COMPOUND CONSUMPTION BY MALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	Control		600 ppm				1,200 ppm				2,500 ppm			
Week	Grams Feed/ Day (a)	Body Wt (g)	Grams Feed/ Day (a)	Body Wt (g)	Low/ Cont (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Wt (g)	Mid/ Cont (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Wt (g)	High/ Cont (b)	Dose/ Day (c)
5	7	29.9	8	30.0	1.1	160	7	29.0	1.0	290	8	29.3	1.1	683
9	7	32.7	8	34.2	1.1	140	8	32.5	1.1	295	8	33.9	1.1	590
13	6	34.8	6	35.8	1.0	101	6	34.5	1.0	209	6	35.8	1.0	419
19	7	36.3	6	37.6	0.9	96	6	36.0	0.9	200	7	37.7	1.0	464
23	8	38.2	8	39.2	1.0	122	7	38.0	0.9	221	7	39.5	0.9	443
28	7	38.7	7	39.3	1.0	107	7	37.6	1.0	223	7	40.0	1.0	438
32	8	40.0	7	41.0	0.9	102	8	38.3	1.0	251	7	40.8	0.9	429
36	9	41.3	8	43.1	0.9	111	8	40.4	0.9	238	8	42.1	0.9	475
39	8	40.8	8	43.7	1.0	110	7	37.4	0.9	225	8	41.9	1.0	477
45	8	42.4	7	44.6	0.9	94	7	41.1	0.9	204	7	43.7	0.9	400
49	9	43.4	8	44.7	0.9	107	7	40.3	0.8	208	9	43.6	1.0	516
54	8	44.1	7	45.6	0.9	92	8	41.6	1.0	231	8	43.1	1.0	464
58	9	44.0	7	45.1	0.8	93	8	40.9	0.9	235	8	42.7	0.9	468
61	8	43.4	7	44.3	0.9	95	7	40.8	0.9	206	8	42.1	1.0	475
66	8	43.3	7	44.5	0.9	94	7	41.0	0.9	205	8	41.9	1.0	477
69	9	43.9	8	43.8	0.9	110	8	41.1	0.9	234	9	41.5	1.0	542
73	9	41.1	8	43.6	0.9	110	8	40.7	0.9	236	10	41.5	1.1	602
78	9	43.0	7	42.4	0.8	99	7	40.8	0.8	206	9	41.1	1.0	547
83	9	42.4	7	41.8	0.8	100	8	40.1	0.9	239	8	39.7	0.9	504
87	9	42.5	8	41.8	0.9	115	8	39.7	0.9	242	10	39.4	1.1	635
91	9	41.4	8	41.5	0.9	116	9	38.4	1.0	281	11	39.4	1.2	698
96	11	39.5	10	39.9	0.9	150	11	38.8	1.0	340	13	39.3	1.2	827
100	12	40.3	10	39.3	0.8	153	9	38.1	0.8	283	13	38.3	1.1	849
Mean	8.4	40.3	7.6	41.2	0.9	112	7.7	38.6	0.9	239	8.6	39.9	1.0	540
SD (d)	1.3		1.0		0.1	20	1.1		0.1	36	1.8		0.1	124
CV (e)	15.5		13.2		11.1	17.9	14.3		11.1	15.1	20.9		10.0	23.0

(a) Grams of feed removed from feeder per day. Not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of C.I. Disperse Blue 1 consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE L4. FEED AND COMPOUND CONSUMPTION BY FEMALE MICE IN THE TWO-YEAR FEED STUDY OF C.I. DISPERSE BLUE 1

	Control		600 ppm				1,200 ppm				2,500 ppm			
Week	Grams Feed/ Day (a)	Body Wt (g)	Grams Feed/ Day (a)	Body Wt (g)	Low/ Cont (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Wt (g)	Mid/ Cont (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Wt (g)	High/ Cont (b)	Dose/ Day (c)
5	8	21.7	7	22.8	0.9	184	8	22.9	1.0	419	8	23.1	1.0	866
9	6	24.0	7	25.3	1.2	166	7	24.8	1.2	339	7	25.1	1.2	697
13	5	26.2	6	27.0	1.2	133	5	26.1	1.0	230	6	26.3	1.2	570
19	5	28.4	5	30.1	1.0	100	5	28.2	1.0	213	6	28.6	1.2	524
23	7	30.2	6	30.7	0.9	117	7	29.7	1.0	283	7	30.4	1.0	576
28	6	31.6	7	33.2	1.2	127	7	32.1	1.2	262	7	32.2	1.2	543
32	6	33.2	7	34.7	1.2	121	7	33.1	1.2	254	7	34.2	1.2	512
36	7	35.9	7	38.5	1.0	109	8	36.2	1.1	265	7	36.3	1.0	482
39	7	37.8	7	41.4	1.0	101	8	37.9	1.1	253	8	37.7	1.1	531
45	7	39.0	7	42.9	1.0	98	7	39.4	1.0	213	7	39.4	1.0	444
49	8	42.5	7	46.1	0.9	91	8	42.4	1.0	226	8	41.1	1.0	487
54	7	43.0	7	47.1	1.0	89	8	43.5	1.1	221	8	40.8	1.1	490
58	7	41.7	7	47.0	1.0	89	8	42.7	1.1	225	8	41.0	1.1	488
61	7	42.4	7	47.0	1.0	89	7	43.8	1.0	192	7	40.4	1.0	433
66	7	43.8	6	48.1	0.9	75	7	45.0	1.0	187	7	40.7	1.0	430
69	7	44.1	7	48.9	1.0	86	9	44.8	1.3	241	8	40.7	1.1	491
73	7	44.1	7	49.3	1.0	85	7	45.8	1.0	183	8	42.2	1.1	474
78	7	43.7	8	48.4	1.1	99	7	45.5	1.0	185	7	40.8	1.0	429
83	7	44.2	7	47.4	1.0	89	7	45.1	1.0	186	7	40.3	1.0	434
87	8	45.3	8	49.2	1.0	98	7	45.4	0.9	185	8	41.3	1.0	484
91	8	44.1	9	50.1	1.1	108	7	45.6	0.9	184	8	41.9	1.0	477
96	8	44.6	9	49.2	1.1	110	9	46.5	1.1	232	9	41.1	1.1	547
100	8	45.8	10	49.8	1.3	120	9	47.3	1.1	228	9	40.7	1.1	553
Mean	7.0	38.1	7.2	41.5	1.0	108	7.3	38.9	1.1	235	7.5	36.8	1.1	520
SD (d)	0.9		1.1		0.1	26	1.0		0.1	55	0.8		0.1	97
CV (e)	12.9		15.3		10.0	24.1	13.7		9.1	23.4	10.7		9.1	18.7

(a) Grams of feed removed from feeder per day. Not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimated milligrams of C.I. Disperse Blue 1 consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

APPENDIX M

GENETIC TOXICOLOGY OF C.I. DISPERSE BLUE 1

TABLE M1. MUTAGENICITY OF C.I. DISPERSE BLUE 1 IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0	142 ± 4.9	139 ± 5.9	111 ± 4.0
	10	--	155 ± 3.2	134 ± 3.2
	33	177 ± 3.5	--	--
	100	160 ± 2.8	157 ± 2.5	147 ± 9.2
	333	174 ± 9.2	175 ± 4.7	154 ± 3.8
	1,000	151 ± 10.1	179 ± 1.2	128 ± 35.2
	2,000	122 ± 11.0	152 ± 20.2	91 ± 15.6
TA1535	0	29 ± 1.9	11 ± 1.0	11 ± 0.9
	10	--	17 ± 1.8	12 ± 2.6
	33	32 ± 1.8	--	--
	100	31 ± 1.8	21 ± 5.5	24 ± 0.7
	333	38 ± 3.3	24 ± 0.6	25 ± 3.5
	1,000	43 ± 6.1	28 ± 0.3	34 ± 1.8
	2,000	43 ± 3.3	44 ± 1.9	38 ± 7.2
TA97	0	95 ± 3.5	142 ± 1.8	119 ± 2.5
	0.1	99 ± 9.0	--	--
	0.3	110 ± 6.7	--	--
	1.0	118 ± 10.5	151 ± 2.7	135 ± 6.8
	3.3	163 ± 4.4	146 ± 4.7	140 ± 5.2
	10.0	198 ± 6.2	189 ± 4.5	178 ± 8.0
	33.0	--	177 ± 4.5	163 ± 14.5
	100.0	--	176 ± 18.2	127 ± 23.8
TA98	0	17 ± 0.6	38 ± 4.9	35 ± 2.0
	10	--	69 ± 6.2	74 ± 5.2
	33	49 ± 2.0	--	--
	100	45 ± 5.5	140 ± 9.7	131 ± 6.5
	333	66 ± 8.9	137 ± 1.0	161 ± 8.0
	1,000	84 ± 4.6	92 ± 5.8	159 ± 0.9
	2,000	115 ± 1.5	68 ± 13.8	86 ± 8.3

(a) The S9 fractions were prepared from the livers of Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters. Cells and test compound or solvent (DMSO) were incubated for 20 minutes at 37° C in the presence of either S9 or buffer. After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37° C for 48 hours (Haworth et al., 1983). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.
(b) Mean ± standard error

APPENDIX N

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

Meal Diet: December 1979 to January 1982

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

TABLE N1. 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
Brewer's dried 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) NIH, 1978; NCI, 1976
(b) Ingredients should be ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE N2. 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 activity
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 N3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrient	Mean ± Standard Deviation	Range	No. of Samples
Crude protein (percent by weight)	24.30 ± 1.04	22.9-26.3	24
Crude fat (percent by weight)	4.92 ± 0.43	4.4-6.0	24
Crude fiber (percent by weight)	3.36 ± 0.59	1.4-4.2	24
Ash (percent by weight)	6.71 ± 0.44	5.97-7.42	24
Essential Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.827-0.840	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	10,800 ± 2,250	7,900 ± 17,000	24
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	17.3 ± 0.61	7.3-26.0	(b) 23
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.30 ± 0.20	0.81-1.6	24
Phosphorous (percent)	1.01 ± 0.09	0.82-1.10	24
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

(a) One or two batches of feed analyzed for nutrients reported in this table were manufactured in January and/or April 1983.
(b) One batch (7/22/81) not analyzed for thiamine

TABLE N4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminant	Mean ± Standard Deviation	Range	No. of Samples
Arsenic (ppm)	0.36 ± 0.18	<0.05-0.93	24
Cadmium (ppm) (a)	0.11 ± 0.07	<0.1-0.40	24
Lead (ppm)	1.03 ± 0.61	0.57-2.62	24
Mercury (ppm) (b)	<0.05		
Selenium (ppm)	0.29 ± 0.08	0.10-0.48	24
Aflatoxins (ppb) (b,c)	<10		24
Nitrate nitrogen (ppm) (d,e)	7.32 ± 4.14	<0.1-13.0	24
Nitrite nitrogen (ppm) (d,e)	1.77 ± 1.28	<0.1-3.7	24
BHA (ppm) (f,g)	3.51 ± 2.83	<0.4-11.0	24
BHT (ppm) (f)	2.72 ± 1.22	1.2-5.3	24
Aerobic plate count (CFU/g)	70,896 ± 50,153	7,000-210,000	24
Coliform (MPN/g) (h)	96 ± 119	<3-460	16
Coliform (MPN/g) (i)	593 ± 814	<3-2,400	24
E. Coli (MPN/g) (j)	7.50 ± 7.68	<3-23	24
Total nitrosamines (ppb) (k,l)	7.12 ± 6.56	<1.8-24.5	22
Total nitrosamines (ppb) (k,m)	14.93 ± 27.23	<1.8-101.6	24
N-Nitrosodimethylamine (ppb) (k,l)	5.37 ± 5.98	0.7-20.0	22
N-Nitrosodimethylamine (ppb) (k,m)	13.13 ± 26.89	0.7-101.6	24
N-Nitrosopyrrolidine (ppb)	1.27 ± 0.80	<0.5-3.5	24
Pesticides (ppm)			
α-BHC (b,n)	<0.01		24
β-BHC (b)	<0.02		24
γ-BHC-Lindane (b)	<0.01		24
δ-BHC (b)	<0.01		24
Heptachlor (b)	<0.01		24
Aldrin (b)	<0.01		24
Heptachlor epoxide (b)	<0.01		24
DDE (b,o)	<0.01	0.05 (7/14/81)	24
DDD (b)	<0.01		24
DDT (b)	<0.01		24
HCB (b)	<0.01		24
Mirex (b)	<0.01		24
Methoxychlor (b,o)	<0.05	0.13 (8/25/81)	24
Dieldrin (b)	<0.01		24
Endrin (b)	<0.01		24
Telodrin (b)	<0.01		24
Chlordane (b)	<0.05		24
Toxaphene (b)	<0.1		24
Estimated PCB's (b)	<0.2		24
Ronnel (b)	<0.01		24
Ethion (b)	<0.02		24
Trithion (b)	<0.05		24
Diazinon (b)	<0.1		24
Methyl parathion (b)	<0.02		24
Ethyl parathion (b)	<0.02		24
Malathion (p)	0.08 ± 0.05	<0.05-0.25	24
Endosulfan I (b)	<0.01		24
Endosulfan II (b)	<0.01		24
Endosulfan sulfate (b)	<0.03		24

TABLE N4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) Two batches contained more than 0.1 ppm.
(b) All values were less than the detection limit, given in the table as the mean.
(c) The detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(d) Source of contamination: Alfalfa, grains, and fish meal
(e) Two batches contained less than 0.2 ppm.
(f) Source of contamination: Soy oil and fish meal
(g) Three batches contained less than 0.5 ppm.
(h) Excludes eight very high values in the range 1,100-2,400 obtained in batches produced on 11/25/80, 12/16/80, 5/26/81, 7/14/81, 9/25/81, 10/23/81, 11/27/81, and 4/26/82
(i) Includes the high values listed in footnote h
(j) MPN = most probable number
(k) All values were corrected for percent recovery.
(l) Mean, standard deviation, and range exclude two very high values of 101.6 and 100.3 ppb in batches produced on 1/26/81 and 4/27/81.
(m) Mean, standard deviation, and range include the very high values given in footnote l.
(n) BHC = hexachlorocyclohexane or benzene hexachloride
(o) There was one observation above the detection limit. The value and the date it was obtained are given under the range.
(p) Eight batches contained more than 0.05 ppm.

APPENDIX O

DATA AUDIT SUMMARY

APPENDIX O. DATA AUDIT SUMMARY

An audit was conducted on the archival data and pathology materials for the 2-year toxicology and carcinogenesis studies of C.I. Disperse Blue 1 in rats and mice. The animal studies were performed at Southern Research Institute, Birmingham, Alabama, under a subcontract with Tracor Jitco, Inc., from the National Cancer Institute. The 2-year studies were conducted from March 1980 to March 1982 and was initiated before the requirement of compliance to Good Laboratory Practice by NTP in October 1981. The audit was conducted at the NTP Archives, Rockville, Maryland, and involved the following personnel: C. Dippel, M.S., F. Garner, D.V.M., J. Konz, M.S.P.H., J. Plautz, M.S., R. Schueler, D.V.M., C. Sexsmith, B.S., and P. Wennerberg, D.V.M. (Dynamac Corporation); A. Grant and R. Joftes (NTP); S. Corson (Pathology Associates, Inc.); and M. Pielmeier, G. Heuckeroth, and M. Plein (Tracor Jitco, Inc). The audit consisted of an in-depth review of the data and pathology materials collected during the conduct of the studies as well as review of the correspondence, laboratory final report, and draft Technical Report.

For the inlife toxicology data, 100% of the records on animal receipt and husbandry, mortality, environmental conditions, sentinel animals, and dosing and 10% of the animal data on body weight, clinical observation, and food consumption were examined. Records of the randomization of animals were not available for review. Review of the mortality data for the mice identified two animals that possibly had received incorrect disposition codes, and the audit of the clinical observations data found indications that the animal room technicians had difficulties in palpating tissue masses and in identifying and locating lesions of the urinary bladder by palpation. Validation of the draft Technical Report found that all of the procedures and data were accurately reported, with the exception of the feed consumption data. The feed consumption data accurately reflected the data in CBDS, but the data submitted to CBDS did not accurately reflect the laboratory records. Revised data were submitted to CBDS and are incorporated in this Technical Report.

In the review of the chemistry data associated with the studies, all of the records were examined pertaining to receipt and use of the chemical, analyses of the bulk chemical and diets by the contract laboratory, and characterization of the bulk chemical and analysis of the formulated diets by the referee laboratory. Review of the analytical chemistry data showed that all the appropriate data were present and that the chemical concentrations in the diet were near the target concentrations throughout the study.

The audit of the pathology materials included review of 100% of the Individual Animal Data Records (IADR's) for correlation between gross observation and microscopic diagnosis and for clerical errors, examination of the wet tissues of 10% of the animals for unidentified lesions and 100% of the animals for correct identification, correlation of slides and tissue blocks for six of eight groups, and verification of the reported pathology on a 10% sample of the animals. Review of the pathology data found no significant problems in the number of preserved tissue bags, slide/block match, tissue accountability, clerical errors on IADR's, or individual pathology tables. Discrepancies were found in the correlation of gross necropsy observations and microscopic diagnoses; however, the majority of these resulted from observations at necropsy which would not necessarily correspond with pathologic changes seen microscopically. Only a few untrimmed lesions were found during review of the wet tissues: two eye lesions, one enlarged lymph node, one enlarged bulbocavernosis muscle, and one dark raised area on the liver (in rats); two untrimmed liver nodules, one enlarged atrium, and an enlarged spleen (in mice).

The combination of microscopic and wet tissue examination revealed the following total number of lesions: For the rats, no potential tumors in target organs were found, and 11 potential neoplastic lesions were found in nontarget organs; for the mice, 4 potential tumors in target organs, 9 potential nonneoplastic lesions in target organs, and 24 potential neoplastic lesions in nontarget organs were recorded by the auditing pathologist. All uncut lesions that were perceived to be potential tumors were trimmed, sectioned, stained, and examined. All potential tumors found in the audit of the

stained slides from the studies were reexamined. These findings were added to the data from the studies. Likewise, additional nontumor pathology data that were discovered in the audit were added to the study data.

Although some problems and discrepancies were identified as discussed in the audit report, these were adequately resolved or were determined not to affect the outcome of the studies. In conclusion, the data examined in this audit are considered adequate to meet the objectives of the studies.

*U.S. GOVERNMENT PRINTING OFFICE: 1986-491-292:41083