

**NATIONAL TOXICOLOGY PROGRAM**  
**Technical Report Series**  
**No. 222**



**CARCINOGENESIS BIOASSAY**  
**OF**  
**C. I. DISPERSE YELLOW 3**  
**(CAS NO. 2832-40-8)**  
**IN F344/N RATS AND B6C3F<sub>1</sub> MICE**  
**(FEED STUDY)**

**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 chemically induced 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.

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NTP Technical Report  
on the  
CARCINOGENESIS BIOASSAY  
of  
C. I. DISPERSE YELLOW 3  
(CAS No. 2832-40-8)  
IN F344/N RATS AND B6C3F<sub>1</sub>/N MICE  
(FEED STUDY)



NATIONAL TOXICOLOGY PROGRAM  
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National Institutes of Health

#### NOTE TO THE READER

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

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

Comments and questions about the National Toxicology Program Technical Reports on Carcinogenesis Bioassays should be directed to the National Toxicology Program, located at Room A-306, Landow Building, Bethesda, MD 20205 (301-496-1152) or at Research Triangle Park, NC 27709 (919-541-3991).

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## ABSTRACT

A carcinogenesis bioassay of C. I. Disperse Yellow 3 (87.6% dye), a textile dye, was conducted by feeding diets containing 5,000 or 10,000 ppm of the test substance to groups of 50 F344 rats of either sex for 103 weeks. Similar groups of 50 B6C3F1 mice received diets containing 2,500 or 5,000 ppm of the test substance for 103 weeks. Groups of 50 untreated rats and mice of each sex served as controls.

Throughout the bioassay, mean body weights of dosed rats and mice of either sex were lower than those of the controls. Survival of dosed rats of either sex was significantly greater than that of the corresponding controls. No other compound-related clinical signs or effects on survival were observed.

A significant increase in neoplastic nodules of the liver occurred in dosed male rats as compared to controls (controls 1/49, 2%; low-dose 15/50, 30%;  $P < 0.001$ ; high-dose, 10/50, 20%;  $P < 0.01$ ). No increase was observed for female rats.

Stomach tumors, rare in F344 rats (10/2960, 0.3%), were found in the dosed male rats: one adenocarcinoma and a sarcoma in a high-dose male and in the low-dose group a squamous cell papilloma, fibrosarcoma, adenoma, and mucinous adenocarcinoma. The incidence of these tumors was not significantly greater than that in controls; thus, the association between the administration of C. I. Disperse Yellow 3 and the stomach tumors in male rats is not clearly established.

Negative trends in the incidences of certain primary tumors in dosed rats included: decreased lymphocytic leukemia in both sexes; decreased malignant mesothelioma and C-cell carcinoma of the thyroid in males; and decreased pituitary chromophobe adenoma and endometrial stromal polyps in females.

Hepatocellular adenomas occurred in dosed female mice at incidences significantly higher than that in the controls (control 0/50, 0%; low-dose 6/50, 12%,  $P < 0.05$ ; high-dose 12/50, 24%,  $P < 0.001$ ). The incidences of hepatocellular carcinomas were also higher in the dosed female mice than in the controls, but the increased incidences were not statistically significant (2/50, 4/50, 5/50). A significantly ( $P < 0.05$ ) lower incidence of hepatocellular adenomas was detected among low-dose (7/50, 1/49, 7/49) male mice.

Alveolar/bronchiolar adenomas occurred in high-dose male mice at an incidence significantly ( $P < 0.05$ ) higher than that in the controls (control 2/50, 4%; low-dose 6/49, 12%; high-dose 9/49, 18%). However, the high-dose effect was not significant when adenomas and carcinomas were combined; the incidence among low-dose female mice was significantly reduced as compared with controls. Thus, the incidence of alveolar/bronchiolar adenomas among males is not considered to be related to treatment with C. I. Disperse Yellow 3.

Malignant lymphomas occurred in a dose-related ( $P < 0.05$ ) trend in female mice and at incidences greater ( $P < 0.05$ ) in the high-dose group than that in the controls (10/50, 16/50, 19/50). However, because of the range of variability in the historical incidence of this tumor and because of the lack of a similar effect in male mice or in male and female rats, this increase was not regarded as being unequivocally related to the administration of C. I. Disperse Yellow 3.

Under the conditions of this bioassay, C. I. Disperse Yellow 3 was considered carcinogenic for male F344 rats, causing an increased incidence of neoplastic nodules of the liver; this dye was not carcinogenic for female F344 rats. In addition, the stomach tumors found in the male rats may have been induced by the administration of the test chemical. C. I. Disperse Yellow 3 was carcinogenic for female B6C3F1 mice, as evidenced by the increased incidence of hepatocellular adenomas; C. I. Disperse Yellow 3 was not carcinogenic for male B6C3F1 mice. Also, the increased incidence of malignant lymphoma in female mice may have been associated with the administration of C. I. Disperse Yellow 3.

## CONTRIBUTORS

This bioassay was conducted at Battelle Columbus Laboratories, Columbus, Ohio, under a subcontract to Tracor Jitco, Inc., Rockville, Maryland, prime contractor for the NCI/NTP Carcinogenesis Testing Program. The prechronic studies were initiated in June 1976 and finished in December 1976. The chronic studies were begun in March 1977 and finished in April 1979.

Dr. A. Peters (1) was the principal investigator for this study. Doses of the test chemical were selected by Drs. A. Peters and J. Robens (2,3). Drs. A. Peters, H. Harroff (1), and P. Stromberg (1) were in charge of animal care.

Necropsies were directed by Drs. G. S. Dill (1), R. Persing (1), R. Everett (1,4), and D. Thake (1). Histopathologic evaluations were performed by Drs. G. S. Dill (rats) and R. Persing (mice) (1). The pathology report and selected slides were evaluated by the NCI Pathology Working Group as described by Ward et al. (1978). The diagnoses represent a consensus of contracting pathologists and the NCI Pathology Working Group, with final approval by the NCI Pathology Working Group.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (5). Statistical analyses were performed by Dr. J. R. Joiner (2) and Mr. J. Warner (2) using methods selected for the bioassay program by Dr. J. J. Gart (6). Chemical analyses were conducted at Midwest Research Institute (7). Dosage analysis was supervised by Drs. R. Freudenthal (1) and P. Leber (1,8) and by Mr. D. Emmerling (1).

This report was prepared at Tracor Jitco (2) under the direction of Dr. C. Cueto (9), Director of the Bioassay Program; Dr. S. S. Olin, Associate Director; Dr. J. E. Tomaszewski, chemist; Dr. M. A. Stedham, pathologist; Dr. W. D. Theriault, reports manager; Dr. A. C. Jacobs, bioscience writer; and Ms. M. W. Glasser, technical editor.

The following scientists at NCI/NTP (10) were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. J. Fielding Douglas, Dr. Charles Grieshaber, Dr. Larry Hart, Dr. William V. Hartwell, Dr. Joseph Haseman, Dr. James Huff, Dr. Ernest E. McConnell, Dr. John H. Mennear (Chemical Manager), Dr. John A. Moore, Dr. Sherman F. Stinson, Dr. Raymond Tennant, and Dr. Jerrold M. Ward.

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## PEER REVIEW COMMENTS

On February 18, 1981 this report underwent peer review and was approved by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts at an open meeting held in Building 31C, National Institutes of Health, Bethesda, Maryland.

Dr. Williams, as a principal reviewer for the report on the bioassay of C. I. Disperse Yellow 3, agreed with the conclusion that under the conditions of the bioassay Yellow 3 induced liver tumors in F344 male rats and B6C3F1 female mice. In addition, stomach tumors in male rats may have been induced by the chemical. An increased incidence of pulmonary adenomas occurred in male mice, but the higher incidence in historical controls and a negative effect in female mice may limit the significance of this finding. His major concern about the study was that the degree of depression of weight gain in the high-dose rats indicated the maximum tolerated dose was exceeded. In his opinion, the development of a variety of nonneoplastic changes substantiated the observation that the high dose was not a tolerated dose. In spite of these considerations, he proposed that the close structural similarity of C. I. Disperse Yellow 3 to the amino azo dyes indicated the carcinogenic effect could arise from a genotoxic action, and suggested that additional genetic toxicology be performed.

As the second principal reviewer, Dr. Swenberg opined that although there was an increased incidence of hepatic neoplastic nodules in male rats and hepatocellular adenomas in female mice, no apparent progression to hepatic carcinoma was demonstrated in either case. He reiterated the development of stomach tumors in male rats. He commented on striking dose-related decreases in the incidence of lymphocytic leukemia, C-cell carcinoma of the thyroid, and mesotheliomas of multiple organs in male rats, and similar decreases in pituitary adenomas and endometrial stromal polyps of the uterus in females. Based on the evidence, Dr. Swenberg considered C. I. Disperse Yellow 3 to have limited carcinogenic activity in male rats and female mice. He stated that the summary should qualify the significance of several of the tumor diagnoses, should mention the dose-related decrease in several tumor types, and should reflect the limited carcinogenic activity of the chemical.

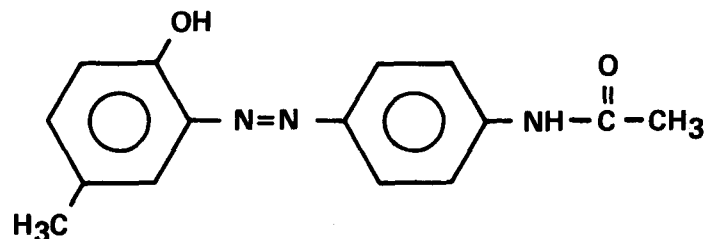
Dr. Highland disagreed with Dr. Swenberg as to the "limited" nature of the evidence for carcinogenicity. Dr. Swenberg said he based his qualification on the facts that the results for the finding of pulmonary adenomas in male mice were equivocal and that the hepatic nodules in rats and adenomas in mice are lesions which sometimes occur spontaneously and are difficult to classify as malignant by histological criteria alone. Drs. Moore and Highland agreed that a possible compromise would be to state that "under the conditions of the bioassay, C. I. Disperse Yellow 3 was found to be a carcinogen as evidenced by an increased induction of hepatic neoplastic nodules in male rats and hepatocellular adenomas in female mice."

Dr. Williams requested that the portion of the discussion in the report dealing with the issue of whether or not hepatic nodules are precursors of carcinomas should be expanded to read along the lines of a similar discussion in the report on the bioassay of C. I. Solvent Yellow 14.

Dr. Williams moved that in the report on the bioassay of C. I. Disperse Yellow 3 adequate evidence exists for the carcinogenicity of the chemical and the report should be accepted with the revisions noted. Dr. Swenberg seconded the motion, and the report was approved unanimously by the Peer Review Panel.



## I. INTRODUCTION



### C. I. DISPERSE YELLOW 3

CAS NO. 2832-40-8

COLOUR INDEX NO. 11855

C. I. Disperse Yellow 3, also known as Disperse Fast Yellow 6 and Acetamine Yellow CG, is a monoazo dye, of low aqueous solubility, used to color nylon, polyvinyl chloride and acrylic fibers, wools and furs, cellulose acetate, polystyrene, and other thermoplastics. Finished products containing C. I. Disperse Yellow 3 include clothing, hosiery, and carpeting (Society of Dyers and Colourists, 1971; Kirk-Othmer, 1978; Gray and Hunter, 1977).

Current production figures are not available (USITC, 1979); however, 1,277,000 kilograms were produced in the United States in 1972 (IARC, 1975).

C. I. Disperse Yellow 3 has been reported to produce allergic eczema in persons wearing nylon hosiery dyed with this compound (Foussereau et al., 1972).

C. I. Disperse Yellow 3 was reported to be "mutagenic in some bacteria," but details of the study were not given (Gray and Hunter, 1977).

Boyland et al. (1964) observed one adenoma and six carcinomas in stock mice (7/25) 25 weeks after the mice received urinary bladder implants of cholesterol pellets containing C. I. Disperse Yellow 3 (concentration not

given). In 77 control animals implanted with cholesterol alone, a total of 4 papillomas and 5 carcinomas were diagnosed. The small number of animals, short duration, exposure method, and reporting render these borderline increases inadequate for evaluation.

C. I. Disperse Yellow 3 was tested by the Carcinogenesis Testing Program because of its widespread use and because the only previous test (Boyland et al., 1964) was considered to be inadequate.

## II. MATERIALS AND METHODS

### A. Chemical

C. I. Disperse Yellow 3 -- N-(4-((2-hydroxy-5-methylphenyl)azo)phenyl)acetamide -- was obtained from E. I. duPont de Nemours and Company, Wilmington, Delaware. Lot No. 19-007630 was used for the repeated-dose, subchronic, and chronic studies.

The results of analyses performed at Midwest Research Institute (Kansas City, MO) indicated that Lot No. 19-007630 was 87.6% dye based on titration of the azo group with titanous chloride (Appendix E). Results of carbon and nitrogen analyses were 89% and 86%, those of the theoretical values for 100% dye. The separate determinations of chloride and carbonate contents (3.47% and 0.65%, respectively) contribute 5.72% and 1.15% to the total, as sodium salts. The total of these values, the dye content (87.6%), and the water content (6.62%) as determined by Karl Fisher titration was 101% of the theoretical value. Two minor and two trace impurities were indicated by thin-layer chromatography and at least four impurities comprising 2.7% of the major peak were detected by high-pressure liquid chromatography; these impurities were not identified. The ultraviolet, visible, and infrared spectra were consistent with the structure and the literature spectra. This batch of C. I. Disperse Yellow 3 was considered to be representative of C. I. Disperse Yellow 3 commercially available for industrial purposes and was therefore considered suitable for use in the Bioassay Program.

The test chemical was stored in the dark at 23°C, and periodic bulk chemical analysis indicated that the chemical was stable throughout the study.

### B. Dietary Preparation

Diets were formulated by mixing weighed amounts of Purina® Laboratory Chow animal meal (Table 1) and the test chemical in an intensifier-bar equipped Patterson-Kelly® twin-shell blender for 15 minutes. Formulated

**Table 1. Specifications and Sources of Materials Used for Animal Maintenance**

| Item            | Specifications                         | Source                             |
|-----------------|--|------------------------------------|
| Bedding         | Absorb-dri <sup>®</sup> hardwood Chips | Lab Products, Inc. (Garfield, NJ)  |
| Cages           | Solid bottom, polycarbonate            | Lab Products, Inc. (Garfield, NJ)  |
| Feed            | Purina <sup>®</sup> Laboratory Chow    | Ralston Purina Co. (Richmond, IN)  |
| Watering System | Edstrom Automatic                      | Edstrom Industries (Waterford, WI) |

diets containing 100,000 ppm C. I. Disperse Yellow 3 were analyzed at Midwest Research Institute and were found to be stable for 2 weeks at temperatures up to 45°C (Appendix F). Formulated diets were stored at 23°C for no longer than 10 days.

The mean analytical concentrations of C. I. Disperse Yellow 3 in selected batches of formulated diets were within +10% of the desired concentration (Appendix G). Homogeneity of the chemical-diet mix was verified analytically.

#### C. Animals

For both the subchronic and chronic studies, 4-week old F344 rats and B6C3F1 mice of either sex were obtained from NCI Frederick Cancer Research Center (Frederick, MD), isolated and maintained in separate quarters for 2 weeks, and assigned to cages according to a table of random numbers. The cages were then assigned to control or dosed groups according to another table of random numbers.

#### D. Animal Maintenance

Rats and mice were housed five per cage in solid-bottom polycarbonate cages (Table 1) supplied with hardwood chip bedding. Cages and bedding were changed twice per week. Control and test diets were available ad libitum in feed hoppers that were changed weekly. Water was available ad libitum from an automatic watering system.

The temperature in the animal rooms was 21° to 23°C and the relative humidity was 40%-60%. Room air was changed 15 times per hour. Fluorescent lighting was provided 12 hours per day.

Rats and mice fed C. I. Disperse Yellow 3 were housed by species in the same room as animals of the same species on feeding studies of D and C Red No. 9 (CAS No. 5160-02-1) and C. I. Solvent Yellow 14 (CAS No. 842-07-9). Each study had a separate set of controls.

#### E. Single-Day Dosing and Repeated-Dose Studies

Single-day dosing and 14-day repeated-dose studies were conducted using F344 rats and B6C3F1 mice to determine the concentrations of C. I. Disperse Yellow 3 to be used in the subchronic studies.

In the single-day dosing study, animals were randomized into groups of five males and five females of each species according to a table of random numbers. Groups of animals of each sex and species were offered diets containing 6,000, 12,500, 25,000, 50,000, or 100,000 ppm C. I. Disperse Yellow 3 for 24 hours and then laboratory chow for the remainder of the study. Feed consumption by rats was inversely proportional to dose during the 24-hour period when dosed feed was available (Table 2). Mice ate negligible amounts of feed. All animals were killed on day 15. No deaths occurred among the rats or mice and no overt signs of toxicity were observed.

In the repeated-dose study, groups of five males and five females of each species were fed diets containing 0, 6,000, 12,500, 25,000, 50,000, or 100,000 ppm for 2 weeks. All surviving animals were killed on day 15.

Weight gain was depressed by 15% or more in all groups of dosed rats as compared with controls (Table 3). Rats receiving 50,000 ppm or 100,000 ppm lost weight. Weight gain was depressed by 25% or more in all groups of dosed mice except for males receiving 6,000 ppm and females receiving 12,500 or 50,000 ppm (Table 4). Feed consumption was not measured, but it was estimated to be 25%-35% less for rats and mice receiving 50,000 or 100,000 ppm as compared with controls.

All rats receiving the 100,000-ppm diet and 1/5 male and 1/5 female rats receiving 50,000 ppm died. The rats receiving the 100,000-ppm diet were emaciated; the fat deposits, usually observed around the kidneys, adrenals, and heart, were depleted. Spleens, kidneys, and livers were uniformly dark red to black. Similar, but milder changes were present in rats fed the 50,000-ppm diet. Rats receiving 25,000 ppm had the normal amount of body fat and livers of normal color, although spleens and kidneys were dark red.

Table 2. Feed Consumption in the Single-Day Dosing Study of  
C. I. Disperse Yellow 3

| Dose<br>(ppm) | <u>Average Feed Consumption per Animal (grams)</u> |        |             |        |
|---------------|--|--------|-------------|--------|
|               | <u>Rats</u>  |        | <u>Mice</u> |        |
|               | Male   | Female | Male        | Female |
| 6,000         | 13.6   | 10.8   | 0           | 0      |
| 12,500        | 10.4   | 10.2   | 0           | 1      |
| 25,000        | 8.0  | 7.4    | 0           | 0      |
| 50,000        | 7.0  | 4.2    | 0           | 0.4    |
| 100,000       | 6.2  | 2.4    | 1           | 0      |

Table 3. Dosage, Survival, and Mean Body Weight Gain of Rats Fed Diets Containing C. I. Disperse Yellow 3 for 14 Days

| Dose<br>(ppm) | Survival (a)<br>(day of death) | Mean Body Weights (b) |              |               | Weight Change<br>Relative to<br>Controls<br>(Percent) (c) |
|---------------|--------------------------------|-----------------------|--------------|---------------|---|
|               |                                | Initial<br>(g)        | Final<br>(g) | Change<br>(g) |   |
| <u>Male</u>   |                                |                       |              |               |   |
| 0             | 5/5                            | 107                   | 127          | +20           |   |
| 6,000         | 5/5                            | 112                   | 118          | + 6           | - 70  |
| 12,500        | 5/5                            | 102                   | 119          | +17           | - 15  |
| 25,000        | 5/5                            | 101                   | 106          | + 5           | - 75  |
| 50,000        | 4/5(11)                        | 93                    | 75           | -18           | -190  |
| 100,000       | 0/5(6,7,10,<br>10,11)          | 92                    | -            | -             | -   |
| <u>Female</u> |                                |                       |              |               |   |
| 0             | 5/5                            | 101                   | 121          | +20           |   |
| 6,000         | 5/5                            | 101                   | 113          | +12           | - 40  |
| 12,500        | 5/5                            | 101                   | 108          | + 7           | - 65  |
| 25,000        | 5/5                            | 87                    | 97           | +10           | - 50  |
| 50,000        | 4/5(13)                        | 96                    | 85           | -11           | -155  |
| 100,000       | 0/5(9,14,14,<br>15,15)         | 96                    | 67           | -29           | -245  |

(a) Number surviving/number per group.

(b) Animals were weighed by cage.

(c) Weight Change Relative to Controls =

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



Table 4. Dosage, Survival, and Mean Body Weight Gain of Mice Fed  
C. I. Disperse Yellow 3 for 14 Days

| Dose<br>(ppm) | Survival (a)<br>(day of death) | Mean Body Weights (b) |              |               | Weight Change<br>Relative to<br>Controls<br>(Percent) (c) |
|---------------|--------------------------------|-----------------------|--------------|---------------|---|
|               |                                | Initial<br>(g)        | Final<br>(g) | Change<br>(g) |   |
| <u>Male</u>   |                                |                       |              |               |   |
| 0             | 5/5                            | 26                    | 30           | + 4           |   |
| 6,000         | 5/5                            | 24                    | 29           | + 5           | + 25  |
| 12,500        | 5/5                            | 25                    | 28           | + 3           | - 25  |
| 25,000        | 5/5                            | 23                    | 26           | + 3           | - 25  |
| 50,000        | 5/5                            | 25                    | 26           | + 1           | - 75  |
| 100,000       | 1/5(10,10,11,<br>11)           | 26                    | 22           | - 4           | -200  |
| <u>Female</u> |                                |                       |              |               |   |
| 0             | 5/5                            | 19                    | 21           | + 2           |   |
| 6,000         | 5/5                            | 20                    | 21           | + 1           | - 50  |
| 12,500        | 5/5                            | 20                    | 22           | + 2           | 0   |
| 25,000        | 5/5                            | 20                    | 19           | - 1           | -150  |
| 50,000        | 5/5                            | 19                    | 22           | + 3           | + 50  |
| 100,000       | 3/5(11,14)                     | 20                    | 20           | 0             | -100  |

(a) Number surviving/number per group.

(b) Animals were weighed by cage.

(c) Weight Change Relative to controls =

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

Among the mice receiving 100,000 ppm, 4/5 males and 2/5 females died. The spleens and kidneys were dark red to black and the livers were reddish tan; the changes were less severe than those found in rats at the same dose level. Enlarged spleens and dark red to black kidneys and spleens were observed in mice receiving 25,000 or 50,000 ppm.

#### F. Subchronic Studies

Subchronic studies were conducted to determine the dietary concentrations of C. I. Disperse Yellow 3 to be used in the chronic studies. Animals were randomized into groups of 10 males and 10 females of each species and were fed diets containing 0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm C. I. Disperse Yellow 3 for 91 days (Table 5 and Table 6). Animals were observed for mortality twice daily and individual animals were weighed weekly. At the end of the dosing period, the animals were killed, necropsies were performed, and tissues (as described in section H) were taken for histopathologic examination.

Rats: One male receiving 1,250 ppm and one female receiving 20,000 ppm died. Weight gain was depressed by 18% or more among rats fed diets containing 10,000 or 20,000 ppm. Feed consumption by male or female rats fed 20,000 ppm was 58% that of the controls. Feed consumption by male or female rats fed 10,000 ppm was 98% and 89%, respectively, that of the controls (Table 5).

The compound-related histopathologic findings are summarized in Table 7. Thyroid hyperplasia, splenic discoloration and mild hypertrophy, and kidney discoloration were observed at necropsy in rats fed 20,000 ppm. Rats fed 20,000 ppm had nonneoplastic lesions in the pituitary, thyroid, spleen, and kidney, including vacuolar degeneration of the pituitary pars distalis in 10/10 males and 6/6 females; thickened fibrous capsules in the thyroid in 10/10 males and 9/9 females; follicular hyperplasia in 10/10 males and in 9/9 females; follicular-cell adenomas in the thyroid in 3/10 males and 1/9 females; hemosiderosis in the spleen in 10/10 males and in 9/9

Table 5. Dosage, Survival, and Mean Body Weights of Rats Fed Diets Containing C. I. Disperse Yellow 3 for 91 Days

| Dose (ppm)    | Survival (a) | Mean Body Weights (grams) (b) |             |              | Weight Change Relative to Controls (%) (c) | Mean Total Feed Consumption Per Animal (grams) |
|---------------|--------------|-------------------------------|-------------|--------------|--|--|
|               |              | Initial                       | Final       | Change       |  |  |
| <b>Male</b>   |              |                               |             |              |  |  |
| 0             | 10/10        | 115.3(3.84)                   | 286.1(6.65) | +170.8(6.10) |  | 1270   |
| 1,250         | 9/10(d)      | 117.6(2.64)                   | 287.9(3.33) | +170.3(3.97) | 0  | 1370   |
| 2,500         | 10/10        | 113.4(2.75)                   | 292.8(9.55) | +179.4(7.66) | + 5  | 1380   |
| 5,000         | 10/10        | 124.7(6.10)                   | 276.4(4.32) | +151.7(5.15) | -11  | 1350   |
| 10,000        | 10/10        | 111.0(3.07)                   | 251.5(5.25) | +140.5(4.66) | -18  | 1240   |
| 20,000        | 10/10        | 110.3(3.40)                   | 182.3(5.02) | + 72.0(4.08) | -58  | 880  |
| <b>Female</b> |              |                               |             |              |  |  |
| 0             | 10/10        | 99.9(3.27)                    | 185.1(3.25) | +85.2(3.48)  |  | 990  |
| 1,250         | 10/10        | 102.4(3.42)                   | 182.3(3.32) | +79.9(3.71)  | - 6  | 950  |
| 2,500         | 9/9          | 96.3(2.96)                    | 182.1(4.22) | +85.8(2.62)  | + 1  | 970  |
| 5,000         | 10/10        | 92.8(2.95)                    | 173.4(3.26) | +80.6(2.40)  | - 5  | 940  |
| 10,000        | 10/10        | 94.1(2.81)                    | 160.9(2.07) | +66.8(1.66)  | -22  | 880  |
| 20,000        | 9/10(e)      | 96.7(3.56)                    | 132.8(2.11) | +36.1(1.88)  | -58  | 570  |

(a) Number surviving/number initially in the group.

(b) Mean weight change of the survivors of the group and standard error of the mean (in parentheses).

(c) Mean weight change of dosed survivors relative to the survivors of the controls =

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

(d) One animal died at week 7.

(e) One animal died at week 3.

Table 6. Dosage, Survival, and Mean Body Weights of Mice Fed Diets Containing C. I. Disperse Yellow 3 for 91 Days

| Dose (ppm)    | Survival (a) | Mean Body Weights (grams) |            |            | Weight Change Relative to Controls (%) (c) |
|---------------|--------------|---------------------------|------------|------------|--|
|               |              | Initial                   | Final      | Change (b) |  |
| <u>Male</u>   |              |                           |            |            |  |
| 0             | 10/10        | 23.7(0.63)                | 32.2(0.92) | +8.5(0.48) |  |
| 1,250         | 10/10        | 23.2(0.61)                | 32.3(0.78) | +9.1(0.59) | + 7  |
| 2,500         | 10/10        | 24.3(0.54)                | 32.1(0.69) | +7.8(0.55) | - 8  |
| 5,000         | 10/10        | 24.0(0.39)                | 30.9(0.28) | +6.9(0.23) | -19  |
| 10,000        | 10/10        | 24.6(0.31)                | 31.8(0.66) | +7.2(0.44) | -15  |
| 20,000        | 10/10        | 23.4(0.50)                | 29.2(0.36) | +5.8(0.29) | -32  |
| <u>Female</u> |              |                           |            |            |  |
| 0             | 10/10        | 18.5(0.31)                | 23.4(0.43) | +4.9(0.31) |  |
| 1,250         | 10/10        | 19.1(0.41)                | 23.9(0.50) | +4.8(0.33) | - 2  |
| 2,500         | 10/10        | 18.5(0.22)                | 24.0(0.42) | +5.5(0.34) | +12  |
| 5,000         | 10/10        | 19.0(0.30)                | 23.5(0.43) | +4.5(0.37) | - 8  |
| 10,000        | 10/10        | 19.0(0.42)                | 23.4(0.34) | +4.4(0.27) | -10  |
| 20,000        | 10/10        | 18.2(0.36)                | 21.9(0.31) | +3.7(0.30) | -25  |

(a) Number surviving/number initially in the group.

(b) Mean weight change of the group and standard error of the mean (in parentheses).

(c) Mean weight change of dosed mice relative to that of controls =

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

Table 7. Compound-Related Histopathologic Findings in Rats Fed Diets Containing C. I. Disperse Yellow 3 for 91 Days

|  | Dose (ppm) |        |       |        |       |        |       |        |        |        |        |           |
|--|------------|--------|-------|--------|-------|--------|-------|--------|--------|--------|--------|-----------|
|  | Control    |        | 1,250 |        | 2,500 |        | 5,000 |        | 10,000 |        | 20,000 |           |
|  | Male       | Female | Male  | Female | Male  | Female | Male  | Female | Male   | Female | Male   | Female(b) |
| Pituitary, pars distalis<br>vacuolar degeneration                          | 0/10       | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10   | 0/10   | 10/10  | 6/6(a)    |
| Thyroid, capsule, fibrous<br>thickening                                    | 0/10       | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 10/10  | 0/10   | 10/10  | 9/9       |
| Thyroid, follicular hyper-<br>plasia, mild                                 | 0/10       | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 10/10  | 10/10  | 0/10   | 0/9       |
| Thyroid, follicular hyper-<br>plasia, moderate                             | 0/10       | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10   | 0/10   | 10/10  | 9/9       |
| Thyroid, adenomatous<br>hyperplasia  | 0/10       | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10   | 0/10   | 0/10   | 1/9       |
| Thyroid, adenoma   | 0/10       | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10   | 0/10   | 3/10   | 1/9       |
| Thyroid, capsule,<br>inflammatory infil-<br>trate, nonsuppurative,<br>mild | 0/10       | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10   | 0/10   | 1/10   | 0/9       |

Table 7. Compound-Related Histopathologic Findings in Rats Fed Diets  
Containing C. I. Disperse Yellow 3 for 91 Days

(Continued)

|   | Dose (ppm) |        |       |        |       |        |       |        |        |        |        |           |
|---|------------|--------|-------|--------|-------|--------|-------|--------|--------|--------|--------|-----------|
|   | Control    |        | 1,250 |        | 2,500 |        | 5,000 |        | 10,000 |        | 20,000 |           |
|   | Male       | Female | Male  | Female | Male  | Female | Male  | Female | Male   | Female | Male   | Female(b) |
| Spleen, hemosiderosis,<br>mild                                      | 0/10       | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 4/10  | 8/10   | 10/10  | 10/10  | 0/10   | 0/9       |
| Spleen, hemosiderosis,<br>moderate                                  | 0/10       | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10   | 0/10   | 10/10  | 9/9       |
| Spleen, lymphocytic<br>depletion, mild                              | 0/10       | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10   | 0/10   | 10/10  | 8/9       |
| <sup>28</sup> Kidney, cortical tubules,<br>pigment deposition, mild | 0/10       | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 10/10  | 10/10  | 0/10   | 0/9       |
| Kidney, cortical tubules,<br>pigment deposition,<br>moderate        | 0/10       | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10  | 0/10   | 0/10   | 0/10   | 10/10  | 9/9       |

(a) Three pituitaries missing.

(b) One female died early.

females; and pigment deposition in the cortical tubules of the kidney in 10/10 males and 9/9 females. These lesions were present to a lesser extent in rats fed 5,000 or 10,000 ppm but were not seen in the controls or animals fed the 1,250 and 2,500 ppm diets.

Doses selected for the chronic study with rats were 5,000 and 10,000 ppm C. I. Disperse Yellow 3 in feed. Because of weight gain depression and the severity of histopathologic effects, 5,000 ppm could have been selected as the high dose. However, 10,000 ppm was selected as the high dose to maximize the possibility of reproducing the thyroid pathology detected during the subchronic study.

Mice: None of the mice died. Mean weight gain was depressed 10% or more in male mice receiving 5,000-20,000 ppm and in female mice receiving 10,000 or 20,000 ppm. Feed consumption data could not be interpreted because of fecal matter and urine in the feed containers. Hemosiderosis of the renal tubular epithelium was observed in all mice receiving 10,000 or 20,000 ppm; hemosiderosis of the spleen was observed in all mice receiving 5,000 ppm or more; and cytoplasmic swelling of the centrilobular hepatocytes was observed in 6/10 males and 6/10 females receiving 10,000 ppm and in 10/10 males and 8/10 females receiving 20,000 ppm (Table 8).

In the subchronic study, mild hemosiderosis of the spleen was the only histopathologic effect seen at 5,000 ppm. Although weight gain depression for male mice receiving 5,000 ppm was greater than 10% as compared with controls, the 15% weight gain depression for male mice receiving 10,000 ppm was less than that seen in mice receiving 5,000 ppm. Weight gain depression for female mice receiving 5,000 ppm was less than 10% as compared with controls.

Doses selected for mice for the chronic study were 2,500 and 5,000 ppm C. I. Disperse Yellow 3 in the feed.

#### G. Chronic Studies

The test groups, doses administered, and durations of the chronic studies are shown in Table 9.

Table 8. Compound-Related Histopathologic Findings in Mice Fed Diets Containing C. I. Disperse Yellow 3 for 91 Days

| Dose (ppm)     | Kidney, Cortex, Proximal Tubules, Hemosiderosis | Spleen, Hemosiderosis | Liver, Centrilobular Hepatocyte, Swelling |
|----------------|---|-----------------------|---|
| <u>MALES</u>   |   |                       |   |
| Control        | 0/10  | 0/10                  | 0/10                                      |
| 1,250          | 0/10  | 0/10                  | 0/10                                      |
| 2,500          | 0/10  | 0/10                  | 0/10                                      |
| 5,000          | 0/10  | 10/10                 | 0/10                                      |
| 10,000         | 10/10   | 10/10                 | 6/10                                      |
| 20,000         | 10/10   | 10/10                 | 10/10                                     |
| <u>FEMALES</u> |   |                       |   |
| Control        | 0/10  | 0/10                  | 0/10                                      |
| 1,250          | 0/10  | 0/10                  | 0/10                                      |
| 2,500          | 0/10  | 0/10                  | 0/10                                      |
| 5,000          | 0/10  | 10/10                 | 0/10                                      |
| 10,000         | 10/10   | 10/10                 | 6/10                                      |
| 20,000         | 10/10   | 10/10                 | 8/10                                      |



Table 9. Experimental Design of Chronic Feeding Studies with  
C. I. Disperse Yellow 3 in Rats and Mice

| Test Group (a)     | Initial No. of Animals | C. I. Disperse Yellow 3 (ppm) | Weeks on Study (b) |          |
|--------------------|------------------------|-------------------------------|--------------------|----------|
|                    |                        |                               | Dosed              | Observed |
| <u>Male Rats</u>   |                        |                               |                    |          |
| Control            | 50                     | 0                             | 0                  | 104      |
| Low-Dose           | 50                     | 5,000                         | 103                | 1        |
| High-Dose          | 50                     | 10,000                        | 103                | 1        |
| <u>Female Rats</u> |                        |                               |                    |          |
| Control            | 50                     | 0                             | 0                  | 104      |
| Low-Dose           | 50                     | 5,000                         | 103                | 1        |
| High-Dose          | 50                     | 10,000                        | 103                | 1        |
| <u>Male Mice</u>   |                        |                               |                    |          |
| Control            | 50                     | 0                             | 0                  | 104      |
| Low-Dose           | 50                     | 2,500                         | 103                | 2        |
| High-Dose          | 50                     | 5,000                         | 103                | 2        |
| <u>Female Mice</u> |                        |                               |                    |          |
| Control            | 50                     | 0                             | 0                  | 105      |
| Low-Dose           | 50                     | 2,500                         | 103                | 2        |
| High-Dose          | 50                     | 5,000                         | 103                | 2        |

(a) The control and dosed animals were of the same strain, sex, and age range and from the same source and shipment. All animals of the same strain shared the same room, and all aspects of animal care and maintenance were similar. Animals were randomized to dosed and control groups as described in Section IIc.

(b) The start dates were March 10, 1977, for male rats, March 23, 1977, for female rats, April 8, 1977, for male mice, and April 14, 1977, for female mice.

## H. Clinical Examinations and Pathology

All animals were observed twice daily to discern sick or moribund animals. Clinical examinations and palpation for masses were performed each month, and the animals were weighed (by cage) every 4 weeks. Moribund animals and animals that survived to the end of the bioassay were killed using carbon dioxide and necropsied.

Gross and microscopic examinations were performed on major tissues, major organs, and all gross lesions from killed animals and from animals found dead. The tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following tissues were examined microscopically: skin (abdominal), lungs and bronchi, trachea, bone, bone marrow (femur), thigh muscle, spleen, lymph nodes, thymus, heart, salivary glands, liver, pancreas, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, mammary gland, uterus, ovary, brain, epididymus, eye, and all tissue masses.

Necropsies were performed on all animals found dead, unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and does not necessarily represent the number of animals that were placed on study in each group.

## I. Data Recording and Statistical Analyses

Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died

of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is reported only when its two-tailed P value is less than 0.05.

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

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of dosed animals at each dose level. When the results from two dosed groups are compared simultaneously with that for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality criterion (Miller, 1966) requires that the P values for any comparison be less than or equal to 0.025. When this correction was used, it is discussed in the narrative section. It is not presented in the tables, where the Fisher exact P values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. Under the assumption of a linear trend, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance.

Unless otherwise noted, the direction of the significant trend is a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

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

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

a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical, which could not be detected under the conditions of this test.



### III. RESULTS - RATS

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

Throughout the bioassay, mean body weights of dosed rats of either sex were lower than those of the corresponding controls, and the decrements in mean body weight gain were dose related (Figure 1 and Table 10). No other compound-related clinical signs were observed. Feed consumption by dosed and control groups was comparable (Appendix H).

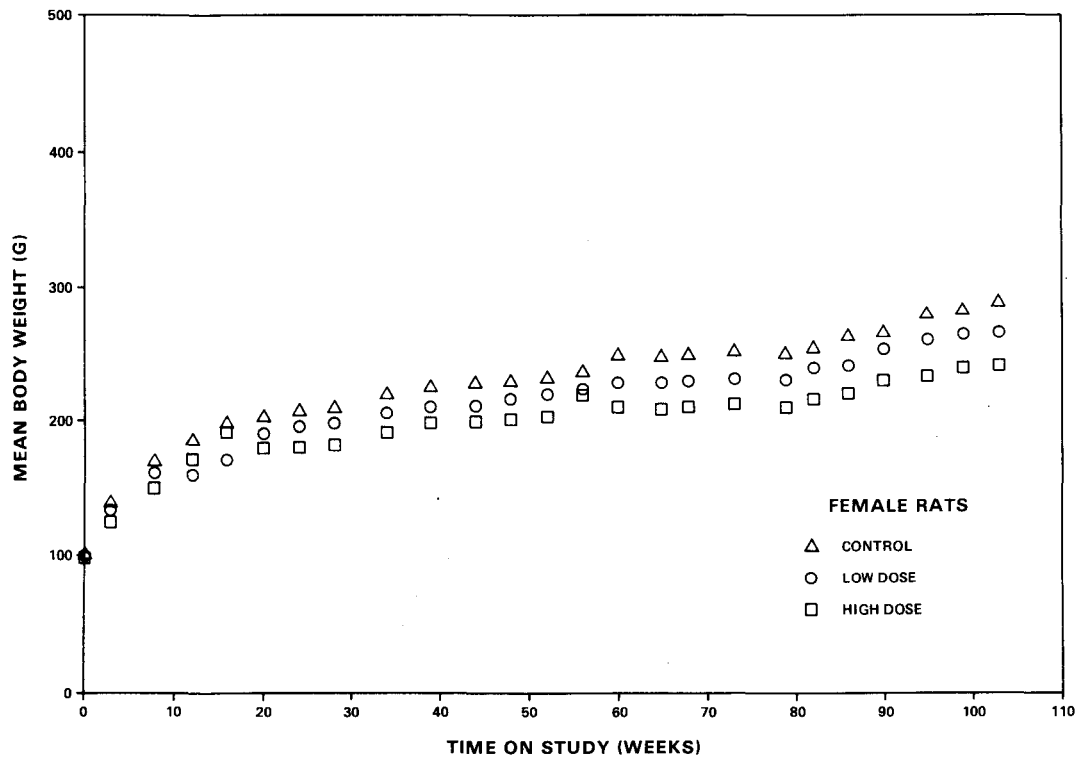
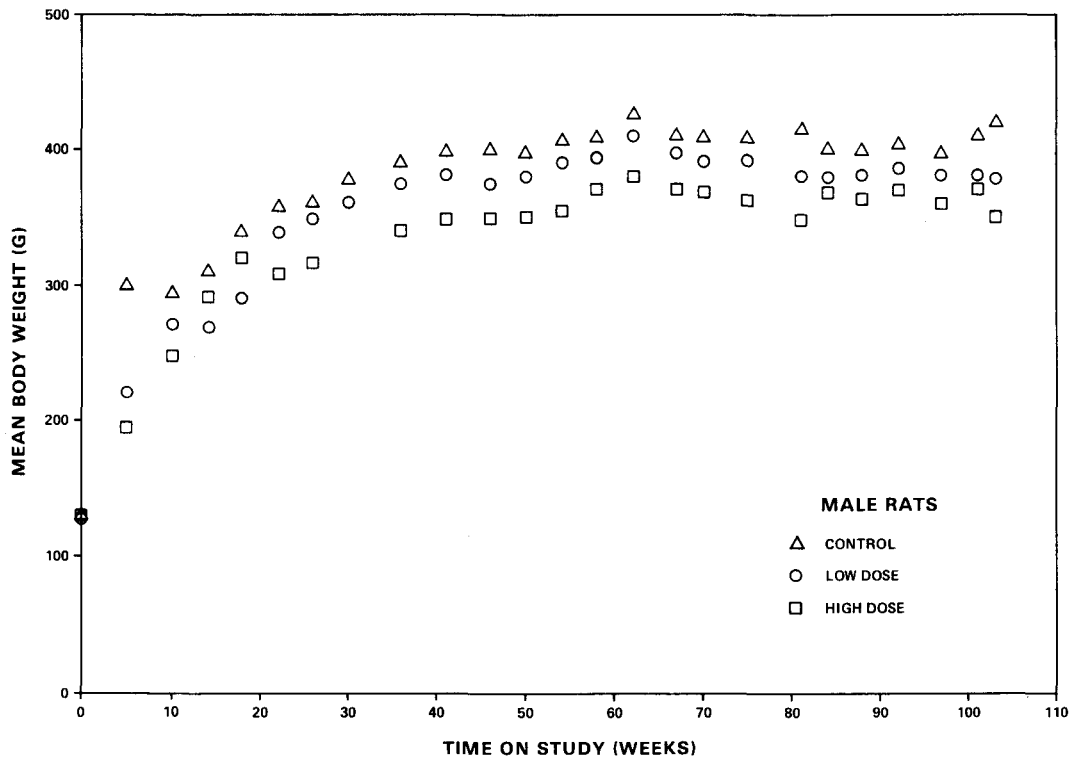
#### B. Survival (Rats)

Estimates of the probabilities of survival of male and female rats administered C. I. Disperse Yellow 3 at the concentrations of this bioassay, together with those of the control group, are shown by the Kaplan and Meier curves in Figure 2. Both sexes of rats had a wide range of survival between the different groups. In males, the low-dose group had significantly ( $P < 0.05$ ) greater survival than did the controls, with the high-dose intermediate between the two. In females, the high-dose group had significantly ( $P < 0.05$ ) greater survival than did the controls, with the low-dose intermediate between them.

In male rats, 31/50 (62%) of the control group, 45/50 (90%) of the low-dose group, and 39/50 (78%) of the high-dose group lived to the end of the study at 104 weeks. In female rats, 33/50 (66%) of the control group, 40/50 (80%) of the low-dose group, and 46/50 (92%) of the high-dose group lived to the end of the study at 104 weeks.

#### C. Pathology (Rats)

Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; Tables A3 and A4 give the survival and tumor status for each individual animal in the male and female rat studies. Findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2.



**Figure 1. Growth Curves for Rats Fed Diets Containing C. I. Disperse Yellow 3**



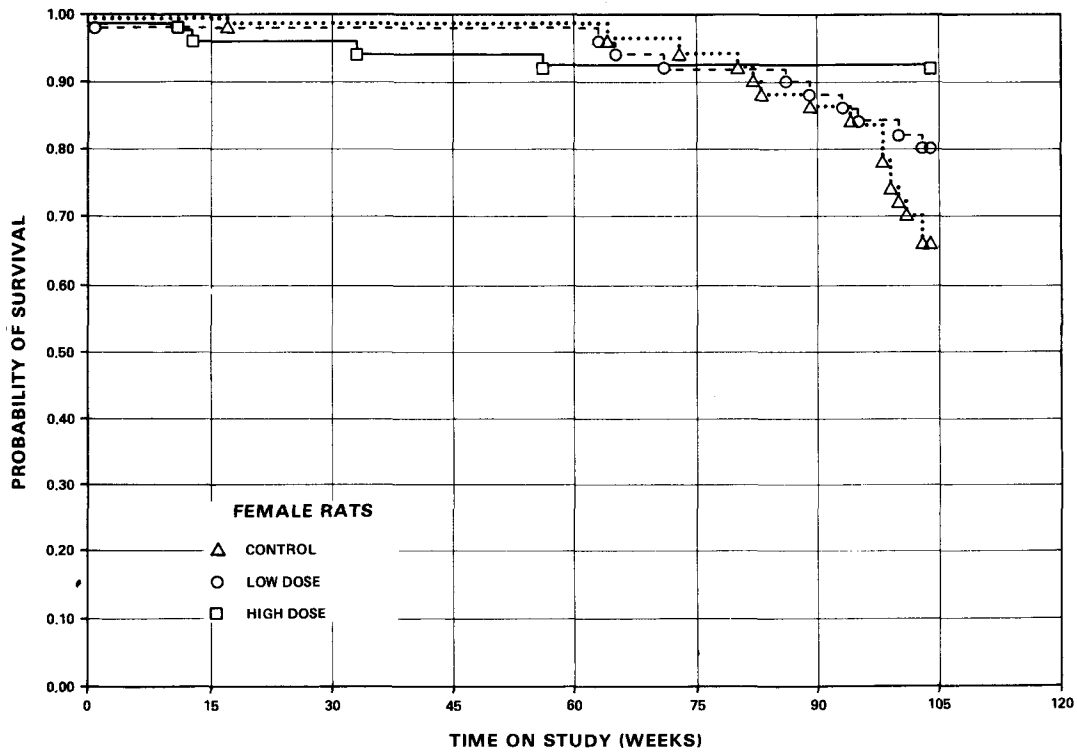
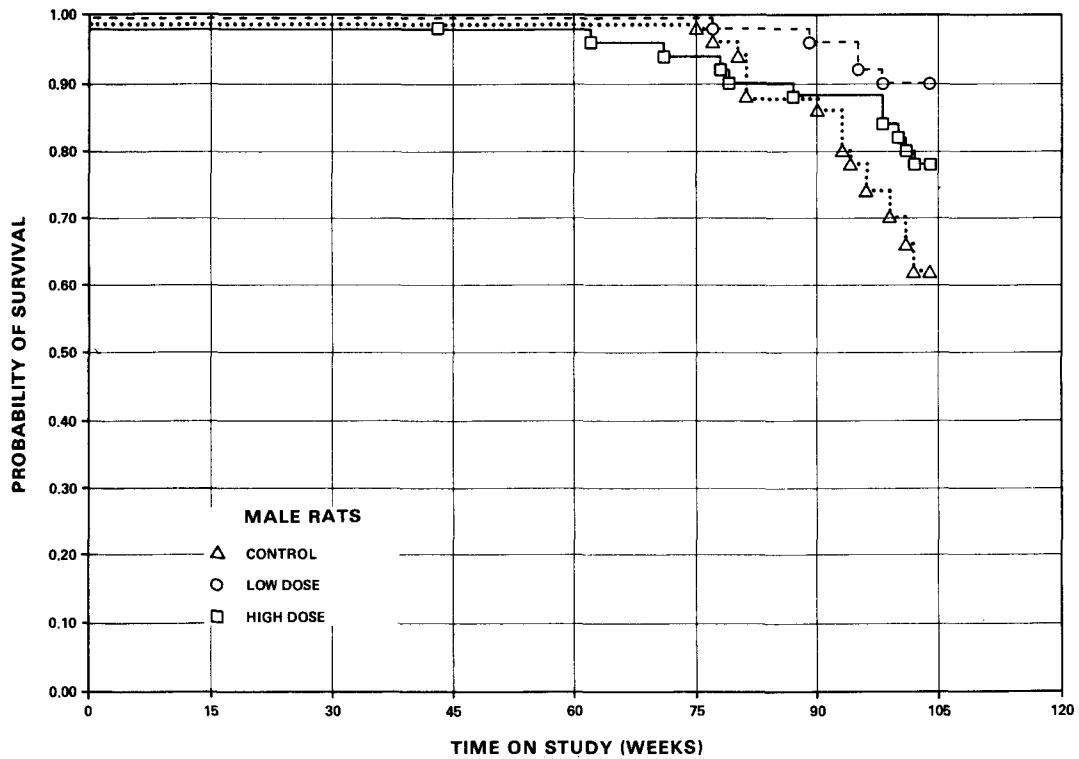
Table 10. Mean Body Weight Change (Relative to Controls) of Rats Fed Diets Containing C. I. Disperse Yellow 3

|               | Week No. | Mean Body Weight Change From Week 1<br>(grams) |          |           | Weight Change Relative<br>to Control (Percent) (a) |           |
|---------------|----------|--|----------|-----------|--|-----------|
|               |          | Control  | Low Dose | High Dose | Low Dose   | High Dose |
| <b>Male</b>   |          |  |          |           |  |           |
| Rats          | 1        | 129 (b)  | 127 (b)  | 128 (b)   |  |           |
|               | 5        | 171  | 92       | 66        | -46  | -61       |
|               | 26       | 233  | 221      | 189       | - 5  | -19       |
|               | 46       | 271  | 248      | 221       | - 8  | -18       |
|               | 67       | 284  | 270      | 243       | - 5  | -14       |
|               | 88       | 271  | 254      | 236       | - 6  | -13       |
|               | 103      | 291  | 251      | 225       | -14  | -23       |
| <b>Female</b> |          |  |          |           |  |           |
| Rats          | 1        | 102 (b)  | 100 (b)  | 98 (b)    |  |           |
|               | 3        | 37   | 34       | 27        | - 8  | -27       |
|               | 24       | 105  | 96       | 82        | - 9  | -22       |
|               | 44       | 126  | 112      | 100       | -11  | -21       |
|               | 65       | 145  | 128      | 111       | -12  | -23       |
|               | 86       | 162  | 141      | 123       | -13  | -24       |
|               | 103      | 187  | 166      | 142       | -11  | -24       |

(a) Weight Change Relative to Controls =

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

(b) Weight at end of week 1.



**Figure 2. Survival Curves for Rats Fed Diets Containing C. I. Disperse Yellow 3**

Various neoplasms were detected among both dosed and control animals. These lesions have been encountered previously in aging control F344 rats (Goodman et al., 1979).

Focal hepatic cellular change in males was dose related (controls 1/49; low-dose 4/50; and high-dose 17/50). These foci were different than the usual basophilic type found in controls and were usually composed of vacuolated, clear, or eosinophilic hepatocytes. The neoplastic nodules in dosed males were frequently multiple, of moderate to small size, and composed of basophilic hepatocytes. A few nodules were composed of eosinophilic cells. Carcinomas were trabecular in type.

The incidence of neoplastic nodules in the livers of the male rats fed the chemical was markedly increased over that in the controls (controls 1/49, 2%; low-dose 15/50, 30%; high-dose 10/50, 20%). Hepatocellular carcinomas were also seen in one control and two high-dose male rats.

Stomach tumors were seen in five male rats (controls 0/49; low-dose 4/50; high-dose 1/50). The lesions in the high-dose rat were an adenocarcinoma and a sarcoma of the glandular portion of the stomach, while those in the low-dose group included two tumors (squamous papilloma and fibrosarcoma) in the nonglandular portion and two tumors (adenoma and mucinous adenocarcinoma) in the glandular portion. One low-dose and two high-dose male rats had gastric epithelial hyperplasia.

Various nonneoplastic lesions were observed among both control and dosed animals. These lesions have been encountered previously as spontaneous lesions in F344 rats (Goodman et al., 1979).

Renal pigmentation appeared to be related to dosing in female rats (0/50 controls; 8/50 low-dose; and 34/50 high-dose). In male rats, the incidences of renal pigmentation were 0/50 for controls, 1/50 for the low-dose group, and 3/50 in the high-dose group. The pigment was not identified.

The results of histopathologic examination provided evidence that C. I. Disperse Yellow 3 may have induced liver and stomach tumors in F344 male rats under the conditions of this bioassay.

#### D. Statistical Analyses of Results (Rats)

Tables 11 and 12 contain the statistical analyses of those primary tumors that occurred in at least two animals of one group and with an incidence of at least 5% in one or more groups.

Neoplastic nodules of the liver in male rats were observed in a statistically significant positive association in the dosed groups compared with the control group (1/49, 2% in the controls; 15/50, 30% in the low-dose; 10/50, 20% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant in the positive direction ( $P=0.014$ ), but there was a departure from linear trend ( $P=0.004$ ) due to the higher incidence in the low-dose group compared with the other two groups. The Fisher exact test between the control group and either dosed group was significant ( $P=0.004$  in the high-dose and  $P$  less than 0.001 in the low-dose). This tumor has been observed in 40/2,960 (1.4%) male F344 control rats in the Bioassay Program and in 5/140 (3.6%) F344 male rats at this laboratory. This tumor was not observed in statistically significant proportions in female rats.

Lymphocytic leukemia of the hematopoietic system in male rats was observed in a statistically significant negative relation in the dosed groups compared with the controls (13/50, 26% in the controls; 2/50, 4% in the low-dose; and 1/50, 2% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant in the negative direction ( $P$  less than 0.001). The Fisher exact test between the control group and either of the dosed groups was significant ( $P$  less than 0.001 in the high-dose and  $P=0.002$  in the low-dose). This tumor was also found in female rats in a statistically significant negative relation (8/50, 16% in the controls; 2/50, 4% in the low-dose; 1/50, 2% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant in the negative

direction ( $P=0.007$ ). The Fisher exact tests between the dosed groups and the controls were significant ( $P=0.015$  in the high-dose and  $P=0.046$  in the low-dose), but the value of  $P=0.046$  is above the value of  $P=0.025$  required by the Bonferroni inequality criterion for an overall significance of  $P=0.05$  when two dosed groups are compared with a common control group. The historical incidence of rats with leukemia at this laboratory is 73/240 (30%) for males and 50/238 (21%) for females.

C-Cell carcinomas of the thyroid in male rats were observed in decreasing incidence (4/49, 8% in the controls; 1/50, 2% in the low-dose; 0/48, 0% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant in the negative direction ( $P=0.026$ ). The Fisher exact tests were not significant. In female rats, this tumor was not observed in statistically significant proportions.

Mesotheliomas, malignant in multiple organs, were observed in male rats in decreasing incidence (4/50, 8% in the controls; 2/50, 4% in the low-dose; 0/50, 0% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant in the negative direction ( $P=0.037$ ). The Fisher exact tests were not significant. In female rats, this tumor was not observed in a statistically significant proportion.

Chromophobe adenomas of the pituitary in female rats were observed in decreased incidence in the dosed groups, compared with the control group (15/44, 34% in the controls; 15/48, 31% in the low-dose; 8/49, 16% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant in the negative direction ( $P=0.033$ ). The Fisher exact test between the high-dose group and the matched control group was significant ( $P=0.041$ ), but this is above the value of  $P=0.025$  required by the Bonferroni inequality criterion for an overall significance of  $P=0.05$  when two dosed groups are compared with a common control group. In male rats, this tumor was not observed in statistically significant proportions.

Endometrial stromal polyps of the uterus in female rats were observed in a statistically significant negative relation (14/50, 28% in the controls;

7/48, 15% in the low-dose; 3/50, 6% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant in the negative direction ( $P=0.002$ ). The Fisher exact test between the high-dose group and the control group was significant ( $P=0.003$ ). No significant incidence was observed in the low-dose group; however, this tumor occurred in decreased incidence in the low-dose group compared with the control group.

Fibroadenomas of the mammary gland in female rats and tumors of the stomach in male rats were observed in increased incidences in the low-dose groups compared with the other two groups. The Cochran-Armitage tests for linear trend were not significant. Departures from linear trend occurred due to increased incidences in the low-dose groups. The Fisher exact tests were not significant.

One high-dose male rat and five female rats (one control, one low dose, and three high dose) died before 52 weeks, and time-adjusted tests were not significantly different from those reported above.

Life table analysis based on the time to observation of tumors did not materially alter the above results.

Table 11. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing C. I. Disperse Yellow 3 (a)

|   | Control                 | Low Dose   | High Dose               |
|---|-------------------------|------------|-------------------------|
| Subcutaneous Tissue: Fibroma (b)                  | 3/50(6)                 | 1/50(2)    | 1/50(2)                 |
| P Values (c), (d)                                 | N.S.                    | N.S.       | N.S.                    |
| Relative Risk (Control) (e)                       |                         | 0.333      | 0.333                   |
| Lower Limit                                       |                         | 0.006      | 0.006                   |
| Upper Limit                                       |                         | 3.983      | 3.983                   |
| Weeks to First Observed Tumor                     | 93                      | 104        | 104                     |
| <hr/>   |                         |            |                         |
| Hematopoietic System:<br>Lymphocytic Leukemia (b) | 13/50(26)               | 2/50(4)    | 1/50(2)                 |
| P Values (c), (d)                                 | P less than<br>0.001(N) | P=0.002(N) | P less than<br>0.001(N) |
| Relative Risk (Control) (e)                       |                         | 0.154      | 0.077                   |
| Lower Limit                                       |                         | 0.018      | 0.002                   |
| Upper Limit                                       |                         | 0.632      | 0.480                   |
| Weeks to First Observed Tumor                     | 81                      | 98         | 98                      |
| <hr/>   |                         |            |                         |
| Hematopoietic System:<br>Lymphoma or Leukemia (b) | 13/50(26)               | 3/50(6)    | 1/50(2)                 |
| P Values (c), (d)                                 | P less than<br>0.001(N) | P=0.006(N) | P less than<br>0.001(N) |
| Relative Risk (Control) (e)                       |                         | 0.231      | 0.077                   |
| Lower Limit                                       |                         | 0.045      | 0.002                   |
| Upper Limit                                       |                         | 0.777      | 0.480                   |
| Weeks to First Observed Tumor                     | 81                      | 98         | 98                      |

Table 11. Analyses of the Incidence of Primary Tumors in Male Rats  
Fed Diets Containing C. I. Disperse Yellow 3 (a)

(Continued)

|   | Control | Low<br>Dose          | High<br>Dose |
|---|---------|----------------------|--------------|
| Liver: Neoplastic Nodule (b)                                | 1/49(2) | 15/50(30)            | 10/50(20)    |
| P Values (c), (d)   | P=0.014 | P less than<br>0.001 | P=0.004      |
| Departure from Linear Trend (f)                             | P=0.004 |                      |              |
| Relative Risk (Control) (e)                                 |         | 14.700               | 9.800        |
| Lower Limit   |         | 2.419                | 1.482        |
| Upper Limit   |         | 601.480              | 414.931      |
| Weeks to First Observed Tumor                               | 104     | 104                  | 104          |
| Liver: Neoplastic Nodule or<br>Hepatocellular Carcinoma (b) | 2/49(4) | 15/50(30)            | 11/50(22)    |
| P Values (c), (d)   | P=0.016 | P=0.001              | P=0.008      |
| Departure from Linear Trend (f)                             | P=0.012 |                      |              |
| Relative Risk (Control) (e)                                 |         | 7.350                | 5.390        |
| Lower Limit   |         | 1.844                | 1.262        |
| Upper Limit   |         | 63.184               | 47.937       |
| Weeks to First Observed Tumor                               | 104     | 104                  | 104          |
| Stomach, Cardiac Stomach, or Pylorus:<br>All Tumors (b)     | 0/49(0) | 4/50(8)              | 1/50(2)      |
| P Values (c), (d)   | N.S.    | N.S.                 | N.S.         |
| Departure from Linear Trend (f)                             | P=0.025 |                      |              |
| Relative Risk (Control) (e)                                 |         | Infinite             | Infinite     |
| Lower Limit   |         | 0.909                | 0.053        |
| Upper Limit   |         | Infinite             | Infinite     |
| Weeks to First Observed Tumor                               | --      | 104                  | 104          |



Table 11. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing C. I. Disperse Yellow 3 (a)

(Continued)

|  | Control  | Low Dose | High Dose |
|--|----------|----------|-----------|
| Pituitary: Chromophobe Adenoma (b)       | 5/47(11) | 7/49(14) | 4/46(9)   |
| P Values (c), (d)                        | N.S.     | N.S.     | N.S.      |
| Relative Risk (Control) (e)              |          | 1.343    | 0.817     |
| Lower Limit                              |          | 0.396    | 0.172     |
| Upper Limit                              |          | 5.010    | 3.557     |
| Weeks to First Observed Tumor            | 81       | 104      | 104       |
| Adrenal: Pheochromocytoma (b)            | 6/50(12) | 8/50(16) | 3/49(6)   |
| P Values (c), (d)                        | N.S.     | N.S.     | N.S.      |
| Relative Risk (Control) (e)              |          | 1.333    | 0.510     |
| Lower Limit                              |          | 0.438    | 0.087     |
| Upper Limit                              |          | 4.331    | 2.243     |
| Weeks to First Observed Tumor            | 94       | 104      | 104       |
| Adrenal: Pheochromocytoma, Malignant (b) | 1/50(2)  | 3/50(6)  | 2/49(4)   |
| P Values (c), (d)                        | N.S.     | N.S.     | N.S.      |
| Relative Risk (Control) (e)              |          | 3.000    | 2.041     |
| Lower Limit                              |          | 0.251    | 0.110     |
| Upper Limit                              |          | 154.270  | 117.931   |
| Weeks to First Observed Tumor            | 104      | 77       | 104       |

Table 11. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing C. I. Disperse Yellow 3 (a)

(Continued)

|  | Control    | Low Dose  | High Dose |
|--|------------|-----------|-----------|
| Thyroid: C-Cell Carcinoma (b)            | 4/49(8)    | 1/50(2)   | 0/48(0)   |
| P Values (c), (d)                        | P=0.026(N) | N.S.      | N.S.      |
| Relative Risk (Control) (e)              |            | 0.245     | 0.000     |
| Lower Limit                              |            | 0.005     | 0.000     |
| Upper Limit                              |            | 2.362     | 1.100     |
| Weeks to First Observed Tumor            | 96         | 104       | --        |
| Thyroid: C-Cell Adenoma or Carcinoma (b) | 4/49(8)    | 2/50(4)   | 0/48(0)   |
| P Values (c), (d)                        | P=0.038(N) | N.S.      | N.S.      |
| Relative Risk (Control) (e)              |            | 0.490     | 0.000     |
| Lower Limit                              |            | 0.046     | 0.000     |
| Upper Limit                              |            | 3.251     | 1.100     |
| Weeks to First Observed Tumor            | 96         | 104       | --        |
| Testis: Interstitial-Cell Tumor (b)      | 46/49(94)  | 48/49(98) | 43/50(86) |
| P Values (c), (d)                        | N.S.       | N.S.      | N.S.      |
| Relative Risk (Control) (e)              |            | 1.043     | 0.916     |
| Lower Limit                              |            | 0.950     | 0.826     |
| Upper Limit                              |            | 1.088     | 1.066     |
| Weeks to First Observed Tumor            | 75         | 89        | 71        |

Table 11. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing C. I. Disperse Yellow 3 (a)

(Continued)

|                               | Control    | Low Dose | High Dose |
|-------------------------------|------------|----------|-----------|
| <b>Tunica Vaginalis:</b>      |            |          |           |
| Mesothelioma, NOS (b)         | 1/50(2)    | 3/50(6)  | 1/50(2)   |
| P Values (c), (d)             | N.S.       | N.S.     | N.S.      |
| Relative Risk (Control) (e)   |            | 3.000    | 1.000     |
| Lower Limit                   |            | 0.251    | 0.013     |
| Upper Limit                   |            | 154.270  | 76.790    |
| Weeks to First Observed Tumor | 104        | 104      | 104       |
| <b>Multiple Organs:</b>       |            |          |           |
| Mesothelioma, Malignant (b)   | 4/50(8)    | 2/50(4)  | 0/50(0)   |
| P Values (c), (d)             | P=0.037(N) | N.S.     | N.S.      |
| Relative Risk (Control) (e)   |            | 0.500    | 0.000     |
| Lower Limit                   |            | 0.047    | 0.000     |
| Upper Limit                   |            | 3.318    | 1.079     |
| Weeks to First Observed Tumor | 80         | 104      | --        |

- (a) Dosed groups received doses of 5,000 or 10,000 ppm in the diet.
- (b) Number of tumor-bearing animals/number of animals examined at site (percent).
- (c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
- (d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
- (e) The 95 percent confidence interval of the relative risk between each dosed group and the control group.
- (f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

Table 12. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing C. I. Disperse Yellow 3 (a)

|                               | Control    | Low Dose   | High Dose  |
|-------------------------------|------------|------------|------------|
| <hr/>                         |            |            |            |
| Hematopoietic System:         |            |            |            |
| Lymphocytic Leukemia (b)      | 8/50(16)   | 2/50(4)    | 1/50(2)    |
| P Values (c), (d)             | P=0.007(N) | P=0.046(N) | P=0.015(N) |
| Relative Risk (Control) (e)   |            | 0.250      | 0.125      |
| Lower Limit                   |            | 0.027      | 0.003      |
| Upper Limit                   |            | 1.176      | 0.880      |
| Weeks to First Observed Tumor | 82         | 1          | 104        |
| <hr/>                         |            |            |            |
| Hematopoietic System:         |            |            |            |
| Lymphoma or Leukemia (b)      | 10/50(20)  | 4/50(8)    | 3/50(6)    |
| P Values (c), (d)             | P=0.020(N) | N.S.       | P=0.036(N) |
| Relative Risk (Control) (e)   |            | 0.400      | 0.300      |
| Lower Limit                   |            | 0.098      | 0.056      |
| Upper Limit                   |            | 1.284      | 1.083      |
| Weeks to First Observed Tumor | 17         | 1          | 13         |
| <hr/>                         |            |            |            |
| Liver: Neoplastic Nodule (b)  | 2/50(4)    | 1/49(2)    | 2/50(4)    |
| P Values (c), (d)             | N.S.       | N.S.       | N.S.       |
| Relative Risk (Control) (e)   |            | 0.510      | 1.000      |
| Lower Limit                   |            | 0.009      | 0.075      |
| Upper Limit                   |            | 9.474      | 13.326     |
| Weeks to First Observed Tumor | 104        | 104        | 104        |
| <hr/>                         |            |            |            |

Table 12. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing C. I. Disperse Yellow 3 (a)

(Continued)

|  | Control    | Low Dose  | High Dose  |
|--|------------|-----------|------------|
| Liver: Neoplastic Nodule or Hepatocellular Carcinoma (b) | 2/50(4)    | 1/49(2)   | 3/50(6)    |
| P Values (c), (d)  | N.S.       | N.S.      | N.S.       |
| Relative Risk (Control) (c)                              |            | 0.510     | 1.500      |
| Lower Limit  |            | 0.009     | 0.180      |
| Upper Limit  |            | 9.474     | 17.329     |
| Weeks to First Observed Tumor                            | 104        | 104       | 104        |
| Pituitary: Chromophobe Adenoma (b)                       | 15/44(34)  | 15/48(31) | 8/49(16)   |
| P Values (c), (d)  | P=0.033(N) | N.S.      | P=0.041(N) |
| Relative Risk (Control) (e)                              |            | 0.917     | 0.479      |
| Lower Limit  |            | 0.478     | 0.197      |
| Upper Limit  |            | 1.768     | 1.080      |
| Weeks to First Observed Tumor                            | 89         | 93        | 56         |
| Adrenal: Pheochromocytoma (b)                            | 2/50(4)    | 3/50(6)   | 0/50(0)    |
| P Values (c), (d)  | N.S.       | N.S.      | N.S.       |
| Relative Risk (Control) (e)                              |            | 1.500     | 0.000      |
| Lower Limit  |            | 0.180     | 0.000      |
| Upper Limit  |            | 17.329    | 3.381      |
| Weeks to First Observed Tumor                            | 98         | 103       | --         |

Table 12. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing C. I. Disperse Yellow 3 (a)

(Continued)

|                                       | Control    | Low Dose  | High Dose  |
|---------------------------------------|------------|-----------|------------|
| Thyroid: C-Cell Carcinoma (b)         | 1/49(2)    | 2/49(4)   | 3/50(6)    |
| P Values (c), (d)                     | N.S.       | N.S.      | N.S.       |
| Relative Risk (Control) (e)           |            | 2.000     | 2.940      |
| Lower Limit                           |            | 0.108     | 0.246      |
| Upper Limit                           |            | 115.581   | 151.180    |
| Weeks to First Observed Tumor         | 104        | 104       | 104        |
| Mammary Gland: Fibroadenoma (b)       | 7/50(14)   | 11/50(22) | 3/50(6)    |
| P Values (c), (d)                     | N.S.       | N.S.      | N.S.       |
| Departure from Linear Trend (f)       | P=0.045    |           |            |
| Relative Risk (Control) (e)           |            | 1.571     | 0.429      |
| Lower Limit                           |            | 0.608     | 0.075      |
| Upper Limit                           |            | 4.394     | 1.759      |
| Weeks to First Observed Tumor         | 104        | 104       | 104        |
| Uterus: Endometrial Stromal Polyp (b) | 14/50(28)  | 7/48(15)  | 3/50(6)    |
| P Values (c), (d)                     | P=0.002(N) | N.S.      | P=0.003(N) |
| Relative Risk (Control) (e)           |            | 0.521     | 0.214      |
| Lower Limit                           |            | 0.195     | 0.042      |
| Upper Limit                           |            | 1.250     | 0.709      |
| Weeks to First Observed Tumor         | 94         | 100       | 104        |

Table 12. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing C. I. Disperse Yellow 3 (a)

(Continued)

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- (a) Dosed groups received doses of 5,000 or 10,000 ppm in the diet.
- (b) Number of tumor-bearing animals/number of animals examined at site (percent).
- (c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
- (d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
- (e) The 95 percent confidence interval of the relative risk between each dosed group and the control group.
- (f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.





#### IV. RESULTS - MICE

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

Throughout the bioassay, mean body weights of dosed mice of either sex tended to be lower than those of the controls (Figure 3 and Table 13). Clinical signs and feed consumption by dosed and control animals were comparable (Appendix H).

##### B. Survival (Mice)

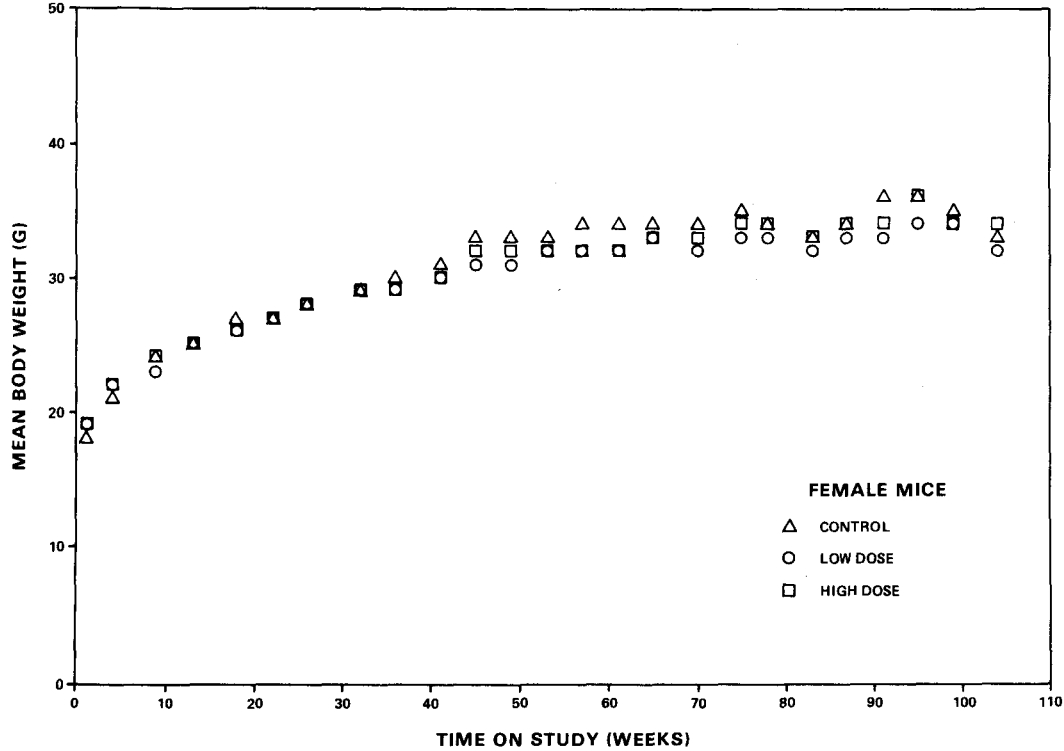
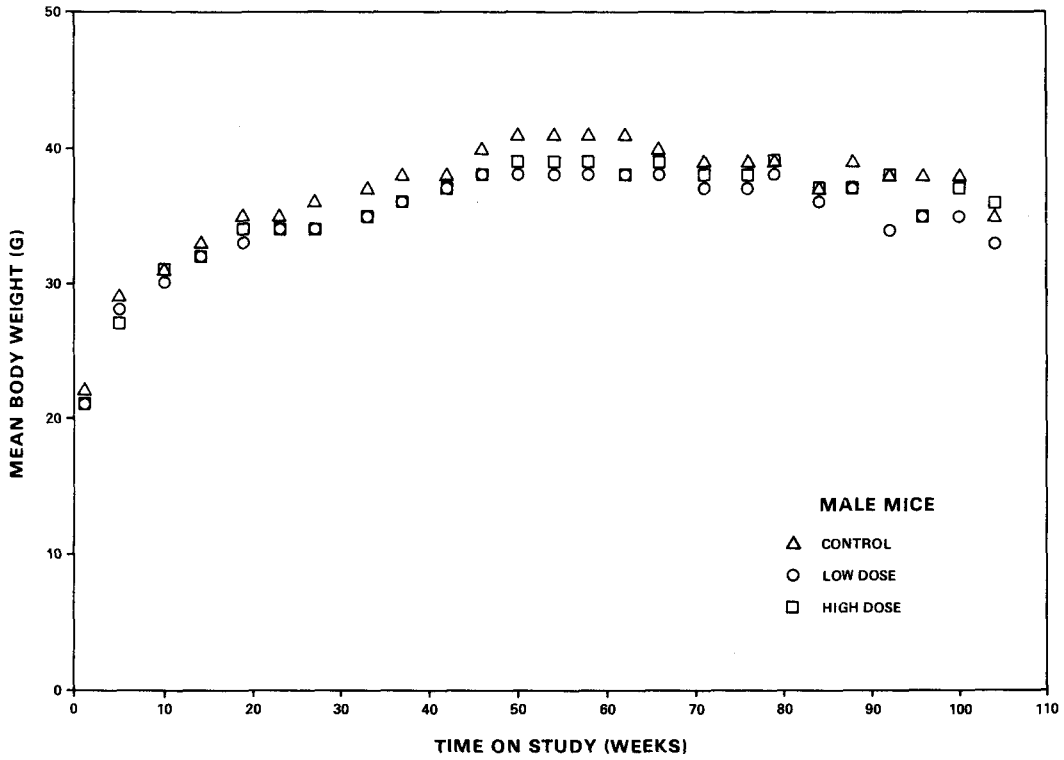
Estimates of the probabilities of survival of male and female mice administered C. I. Disperse Yellow 3 at the concentrations of this bioassay, together with those of the control group, are shown by the Kaplan and Meier curves in Figure 4. All the groups of mice had similar survival, and there were no significant differences between any of the groups of either sex.

In male mice, 43/50 (86%) of the control group, 39/50 (78%) of the low-dose group, and 42/50 (84%) of the high-dose group lived to the end of the study at 104-105 weeks. In female mice, 44/50 (88%) of the control group, 39/50 (78%) of the low-dose group, and 42/50 (84%) of the high-dose group lived to the end of the study at 105 weeks.

##### C. Pathology (Mice)

Histopathologic findings on neoplasms in mice are summarized in Appendix B, Tables B1 and B2; Tables B3 and B4 give the survival and tumor status for individual animals in the male and female mouse studies. Findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2.

Tumors were uniformly distributed among dosed and control groups of mice except for tumors of the lung, liver, and hematopoietic system. Compared with controls, dosed male mice had a higher incidence of alveolar/bronchiolar adenomas (controls, 2/50; low-dose, 6/49; high-dose, 9/49) and



**Figure 3. Growth Curves for Mice Fed Diets Containing C. I. Disperse Yellow 3**

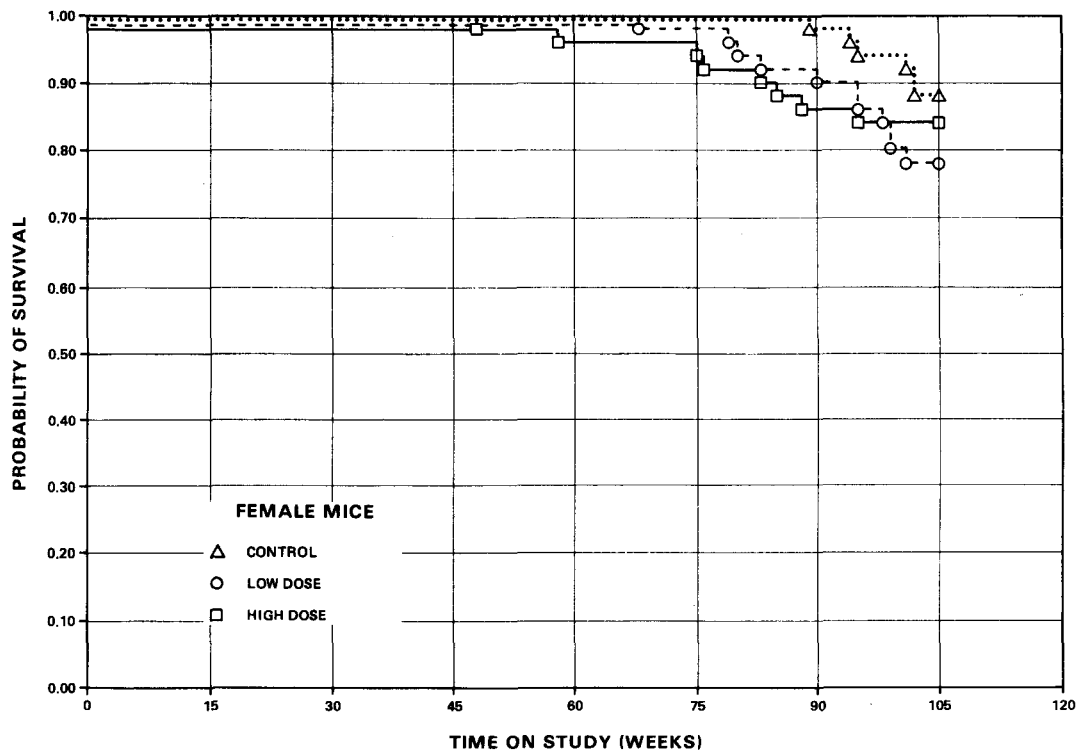
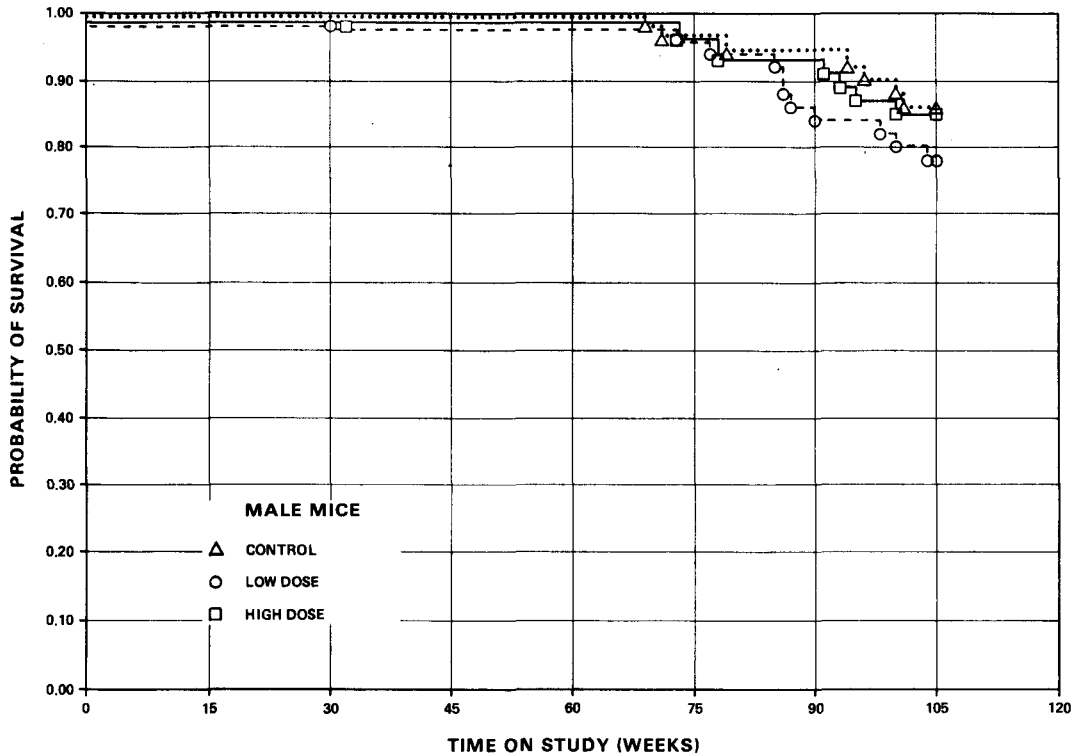
Table 13. Mean Body Weight Change (Relative to Controls) of Mice Fed Diets Containing C. I. Disperse Yellow 3

|               |     | Mean Body Weight Change From Week 1<br>(grams) |          |           | Weight Change Relative<br>to Controls (%) (b) |           |
|---------------|-----|--|----------|-----------|---|-----------|
| Week No.      |     | Control  | Low Dose | High Dose | Low Dose                                      | High Dose |
| <b>Male</b>   |     |  |          |           |   |           |
| Mice          | 1   | 22(b)  | 21(b)    | 21(b)     |   |           |
|               | 5   | 7  | 7        | 6         | 0   | -14       |
|               | 23  | 13   | 13       | 13        | 0   | 0         |
|               | 42  | 16   | 16       | 16        | 0   | 0         |
|               | 62  | 19   | 17       | 17        | -11   | -11       |
|               | 84  | 15   | 15       | 16        | 0   | +7        |
|               | 104 | 13   | 12       | 15        | -8  | +15       |
| <b>Female</b> |     |  |          |           |   |           |
| Mice          | 1   | 18 (b)   | 19 (b)   | 19 (b)    |   |           |
|               | 4   | 3  | 3        | 3         | 0   | 0         |
|               | 22  | 9  | 8        | 8         | -11   | -11       |
|               | 41  | 13   | 11       | 11        | -15   | -15       |
|               | 61  | 16   | 13       | 13        | -19   | -19       |
|               | 83  | 15   | 13       | 14        | -13   | -7        |
|               | 104 | 15   | 13       | 15        | -13   | 0         |

(a) Weight Change Relative to Controls =

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

(b) Weight at the end of week 1.



**Figure 4. Survival Curves for Mice Fed Diets Containing C. I. Disperse Yellow 3**

dosed females had higher incidences of hepatocellular adenomas (controls, 0/50; low-dose, 6/50; high-dose, 12/50) and lymphomas (controls, 10/50; low-dose, 16/50; high-dose, 19/50). The hepatocellular adenomas were composed of well-circumscribed solid sheets of cells which had basophilic or eosinophilic cytoplasm. Hepatocellular carcinomas had prominent trabecular areas. One control and one high-dose female mouse had a metastatic hepatocellular carcinoma in the lung.

All other microscopic abnormalities were considered to be age-associated lesions seen in B6C3F1 mice.

Histopathologic examination provided evidence that administration of C. I. Disperse Yellow 3 was associated with lung, liver, and possibly hematopoietic tumors in B6C3F1 mice under the conditions of this bioassay.

#### D. Statistical Analyses of Results (Mice)

Tables 14 and 15 contain the statistical analyses of those primary tumors that occurred in at least two animals of one group and with an incidence of at least 5% in one or more groups.

Alveolar/bronchiolar adenomas of the lung in male mice were observed in a statistically significant positive relation (2/50, 4% in the controls; 6/49, 12% in the low-dose; and 9/49, 18% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant in the positive direction ( $P=0.019$ ). The Fisher exact test between the high-dose group and the matched control group was significant ( $P=0.023$ ). No significant incidence was observed in the low-dose group; however, this tumor occurred in increased incidence in the low-dose group compared with the control group. The historical control incidence of male mice with this tumor at this laboratory is 19/295 (6.4%). Fisher exact tests for male mice with adenomas or carcinomas of the lung (3/50, 6% in the control; 7/49, 14% in the low-dose; and 9/49, 18% in the high-dose) were not significant, but

the Cochran-Armitage test for linear trend was significant ( $P=0.046$ ). Alveolar/bronchiolar adenomas of the lung in female mice were observed in decreased incidence in the low-dose group compared with the other two groups. The Cochran-Armitage test for linear trend was not significant, but there was a departure from linear trend due to decreased incidence in the low-dose compared with the other two dosed groups. The Fisher exact test between the low-dose group and the control group was significant ( $P=0.028$ ). No significant incidence was observed in the high-dose group. Because of the higher incidences seen in other control groups at this laboratory, the negative result in the female mice, and the lack of significant Fisher exact tests between the dosed groups and the control group when the incidence of male mice with adenomas or carcinomas is analyzed, the association of these tumors in male mice with the administration of C. I. Disperse Yellow 3 is not clearly established.

Hepatocellular adenomas in female mice were observed in a statistically significant positive relation in the dosed groups compared with the control group (0/50, 0% in the controls; 6/50, 12% in the low-dose; 12/50, 24% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant in the positive direction ( $P$  less than 0.001). The Fisher exact test between the control group and either of the dosed groups was significant ( $P$  less than 0.001 in the high-dose and  $P=0.013$  in the low-dose). Adenomas in the liver have been observed in 72/3,617 (2.0%) of the control female mice in the bioassay program and in 3/298 (1.0%) of the female mice at this laboratory. Life table analysis of the time to observation of these liver tumors in female mice indicates a significant trend ( $P$  less than 0.001). The incidences of carcinomas of the liver in female mice were not statistically significant, and there were no significant increases in liver tumors in male mice.

Lymphomas of the hematopoietic system in female mice were observed in increased incidence in the dosed groups compared with the matched control group (10/50, 20% in the controls; 16/50, 32% in the low-dose; 19/50, 38% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant in the positive direction ( $P=0.032$ ). The Fisher

exact test between the high-dose group and the control group indicated a value of  $P=0.038$ .

The incidence of female mice with lymphomas or leukemia was increased in the dosed groups (control, 10/50, 20%; low-dose, 17/50, 34%; high-dose, 20/50, 40%). The Cochran-Armitage test for linear trend was statistically significant in the positive direction ( $P=0.020$ ). The Fisher exact test between the high-dose group and the control group indicated a value of  $P=0.024$ . The high-dose incidence is also significantly ( $P<0.05$ ) different from the historical incidence of female mice with lymphomas or leukemia at this laboratory [ 70/300 (23.3%; range 10/50 to 16/50)].

One female and two male mice died before 52 weeks on study, and neither time adjusted tests nor life table analyses materially altered the results reported above.

Table 14. Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing C. I. Disperse Yellow 3 (a)

|  | Control  | Low Dose | High Dose |
|--|----------|----------|-----------|
| Lung: Alveolar/Bronchiolar Adenoma (b)                               | 2/50(4)  | 6/49(12) | 9/49(18)  |
| P Values (c), (d)  | P=0.019  | N.S.     | P=0.023   |
| Relative Risk (Control) (e)  |          | 3.061    | 4.592     |
| Lower Limit  |          | 0.581    | 1.015     |
| Upper Limit  |          | 29.826   | 41.883    |
| Weeks to First Observed Tumor  | 104      | 98       | 91        |
| Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)                  | 3/50(6)  | 7/49(14) | 9/49(18)  |
| P Values (c), (d)  | P=0.046  | N.S.     | N.S.      |
| Relative Risk (Control) (e)  |          | 2.381    | 3.061     |
| Lower Limit  |          | 0.581    | 0.820     |
| Upper Limit  |          | 13.550   | 16.653    |
| Weeks to First Observed Tumor  | 94       | 98       | 91        |
| Hematopoietic System:<br>Malignant Lymphoma,<br>Histiocytic Type (b) | 5/50(10) | 3/49(6)  | 1/49(2)   |
| P Values (c), (d)  | N.S.     | N.S.     | N.S.      |
| Relative Risk (Control) (e)  |          | 0.612    | 0.204     |
| Lower Limit  |          | 0.100    | 0.004     |
| Upper Limit  |          | 2.967    | 1.733     |
| Weeks to First Observed Tumor  | 100      | 86       | 105       |



Table 14. Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing C. I. Disperse Yellow 3 (a)

(Continued)

|                               | Control  | Low Dose | High Dose |
|-------------------------------|----------|----------|-----------|
| <b>Hematopoietic System:</b>  |          |          |           |
| Malignant Lymphoma, NOS (b)   | 2/50(4)  | 3/49(6)  | 3/49(6)   |
| P Values (c), (d)             | N.S.     | N.S.     | N.S.      |
| Relative Risk (Control) (e)   |          | 1.531    | 1.531     |
| Lower Limit                   |          | 0.183    | 0.183     |
| Upper Limit                   |          | 17.671   | 17.671    |
| Weeks to First Observed Tumor | 96       | 104      | 100       |
| <b>Hematopoietic System:</b>  |          |          |           |
| Malignant Lymphoma (b)        | 8/50(16) | 6/49(12) | 4/49(8)   |
| P Values (c), (d)             | N.S.     | N.S.     | N.S.      |
| Relative Risk (Control) (e)   |          | 0.765    | 0.510     |
| Lower Limit                   |          | 0.236    | 0.120     |
| Upper Limit                   |          | 2.325    | 1.771     |
| Weeks to First Observed Tumor | 96       | 86       | 100       |
| <b>Hematopoietic System:</b>  |          |          |           |
| Lymphoma or Leukemia (b)      | 8/50(16) | 6/49(12) | 5/49(10)  |
| P Values (c), (d)             | N.S.     | N.S.     | N.S.      |
| Relative Risk (Control) (e)   |          | 0.765    | 0.638     |
| Lower Limit                   |          | 0.236    | 0.176     |
| Upper Limit                   |          | 2.325    | 2.049     |
| Weeks to First Observed Tumor | 96       | 86       | 100       |

Table 14. Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing C. I. Disperse Yellow 3 (a)

(Continued)

|  | Control   | Low Dose   | High Dose |
|--|-----------|------------|-----------|
| Liver: Hepatocellular Adenoma (b)              | 7/50(14)  | 1/49(2)    | 7/49(14)  |
| P Values (c), (d)                              | N.S.      | P=0.032(N) | N.S.      |
| Departure from Linear Trend (f)                | P=0.022   |            |           |
| Relative Risk (Control) (e)                    |           | 0.146      | 1.020     |
| Lower Limit                                    |           | 0.003      | 0.330     |
| Upper Limit                                    |           | 1.073      | 3.155     |
| Weeks to First Observed Tumor                  | 104       | 105        | 105       |
| Liver: Hepatocellular Carcinoma (b)            | 14/50(28) | 11/49(22)  | 12/49(24) |
| P Values (c), (d)                              | N.S.      | N.S.       | N.S.      |
| Relative Risk (Control) (e)                    |           | 0.802      | 0.875     |
| Lower Limit                                    |           | 0.367      | 0.413     |
| Upper Limit                                    |           | 1.706      | 1.823     |
| Weeks to First Observed Tumor                  | 69        | 77         | 73        |
| Liver: Hepatocellular Adenoma or Carcinoma (b) | 20/50(40) | 12/49(24)  | 16/49(33) |
| P Values (c), (d)                              | N.S.      | N.S.       | N.S.      |
| Relative Risk (Control) (e)                    |           | 0.612      | 0.816     |
| Lower Limit                                    |           | 0.310      | 0.453     |
| Upper Limit                                    |           | 1.162      | 1.449     |
| Weeks to First Observed Tumor                  | 69        | 77         | 73        |

Table 14. Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing C. I. Disperse Yellow 3 (a)

(Continued)

|                               | Control | Low Dose | High Dose |
|-------------------------------|---------|----------|-----------|
| Eye/Lacrimal Gland:           |         |          |           |
| Papillary Adenoma (b)         | 2/50(4) | 1/49(2)  | 3/49(6)   |
| P Values (c), (d)             | N.S.    | N.S.     | N.S.      |
| Relative Risk (Control) (e)   |         | 0.510    | 1.531     |
| Lower Limit                   |         | 0.009    | 0.183     |
| Upper Limit                   |         | 9.474    | 17.671    |
| Weeks to First Observed Tumor | 104     | 105      | 105       |

- (a) Dosed groups received doses of 2,500 or 5,000 ppm in the diet.
- (b) Number of tumor-bearing animals/number of animals examined at site (percent).
- (c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
- (d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
- (e) The 95 percent confidence interval of the relative risk between each dosed group and the control group.
- (f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

Table 15. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing C. I. Disperse Yellow 3 (a)

|  | Control  | Low Dose   | High Dose |
|--|----------|------------|-----------|
| Lung: Alveolar/Bronchiolar Adenoma (b)                         | 5/50(10) | 0/50(0)    | 3/50(6)   |
| P Values (c), (d)  | N.S.     | P=0.028(N) | N.S.      |
| Departure from Linear Trend (e)                                | P=0.039  |            |           |
| Relative Risk (Control) (f)                                    |          | 0.000      | 0.600     |
| Lower Limit  |          | 0.000      | 0.098     |
| Upper Limit  |          | 0.793      | 2.910     |
| Weeks to First Observed Tumor                                  | 105      | --         | 105       |
| Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)            | 6/50(12) | 0/50(0)    | 4/50(8)   |
| P Values (c), (d)  | N.S.     | P=0.013(N) | N.S.      |
| Departure from Linear Trend (e)                                | P=0.021  |            |           |
| Relative Risk (Control) (f)                                    |          | 0.000      | 0.667     |
| Lower Limit  |          | 0.000      | 0.147     |
| Upper Limit  |          | 0.625      | 2.635     |
| Weeks to First Observed Tumor                                  | 105      | --         | 105       |
| Hematopoietic System: Malignant Lymphoma, Histiocytic Type (b) | 5/50(10) | 11/50(22)  | 9/50(18)  |
| P Values (c), (d)  | N.S.     | N.S.       | N.S.      |
| Relative Risk (Control) (e)                                    |          | 2.200      | 1.800     |
| Lower Limit  |          | 0.765      | 0.586     |
| Upper Limit  |          | 7.508      | 6.377     |
| Weeks to First Observed Tumor                                  | 102      | 68         | 48        |

Table 15. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing C. I. Disperse Yellow 3 (a)

(Continued)

|                               | Control   | Low Dose  | High Dose |
|-------------------------------|-----------|-----------|-----------|
| <hr/>                         |           |           |           |
| Hematopoietic System:         |           |           |           |
| Malignant Lymphoma, NOS (b)   | 6/50(12)  | 3/50(6)   | 7/50(14)  |
| P Values (c), (d)             | N.S.      | N.S.      | N.S.      |
| Relative Risk (Control) (e)   |           | 0.500     | 1.167     |
| Lower Limit                   |           | 0.085     | 0.361     |
| Upper Limit                   |           | 2.200     | 3.911     |
| Weeks to First Observed Tumor | 94        | 105       | 95        |
| <hr/>                         |           |           |           |
| Hematopoietic System:         |           |           |           |
| Malignant Lymphoma (b)        | 10/50(20) | 16/50(32) | 19/50(38) |
| P Values (c), (d)             | P=0.032   | N.S.      | P=0.038   |
| Relative Risk (Control) (e)   |           | 1.600     | 1.900     |
| Lower Limit                   |           | 0.761     | 0.942     |
| Upper Limit                   |           | 3.540     | 4.074     |
| Weeks to First Observed Tumor | 94        | 68        | 48        |
| <hr/>                         |           |           |           |
| Hematopoietic System:         |           |           |           |
| Lymphoma or Leukemia (b)      | 10/50(20) | 17/50(34) | 20/50(40) |
| P Values (c), (d)             | P=0.020   | N.S.      | P=0.024   |
| Relative Risk (Control) (e)   |           | 1.700     | 2.000     |
| Lower Limit                   |           | 0.821     | 1.004     |
| Upper Limit                   |           | 3.719     | 4.249     |
| Weeks to First Observed Tumor | 94        | 68        | 48        |
| <hr/>                         |           |           |           |

Table 15. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing C. I. Disperse Yellow 3 (a)

(Continued)

|  | Control           | Low Dose  | High Dose         |
|--|-------------------|-----------|-------------------|
| Liver: Hepatocellular Adenoma (b)              | 0/50(0)           | 6/50(12)  | 12/50(24)         |
| P Values (c), (d)                              | P less than 0.001 | P=0.013   | P less than 0.001 |
| Relative Risk (Control) (e)                    |                   | Infinite  | Infinite          |
| Lower Limit                                    |                   | 1.600     | 3.667             |
| Upper Limit                                    |                   | Infinite  | Infinite          |
| Weeks to First Observed Tumor                  | -                 | 105       | 105               |
| Liver: Hepatocellular Carcinoma (b)            | 2/50(4)           | 4/50(8)   | 5/50(10)          |
| P Values (c), (d)                              | N.S.              | N.S.      | N.S.              |
| Relative Risk (Control) (e)                    |                   | 2.000     | 2.500             |
| Lower Limit                                    |                   | 0.301     | 0.432             |
| Upper Limit                                    |                   | 21.316    | 25.286            |
| Weeks to First Observed Tumor                  | 102               | 99        | 83                |
| Liver: Hepatocellular Adenoma or Carcinoma (b) | 2/50(4)           | 10/50(20) | 17/50(34)         |
| P Values (c), (d)                              | P less than 0.001 | P=0.014   | P less than 0.001 |
| Relative Risk (Control) (e)                    |                   | 5.000     | 8.500             |
| Lower Limit                                    |                   | 1.140     | 2.180             |
| Upper Limit                                    |                   | 45.011    | 72.178            |
| Weeks to First Observed Tumor                  | 102               | 99        | 83                |

Table 15. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing C. I. Disperse Yellow 3 (a)

(Continued)

|   | Control | Low Dose | High Dose |
|---|---------|----------|-----------|
| Pituitary: Chromophobe Adenoma (b)        | 1/38(3) | 1/30(3)  | 4/42(10)  |
| P Values (c), (d)                         | N.S.    | N.S.     | N.S.      |
| Relative Risk (Control) (e)               |         | 1.267    | 3.619     |
| Lower Limit                               |         | 0.017    | 0.380     |
| Upper Limit                               |         | 96.122   | 173.681   |
| Weeks to First Observed Tumor             | 105     | 95       | 105       |
| Eye/Lacrimal Gland: Papillary Adenoma (b) | 1/50(2) | 3/50(6)  | 1/50(2)   |
| P Values (c), (d)                         | N.S.    | N.S.     | N.S.      |
| Relative Risk (Control) (e)               |         | 3.000    | 1.000     |
| Lower Limit                               |         | 0.251    | 0.013     |
| Upper Limit                               |         | 154.270  | 76.970    |
| Weeks to First Observed Tumor             | 105     | 105      | 105       |

- (a) Dosed groups received doses of 2,500 or 5,000 ppm in the diet.
- (b) Number of tumor-bearing animals/number of animals examined at site (percent).
- (c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.
- (d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.
- (e) The 95 percent confidence interval of the relative risk between each dosed group and the control group.
- (f) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.





## V. DISCUSSION

During the 2-year study, body weight gains by C. I. Disperse Yellow 3 dosed rats were depressed in a dose-related fashion. Also, weight gains by dosed mice tended to be depressed, but the magnitude of the effect was less than that observed among dosed rats, and dose-response relationships were not always obvious. However, feed consumption by dosed and control groups in the chronic study were comparable (Appendix H), and the observed weight gain decrements may be attributed to consumption of the test chemical.

The NCI guidelines (NCI 1976) for chronic feeding dosage selection were not strictly adhered to during this study. These guidelines suggest that dosage levels that cause greater than 10% decrements in body weight gains during prechronic testing should not be employed in the 2-year feeding study. In the 13-week studies, 17.7% and 21.6% decrements in weight gains by male and female rats were associated with dietary levels of 10,000 ppm C. I. Disperse Yellow 3. Similarly, dietary levels of 5,000 ppm caused 18.8% and 8.2% decrements in male and female mice, whereas the 10,000 ppm levels caused a decrease in body weight gain of 15% (male) and 10% (female). These dosage levels were selected to maximize the likelihood of reproducing the thyroid lesions observed in rats during the 90-day study. Although the thyroid effects were not observed in the two-year test, the dosage levels of C. I. Disperse Yellow 3 used in this study are judged to be adequate.

Despite the effects of compound administration on body weight gains, C. I. Disperse Yellow 3 did not adversely affect either rat or mouse survival. In fact, dosed rats survived significantly longer than did control rats. The survival rate for control female rats in this study was consistent with control rates in three previous groups (190 animals) utilized in these laboratories, and control male rat survival was consistent with that in two of the three previous control groups. The excellent survival rates of dosed rats and mice indicate that the maximum tolerated doses of C. I. Disperse Yellow 3 were not exceeded during this study.

An explanation for the improved survival of rats administered C. I. Disperse Yellow 3 is not obvious. A combination of negative trends related to certain primary tumors in dosed rats (as identified below) may have influenced survival, but the effect cannot be attributed to any single decrease in tumor incidence. With the exception of the decreased incidences of lymphoma or leukemia, all negative trends were seen in either male or female animals but not in both sexes. Among males, the decreased incidence of malignant mesothelioma and C-cell carcinoma of the thyroid are not considered to be sufficient to account for a significant increase in survival rate. Among female rats, a decreased incidence of pituitary adenoma could influence survival but a decrease in endometrial stromal polyps (which was probably secondary to decreased pituitary adenomas) would not.

Although a treatment-related decrease in lymphoma or leukemia was detected in both sexes of rats, the results of earlier studies do not support a relationship between this effect and increased survival. At least four other test agents--C. I. Acid Orange 10, C. I. Acid Red 14, C. I. Solvent Yellow 14, and D & C Red No. 9 (NTP 1982, 1982a, 1982b, 1982c)--have been found to decrease the incidence of lymphoma or leukemia in F344 rats. These decreases were not associated with significant increases in survival.

Lymphomas or leukemias occurred in a dose-related trend among female mice with a statistically significant ( $P < 0.05$ ) difference between high-dose and control groups. The high-dose incidence is also significantly ( $P < 0.05$ ) greater than the historical control rate for female mice with lymphoma or leukemia at this laboratory (23%, range 20%-32%). However, the incidence of these tumors shows considerable variability throughout the Bioassay Program (historical control range: 8-62%); further, since the increase in this study was observed only for female mice, this induced tumor was not regarded as clearly related to the administration of C. I. Disperse Yellow 3.

Although not statistically significant, the appearance of stomach tumors among C. I. Disperse Yellow 3 dosed male rats deserves mention. These rare stomach tumors were observed in 4/50 low-dose and 1/50 high-dose F344 rats.

The historical incidence of this tumor is only 10/2,960 (0.3%) in control male rats. Despite the lack of a dose-response relationship, the occurrence of these lesions may be treatment related.

Significant increases in hepatic neoplastic nodules were detected in both dosed groups of male rats, and a significant and dose-related increase in hepatocellular adenoma was detected in female mice. The incidence of hepatocellular carcinoma was not significantly altered by administration of the test chemical, although in female mice the incidences were higher in both dosed groups compared with controls. Hepatic neoplastic nodules and adenomas are populations of lesions, some of which may regress while others may progress to hepatocellular carcinoma. At the present time, it is impossible to differentiate between lesions that will regress and those that will progress. Consequently, one should consider these nodules and adenomas to exist at some ill-defined point along a continuum between benign and malignant with various factors being capable of influencing their final disposition. Teebor and Becker (1971), working with the hepatocarcinogen N-2-fluorenylacetamide (2-AAF), presented evidence that the fate of hepatic neoplastic nodules in Sprague-Dawley rats can be influenced by the duration of carcinogen administration. Nodules induced by a 3-month exposure to the carcinogen tended to regress when the treatment was stopped. This exposure was associated with a low incidence of hepatocellular carcinomas. Nodules produced by 4 months of treatment, however, were more persistent and were associated with a high incidence of hepatocellular carcinomas. Hirota and Williams (1979) in a similar study did not report regression of the nodules in F344 rats but observed that the nodules grew progressively in size.

The National Academy of Sciences (Stewart et al., 1980) considers the hepatic neoplastic nodule (and hepatic cell adenoma) to be a manifestation of the process of hepatocarcinogenesis which is induced by a variety of hepatocarcinogens but not by noncarcinogenic agents. The NAS defined neoplastic nodules as hepatocellular carcinomas, differentiated or grade 1. National and international organizations have stated that few, if any, chemicals produce only benign tumors in any species and that agents that markedly increase the incidence of benign tumors are now viewed with as much

suspicion as they would have been had the induced tumors been malignant (IARC, 1980; IRLG, 1979; Fed. Reg., 1980). Therefore, C. I. Disperse Yellow 3 is considered to be a carcinogen in F344 male rats and in B6C3F1 female mice. It is impossible to state if this carcinogenic effect is mediated through genetic or nongenetic mechanisms. It should be pointed out, however, that this azo dye could undergo metabolic reduction to form aromatic amines. The carcinogenicity of numerous aromatic amines has been well established. Additional studies would be required to clarify this point.

Significantly decreased incidences of two primary tumors, hepatocellular adenomas in males and alveolar/bronchiolar adenomas in females, were observed in C. I. Disperse Yellow 3 dosed mice. These decreases are not considered to be associated with administration of the dye because these were evident only for mice at the low doses and were not consistent across sexes.

An increased incidence of alveolar/bronchiolar adenomas was observed among male mice, while a significantly lower incidence was detected in low-dose females. Although the increase among males was significant ( $P=0.023$ ) and dose-related ( $P=0.019$ ), the control incidence (2/50, 4%) was lower than the mean (6.4%) of the historical controls encountered in this laboratory. Also, when the adenomas were combined with alveolar/bronchiolar carcinomas, there were no statistically significant differences between controls and dosed groups; the dose-related trend remained significant ( $P=0.046$ ). Because of the historical data, the significantly lower incidence among low-dose females, and the loss of statistical significance when adenomas and carcinomas were combined, relating this change to the administration of C. I. Disperse Yellow 3 lacks convincing support. However, the results cannot be dismissed and should be interpreted in light of the other experimental findings.

## VI. CONCLUSIONS

Under the conditions of this bioassay, C. I. Disperse Yellow 3 was considered to be carcinogenic for male F344 rats, causing an increased incidence of neoplastic nodules of the liver; this dye was not carcinogenic for female F344 rats. In addition, the stomach tumors found in the male rats may have been induced by the administration of the test chemical. C. I. Disperse Yellow 3 was carcinogenic for female B6C3F1 mice, as evidenced by the increased incidence of hepatocellular adenomas. C. I. Disperse Yellow 3 was not carcinogenic for male B6C3F1 mice. Also, the increased incidence of malignant lymphoma in female mice may have been associated with the administration of C. I. Disperse Yellow 3.



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**APPENDIX A**

**Summary of the Incidence of Neoplasms in Rats  
Fed Diets Containing C. I. Disperse Yellow 3**



TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED  
DIETS CONTAINING C. I. DISPERSE YELLOW 3

|                                      | CONTROL  | LOW DOSE | HIGH DOSE |
|--------------------------------------|----------|----------|-----------|
| ANIMALS INITIALLY IN STUDY           | 50       | 50       | 50        |
| ANIMALS NECROPSIED                   | 50       | 50       | 50        |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50       | 50       | 50        |
| INTEGUMENTARY SYSTEM                 |          |          |           |
| *SKIN                                | (50)     | (50)     | (50)      |
| SQUAMOUS CELL CARCINOMA              |          | 1 (2%)   |           |
| BASAL-CELL CARCINOMA                 | 1 (2%)   |          |           |
| *SUBCUT TISSUE                       | (50)     | (50)     | (50)      |
| SQUAMOUS CELL CARCINOMA              | 1 (2%)   |          | 1 (2%)    |
| BASAL-CELL CARCINOMA                 | 1 (2%)   |          | 1 (2%)    |
| SARCOMA, NOS                         |          |          | 1 (2%)    |
| FIBROMA                              | 3 (6%)   | 1 (2%)   | 1 (2%)    |
| FIBROSARCOMA                         |          |          | 2 (4%)    |
| FIBROSARCOMA, INVASIVE               | 1 (2%)   |          |           |
| LIPOMA                               |          |          | 1 (2%)    |
| OSTEOSARCOMA                         |          |          | 1 (2%)    |
| RESPIRATORY SYSTEM                   |          |          |           |
| *NASAL CAVITY                        | (50)     | (50)     | (50)      |
| SQUAMOUS CELL CARCINOMA, INVASIV     | 1 (2%)   |          |           |
| #LUNG                                | (50)     | (50)     | (50)      |
| SQUAMOUS CELL CARCINOMA              |          | 1 (2%)   |           |
| SQUAMOUS CELL CARCINOMA, METASTA     |          |          | 1 (2%)    |
| ALVEOLAR/BRONCHIOLAR ADENOMA         | 1 (2%)   |          |           |
| ALVEOLAR/BRONCHIOLAR CARCINOMA       | 1 (2%)   |          |           |
| OSTEOSARCOMA, METASTATIC             |          |          | 2 (4%)    |
| HEMATOPOIETIC SYSTEM                 |          |          |           |
| *MULTIPLE ORGANS                     | (50)     | (50)     | (50)      |
| LYMPHOCYTIC LEUKEMIA                 | 13 (26%) | 2 (4%)   | 1 (2%)    |
| *SPLEEN                              | (50)     | (50)     | (50)      |
| MALIG. LYMPHOMA, HISTIOCYTIC TYPE    |          | 1 (2%)   |           |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

\* NUMBER OF ANIMALS NECROPSIED

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

|  | CONTROL                  | LOW DOSE                 | HIGH DOSE                  |
|--|--------------------------|--------------------------|----------------------------|
| #MANDIBULAR L. NODE<br>SQUAMOUS CELL CARCINOMA, METASTA                    | (47)                     | (48)                     | (45)<br>1 (2%)             |
| #PRETRACHEAL LYMPH NO<br>C-CELL CARCINOMA, METASTATIC                      | (47)<br>1 (2%)           | (48)                     | (45)                       |
| CIRCULATORY SYSTEM   |                          |                          |                            |
| #ENDOCARDIUM<br>NEURILEMOMA, MALIGNANT                                     | (50)                     | (50)                     | (49)<br>1 (2%)             |
| *MIDDLE MENINGEAL ART<br>SQUAMOUS CELL CARCINOMA, METASTA                  | (50)<br>1 (2%)           | (50)                     | (50)                       |
| DIGESTIVE SYSTEM   |                          |                          |                            |
| #SALIVARY GLAND<br>FIBROSARCOMA  | (46)<br>1 (2%)           | (50)                     | (49)                       |
| #LIVER<br>NEOPLASTIC NODULE<br>HEPATOCELLULAR CARCINOMA                    | (49)<br>1 (2%)<br>1 (2%) | (50)<br>15 (30%)         | (50)<br>10 (20%)<br>2 (4%) |
| #STOMACH<br>ADENOCARCINOMA, NOS<br>MUCINOUS ADENOCARCINOMA<br>SARCOMA, NOS | (49)                     | (50)<br>1 (2%)           | (50)<br>1 (2%)<br>1 (2%)   |
| #CARDIAC STOMACH<br>SQUAMOUS CELL PAPILLOMA<br>FIBROSARCOMA                | (49)                     | (50)<br>1 (2%)<br>1 (2%) | (50)                       |
| #PYLORUS<br>ADENOMA, NOS   | (49)                     | (50)<br>1 (2%)           | (50)                       |
| URINARY SYSTEM   |                          |                          |                            |
| #KIDNEY<br>TUBULAR-CELL ADENOMA<br>TUBULAR-CELL ADENOCARCINOMA             | (50)                     | (50)                     | (50)<br>1 (2%)<br>1 (2%)   |
| #URINARY BLADDER<br>LEIOMYOMA  | (45)                     | (50)                     | (48)<br>1 (2%)             |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

\* NUMBER OF ANIMALS NECROPSIED

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

|                                  | CONTROL  | LOW DOSE | HIGH DOSE |
|----------------------------------|----------|----------|-----------|
| ENDOCRINE SYSTEM                 |          |          |           |
| #PITUITARY                       | (47)     | (49)     | (46)      |
| ADENOMA, NOS                     | 1 (2%)   |          |           |
| CHROMOPHOBE ADENOMA              | 5 (11%)  | 7 (14%)  | 4 (9%)    |
| CHROMOPHOBE CARCINOMA            | 1 (2%)   |          |           |
| ACIDOPHIL ADENOMA                |          |          | 1 (2%)    |
| #ADRENAL                         | (50)     | (50)     | (49)      |
| PHEOCHROMOCYTOMA                 | 6 (12%)  | 8 (16%)  | 3 (6%)    |
| PHEOCHROMOCYTOMA, MALIGNANT      | 1 (2%)   | 3 (6%)   | 2 (4%)    |
| #THYROID                         | (49)     | (50)     | (48)      |
| PAPILLARY ADENOMA                |          | 1 (2%)   |           |
| FOLLICULAR-CELL ADENOMA          |          | 1 (2%)   |           |
| C-CELL ADENOMA                   |          | 1 (2%)   |           |
| C-CELL CARCINOMA                 | 4 (8%)   | 1 (2%)   |           |
| #PANCREATIC ISLETS               | (48)     | (50)     | (49)      |
| ISLET-CELL ADENOMA               |          | 2 (4%)   |           |
| ISLET-CELL CARCINOMA             | 2 (4%)   | 1 (2%)   | 2 (4%)    |
| REPRODUCTIVE SYSTEM              |          |          |           |
| *MAMMARY GLAND                   | (50)     | (50)     | (50)      |
| FIBROADENOMA                     |          |          | 1 (2%)    |
| *PREPUTIAL GLAND                 | (50)     | (50)     | (50)      |
| CARCINOMA, NOS                   |          | 2 (4%)   |           |
| ADENOMA, NOS                     |          |          | 2 (4%)    |
| #TESTIS                          | (49)     | (49)     | (50)      |
| INTERSTITIAL-CELL TUMOR          | 46 (94%) | 48 (98%) | 43 (86%)  |
| NERVOUS SYSTEM                   |          |          |           |
| #BRAIN                           | (50)     | (50)     | (50)      |
| GRANULAR-CELL TUMOR, BENIGN      |          |          | 1 (2%)    |
| GLIOMA, NOS                      |          |          | 1 (2%)    |
| ASTROCYTOMA                      |          | 1 (2%)   | 2 (4%)    |
| #OLFACTORY BULB                  | (50)     | (50)     | (50)      |
| SQUAMOUS CELL CARCINOMA, INVASIV | 1 (2%)   |          |           |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

\* NUMBER OF ANIMALS NECROPSIED

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

|                                   | CONTROL | LOW DOSE | HIGH DOSE |
|-----------------------------------|---------|----------|-----------|
| <b>SPECIAL SENSE ORGANS</b>       |         |          |           |
| *EAR CANAL                        | (50)    | (50)     | (50)      |
| SQUAMOUS CELL PAPILLOMA           | 1 (2%)  |          |           |
| SQUAMOUS CELL CARCINOMA           | 1 (2%)  |          |           |
| *ZYMBAL'S GLAND                   | (50)    | (50)     | (50)      |
| SQUAMOUS CELL CARCINOMA           | 1 (2%)  |          |           |
| <b>MUSCULOSKELETAL SYSTEM</b>     |         |          |           |
| *SKULL                            | (50)    | (50)     | (50)      |
| OSTEOMA                           |         |          | 1 (2%)    |
| <b>BODY CAVITIES</b>              |         |          |           |
| *MEDIASTINUM                      | (50)    | (50)     | (50)      |
| NONCHROMAFFIN PARAGANGLIOMA       |         |          | 1 (2%)    |
| *PELVIS                           | (50)    | (50)     | (50)      |
| OSTEOSARCOMA                      |         |          | 1 (2%)    |
| *TUNICA VAGINALIS                 | (50)    | (50)     | (50)      |
| MESOTHELICMA, NOS                 | 1 (2%)  | 3 (6%)   | 1 (2%)    |
| <b>ALL OTHER SYSTEMS</b>          |         |          |           |
| *MULTIPLE ORGANS                  | (50)    | (50)     | (50)      |
| MESOTHELIOMA, MALIGNANT           | 4 (8%)  | 2 (4%)   |           |
| TAIL                              |         |          |           |
| SQUAMOUS CELL PAPILLOMA           |         | 1        |           |
| <b>ANIMAL DISPOSITION SUMMARY</b> |         |          |           |
| ANIMALS INITIALLY IN STUDY        | 50      | 50       | 50        |
| NATURAL DEATH <sup>a</sup>        | 15      | 4        | 8         |
| MORIBUND SACRIFICE                | 4       | 1        | 3         |
| SCHEDULED SACRIFICE               |         |          |           |
| ACCIDENTALLY KILLED               |         |          |           |
| TERMINAL SACRIFICE                | 31      | 45       | 39        |
| ANIMAL MISSING                    |         |          |           |

<sup>a</sup> INCLUDES AUTOLYZED ANIMALS

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



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

|   | CONTROL | LOW DOSE | HIGH DOSE |
|---|---------|----------|-----------|
| TUMOR SUMMARY   |         |          |           |
| TOTAL ANIMALS WITH PRIMARY TUMORS*  | 50      | 50       | 47        |
| TOTAL PRIMARY TUMORS  | 98      | 107      | 93        |
| TOTAL ANIMALS WITH BENIGN TUMORS  | 48      | 49       | 46        |
| TOTAL BENIGN TUMORS   | 63      | 72       | 61        |
| TOTAL ANIMALS WITH MALIGNANT TUMORS   | 28      | 15       | 16        |
| TOTAL MALIGNANT TUMORS  | 33      | 17       | 21        |
| TOTAL ANIMALS WITH SECONDARY TUMORS#  | 3       |          | 3         |
| TOTAL SECONDARY TUMORS  | 5       |          | 4         |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-<br>BENIGN OR MALIGNANT                     | 2       | 17       | 11        |
| TOTAL UNCERTAIN TUMORS  | 2       | 18       | 11        |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-<br>PRIMARY OR METASTATIC                   |         |          |           |
| TOTAL UNCERTAIN TUMORS  |         |          |           |
| * PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS                            |         |          |           |
| # SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN |         |          |           |

TABLE A2.

**SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS FED  
DIETS CONTAINING C. I. DISPERSE YELLOW 3**

|  | CONTROL | LOW DOSE | HIGH DOSE |
|--|---------|----------|-----------|
| ANIMALS INITIALLY IN STUDY                               | 50      | 50       | 50        |
| ANIMALS NECROPSIED                                       | 50      | 50       | 50        |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY                     | 50      | 50       | 50        |
| INTEGUMENTARY SYSTEM                                     |         |          |           |
| *SUBCUT TISSUE   | (50)    | (50)     | (50)      |
| SQUAMOUS CELL CARCINOMA                                  |         | 1 (2%)   |           |
| C-CELL CARCINOMA, INVASIVE                               |         |          | 1 (2%)    |
| SARCOMA, NOS   |         | 1 (2%)   |           |
| FIBROMA  |         | 1 (2%)   |           |
| FIBROSARCOMA   | 1 (2%)  |          |           |
| LEIOMYOSARCOMA   |         | 1 (2%)   |           |
| RESPIRATORY SYSTEM                                       |         |          |           |
| *NASAL CAVITY  | (50)    | (50)     | (50)      |
| SQUAMOUS CELL CARCINOMA, INVASIV                         |         | 1 (2%)   |           |
| #LUNG  | (49)    | (50)     | (50)      |
| C-CELL CARCINOMA, METASTATIC                             |         |          | 1 (2%)    |
| GANGLIONEUROBLASTOMA, METASTATIC                         |         | 1 (2%)   |           |
| HEMATOPOIETIC SYSTEM                                     |         |          |           |
| *MULTIPLE ORGANS   | (50)    | (50)     | (50)      |
| MALIG.LYMPHOMA, LYMPHOCYTIC TYPE                         | 1 (2%)  | 2 (4%)   | 2 (4%)    |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE                         | 1 (2%)  |          |           |
| LYMPHOCYTIC LEUKEMIA                                     | 7 (14%) | 2 (4%)   |           |
| #SPLEEN  | (48)    | (50)     | (50)      |
| FIBROSARCOMA   |         |          | 1 (2%)    |
| LYMPHOCYTIC LEUKEMIA                                     | 1 (2%)  |          | 1 (2%)    |
| #LYMPH NODE  | (48)    | (44)     | (44)      |
| FIBROSARCOMA, METASTATIC                                 | 1 (2%)  |          |           |
| #BRONCHIAL LYMPH NODE                                    | (48)    | (44)     | (44)      |
| FIBROSARCOMA, METASTATIC                                 |         |          | 1 (2%)    |
| # NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY |         |          |           |
| * NUMBER OF ANIMALS NECROPSIED                           |         |          |           |

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

|   | CONTROL                                | LOW DOSE   | HIGH DOSE                          |
|---|--|--|------------------------------------|
| #MEDIASTINAL L.NODE<br>C-CELL CARCINOMA, METASTATIC   | (48)                                   | (44)   | (44)<br>1 (2%)                     |
| CIRCULATORY SYSTEM  |  |  |                                    |
| #HEART<br>NEURILEMOMA   | (50)                                   | (50)<br>1 (2%)                                   | (49)                               |
| DIGESTIVE SYSTEM  |  |  |                                    |
| #LIVER<br>NEOPLASTIC NODULE<br>HEPATOCELLULAR CARCINOMA<br>FIBROSARCOMA, METASTATIC   | (50)<br>2 (4%)                         | (49)<br>1 (2%)                                   | (50)<br>2 (4%)<br>1 (2%)<br>1 (2%) |
| #PANCREAS<br>FIBROSARCOMA, INVASIVE   | (48)                                   | (50)   | (50)<br>1 (2%)                     |
| URINARY SYSTEM  |  |  |                                    |
| #KIDNEY<br>TUBULAR-CELL ADENOCARCINOMA  | (50)<br>1 (2%)                         | (50)   | (50)                               |
| ENDOCRINE SYSTEM  |  |  |                                    |
| #PITUITARY<br>CARCINOMA, NOS<br>ADENOMA, NOS<br>CHROMOPHOBE ADENOMA<br>CHROMOPHOBE CARCINOMA  | (44)<br><br>15 (34%)<br>1 (2%)         | (48)<br><br>1 (2%)<br>15 (31%)                   | (49)<br><br>1 (2%)<br>8 (16%)      |
| #ADRENAL<br>CORTICAL ADENOMA<br>CORTICAL CARCINOMA<br>PHEOCHROMOCYTOMA<br>PHEOCHROMOCYTOMA, MALIGNANT<br>GANGLIONEUROMA<br>GANGLIONEUROBLASTOMA | (50)<br><br>1 (2%)<br>2 (4%)<br>1 (2%) | (50)<br><br>1 (2%)<br>3 (6%)<br>1 (2%)<br>1 (2%) | (50)                               |
| #ZONA FASCICULATA<br>ADENOMA, NOS   | (50)                                   | (50)   | (50)<br>1 (2%)                     |

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

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

|                               | CONTROL        | LOW DOSE       | HIGH DOSE      |
|-------------------------------|----------------|----------------|----------------|
| #THYROID<br>C-CELL CARCINOMA  | (49)<br>1 (2%) | (49)<br>2 (4%) | (50)<br>3 (6%) |
| <b>REPRODUCTIVE SYSTEM</b>    |                |                |                |
| *MAMMARY GLAND                | (50)           | (50)           | (50)           |
| ADENOMA, NOS                  | 1 (2%)         | 1 (2%)         |                |
| ADENOCARCINOMA, NOS           |                | 1 (2%)         |                |
| CARCINOSARCOMA                |                | 1 (2%)         |                |
| FIBROADENOMA                  | 7 (14%)        | 11 (22%)       | 3 (6%)         |
| *MAMMARY DUCT                 | (50)           | (50)           | (50)           |
| ADENOCARCINOMA, NOS           |                | 1 (2%)         |                |
| *PREPUTIAL GLAND              | (50)           | (50)           | (50)           |
| SQUAMOUS CELL CARCINOMA       | 1 (2%)         |                |                |
| *CLITORAL GLAND               | (50)           | (50)           | (50)           |
| ADENOCARCINOMA, NOS           | 1 (2%)         |                |                |
| #UTERUS                       | (50)           | (48)           | (50)           |
| ENDOMETRIAL STROMAL POLYP     | 14 (28%)       | 7 (15%)        | 3 (6%)         |
| CARCINOSARCOMA                |                | 1 (2%)         |                |
| #OVARY                        | (50)           | (49)           | (50)           |
| GRANULOSA-CELL TUMOR          |                | 1 (2%)         | 1 (2%)         |
| FIBROSARCOMA                  |                |                | 1 (2%)         |
| <b>NERVOUS SYSTEM</b>         |                |                |                |
| #BRAIN                        | (50)           | (50)           | (49)           |
| GRANULAR-CELL TUMOR, BENIGN   |                | 1 (2%)         |                |
| ASTROCYTOMA                   | 1 (2%)         |                |                |
| <b>SPECIAL SENSE ORGANS</b>   |                |                |                |
| NONE                          |                |                |                |
| <b>MUSCULOSKELETAL SYSTEM</b> |                |                |                |
| NONE                          |                |                |                |

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

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

|   | CONTROL | LOW DOSE | HIGH DOSE |
|---|---------|----------|-----------|
| BODY CAVITIES   |         |          |           |
| NONE  |         |          |           |
| ALL OTHER SYSTEMS   |         |          |           |
| *MULTIPLE ORGANS  | (50)    | (50)     | (50)      |
| SQUAMOUS CELL CARCINOMA, METASTA  | 1 (2%)  |          |           |
| LEIOMYOSARCOMA  |         | 1 (2%)   |           |
| ANIMAL DISPOSITION SUMMARY  |         |          |           |
| ANIMALS INITIALLY IN STUDY  | 50      | 50       | 50        |
| NATURAL DEATH <sup>a</sup>  | 11      | 7        | 3         |
| MORIBUND SACRIFICE  | 6       | 3        | 1         |
| SCHEDULED SACRIFICE   |         |          |           |
| ACCIDENTALLY KILLED   |         |          |           |
| TERMINAL SACRIFICE  | 33      | 40       | 46        |
| ANIMAL MISSING  |         |          |           |
| <sup>a</sup> INCLUDES AUTOLYZED ANIMALS   |         |          |           |
| TUMOR SUMMARY   |         |          |           |
| TOTAL ANIMALS WITH PRIMARY TUMORS*  | 38      | 40       | 25        |
| TOTAL PRIMARY TUMORS  | 60      | 61       | 28        |
| TOTAL ANIMALS WITH BENIGN TUMORS  | 29      | 30       | 15        |
| TOTAL BENIGN TUMORS   | 40      | 43       | 15        |
| TOTAL ANIMALS WITH MALIGNANT TUMORS   | 17      | 15       | 9         |
| TOTAL MALIGNANT TUMORS  | 18      | 16       | 10        |
| TOTAL ANIMALS WITH SECONDARY TUMORS#  | 2       | 2        | 2         |
| TOTAL SECONDARY TUMORS  | 2       | 2        | 6         |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-<br>BENIGN OR MALIGNANT                     | 2       | 2        | 3         |
| TOTAL UNCERTAIN TUMORS  | 2       | 2        | 3         |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-<br>PRIMARY OR METASTATIC                   |         |          |           |
| TOTAL UNCERTAIN TUMORS  |         |          |           |
| * PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS                            |         |          |           |
| # SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN |         |          |           |





TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY TABLES OF MALE RATS IN THE 2-YEAR STUDY OF C.I. DISPERSE YELLOW 3

LOW DOSE

| ANIMAL NUMBER   | 0              |   | 1 |   | 2 |   | 3 |   | 4 |   | 5 |    | 6  |    | 7  |    | 8  |    | 9  |    | 10 |    | 11 |    | 12 |    | 13 |    | 14 |    | 15 |    | 16 |    | 17 |    | 18 |    | 19 |    | 20 |    | 21 |    | 22 |    | 23 |    | 24 |    | 25 |    | 26 |    | 27 |    | 28 |    | 29 |    | 30 |    | 31 |    | 32 |    | 33 |    | 34 |    | 35 |    | 36 |    | 37 |    | 38 |    | 39 |    | 40 |    | 41 |    | 42 |    | 43 |    | 44 |    | 45 |    | 46 |    | 47 |    | 48 |    | 49 |    | 50 |     | 51  |     | 52  |     | 53  |     | 54  |     | 55  |     | 56  |     | 57  |     | 58  |     | 59  |     | 60  |     | 61  |     | 62  |     | 63  |     | 64  |     | 65  |     | 66  |     | 67  |     | 68  |     | 69  |     | 70  |     | 71  |     | 72  |     | 73  |     | 74  |     | 75  |     | 76  |     | 77  |     | 78  |     | 79  |     | 80  |     | 81  |     | 82  |     | 83  |     | 84  |     | 85  |     | 86  |     | 87  |     | 88  |     | 89  |     | 90  |     | 91  |     | 92  |     | 93  |     | 94  |     | 95  |     | 96  |     | 97  |     | 98  |     | 99  |     | 100 |     | 101 |  | 102 |  | 103 |  | 104 |  | 105 |  | 106 |  | 107 |  | 108 |  | 109 |  | 110 |  | 111 |  | 112 |  | 113 |  | 114 |  | 115 |  | 116 |  | 117 |  | 118 |  | 119 |  | 120 |  | 121 |  | 122 |  | 123 |  | 124 |  | 125 |  | 126 |  | 127 |  | 128 |  | 129 |  | 130 |  | 131 |  | 132 |  | 133 |  | 134 |  | 135 |  | 136 |  | 137 |  | 138 |  | 139 |  | 140 |  | 141 |  | 142 |  | 143 |  | 144 |  | 145 |  | 146 |  | 147 |  | 148 |  | 149 |  | 150 |  | 151 |  | 152 |  | 153 |  | 154 |  | 155 |  | 156 |  | 157 |  | 158 |  | 159 |  | 160 |  | 161 |  | 162 |  | 163 |  | 164 |  | 165 |  | 166 |  | 167 |  | 168 |  | 169 |  | 170 |  | 171 |  | 172 |  | 173 |  | 174 |  | 175 |  | 176 |  | 177 |  | 178 |  | 179 |  | 180 |  | 181 |  | 182 |  | 183 |  | 184 |  | 185 |  | 186 |  | 187 |  | 188 |  | 189 |  | 190 |  | 191 |  | 192 |  | 193 |  | 194 |  | 195 |  | 196 |  | 197 |  | 198 |  | 199 |  | 200 |  |
|---|----------------|---|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|-----|--|
|   | WEEKS ON STUDY | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 | 61 | 62 | 63 | 64 | 65 | 66 | 67 | 68 | 69 | 70 | 71 | 72 | 73 | 74 | 75 | 76 | 77 | 78 | 79 | 80 | 81 | 82 | 83 | 84 | 85 | 86 | 87 | 88 | 89 | 90 | 91 | 92 | 93 | 94 | 95 | 96 | 97 | 98 | 99 | 100 | 101 | 102 | 103 | 104 | 105 | 106 | 107 | 108 | 109 | 110 | 111 | 112 | 113 | 114 | 115 | 116 | 117 | 118 | 119 | 120 | 121 | 122 | 123 | 124 | 125 | 126 | 127 | 128 | 129 | 130 | 131 | 132 | 133 | 134 | 135 | 136 | 137 | 138 | 139 | 140 | 141 | 142 | 143 | 144 | 145 | 146 | 147 | 148 | 149 | 150 | 151 | 152 | 153 | 154 | 155 | 156 | 157 | 158 | 159 | 160 | 161 | 162 | 163 | 164 | 165 | 166 | 167 | 168 | 169 | 170 | 171 | 172 | 173 | 174 | 175 | 176 | 177 | 178 | 179 | 180 | 181 | 182 | 183 | 184 | 185 | 186 | 187 | 188 | 189 | 190 | 191 | 192 | 193 | 194 | 195 | 196 | 197 | 198 | 199 | 200 |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| INTEGUMENTARY SYSTEM  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| SKIN SQUAMOUS CELL CARCINOMA  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| SUBCUTANEOUS TISSUE FIBROMA   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| RESPIRATORY SYSTEM  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| LUNGS AND BRONCHI SQUAMOUS CELL CARCINOMA   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| TRACHEA   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| HEMATOPOIETIC SYSTEM  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| BONE MARROW   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| SPLEEN MALIG. LYMPHOMA, HISTIOCYTIC TYPE  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| LYMPH NODES   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| THYMUS  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| CIRCULATORY SYSTEM  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| HEART   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| DIGESTIVE SYSTEM  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| SALIVARY GLAND  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| LIVER NEOPLASTIC MODULE   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| BILE DUCT   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| GALLBLADDER & COMMON BILE DUCT  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| PANCREAS  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| ESOPHAGUS   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| STOMACH SQUAMOUS CELL PAPILLOMA ADENOMA, NOS MUCINOUS ADENOCARCINOMA FIBROSARCOMA |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| SMALL INTESTINE   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| LARGE INTESTINE   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| URINARY SYSTEM  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| KIDNEY  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| URINARY BLADDER   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| ENDOCRINE SYSTEM  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| PITUITARY CHROMOPHOBE ADENOMA   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| ADRENAL PHEOCHROMOCYTOMA, MALIGNANT   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| THYROID PAPILLARY ADENOMA FOLLICULAR-CELL ADENOMA C-CELL ADENOMA C-CELL CARCINOMA |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| PARATHYROID   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| PANCREATIC ISLETS ISLET-CELL ADENOMA ISLET-CELL CARCINOMA                         |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| REPRODUCTIVE SYSTEM   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| MAMMARY GLAND   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| TESTIS INTERSTITIAL-CELL TUMOR  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| PROSTATE  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| PREPUTIAL/CLITORAL GLAND CARCINOMA, NOS   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| NERVOUS SYSTEM  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| BRAIN ASTROCYTOMA   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| BODY CAVITIES   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| TUNICA VAGINALIS MESOTHELIOMA, NOS  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| ALL OTHER SYSTEMS   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| MULTIPLE ORGANS NOS MESOTHELIOMA, MALIGNANT LYMPHOCTIC LEUKEMIA                   |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |
| TAIL SQUAMOUS CELL PAPILLOMA  |                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |     |  |

+ : TISSUE EXAMINED MICROSCOPICALLY  
- : REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY  
X : TUMOR INCIDENCE  
M : NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION  
: NO TISSUE INFORMATION SUBMITTED  
C : NECROPSY, NO HISTOLOGY DUE TO PROTOCOL  
A : AUTOLYSIS  
M : ANIMAL MISSING  
B : NO NECROPSY PERFORMED



TABLE A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

|                                   | ANIMAL NUMBER  |   |   |   |   |   |   |   |   |    |    |    | TOTAL TISSUES TUMORS |   |   |   |   |   |   |   |   |   |    |    |   |    |
|-----------------------------------|----------------|---|---|---|---|---|---|---|---|----|----|----|----------------------|---|---|---|---|---|---|---|---|---|----|----|---|----|
|                                   | 1              | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |                      |   |   |   |   |   |   |   |   |   |    |    |   |    |
|                                   | WEEKS ON STUDY |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   |    |
|                                   | 0              | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9  | 10 | 11 | 0                    | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |   |    |
| <b>INTEGUMENTARY SYSTEM</b>       |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   |    |
| SKIN                              | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 50 |
| SQUAMOUS CELL CARCINOMA           |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   | 1  |
| SUBCUTANEOUS TISSUE               | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 50 |
| FIBROMA                           |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   | 1  |
| <b>RESPIRATORY SYSTEM</b>         |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   |    |
| LUNGS AND BRONCHI                 | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 50 |
| SQUAMOUS CELL CARCINOMA           |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    | X  |   | 1  |
| TRACHEA                           | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 50 |
| <b>HEMATOPOIETIC SYSTEM</b>       |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   |    |
| BONE MARROW                       | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 50 |
| SPLEEN                            | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 50 |
| MALIG. LYMPHOMA, HISTIOCYTIC TYPE |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    | X  |   | 1  |
| LYMPH NODES                       | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 48 |
| THYMUS                            | -              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 45 |
| <b>CIRCULATORY SYSTEM</b>         |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   |    |
| HEART                             | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 50 |
| <b>DIGESTIVE SYSTEM</b>           |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   |    |
| SALIVARY GLAND                    | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 50 |
| LIVER                             | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 50 |
| NEOPLASTIC MODULE                 |                |   |   | X |   |   |   |   |   | X  | X  |    |                      | X | X |   |   |   | X |   | X | X |    |    |   | 19 |
| 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           |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   | 1  |
| ADENOMA, NOS                      |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   | 1  |
| MUCINOUS ADENOCARCINOMA           |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   | 1  |
| FIBROSARCOMA                      |                |   |   | X |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   | 1  |
| SMALL INTESTINE                   | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 50 |
| LARGE INTESTINE                   | -              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 45 |
| <b>URINARY SYSTEM</b>             |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   |    |
| KIDNEY                            | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 50 |
| URINARY BLADDER                   | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 50 |
| <b>ENDOCRINE SYSTEM</b>           |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   |    |
| PITUITARY                         | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 49 |
| CHROMOPHOBE ADENOMA               |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   | X  |    |   | 7  |
| ADRENAL                           | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 50 |
| PHEOCHROMOCYTOMA                  |                | X |   | X |   |   |   | X |   |    | X  |    |                      |   |   | X |   |   |   |   |   | X |    | X  |   | 8  |
| PHEOCHROMOCYTOMA, MALIGNANT       |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   | 3  |
| THYROID                           | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 50 |
| PAPILLARY ADENOMA                 |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    | X  |   | 1  |
| FOLLICULAR-CELL ADENOMA           |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   | 1  |
| C-CELL ADENOMA                    |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   | 1  |
| C-CELL CARCINOMA                  |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   | X  |    |   | 1  |
| PARATHYROID                       | -              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 43 |
| PANCREATIC ISLETS                 | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 50 |
| ISLET-CELL ADENOMA                |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    | X  |   | 2  |
| ISLET-CELL CARCINOMA              |                |   |   | X |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   | 1  |
| <b>REPRODUCTIVE SYSTEM</b>        |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   |    |
| MAMMARY GLAND                     | N              | N | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | N | 50 |
| TESTIS                            | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 49 |
| 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 | 48 |
| PROSTATE                          | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 49 |
| 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  |
| <b>NERVOUS SYSTEM</b>             |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   |    |
| BRAIN                             | +              | + | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 50 |
| ASTROCYTOMA                       |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   | 1  |
| <b>BODY CAVITIES</b>              |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   |    |
| TUNICA VAGINALIS                  | +              | N | + | + | + | + | + | + | + | +  | +  | +  | +                    | + | + | + | + | + | + | + | + | + | +  | +  | + | 50 |
| MESOTHELIOA, NOS                  |                |   | X | X |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   | 3  |
| <b>ALL OTHER SYSTEMS</b>          |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   |    |
| 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 |
| MESOTHELIOA, MALIGNANT            |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    | X  |   | 2  |
| LYMPHOCTIC LEUKEMIA               |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   | 2  |
| TAIL                              |                |   |   |   |   |   |   |   |   |    |    |    |                      |   |   |   |   |   |   |   |   |   |    |    |   |    |
| SQUAMOUS CELL PAPILLOMA           |                |   |   |   |   |   |   |   |   |    |    |    | X                    |   |   |   |   |   |   |   |   |   |    |    |   | 1  |

\* ANIMALS NECROPSIED  
 +: TISSUE EXAMINED MICROSCOPICALLY  
 -: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY  
 X: TUMOR INCIDENCE  
 N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION  
 : 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 TABLES OF FEMALE RATS IN THE 2-YEAR STUDY OF C.I. DISPERSE YELLOW 3**

**CONTROL**

|  | ANIMAL NUMBER  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|--|----------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  | 0              | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |   |
|  | WEEKS ON STUDY |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|  | 1              | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 3 | 3 | 3 |
| INTEGUMENTARY SYSTEM                             | +              | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SUBCUTANEOUS TISSUE FIBROSARCOMA                 |                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |
| RESPIRATORY SYSTEM                               | +              | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LUNGS AND BRONCHI                                | +              | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| TRACHEA  | +              | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEMATOPOIETIC SYSTEM                             | +              | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| BONE MARROW                                      |                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SPLEEN LYMPHOCTIC LEUKEMIA                       | +              | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LYMPH NODES FIBROSARCOMA, METASTATIC             |                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |
| 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 TUBULAR-CELL ADENOCARCINOMA               |                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| URINARY BLADDER                                  | +              | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ENDOCRINE SYSTEM                                 | +              | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| PITUITARY CHROMOPHOBE ADENOMA                    |                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| PITUITARY CHROMOPHOBE CARCINOMA                  |                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| ADRENAL CORTICAL CARCINOMA                       | +              | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ADRENAL PHEOCHROMOCYTOMA                         |                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| ADRENAL GANGLIOMEUROMA                           |                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| THYROID C-CELL CARCINOMA                         | +              | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| PARATHYROID                                      | +              | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| REPRODUCTIVE SYSTEM                              | +              | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| MAMMARY GLAND ADENOMA, NOS                       |                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| MAMMARY GLAND FIBROADENOMA                       |                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| PREPUTIAL/CLITORAL GLAND SQUAMOUS CELL CARCINOMA |                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| PREPUTIAL/CLITORAL GLAND ADENOCARCINOMA, NOS     |                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| UTERUS ENDOMETRIAL STROMAL POLYP                 | +              | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| OVARY  | +              | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| NERVOUS SYSTEM                                   | +              | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| BRAIN ASTROCYTOMA                                |                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| ALL OTHER SYSTEMS                                | N              | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| MULTIPLE ORGANS NOS                              |                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SQUAMOUS CELL CARCINOMA, METASTAT                |                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| MALIG. LYMPHOMA, LYMPHOCTIC TYPE                 |                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| MALIG. LYMPHOMA, HISTIOCTIC TYPE                 |                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| LYMPHOCTIC LEUKEMIA                              | X              | X |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   | X |

+: TISSUE EXAMINED MICROSCOPICALLY  
 -: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY  
 X: TUMOR INCIDENCE  
 N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION  
 !: 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 TABLES OF FEMALE RATS IN THE 2-YEAR STUDY OF C.I. DISPERSE YELLOW 3

LOW DOSE

| ANIMAL NUMBER                     | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 |  |
|-----------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|--|
| WEEKS ON STUDY                    | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |  |
| <b>INTEGUMENTARY SYSTEM</b>       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| SUBCUTANEOUS TISSUE               | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| SQUAMOUS CELL CARCINOMA           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| SARCOMA, NOS                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| FIBROMA                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| LEIOMYOSARCOMA                    | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| <b>RESPIRATORY SYSTEM</b>         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| LUNGS AND BRONCHI                 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| GANGLIONEUROBLASTOMA, METASTATIC  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| TRACHEA                           | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| NASAL 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 | N |  |
| SQUAMOUS CELL CARCINOMA, INVASIVE |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| <b>HEMATOPOIETIC SYSTEM</b>       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| BONE MARROW                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| SPLEEN                            | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| LYMPH NODES                       | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| THYMUS                            | + | - | + | - | + | - | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + |  |
| <b>CIRCULATORY SYSTEM</b>         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| HEART                             | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| NEURILEMOMA                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| <b>DIGESTIVE SYSTEM</b>           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| SALIVARY GLAND                    | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| LIVER                             | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| NEOPLASTIC NODULE                 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| 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 | N |  |
| PANCREAS                          | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| ESOPHAGUS                         | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| STOMACH                           | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| SMALL INTESTINE                   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| LARGE INTESTINE                   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| <b>URINARY SYSTEM</b>             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| KIDNEY                            | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| URINARY BLADDER                   | + | + | - | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| <b>ENDOCRINE SYSTEM</b>           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| PITUITARY                         | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| ADENOMA, NOS                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| CHROMOPHOBE ADENOMA               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| ADRENAL                           | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| CORTICAL ADENOMA                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| PHEOCHROMOCYTOMA                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| PHEOCHROMOCYTOMA, MALIGNANT       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| GANGLIONEUROMA                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| GANGLIONEUROBLASTOMA              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| THYROID                           | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| C-CELL CARCINOMA                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| PARATHYROID                       | - | + | + | - | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| <b>REPRODUCTIVE SYSTEM</b>        |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| MAMMARY GLAND                     | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| ADENOMA, NOS                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| ADENOCARCINOMA, NOS               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| CARCINOSARCOMA                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| FIBROADENOMA                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| UTERUS                            | + | + | - | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| ENDOMETRIAL STROMAL POLYP         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| CARCINOSARCOMA                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| OVARY                             | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| GRANULOSA-CELL TUMOR              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| <b>NERVOUS SYSTEM</b>             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| BRAIN                             | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| GRANULAR-CELL TUMOR, BENIGN       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| <b>ALL OTHER SYSTEMS</b>          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| 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 |  |
| LEIOMYOSARCOMA                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| MALIG. LYMPHOMA, LYMPHOCYTIC TYPE |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| LYMPHOCYTIC LEUKEMIA              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |

+: TISSUE EXAMINED MICROSCOPICALLY  
 -: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY  
 X: TUMOR INCIDENCE  
 N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION  
 : NO TISSUE INFORMATION SUBMITTED  
 C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL  
 A: AUTOLYSIS  
 M: ANIMAL MISSING  
 B: NO NECROPSY PERFORMED











**APPENDIX B**

**Summary of the Incidence of Neoplasms in Mice  
Fed Diets Containing C. I. Disperse Yellow 3**



TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED  
DIETS CONTAINING C. I. DISPERSE YELLOW 3

|                                      | CONTROL | LOW DOSE | HIGH DOSE |
|--------------------------------------|---------|----------|-----------|
| ANIMALS INITIALLY IN STUDY           | 50      | 50       | 50        |
| ANIMALS MISSING                      |         |          | 1         |
| ANIMALS NECROPSIED                   | 50      | 49       | 49        |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50      | 49       | 49        |
| INTEGUMENTARY SYSTEM                 |         |          |           |
| *SKIN                                | (50)    | (49)     | (49)      |
| FIBROSARCOMA                         |         | 2 (4%)   |           |
| *SUBCUT TISSUE                       | (50)    | (49)     | (49)      |
| FIBROMA                              |         | 1 (2%)   |           |
| LEIOMYOSARCOMA                       | 1 (2%)  |          | 1 (2%)    |
| RESPIRATORY SYSTEM                   |         |          |           |
| #LUNG                                | (50)    | (49)     | (49)      |
| NEOPLASM, NOS, METASTATIC            |         |          | 1 (2%)    |
| HEPATOCELLULAR CARCINOMA, METAST     | 3 (6%)  | 3 (6%)   |           |
| ALVEOLAR/BRONCHIOLAR ADENOMA         | 2 (4%)  | 6 (12%)  | 9 (18%)   |
| ALVEOLAR/BRONCHIOLAR CARCINOMA       | 1 (2%)  | 1 (2%)   |           |
| TUBULAR-CELL ADENOCARCINOMA, MET     |         |          | 1 (2%)    |
| SARCOMA, NOS, METASTATIC             |         | 1 (2%)   |           |
| FIBROSARCOMA, METASTATIC             | 1 (2%)  |          |           |
| HEMATOPOIETIC SYSTEM                 |         |          |           |
| *MULTIPLE ORGANS                     | (50)    | (49)     | (49)      |
| MALIGNANT LYMPHOMA, NOS              | 2 (4%)  | 1 (2%)   | 1 (2%)    |
| MALIG. LYMPHOMA, LYMPHOCYTIC TYPE    | 1 (2%)  |          |           |
| MALIG. LYMPHOMA, HISTIOCYTIC TYPE    | 4 (8%)  | 2 (4%)   | 1 (2%)    |
| MAST-CELL LEUKEMIA                   |         |          | 1 (2%)    |
| *SUBCUT TISSUE                       | (50)    | (49)     | (49)      |
| MAST-CELL TUMOR                      |         |          | 1 (2%)    |
| #SPLEEN                              | (50)    | (49)     | (48)      |
| MALIGNANT LYMPHOMA, NOS              |         |          | 2 (4%)    |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

\* NUMBER OF ANIMALS NECROPSIED

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

|   | CONTROL         | LOW DOSE       | HIGH DOSE       |
|---|-----------------|----------------|-----------------|
| #LYMPH NODE<br>MALIG.LYMPHOMA, HISTIOCYTIC TYPE         | (37)<br>1 (3%)  | (39)           | (36)            |
| #MESENTERIC L. NODE<br>MALIG.LYMPHOMA, HISTIOCYTIC TYPE | (37)            | (39)<br>1 (3%) | (36)            |
| #PANCREAS<br>MALIGNANT LYMPHOMA, NOS                    | (50)            | (48)<br>1 (2%) | (47)            |
| #PEYER'S PATCH<br>MALIGNANT LYMPHOMA, NOS               | (47)            | (49)<br>1 (2%) | (46)            |
| CIRCULATORY SYSTEM                                      |                 |                |                 |
| #SPLEEN<br>HEMANGIOSARCOMA                              | (50)<br>1 (2%)  | (49)           | (48)            |
| #MESENTERIC L. NODE<br>ANGIOMA                          | (37)            | (39)<br>1 (3%) | (36)<br>1 (3%)  |
| #HEART<br>TUBULAR-CELL ADENOCARCINOMA, MET              | (50)            | (49)           | (49)<br>1 (2%)  |
| #LEFT VENTRICLE<br>ANGIOSARCOMA                         | (50)            | (49)           | (49)<br>1 (2%)  |
| #LIVER<br>ANGIOMA                                       | (50)            | (49)<br>1 (2%) | (49)<br>1 (2%)  |
| DIGESTIVE SYSTEM  |                 |                |                 |
| #LIVER<br>HEPATOCELLULAR ADENOMA                        | (50)<br>7 (14%) | (49)<br>1 (2%) | (49)<br>7 (14%) |
| HEPATOCELLULAR CARCINOMA                                | 14 (28%)        | 11 (22%)       | 12 (24%)        |
| #LIVER/KUPFFER CELL<br>SARCOMA, NOS                     | (50)            | (49)<br>1 (2%) | (49)            |
| URINARY SYSTEM  |                 |                |                 |
| #KIDNEY<br>ALVEOLAR/BRONCHIOULAR CA, METASTA            | (50)<br>1 (2%)  | (49)           | (49)            |

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

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

|  | CONTROL        | LOW DOSE       | HIGH DOSE      |
|--|----------------|----------------|----------------|
| TUBULAR-CELL ADENOCARCINOMA              |                |                | 1 (2%)         |
| #KIDNEY/CORTEX<br>TUBULAR-CELL ADENOMA   | (50)           | (49)           | (49)<br>1 (2%) |
| ENDOCRINE SYSTEM                         |                |                |                |
| #PITUITARY<br>CHROMOPHOBE CARCINOMA      | (43)<br>1 (2%) | (34)           | (32)           |
| #ADRENAL<br>PHEOCHROMOCYTOMA             | (50)<br>1 (2%) | (47)<br>2 (4%) | (47)<br>1 (2%) |
| #ADRENAL/CAPSULE<br>ADENOMA, NOS         | (50)<br>1 (2%) | (47)           | (47)           |
| #THYROID<br>FOLLICULAR-CELL ADENOMA      | (49)           | (48)           | (47)<br>1 (2%) |
| REPRODUCTIVE SYSTEM                      |                |                |                |
| NONE                                     |                |                |                |
| NERVOUS SYSTEM                           |                |                |                |
| NONE                                     |                |                |                |
| SPECIAL SENSE ORGANS                     |                |                |                |
| *EYE/LACRIMAL GLAND<br>PAPILLARY ADENOMA | (50)<br>2 (4%) | (49)<br>1 (2%) | (49)<br>3 (6%) |
| MUSCULOSKELETAL SYSTEM                   |                |                |                |
| NONE                                     |                |                |                |
| BODY CAVITIES                            |                |                |                |
| *MEDIASTINUM<br>FIBROSARCOMA, METASTATIC | (50)<br>1 (2%) | (49)           | (49)           |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

\* NUMBER OF ANIMALS NECROPSIED

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

|   | CONTROL | LOW DOSE | HIGH DOSE |
|---|---------|----------|-----------|
| ALL OTHER SYSTEMS   |         |          |           |
| NONE  |         |          |           |
| ANIMAL DISPOSITION SUMMARY  |         |          |           |
| ANIMALS INITIALLY IN STUDY  | 50      | 50       | 50        |
| NATURAL DEATH <sup>a</sup>  | 5       | 9        | 7         |
| MORIBUND SACRIFICE  | 2       | 2        |           |
| SCHEDULED SACRIFICE   |         |          |           |
| ACCIDENTALLY KILLED   |         |          |           |
| TERMINAL SACRIFICE  | 43      | 39       | 42        |
| ANIMAL MISSING  |         |          | 1         |
| <sup>a</sup> INCLUDES AUTOLYZED ANIMALS   |         |          |           |
| TUMOR SUMMARY   |         |          |           |
| TOTAL ANIMALS WITH PRIMARY TUMORS*  | 33      | 26       | 33        |
| TOTAL PRIMARY TUMORS  | 39      | 34       | 45        |
| TOTAL ANIMALS WITH BENIGN TUMORS  | 13      | 11       | 20        |
| TOTAL BENIGN TUMORS   | 13      | 13       | 24        |
| TOTAL ANIMALS WITH MALIGNANT TUMORS   | 23      | 18       | 20        |
| TOTAL MALIGNANT TUMORS  | 26      | 21       | 20        |
| TOTAL ANIMALS WITH SECONDARY TUMORS#  | 4       | 4        | 2         |
| TOTAL SECONDARY TUMORS  | 6       | 4        | 3         |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-<br>BENIGN OR MALIGNANT                     |         |          | 1         |
| TOTAL UNCERTAIN TUMORS  |         |          | 1         |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-<br>PRIMARY OR METASTATIC                   |         |          |           |
| TOTAL UNCERTAIN TUMORS  |         |          |           |
| * PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS                            |         |          |           |
| # SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN |         |          |           |



TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE FED  
DIETS CONTAINING C. I. DISPERSE YELLOW 3

|  | CONTROL | LOW DOSE | HIGH DOSE |
|--|---------|----------|-----------|
| ANIMALS INITIALLY IN STUDY                               | 50      | 50       | 50        |
| ANIMALS NECROPSIED                                       | 50      | 50       | 50        |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY                     | 50      | 50       | 50        |
| INTEGUMENTARY SYSTEM                                     |         |          |           |
| *SKIN  | (50)    | (50)     | (50)      |
| MALIGNANT MELANOMA                                       |         |          | 1 (2%)    |
| *SUBCUT TISSUE   | (50)    | (50)     | (50)      |
| SARCOMA, NOS   |         | 1 (2%)   |           |
| FIBROSARCOMA   | 1 (2%)  |          |           |
| RESPIRATORY SYSTEM                                       |         |          |           |
| *NASAL CAVITY  | (50)    | (50)     | (50)      |
| ADENOCARCINOMA, NOS, INVASIVE                            |         |          | 1 (2%)    |
| #LUNG  | (50)    | (50)     | (50)      |
| ADENOCARCINOMA, NOS, METASTATIC                          |         |          | 1 (2%)    |
| HEPATOCELLULAR CARCINOMA, METAST                         | 1 (2%)  |          | 1 (2%)    |
| ALVEOLAR/BRONCHIOLAR ADENOMA                             | 5 (10%) |          | 3 (6%)    |
| ALVEOLAR/BRONCHIOLAR CARCINOMA                           | 1 (2%)  |          | 1 (2%)    |
| HEMATOPOIETIC SYSTEM                                     |         |          |           |
| *MULTIPLE ORGANS   | (50)    | (50)     | (50)      |
| MALIGNANT LYMPHOMA, NOS                                  | 5 (10%) | 2 (4%)   | 3 (6%)    |
| MALIG. LYMPHOMA, LYMPHOCYTIC TYPE                        |         | 2 (4%)   | 1 (2%)    |
| MALIG. LYMPHOMA, HISTIOCYTIC TYPE                        | 4 (8%)  | 10 (20%) | 7 (14%)   |
| MALIGNANT LYMPHOMA, MIXED TYPE                           |         |          | 1 (2%)    |
| LYMPHOCYTIC LEUKEMIA                                     |         |          | 1 (2%)    |
| GRANULOCYTIC LEUKEMIA                                    |         | 1 (2%)   |           |
| #SPLEEN  | (50)    | (50)     | (49)      |
| MALIGNANT LYMPHOMA, NOS                                  | 1 (2%)  |          | 1 (2%)    |
| MALIG. LYMPHOMA, HISTIOCYTIC TYPE                        |         |          | 1 (2%)    |
| # NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY |         |          |           |
| * NUMBER OF ANIMALS NECROPSIED                           |         |          |           |

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

|  | CONTROL        | LOW DOSE       | HIGH DOSE      |
|--|----------------|----------------|----------------|
| #LYMPH NODE<br>MALIGNANT LYMPHOMA, NOS                   | (40)           | (43)           | (42)<br>2 (5%) |
| #SUBMANDIBULAR L.NODE<br>ADENOCARCINOMA, NOS, METASTATIC | (40)           | (43)           | (42)<br>1 (2%) |
| #PANCREATIC L.NODE<br>MALIG.LYMPHOMA, LYMPHOCYTIC TYPE   | (40)           | (43)           | (42)<br>1 (2%) |
| #MESENTERIC L. NODE<br>MALIG.LYMPHOMA, HISTIOCYTIC TYPE  | (40)           | (43)           | (42)<br>1 (2%) |
| #PANCREAS<br>MALIG.LYMPHOMA, HISTIOCYTIC TYPE            | (50)<br>1 (2%) | (47)           | (50)           |
| #PEYER'S PATCH<br>MALIGNANT LYMPHOMA, NOS                | (48)           | (46)<br>1 (2%) | (46)           |
| #UTERUS<br>MALIG.LYMPHOMA, HISTIOCYTIC TYPE              | (50)           | (50)<br>1 (2%) | (50)           |
| #THYMUS<br>MALIGNANT LYMPHOMA, NOS                       | (41)           | (43)           | (42)<br>1 (2%) |
| CIRCULATORY SYSTEM                                       |                |                |                |
| *SUBCUT TISSUE<br>ANGIOSARCOMA                           | (50)           | (50)           | (50)<br>1 (2%) |
| #SPLEEN<br>HEMANGIOMA<br>HEMANGIOSARCOMA                 | (50)           | (50)<br>1 (2%) | (49)<br>1 (2%) |
| #LUNG<br>ANGIOSARCOMA, METASTATIC                        | (50)           | (50)           | (50)<br>1 (2%) |
| #LIVER<br>ANGIOMA  | (50)           | (50)<br>1 (2%) | (50)<br>1 (2%) |
| #URINARY BLADDER<br>HEMANGIOMA                           | (50)           | (46)<br>1 (2%) | (49)           |
| #UTERUS<br>ANGIOMA                                       | (50)           | (50)<br>1 (2%) | (50)           |

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

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

|                                  | CONTROL | LOW DOSE       | HIGH DOSE |
|----------------------------------|---------|----------------|-----------|
| #OVARY<br>HEMANGIOMA             | (46)    | (48)<br>1 (2%) | (47)      |
| DIGESTIVE SYSTEM                 |         |                |           |
| #LIVER                           | (50)    | (50)           | (50)      |
| HEPATOCELLULAR ADENOMA           |         | 6 (12%)        | 12 (24%)  |
| HEPATOCELLULAR CARCINOMA         | 2 (4%)  | 4 (8%)         | 5 (10%)   |
| #STOMACH                         | (50)    | (48)           | (50)      |
| SQUAMOUS CELL PAPILOMA           |         | 1 (2%)         |           |
| #COLON                           | (49)    | (45)           | (48)      |
| LEIOMYOSARCOMA, INVASIVE         |         | 1 (2%)         |           |
| URINARY SYSTEM                   |         |                |           |
| NONE                             |         |                |           |
| ENDOCRINE SYSTEM                 |         |                |           |
| #PITUITARY                       | (38)    | (30)           | (42)      |
| CHROMOPHOBE ADENOMA              | 1 (3%)  | 1 (3%)         | 4 (10%)   |
| #ADRENAL                         | (46)    | (47)           | (49)      |
| HEPATOCELLULAR CARCINOMA, METAST | 1 (2%)  |                |           |
| #PANCREATIC ISLETS               | (50)    | (47)           | (50)      |
| ISLET-CELL ADENOMA               |         | 1 (2%)         |           |
| ISLET-CELL CARCINOMA             | 1 (2%)  |                |           |
| REPRODUCTIVE SYSTEM              |         |                |           |
| *MAMMARY GLAND                   | (50)    | (50)           | (50)      |
| ADENOCARCINOMA, NOS              |         |                | 1 (2%)    |
| *VAGINA                          | (50)    | (50)           | (50)      |
| SARCOMA, NOS                     |         |                | 1 (2%)    |
| #UTERUS                          | (50)    | (50)           | (50)      |
| SARCOMA, NOS                     |         | 1 (2%)         |           |

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

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

|                            | CONTROL | LOW DOSE | HIGH DOSE |
|----------------------------|---------|----------|-----------|
| LEIOMYOMA                  | 1 (2%)  |          | 1 (2%)    |
| LEIOMYOSARCOMA             |         | 1 (2%)   | 1 (2%)    |
| ENDOMETRIAL STROMAL POLYP  | 1 (2%)  |          | 1 (2%)    |
| #OVARY                     | (46)    | (48)     | (47)      |
| NEOPLASM, NOS              |         |          | 1 (2%)    |
| NERVOUS SYSTEM             |         |          |           |
| #CEREBRUM                  | (50)    | (49)     | (50)      |
| OLIGODENDROGLIOMA          |         | 1 (2%)   |           |
| SPECIAL SENSE ORGANS       |         |          |           |
| *EYE/LACRIMAL GLAND        | (50)    | (50)     | (50)      |
| ADENOMA, NOS               | 1 (2%)  |          |           |
| ADENOCARCINOMA, NOS        |         |          | 1 (2%)    |
| PAPILLARY ADENOMA          | 1 (2%)  | 3 (6%)   | 1 (2%)    |
| MUSCULOSKELETAL SYSTEM     |         |          |           |
| NONE                       |         |          |           |
| BODY CAVITIES              |         |          |           |
| NONE                       |         |          |           |
| ALL OTHER SYSTEMS          |         |          |           |
| *MULTIPLE ORGANS           | (50)    | (50)     | (50)      |
| FIBROSARCOMA, METASTATIC   | 1 (2%)  |          |           |
| ANIMAL DISPOSITION SUMMARY |         |          |           |
| ANIMALS INITIALLY IN STUDY | 50      | 50       | 50        |
| NATURAL DEATH <sup>a</sup> | 5       | 11       | 7         |
| MORIBUND SACRIFICE         | 1       |          | 1         |
| SCHEDULED SACRIFICE        |         |          |           |
| ACCIDENTALLY KILLED        |         |          |           |
| TERMINAL SACRIFICE         | 44      | 39       | 42        |
| ANIMAL MISSING             |         |          |           |

**a INCLUDES AUTOLYZED ANIMALS**

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

\* NUMBER OF ANIMALS NECROPSIED

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

|   | CONTROL | LOW DOSE | HIGH DOSE |
|---|---------|----------|-----------|
| TUMOR SUMMARY   |         |          |           |
| TOTAL ANIMALS WITH PRIMARY TUMORS*  | 20      | 33       | 36        |
| TOTAL PRIMARY TUMORS  | 26      | 42       | 57        |
| TOTAL ANIMALS WITH BENIGN TUMORS  | 9       | 13       | 17        |
| TOTAL BENIGN TUMORS   | 10      | 16       | 24        |
| TOTAL ANIMALS WITH MALIGNANT TUMORS   | 14      | 25       | 26        |
| TOTAL MALIGNANT TUMORS  | 16      | 26       | 32        |
| TOTAL ANIMALS WITH SECONDARY TUMORS#  | 2       | 1        | 3         |
| TOTAL SECONDARY TUMORS  | 3       | 1        | 5         |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-<br>BENIGN OR MALIGNANT                     |         |          | 1         |
| TOTAL UNCERTAIN TUMORS  |         |          | 1         |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-<br>PRIMARY OR METASTATIC                   |         |          |           |
| TOTAL UNCERTAIN TUMORS  |         |          |           |
| * PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS                            |         |          |           |
| # SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN |         |          |           |

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY TABLES OF MALE MICE IN THE 2-YEAR STUDY OF C.I. DISPERSE YELLOW 3

CONTROL

| ANIMAL NUMBER                                 | 0 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|---|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
|   | 0 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| WEEKS ON STUDY                                | 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | 0 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| INTEGUMENTARY SYSTEM                          |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| SUBCUTANEOUS TISSUE                           |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| LEIOMYOSARCOMA                                |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + N + |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| RESPIRATORY SYSTEM                            |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| LUNGS AND BRONCHI                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| HEPATOCELLULAR CARCINOMA, METASTA             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ALVEOLAR/BRONCHIOLAR ADENOMA                  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ALVEOLAR/BRONCHIOLAR CARCINOMA                |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| FIBROSARCOMA, METASTATIC                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| +     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| TRACHEA                                       |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| +     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| HEMATOPOIETIC SYSTEM                          |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| BONE MARROW                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + - +   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| SPLEEN  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| HEMANGIOSARCOMA                               |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| +     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| LYMPH NODES                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| MALIG. LYMPHOMA, HISTIOCYTIC TYPE             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + + + + + + - + + + + + + + + + + + - + + -   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| THYMUS  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + + + + - + - + + + - - + + + + - + + + - +   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CIRCULATORY SYSTEM                            |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| HEART   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| +     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| DIGESTIVE SYSTEM                              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| SALIVARY GLAND                                |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| +     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| LIVER   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| HEPATOCELLULAR ADENOMA                        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| HEPATOCELLULAR CARCINOMA                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| X X X X X X X X X X X X                       |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| BILE DUCT                                     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| +     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| GALLBLADDER & COMMON BILE DUCT                |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + + + + + N + N + + + + + + + + + + + + +     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| PANCREAS                                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| +     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ESOPHAGUS                                     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + + + + + - + + + + + + + + + + + + + + +     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| STOMACH                                       |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| +     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| SMALL INTESTINE                               |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + + + + + - + - + + + + + + + + - + + + +     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| LARGE INTESTINE                               |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| +     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| URINARY SYSTEM                                |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| KIDNEY  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ALVEOLAR/BRONCHIOLAR CA, METASTAT             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + + + + + + + + X + + + + + + + + + + + +     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| URINARY BLADDER                               |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + + + + + + + + + + + + + + + + - + + + + +   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ENDOCRINE SYSTEM                              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| PITUITARY                                     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CHROMOPHOBE CARCINOMA                         |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + + + + + + - + - + + + - + + + + - + + + - + |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ADRENAL                                       |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ADENOMA, NOS                                  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| PHEOCHROMOCYTOMA                              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + + + + + + + + + + + + X + + + + + + + +     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| THYROID                                       |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + + + + + - + + + + + + + + + + + + + + +     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| PARATHYROID                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + - - + + - + - - + - - - - + - + + - +       |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| REPRODUCTIVE SYSTEM                           |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| MAMMARY GLAND                                 |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| N     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| TESTIS  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| - +     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| PROSTATE                                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| +     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| SPECIAL SENSE ORGANS                          |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| LACRIMAL GLAND                                |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| PAPILLARY ADENOMA                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| N N N N N N N N N N N X N N N N N N N N N     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| BODY CAVITIES                                 |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| MEDIASTINUM                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| FIBROSARCOMA, METASTATIC                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| N N N N N N N N N N X N N N N N N N N N N     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ALL OTHER SYSTEMS                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| MULTIPLE ORGANS NOS                           |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| MALIGNANT LYMPHOMA, NOS                       |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| MALIG. LYMPHOMA, LYMPHOCTIC TYPE              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| MALIG. LYMPHOMA, HISTIOCYTIC TYPE             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| X     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

+ : TISSUE EXAMINED MICROSCOPICALLY  
- : REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY  
X : TUMOR INCIDENCE  
N : NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION  
: NO TISSUE INFORMATION SUBMITTED  
C : NECROPSY, NO HISTOLOGY DUE TO PROTOCOL  
A : AUTOLYSIS  
M : ANIMAL MISSING  
B : NO NECROPSY PERFORMED

### TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) CONTROL

| ANIMAL NUMBER  | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9  | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 | 61 | 62 | 63 | 64 | 65 | 66 | 67 | 68 | 69 | 70 | 71 | 72 | 73 | 74 | 75 | 76 | 77 | 78 | 79 | 80 | 81 | 82 | 83 | 84 | 85 | 86 | 87 | 88 | 89 | 90 | 91 | 92 | 93 | 94 | 95 | 96 | 97 | 98 | 99  | 100 |   |
|--|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|-----|-----|---|
| WEEKS ON STUDY   | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 59 | 60 | 61 | 62 | 63 | 64 | 65 | 66 | 67 | 68 | 69 | 70 | 71 | 72 | 73 | 74 | 75 | 76 | 77 | 78 | 79 | 80 | 81 | 82 | 83 | 84 | 85 | 86 | 87 | 88 | 89 | 90 | 91 | 92 | 93 | 94 | 95 | 96 | 97 | 98 | 99 | 100 |     |   |
| TOTAL TISSUES TUMORS   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |   |
| <b>INTEGUMENTARY SYSTEM</b>  |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |   |
| SUBCUTANEOUS TISSUE LEIOMYOSARCOMA   | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | N  |    |    |    |    |    |    |    |    |    | +  |    |    |    |     | 50  | 1 |
| <b>RESPIRATORY SYSTEM</b>  |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |   |
| LUNGS AND BRONCHI HEPATOCELLULAR CARCINOMA, METASTA ALVEOLAR/BRONCHIOLAR ADENOMA ALVEOLAR/BRONCHIOLAR CARCINOMA FIBROSARCOMA, METASTATIC | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | +  |    |    |    |    |    |    |    |    |    | X  |    |    |    |     | 50  | 3 |
| TRACHEA  | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | +  |    |    |    |    |    |    |    |    |    | -  |    |    |    |     | 49  |   |
| <b>HEMATOPOIETIC SYSTEM</b>  |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |   |
| BONE MARROW  | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     | 49  |   |
| SPLEEN HEMANGIOSARCOMA   | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | X  |    |    |    |    |    |    |    |    |    | +  |    |    |    |     | 50  | 1 |
| LYMPH NODES MALIG.LYMPHOMA, HISTIOCYTIC TYPE   | - |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | +  |    |    |    |    |    |    |    |    |    | -  |    |    |    |     | 37  | 1 |
| THYMUS   | - |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | +  |    |    |    |    |    |    |    |    |    | -  |    |    |    |     | 35  |   |
| <b>CIRCULATORY SYSTEM</b>  |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |   |
| HEART  | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     | 50  |   |
| <b>DIGESTIVE SYSTEM</b>  |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |   |
| SALIVARY GLAND   | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     | 50  |   |
| LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA  | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | X  |    |    |    |    |    |    |    |    |    | X  |    |    |    |     | 50  | 7 |
| BILE DUCT  | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     | 50  |   |
| GALLBLADDER & COMMON BILE DUCT   | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | N  |    |    |    |    |    |    |    |    |    | +  |    |    |    |     | 50  | * |
| PANCREAS   | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     | 50  |   |
| ESOPHAGUS  | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     | 49  |   |
| STOMACH  | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     | 50  |   |
| SMALL INTESTINE  | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     | 47  |   |
| LARGE INTESTINE  | - |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | +  |    |    |    |    |    |    |    |    |    | +  |    |    |    |     | 47  |   |
| <b>URINARY SYSTEM</b>  |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |   |
| KIDNEY ALVEOLAR/BRONCHIOLAR CA, METASTAT   | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     | 50  | 1 |
| URINARY BLADDER  | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | -  |    |    |    |    |    |    |    |    |    | +  |    |    |    |     | 48  |   |
| <b>ENDOCRINE SYSTEM</b>  |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |   |
| PITUITARY CHROMOPHOBE CARCINOMA  | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | -  |    |    |    |    |    |    |    |    |    | X  |    |    |    |     | 43  | 1 |
| ADRENAL ADENOMA, NOS PHEOCHROMOCYTOMA  | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | +  |    |    |    |    |    |    |    |    |    | X  |    |    |    |     | 50  | 1 |
| THYROID  | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     | 49  |   |
| PARATHYROID  | - |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     | 18  |   |
| <b>REPRODUCTIVE SYSTEM</b>   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |   |
| MAMMARY GLAND  | N |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     | 50  | * |
| TESTIS   | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     | 49  |   |
| PROSTATE   | + |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     | 50  |   |
| <b>SPECIAL SENSE ORGANS</b>  |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |   |
| LACRIMAL GLAND PAPILLARY ADENOMA   | N |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     | 50  | 2 |
| <b>BODY CAVITIES</b>   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |   |
| MEDIASTINUM FIBROSARCOMA, METASTATIC   | N |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     | 50  | 1 |
| <b>ALL OTHER SYSTEMS</b>   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     |     |   |
| MULTIPLE ORGANS NOS MALIGNANT LYMPHOMA, NOS MALIG.LYMPHOMA, LYMPHOCYTIC TYPE MALIG.LYMPHOMA, HISTIOCYTIC TYPE                            | N |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | X  |    |    |    |    |    |    |    |    |    | X  |    |    |    |     | 50  | 2 |
|  |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |     | 1   | 4 |

\* ANIMALS NECROPSIED  
 +: TISSUE EXAMINED MICROSCOPICALLY  
 -: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY  
 X: TUMOR INCIDENCE  
 N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION  
 : NO TISSUE INFORMATION SUBMITTED  
 C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL  
 A: AUTOLYSIS  
 M: ANIMAL MISSING  
 B: NO NECROPSY PERFORMED





**TABLE B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE**

| ANIMAL NUMBER                     | 0 | 0 | 0 | 0 | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | TOTAL TISSUES TUMORS |
|-----------------------------------|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----------------------|
| WEEKS ON STUDY                    | 1 | 1 | 1 | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 49                   |
| INTEGUMENTARY SYSTEM              | 5 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 49<br>2              |
| SKIN FIBROSARCOMA                 | + | + | A | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | N  | +  | +  | +  | +  | +  | +  | +  | +  | 49<br>1              |
| SUBCUTANEOUS TISSUE FIBROMA       | + | + | A | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | N  | +  | +  | +  | +  | +  | +  | +  | +  | 49<br>1              |
| RESPIRATORY SYSTEM                |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |
| LUNGS AND BRONCHI                 | + | + | A | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 49                   |
| HEPATOCELLULAR CARCINOMA, METASTA |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 3  |                      |
| ALVEOLAR/BRONCHIOLAR ADENOMA      |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 6  |                      |
| ALVEOLAR/BRONCHIOLAR CARCINOMA    |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 1  |                      |
| SARCOMA, NOS, METASTATIC          |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 1  |                      |
| TRACHEA                           | + | + | A | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 47                   |
| HEMATOPOIETIC SYSTEM              |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |
| BONE MARROW                       | + | + | A | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 48                   |
| SPLEEN                            | + | + | A | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 49                   |
| LYMPH NODES                       | + | + | A | + | -  | -  | +  | +  | +  | +  | +  | +  | +  | +  | +  | -  | +  | +  | +  | +  | +  | -  | +  | 39<br>1              |
| ANGIOMA                           |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 1  |                      |
| MALIG. LYMPHOMA, HISTIOCYTIC TYPE |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 1  |                      |
| THYMUS                            | - | - | A | + | -  | +  | +  | -  | +  | +  | -  | +  | +  | -  | +  | -  | +  | -  | +  | +  | -  | +  | -  | 29                   |
| CIRCULATORY SYSTEM                |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |
| HEART                             | + | + | A | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 49                   |
| DIGESTIVE SYSTEM                  |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |
| SALIVARY GLAND                    | + | + | A | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 49                   |
| LIVER                             | + | + | A | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 49                   |
| HEPATOCELLULAR ADENOMA            |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 1  |                      |
| HEPATOCELLULAR CARCINOMA          |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 11 |                      |
| SARCOMA, NOS                      |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 1  |                      |
| ANGIOMA                           |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 1  |                      |
| BILE DUCT                         | + | + | A | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 49                   |
| GALLBLADDER & COMMON BILE DUCT    | + | + | A | + | +  | +  | +  | +  | N  | +  | N  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 49<br>1              |
| PANCREAS                          | + | + | A | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | -  | +  | +  | +  | +  | +  | +  | +  | 48<br>1              |
| MALIGNANT LYMPHOMA, NOS           |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 1  |                      |
| ESOPHAGUS                         | + | + | A | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 49                   |
| STOMACH                           | + | + | A | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | -  | +  | +  | +  | +  | +  | +  | +  | +  | 47                   |
| SMALL INTESTINE                   | + | + | A | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 49                   |
| MALIGNANT LYMPHOMA, NOS           |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 1  |                      |
| LARGE INTESTINE                   | + | + | A | + | +  | -  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 44                   |
| URINARY SYSTEM                    |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |
| KIDNEY                            | + | + | A | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 49                   |
| URINARY BLADDER                   | + | + | A | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 49                   |
| ENDOCRINE SYSTEM                  |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |
| PITUITARY                         | - | + | A | + | -  | -  | +  | -  | -  | +  | -  | +  | -  | +  | -  | -  | +  | -  | -  | +  | +  | -  | +  | 35                   |
| ADRENAL                           | + | + | A | + | +  | +  | +  | +  | -  | +  | -  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 47                   |
| PHEOCHROMOCYTOMA                  |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 2  |                      |
| THYROID                           | + | + | A | + | +  | -  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 48                   |
| PARATHYROID                       | - | + | A | + | -  | -  | +  | -  | -  | -  | -  | +  | -  | +  | -  | -  | +  | -  | -  | +  | -  | -  | -  | 26                   |
| REPRODUCTIVE SYSTEM               |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |
| MAMMARY GLAND                     | N | N | A | N | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | 49<br>1              |
| TESTIS                            | + | + | A | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 49                   |
| PROSTATE                          | + | + | A | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 49                   |
| SPECIAL SENSE ORGANS              |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |
| LACRIMAL GLAND                    | N | N | A | N | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | 49<br>1              |
| PAPILLARY ADENOMA                 |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 1  |                      |
| ALL OTHER SYSTEMS                 |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |
| MULTIPLE ORGANS NOS               | N | N | A | N | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | 49<br>1              |
| MALIGNANT LYMPHOMA, NOS           |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 1  |                      |
| MALIG. LYMPHOMA, HISTIOCYTIC TYPE |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 2  |                      |

\* ANIMALS NECROPSIED  
 +: TISSUE EXAMINED MICROSCOPICALLY  
 -: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY  
 X: TUMOR INCIDENCE  
 N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION  
 : 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 TABLES OF MALE MICE IN THE 2-YEAR**  
**STUDY OF C.I. DISPERSE YELLOW 3**

**HIGH DOSE**

| ANIMAL NUMBER                     | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |   |   |
|-----------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY                    | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 |
| <b>INTEGUMENTARY SYSTEM</b>       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SUBCUTANEOUS TISSUE               | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + |
| LEIOMYOSARCOMA                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| MAST-CELL TUMOR                   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>RESPIRATORY SYSTEM</b>         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| LUNGS AND BRONCHI                 | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| NEOPLASM, NOS, METASTATIC         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| ALVEOLAR/BRONCHIOLAR ADENOMA      | X |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   | X |   |   |   | X | X |   |   |   |
| TUBULAR-CELL ADENOCARCINOMA, META |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| TRACHEA                           | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| <b>HEMATOPOIETIC SYSTEM</b>       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| BONE MARROW                       | + | + | + | + | + | + | + | + | M | + | + | + | - | - | + | + | + | + | + | + | - | + | + | + | + |
| SPLEEN                            | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| MALIGNANT LYMPHOMA, NOS           |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| LYMPH NODES                       | - | - | + | + | - | + | + | + | M | + | + | + | - | + | - | + | - | + | + | + | - | + | + | + | - |
| ANGIOMA                           |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| THYMUS                            | - | + | + | + | - | + | + | + | M | + | + | + | + | - | + | - | + | + | + | + | + | + | + | + | + |
| <b>CIRCULATORY SYSTEM</b>         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| HEART                             | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| TUBULAR-CELL ADENOCARCINOMA, META |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |
| ANGIOSARCOMA                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>DIGESTIVE SYSTEM</b>           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SALIVARY GLAND                    | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LIVER                             | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEPATOCELLULAR ADENOMA            |   |   |   |   |   | X |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |
| HEPATOCELLULAR CARCINOMA          |   |   |   |   |   |   |   |   |   |   | X | X | X |   |   |   |   |   |   |   |   | X |   |   |   |
| ANGIOMA                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| BILE DUCT                         | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| GALLBLADDER & COMMON BILE DUCT    | + | + | + | + | + | + | + | + | M | + | + | + | N | N | + | + | + | + | + | + | + | + | + | + | + |
| PANCREAS                          | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ESOPHAGUS                         | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - |
| STOMACH                           | + | + | + | + | + | + | + | + | M | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SMALL INTESTINE                   | + | + | + | + | + | + | + | + | M | - | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + |
| LARGE INTESTINE                   | + | + | + | + | + | + | + | + | M | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| <b>URINARY SYSTEM</b>             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| KIDNEY                            | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| TUBULAR-CELL ADENOMA              |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| TUBULAR-CELL ADENOCARCINOMA       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |
| URINARY BLADDER                   | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| <b>ENDOCRINE SYSTEM</b>           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| PITUITARY                         | + | - | - | - | + | - | + | - | M | - | + | + | + | - | - | + | + | + | + | + | + | + | + | - | + |
| ADRENAL                           | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| PHEOCHROMOCYTOMA                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |
| THYROID                           | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - |
| FOLLICULAR-CELL ADENOMA           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| PARATHYROID                       | - | - | + | - | + | + | + | + | M | - | + | + | + | - | + | - | - | + | - | + | + | + | + | - | + |
| <b>REPRODUCTIVE SYSTEM</b>        |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| MAMMARY GLAND                     | N | N | N | N | N | N | N | N | M | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| TESTIS                            | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| PROSTATE                          | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| <b>SPECIAL SENSE ORGANS</b>       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| LACRIMAL GLAND                    | N | N | N | N | N | N | N | N | M | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| PAPILLARY ADENOMA                 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |
| <b>ALL OTHER SYSTEMS</b>          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| MULTIPLE ORGANS NOS               | N | N | N | N | N | N | N | N | M | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| MALIGNANT LYMPHOMA, NOS           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| MALIG. LYMPHOMA, HISTIOCYTIC TYPE |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| MAST-CELL LEUKEMIA                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |

|   |    |  |
|---|----|--|
| +: TISSUE EXAMINED MICROSCOPICALLY                    | :  | NO TISSUE INFORMATION SUBMITTED        |
| -: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY       | C: | NECROPSY, NO HISTOLOGY DUE TO PROTOCOL |
| X: TUMOR INCIDENCE                                    | A: | AUTOLYSIS                              |
| N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION | M: | ANIMAL MISSING                         |
|   | B: | NO NECROPSY PERFORMED                  |



TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY TABLES OF FEMALE MICE IN THE 2-YEAR STUDY OF C.I. DISPERSE YELLOW 3

CONTROL

| ANIMAL NUMBER   | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 2 | 3 | 4 | 5 |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY  | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |   |   |   |   |   |   |   |
| <b>INTEGUMENTARY SYSTEM</b>   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SUBCUTANEOUS TISSUE FIBROSARCOMA  | + | N | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | N | + |   |   |   |   |   |
| <b>RESPIRATORY SYSTEM</b>   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| LUNGS AND BRONCHI   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |   |   |   |
| HEPATOCELLULAR CARCINOMA, METASTA   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |
| ALVEOLAR/BRONCHIOLAR ADENOMA  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| ALVEOLAR/BRONCHIOLAR CARCINOMA  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| TRACHEA   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |   |   |   |
| <b>HEMATOPOIETIC SYSTEM</b>   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| BONE MARROW   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + |   |   |   |
| SPLEEN MALIGNANT LYMPHOMA, NOS  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |   |   |
| LYMPH NODES   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |   |   |
| THYMUS  | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |   |   |
| <b>CIRCULATORY SYSTEM</b>   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| HEART   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |   |   |
| <b>DIGESTIVE SYSTEM</b>   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SALIVARY GLAND  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + |   |   |
| LIVER HEPATOCELLULAR CARCINOMA  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |   |
| BILE DUCT   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |   |
| GALLBLADDER & COMMON BILE DUCT  | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + |   |   |
| PANCREAS MALIGNANT LYMPHOMA, HISTIOCYTIC TYPE   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |   |
| ESOPHAGUS   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |   |
| STOMACH   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |   |
| SMALL INTESTINE   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + |   |
| LARGE INTESTINE   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + |
| <b>URINARY SYSTEM</b>   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| KIDNEY  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |
| URINARY BLADDER   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |
| <b>ENDOCRINE SYSTEM</b>   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| PITUITARY CHROMOPHOBE ADENOMA   | + | - | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |
| ADRENAL HEPATOCELLULAR CARCINOMA, METASTA   | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |
| THYROID   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |
| PARATHYROID   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |
| PANCREATIC ISLETS ISLET-CELL CARCINOMA  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |
| <b>REPRODUCTIVE SYSTEM</b>  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| MAMMARY GLAND   | + | N | N | + | + | + | + | + | N | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + |
| UTERUS LEIOMYOMA ENDOMETRIAL STROMAL POLYP  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| OVARY   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| <b>SPECIAL SENSE ORGANS</b>   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| LACRIMAL GLAND ADENOMA, NOS PAPILLARY ADENOMA   | 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 | N | N | N | N | N | N |   |
| <b>ALL OTHER SYSTEMS</b>  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| MULTIPLE ORGANS NOS FIBROSARCOMA, METASTATIC MALIGNANT LYMPHOMA, NOS MALIGNANT LYMPHOMA, HISTIOCYTIC TYPE | 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 | N | N | N | N | N | N |   |

+: TISSUE EXAMINED MICROSCOPICALLY  
 -: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY  
 X: TUMOR INCIDENCE  
 N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION  
 : 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 TABLES OF FEMALE MICE IN THE 2-YEAR STUDY OF C.I. DISPERSE YELLOW 3

HIGH DOSE

| ANIMAL NUMBER  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY   | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| <b>INTEGUMENTARY SYSTEM</b>  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SKIN MALIGNANT MELANOMA  | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SUBCUTANEOUS TISSUE ANGIOSARCOMA   | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| <b>RESPIRATORY SYSTEM</b>  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| LUNGS AND BRONCHI<br>ADENOCARCINOMA, NOS, METASTATIC<br>HEPATOCELLULAR CARCINOMA, METASTATIC<br>ALVEOLAR/BRONCHIOLAR ADENOMA<br>ALVEOLAR/BRONCHIOLAR CARCINOMA<br>ANGIOSARCOMA, METASTATIC | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| TRACHEA  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| NASAL CAVITY<br>ADENOCARCINOMA, NOS, INVASIVE  | 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 |
| <b>HEMATOPOIETIC SYSTEM</b>  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| BONE MARROW  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SPLEEN<br>HEMANGIOMA<br>MALIGNANT LYMPHOMA, NOS<br>MALIG. LYMPHOMA, HISTIOCYTIC TYPE   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LYMPH NODES<br>ADENOCARCINOMA, NOS, METASTATIC<br>MALIGNANT LYMPHOMA, NOS<br>MALIG. LYMPHOMA, LYMPHOCYTIC TYPE<br>MALIG. LYMPHOMA, HISTIOCYTIC TYPE  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| THYMUS<br>MALIGNANT LYMPHOMA, NOS  | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| <b>CIRCULATORY SYSTEM</b>  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| HEART  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| <b>DIGESTIVE SYSTEM</b>  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| SALIVARY GLAND   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LIVER<br>HEPATOCELLULAR ADENOMA<br>HEPATOCELLULAR CARCINOMA<br>ANGIOMA   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| BILE DUCT  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| GALLBLADDER & COMMON BILE DUCT   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| PANCREAS   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ESOPHAGUS  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| STOMACH  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SMALL INTESTINE  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LARGE INTESTINE  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| <b>URINARY SYSTEM</b>  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| KIDNEY   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| URINARY BLADDER  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| <b>ENDOCRINE SYSTEM</b>  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| PITUITARY<br>CHROMOPHOBE ADENOMA   | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ADRENAL  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| THYROID  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| PARATHYROID  | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| <b>REPRODUCTIVE SYSTEM</b>   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| MAMMARY GLAND<br>ADENOCARCINOMA, NOS   | + | N | + | + | + | N | N | + | + | + | N | + | N | + | + | N | N | + | N | + | N | + | N | + | + | + |
| VAGINA<br>SARCOMA, 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 |
| UTERUS<br>LEIOMYOMA<br>LEIOMYOSARCOMA<br>ENDOMETRIAL STROMAL POLYP   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| OVARY<br>NEOPLASM, NOS   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| <b>SPECIAL SENSE ORGANS</b>  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| LACRIMAL GLAND<br>ADENOCARCINOMA, NOS<br>PAPILLARY ADENOMA   | 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 |
| <b>ALL OTHER SYSTEMS</b>   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| MULTIPLE ORGANS NOS<br>MALIGNANT LYMPHOMA, NOS<br>MALIG. LYMPHOMA, LYMPHOCYTIC TYPE<br>MALIG. LYMPHOMA, HISTIOCYTIC TYPE<br>MALIGNANT LYMPHOMA, MIXED TYPE<br>LYMPHOCYTIC LEUKEMIA         | 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 |

+ : TISSUE EXAMINED MICROSCOPICALLY  
 - : REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY  
 X : TUMOR INCIDENCE  
 N : NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION  
 : NO TISSUE INFORMATION SUBMITTED  
 C : NECROPSY, NO HISTOLOGY DUE TO PROTOCOL  
 A : AUTOLYSIS  
 M : ANIMAL MISSING  
 B : NO NECROPSY PERFORMED







APPENDIX C

Summary of the Incidence of Nonneoplastic Lesions  
in Rats Fed Diets Containing C. I. Disperse Yellow 3



TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS  
FED DIETS CONTAINING C. I. DISPERSE YELLOW 3

|  | CONTROL | LOW DOSE | HIGH DOSE |
|--|---------|----------|-----------|
| ANIMALS INITIALLY IN STUDY                               | 50      | 50       | 50        |
| ANIMALS NECROPSIED                                       | 50      | 50       | 50        |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY                     | 50      | 50       | 50        |
| INTEGUMENTARY SYSTEM                                     |         |          |           |
| *SKIN  | (50)    | (50)     | (50)      |
| ULCER, NOS   | 1 (2%)  |          |           |
| RESPIRATORY SYSTEM                                       |         |          |           |
| #TRACHEA   | (48)    | (50)     | (49)      |
| INFLAMMATION, CHRONIC                                    |         |          | 1 (2%)    |
| #LUNG/BRONCHUS   | (50)    | (50)     | (50)      |
| INFLAMMATION, CHRONIC FOCAL                              |         |          | 1 (2%)    |
| #LUNG/BRONCHIOLE   | (50)    | (50)     | (50)      |
| HYPERPLASIA, NOS   | 2 (4%)  | 3 (6%)   |           |
| #LUNG  | (50)    | (50)     | (50)      |
| EDEMA, NOS   |         |          | 2 (4%)    |
| HEMORRHAGE   |         |          | 1 (2%)    |
| HEMORRHAGIC CYST   |         |          | 1 (2%)    |
| INFLAMMATION ACUTE AND CHRONIC                           |         | 1 (2%)   |           |
| PNEUMONIA INTERSTITIAL CHRONIC                           | 1 (2%)  |          | 2 (4%)    |
| INFLAMMATION, CHRONIC FOCAL                              |         |          | 1 (2%)    |
| INFLAMMATION, FOCAL GRANULOMATOUS                        |         |          | 3 (6%)    |
| HYPERPLASIA, ALVEOLAR EPITHELIUM                         | 2 (4%)  | 3 (6%)   |           |
| HISTIOCYTOSIS  | 1 (2%)  | 2 (4%)   |           |
| HEMATOPOIETIC SYSTEM                                     |         |          |           |
| #BONE MARROW   | (48)    | (50)     | (50)      |
| INFLAMMATION, CHRONIC                                    |         |          | 1 (2%)    |
| DEPLETION  |         | 1 (2%)   |           |
| HYPERPLASIA, HEMATOPOIETIC                               | 1 (2%)  |          |           |
| # NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY |         |          |           |
| * NUMBER OF ANIMALS NECROPSIED                           |         |          |           |

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

|  | CONTROL | LOW DOSE | HIGH DOSE        |
|--|---------|----------|------------------|
| HYPERPLASIA, RETICULUM CELL<br>HYPOPLASIA, HEMATOPOIETIC | 2 (4%)  |          | 1 (2%)<br>2 (4%) |
| #SPLEEN  | (50)    | (50)     | (50)             |
| FIBROSIS, FOCAL  | 2 (4%)  |          |                  |
| HEMOSIDEROSIS  | 1 (2%)  |          | 4 (8%)           |
| LYMPHOID DEPLETION                                       |         | 2 (4%)   |                  |
| LIPOMATOSIS  | 2 (4%)  |          |                  |
| #SPLENIC RED PULP  | (50)    | (50)     | (50)             |
| INFLAMMATION, CHRONIC DIFFUSE                            |         | 1 (2%)   |                  |
| FIBROSIS, FOCAL  | 1 (2%)  |          | 1 (2%)           |
| #MANDIBULAR L. NODE                                      | (47)    | (48)     | (45)             |
| INFLAMMATION, ACUTE                                      | 1 (2%)  |          |                  |
| LYMPHOID DEPLETION                                       |         |          | 1 (2%)           |
| PLASMACYTOSIS  | 1 (2%)  |          |                  |
| HYPERPLASIA, LYMPHOID                                    | 1 (2%)  |          |                  |
| #HEPATIC LYMPH NODE                                      | (47)    | (48)     | (45)             |
| EDEMA, NOS   |         |          | 1 (2%)           |
| #MESENTERIC L. NODE                                      | (47)    | (48)     | (45)             |
| HEMORRHAGE   | 1 (2%)  |          |                  |
| HEMOSIDEROSIS  |         | 1 (2%)   |                  |
| LYMPHOID DEPLETION                                       | 1 (2%)  |          | 4 (9%)           |
| #THYMUS  | (40)    | (45)     | (34)             |
| ATROPHY, DIFFUSE   | 1 (3%)  |          |                  |
| CIRCULATORY SYSTEM                                       |         |          |                  |
| #BRAIN   | (50)    | (50)     | (50)             |
| PERIVASCULITIS   |         | 1 (2%)   |                  |
| *THORAX  | (50)    | (50)     | (50)             |
| PERIARTERITIS  | 1 (2%)  |          |                  |
| *SUBCUT TISSUE   | (50)    | (50)     | (50)             |
| PERIARTERITIS  |         |          | 1 (2%)           |
| *MAMMARY GLAND   | (50)    | (50)     | (50)             |
| PERIVASCULITIS   |         |          | 1 (2%)           |
| #MANDIBULAR L. NODE                                      | (47)    | (48)     | (45)             |
| LYMPHANGIECTASIS   | 1 (2%)  | 1 (2%)   | 1 (2%)           |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

\* NUMBER OF ANIMALS NECROPSIED

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

|  | CONTROL          | LOW DOSE                   | HIGH DOSE                |
|--|------------------|----------------------------|--------------------------|
| #MESENTERIC L. NODE<br>LYMPHANGIECTASIS  | (47)<br>1 (2%)   | (48)<br>1 (2%)             | (45)<br>1 (2%)           |
| #LUNG<br>PERIVASCULITIS  | (50)             | (50)                       | (50)<br>1 (2%)           |
| *EPICARDIUM<br>PERIVASCULITIS  | (50)             | (50)                       | (50)<br>1 (2%)           |
| #HEART<br>PERIARTERITIS<br>DEGENERATION, NOS                                       | (50)<br>18 (36%) | (50)<br>1 (2%)<br>27 (54%) | (49)<br>29 (59%)         |
| #HEART/ATRIUM<br>THROMBOSIS, NOS   | (50)             | (50)<br>1 (2%)             | (49)                     |
| #LEFT ATRIUM<br>THROMBOSIS, NOS  | (50)<br>2 (4%)   | (50)<br>1 (2%)             | (49)<br>1 (2%)           |
| #MYOCARDIUM<br>INFLAMMATION, CHRONIC FOCAL<br>DEGENERATION, NOS<br>NECROSIS, FOCAL | (50)             | (50)<br>2 (4%)<br>1 (2%)   | (49)<br>2 (4%)<br>1 (2%) |
| #ENDOCARDIUM<br>INFLAMMATION, CHRONIC<br>INFLAMMATION, CHRONIC FOCAL               | (50)             | (50)<br>1 (2%)             | (49)<br>2 (4%)           |
| #CARDIAC VALVE<br>INFLAMMATION, CHRONIC  | (50)             | (50)<br>1 (2%)             | (49)<br>1 (2%)           |
| *ARTERY<br>PERIVASCULITIS  | (50)             | (50)                       | (50)<br>1 (2%)           |
| *PULMONARY ARTERY<br>ARTERIOSCLEROSIS, NOS   | (50)             | (50)<br>1 (2%)             | (50)                     |
| *TESTICULAR ARTERY<br>INFLAMMATION, CHRONIC NECROTIZIN                             | (50)             | (50)                       | (50)<br>1 (2%)           |
| #PANCREAS<br>PERIARTERITIS   | (48)             | (50)<br>5 (10%)            | (49)<br>1 (2%)           |
| *MESENTERY<br>PERIARTERITIS  | (50)<br>1 (2%)   | (50)                       | (50)                     |

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

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

|   | CONTROL  | LOW DOSE   | HIGH DOSE  |
|---|--|--|--|
| #KIDNEY<br>PERIARTERITIS  | (50)   | (50)   | (50)<br>1 (2%)   |
| <b>DIGESTIVE SYSTEM</b>   |  |  |  |
| *TONGUE<br>ACANTHOSIS   | (50)   | (50)<br>1 (2%)   | (50)   |
| #SALIVARY GLAND<br>CELL-SHAPE, ALTERATION<br>ATROPHY, FOCAL   | (46)   | (50)<br>1 (2%)   | (49)<br>1 (2%)<br>2 (4%)   |
| #LIVER<br>CONGESTION, CHRONIC PASSIVE<br>INFLAMMATION, ACUTE/CHRONIC<br>GRANULOMA, NOS<br>DEGENERATION, NOS<br>DEGENERATION, CYSTIC<br>NECROSIS, FOCAL<br>CYTOPLASMIC VACUOLIZATION<br>BASOPHILIC CYTO CHANGE<br>FOCAL CELLULAR CHANGE<br>ANGIECTASIS | (49)<br>1 (2%)<br><br><br><br>1 (2%)<br>26 (53%)<br>1 (2%) | (50)<br>1 (2%)<br><br>1 (2%)<br>1 (2%)<br>1 (2%)<br>2 (4%)<br>26 (52%)<br>4 (8%) | (50)<br><br><br><br><br>1 (2%)<br>3 (6%)<br>2 (4%)<br>25 (50%)<br>17 (34%)<br>2 (4%) |
| #HEPATIC CAPSULE<br>INFLAMMATION, CHRONIC   | (49)   | (50)<br>1 (2%)   | (50)   |
| #LIVER/CENTRILOBULAR<br>CONGESTION, NOS<br>CONGESTION, ACUTE PASSIVE<br>DEGENERATION, NOS<br>NECROSIS, NOS<br>NECROSIS, FOCAL<br>CYTOPLASMIC VACUOLIZATION  | (49)<br>1 (2%)<br><br><br>1 (2%)<br>2 (4%)                 | (50)<br><br><br>2 (4%)<br>1 (2%)<br>2 (4%)                                       | (50)<br><br><br>1 (2%)<br>1 (2%)<br>1 (2%)<br>1 (2%)                                 |
| #LIVER/PERIPORTAL<br>FIBROSIS, FOCAL  | (49)<br>1 (2%)   | (50)   | (50)   |
| #LIVER/HEPATOCTYES<br>NECROSIS, FOCAL   | (49)   | (50)   | (50)<br>2 (4%)   |
| #BILE DUCT<br>HYPERPLASIA, NOS  | (49)<br>10 (20%)   | (50)   | (50)<br>1 (2%)   |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

\* NUMBER OF ANIMALS NECROPSIED



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

|                           | CONTROL  | LOW DOSE | HIGH DOSE |
|---------------------------|----------|----------|-----------|
| HYPERPLASIA, FOCAL        | 4 (8%)   | 8 (16%)  | 1 (2%)    |
| #PANCREATIC ACINUS        | (48)     | (50)     | (49)      |
| ATROPHY, NOS              | 2 (4%)   | 2 (4%)   | 2 (4%)    |
| ATROPHY, FOCAL            | 6 (13%)  | 7 (14%)  | 12 (24%)  |
| #STOMACH                  | (49)     | (50)     | (50)      |
| ULCER, CHRONIC            | 1 (2%)   |          |           |
| #GASTRIC MUCOSA           | (49)     | (50)     | (50)      |
| MINERALIZATION            |          | 1 (2%)   |           |
| #GASTRIC SUBMUCOSA        | (49)     | (50)     | (50)      |
| EDEMA, NOS                | 1 (2%)   |          |           |
| #CARDIAC STOMACH          | (49)     | (50)     | (50)      |
| EDEMA, NOS                |          |          | 1 (2%)    |
| HYPERPLASIA, EPITHELIAL   |          | 1 (2%)   | 2 (4%)    |
| #GASTRIC FUNDUS           | (49)     | (50)     | (50)      |
| NECROSIS, FOCAL           | 1 (2%)   |          |           |
| #PYLORUS                  | (49)     | (50)     | (50)      |
| ECTOPIA                   |          |          | 1 (2%)    |
| #COLON                    | (49)     | (45)     | (47)      |
| NEMATODIASIS              | 2 (4%)   | 3 (7%)   | 1 (2%)    |
| URINARY SYSTEM            |          |          |           |
| #KIDNEY                   | (50)     | (50)     | (50)      |
| HYDRONEPHROSIS            |          |          | 1 (2%)    |
| CYST, NOS                 |          |          | 1 (2%)    |
| POLYCYSTIC KIDNEY         |          | 1 (2%)   |           |
| NEPHROPATHY               | 38 (76%) | 41 (82%) | 42 (84%)  |
| PIGMENTATION, NOS         |          | 1 (2%)   | 3 (6%)    |
| HYPERPLASIA, TUBULAR CELL |          | 1 (2%)   |           |
| #KIDNEY/CORTEX            | (50)     | (50)     | (50)      |
| CYST, NOS                 |          | 2 (4%)   | 2 (4%)    |
| PIGMENTATION, NOS         | 3 (6%)   |          |           |
| #KIDNEY/PELVIS            | (50)     | (50)     | (50)      |
| MINERALIZATION            | 1 (2%)   |          |           |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

\* NUMBER OF ANIMALS NECROPSIED

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

|                               | CONTROL | LOW DOSE | HIGH DOSE |
|-------------------------------|---------|----------|-----------|
| HYPERPLASIA, EPITHELIAL       |         | 4 (8%)   | 7 (14%)   |
| HYPERPLASIA, PAPILLARY        | 1 (2%)  | 1 (2%)   | 1 (2%)    |
| *URETER                       | (50)    | (50)     | (50)      |
| HYPERPLASIA, EPITHELIAL       |         |          | 1 (2%)    |
| #URINARY BLADDER              | (45)    | (50)     | (48)      |
| HEMORRHAGE                    | 1 (2%)  |          |           |
| HYPERPLASIA, EPITHELIAL       |         |          | 1 (2%)    |
| METAPLASIA, SQUAMOUS          |         |          | 1 (2%)    |
| #U. BLADDER/MUCOSA            | (45)    | (50)     | (48)      |
| NECROSIS, NOS                 | 1 (2%)  |          |           |
| POLYPOID HYPERPLASIA          |         |          | 1 (2%)    |
| ENDOCRINE SYSTEM              |         |          |           |
| #PITUITARY                    | (47)    | (49)     | (46)      |
| CYTOLOGIC DEGENERATION        | 1 (2%)  |          |           |
| HYPERPLASIA, CHROMOPHOBE-CELL | 3 (6%)  | 3 (6%)   | 4 (9%)    |
| #PITUITARY ACIDOPHIL          | (47)    | (49)     | (46)      |
| HYPERPLASIA, FOCAL            |         | 2 (4%)   |           |
| #ADRENAL                      | (50)    | (50)     | (49)      |
| NECROSIS, NOS                 |         |          | 1 (2%)    |
| HYPERPLASIA, NODULAR          |         |          | 2 (4%)    |
| #ADRENAL CORTEX               | (50)    | (50)     | (49)      |
| CYST, NOS                     |         |          | 1 (2%)    |
| LIPIDOSIS                     | 2 (4%)  |          | 5 (10%)   |
| HYPERPLASIA, NODULAR          | 2 (4%)  | 2 (4%)   | 6 (12%)   |
| HYPERPLASIA, FOCAL            | 5 (10%) |          |           |
| #ZONA FASCICULATA             | (50)    | (50)     | (49)      |
| HEMORRHAGE                    |         | 1 (2%)   |           |
| LIPIDOSIS                     |         | 1 (2%)   |           |
| HYPERTROPHY, NOS              |         |          | 1 (2%)    |
| HYPERPLASIA, NODULAR          | 1 (2%)  | 12 (24%) | 7 (14%)   |
| #ADRENAL MEDULLA              | (50)    | (50)     | (49)      |
| HYPERPLASIA, NOS              | 2 (4%)  | 1 (2%)   |           |
| HYPERPLASIA, FOCAL            | 1 (2%)  | 3 (6%)   | 4 (8%)    |
| ANGIECTASIS                   | 1 (2%)  |          |           |

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

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

|                                   | CONTROL  | LOW DOSE | HIGH DOSE |
|-----------------------------------|----------|----------|-----------|
| #THYROID                          | (49)     | (50)     | (48)      |
| THYROGLOSSAL DUCT CYST            |          | 2 (4%)   |           |
| COLLOID CYST                      |          | 3 (6%)   | 1 (2%)    |
| INFLAMMATION, FOCAL GRANULOMATOUS |          |          | 1 (2%)    |
| HYPERPLASIA, C-CELL               | 9 (18%)  | 9 (18%)  | 9 (19%)   |
| #PARATHYROID                      | (34)     | (43)     | (39)      |
| HYPERPLASIA, NOS                  |          | 2 (5%)   |           |
| HYPERPLASIA, FOCAL                | 1 (3%)   |          |           |
| #PANCREATIC ISLETS                | (48)     | (50)     | (49)      |
| HYPERPLASIA, NOS                  | 1 (2%)   |          | 2 (4%)    |
| HYPERPLASIA, FOCAL                |          |          | 3 (6%)    |
| REPRODUCTIVE SYSTEM               |          |          |           |
| *MAMMARY GLAND                    | (50)     | (50)     | (50)      |
| HYPERPLASIA, EPITHELIAL           |          | 5 (10%)  |           |
| HYPERPLASIA, CYSTIC               | 2 (4%)   | 2 (4%)   | 1 (2%)    |
| *MAMMARY ACINUS                   | (50)     | (50)     | (50)      |
| DILATATION, NOS                   | 1 (2%)   |          |           |
| CYST, NOS                         | 2 (4%)   |          |           |
| #PROSTATE                         | (45)     | (49)     | (49)      |
| INFLAMMATION, INTERSTITIAL        | 1 (2%)   |          |           |
| INFLAMMATION, ACUTE NECROTIZING   |          | 1 (2%)   |           |
| INFLAMMATION ACUTE AND CHRONIC    | 2 (4%)   | 2 (4%)   | 2 (4%)    |
| INFLAMMATION, CHRONIC             | 2 (4%)   | 1 (2%)   | 1 (2%)    |
| INFLAMMATION, CHRONIC FOCAL       | 1 (2%)   |          | 1 (2%)    |
| HYPERPLASIA, EPITHELIAL           | 1 (2%)   |          |           |
| HYPERPLASIA, CYSTIC               | 1 (2%)   |          |           |
| #TESTIS                           | (49)     | (49)     | (50)      |
| FIBROSIS, DIFFUSE                 |          | 1 (2%)   |           |
| ATROPHY, NOS                      | 32 (65%) | 40 (82%) | 36 (72%)  |
| ATROPHY, DIFFUSE                  | 7 (14%)  |          |           |
| HYPERPLASIA, INTERSTITIAL CELL    |          | 1 (2%)   | 1 (2%)    |
| NERVOUS SYSTEM                    |          |          |           |
| #BRAIN                            | (50)     | (50)     | (50)      |
| HYDROCEPHALUS, NOS                | 1 (2%)   |          |           |

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

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

|  | CONTROL | LOW DOSE | HIGH DOSE |
|--|---------|----------|-----------|
| HEMORRHAGE   | 1 (2%)  |          |           |
| NECROSIS, HEMORRHAGIC                                    | 1 (2%)  |          |           |
| ATROPHY, PRESSURE  | 2 (4%)  | 1 (2%)   |           |
| #HYPOTHALAMUS  | (50)    | (50)     | (50)      |
| ATROPHY, PRESSURE  | 2 (4%)  |          | 2 (4%)    |
| SPECIAL SENSE ORGANS                                     |         |          |           |
| *EYE   | (50)    | (50)     | (50)      |
| INFLAMMATION, ACUTE/CHRONIC                              |         |          | 1 (2%)    |
| MUSCULOSKELETAL SYSTEM                                   |         |          |           |
| *BONE  | (50)    | (50)     | (50)      |
| FIBROUS OSTEODYSTROPHY                                   |         | 1 (2%)   |           |
| HYPERPLASIA, NOS   |         |          | 1 (2%)    |
| BODY CAVITIES  |         |          |           |
| *ABDOMINAL CAVITY  | (50)    | (50)     | (50)      |
| NECROSIS, FAT  | 1 (2%)  |          |           |
| *MESENTERY   | (50)    | (50)     | (50)      |
| INFLAMMATION, GRANULOMATOUS                              | 1 (2%)  | 1 (2%)   | 1 (2%)    |
| INFLAMMATION, FOCAL GRANULOMATOU                         | 1 (2%)  | 1 (2%)   | 2 (4%)    |
| ALL OTHER SYSTEMS  |         |          |           |
| *MULTIPLE ORGANS   | (50)    | (50)     | (50)      |
| MINERALIZATION   |         | 1 (2%)   |           |
| ADIPOSE TISSUE   |         |          |           |
| INFLAMMATION, FOCAL GRANULOMATOU                         | 1       |          | 1         |
| CRANIOBUCCAL POUCH                                       |         |          |           |
| CYSTIC DUCTS   | 1       | 1        | 5         |
| SPECIAL MORPHOLOGY SUMMARY                               |         |          |           |
| AUTO/NECROPSY/HISTO PERF                                 |         |          | 1         |
| # NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY |         |          |           |
| * NUMBER OF ANIMALS NECROPSIED                           |         |          |           |

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS  
 FED DIETS CONTAINING C. I. DISPERSE YELLOW 3

|                                      | CONTROL | LOW DOSE | HIGH DOSE |
|--------------------------------------|---------|----------|-----------|
| ANIMALS INITIALLY IN STUDY           | 50      | 50       | 50        |
| ANIMALS NECROPSIED                   | 50      | 50       | 50        |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50      | 50       | 50        |
| INTEGUMENTARY SYSTEM                 |         |          |           |
| *SKIN                                | (50)    | (50)     | (50)      |
| EDEMA, NOS                           |         | 1 (2%)   |           |
| *SUBCUT TISSUE                       | (50)    | (50)     | (50)      |
| THYROGLOSSAL DUCT CYST               |         | 1 (2%)   |           |
| EDEMA, NOS                           | 2 (4%)  |          |           |
| RESPIRATORY SYSTEM                   |         |          |           |
| #LUNG                                | (49)    | (50)     | (50)      |
| EDEMA, NOS                           | 2 (4%)  |          |           |
| INFLAMMATION, INTERSTITIAL           | 1 (2%)  | 1 (2%)   |           |
| GRANULOMA, NOS                       | 1 (2%)  | 1 (2%)   | 1 (2%)    |
| INFLAMMATION, FOCAL GRANULOMATOUS    |         |          | 1 (2%)    |
| GRANULOMA, FOREIGN BODY              |         |          | 1 (2%)    |
| HEMOSIDEROSIS                        | 1 (2%)  | 1 (2%)   |           |
| HISTIOCYTOSIS                        |         |          | 4 (8%)    |
| HEMATOPOIETIC SYSTEM                 |         |          |           |
| #BONE MARROW                         | (49)    | (49)     | (50)      |
| HYPERPLASIA, HEMATOPOIETIC           | 1 (2%)  | 2 (4%)   |           |
| HYPERPLASIA, RETICULUM CELL          |         |          | 2 (4%)    |
| HYPOPLASIA, HEMATOPOIETIC            | 1 (2%)  |          |           |
| #SPLEEN                              | (48)    | (50)     | (50)      |
| CONGESTION, NOS                      |         |          | 1 (2%)    |
| PIGMENTATION, NOS                    |         | 1 (2%)   |           |
| HEMOSIDEROSIS                        | 1 (2%)  |          | 1 (2%)    |
| LYMPHOID DEPLETION                   |         |          | 2 (4%)    |
| HYPERPLASIA, RETICULUM CELL          | 1 (2%)  |          |           |

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

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

|                             | CONTROL  | LOW DOSE | HIGH DOSE |
|-----------------------------|----------|----------|-----------|
| HEMATOPOIESIS               | 2 (4%)   | 3 (6%)   |           |
| #MANDIBULAR L. NODE         | (48)     | (44)     | (44)      |
| HEMORRHAGE                  | 1 (2%)   | 1 (2%)   | 1 (2%)    |
| INFLAMMATION, ACUTE/CHRONIC | 1 (2%)   |          |           |
| GRANULOMA, NOS              |          |          | 1 (2%)    |
| HYPERPLASIA, LYMPHOID       | 1 (2%)   |          |           |
| #MESENTERIC L. NODE         | (48)     | (44)     | (44)      |
| HEMORRHAGE                  | 1 (2%)   | 1 (2%)   |           |
| GRANULOMA, NOS              | 1 (2%)   |          | 7 (16%)   |
| NECROSIS, DIFFUSE           | 1 (2%)   |          |           |
| HEMOSIDEROSIS               |          |          | 1 (2%)    |
| LYMPHOID DEPLETION          |          |          | 1 (2%)    |
| #LUNG                       | (49)     | (50)     | (50)      |
| HYPERPLASIA, LYMPHOID       |          |          | 3 (6%)    |
| #THYMUS                     | (37)     | (41)     | (42)      |
| HEMORRHAGE                  |          |          | 1 (2%)    |
| ATROPHY, DIFFUSE            | 1 (3%)   |          |           |
| #THYMIC CORTEX              | (37)     | (41)     | (42)      |
| HYPERPLASIA, LYMPHOID       | 1 (3%)   |          |           |
| -----                       |          |          |           |
| CIRCULATORY SYSTEM          |          |          |           |
| #MANDIBULAR L. NODE         | (48)     | (44)     | (44)      |
| LYMPHANGIECTASIS            | 1 (2%)   |          |           |
| #MESENTERIC L. NODE         | (48)     | (44)     | (44)      |
| LYMPHANGIECTASIS            | 1 (2%)   |          |           |
| #HEART                      | (50)     | (50)     | (49)      |
| THROMBOSIS, NOS             |          | 1 (2%)   |           |
| DEGENERATION, NOS           | 10 (20%) | 20 (40%) | 3 (6%)    |
| #HEART/ATRIUM               | (50)     | (50)     | (49)      |
| THROMBOSIS, NOS             | 1 (2%)   |          |           |
| #RIGHT ATRIUM               | (50)     | (50)     | (49)      |
| THROMBOSIS, NOS             | 1 (2%)   |          |           |
| #LEFT ATRIUM                | (50)     | (50)     | (49)      |
| THROMBOSIS, NOS             |          | 1 (2%)   |           |

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

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

|                                  | CONTROL  | LOW DOSE | HIGH DOSE |
|----------------------------------|----------|----------|-----------|
| THROMBUS, ORGANIZED              | 1 (2%)   |          |           |
| #MYOCARDIUM                      | (50)     | (50)     | (49)      |
| MINERALIZATION                   | 1 (2%)   |          |           |
| INFLAMMATION, CHRONIC FOCAL      | 2 (4%)   | 1 (2%)   | 1 (2%)    |
| #CARDIAC VALVE                   | (50)     | (50)     | (49)      |
| INFLAMMATION, CHRONIC            |          |          | 1 (2%)    |
| INFLAMMATION, CHRONIC FOCAL      |          | 1 (2%)   |           |
| *CORONARY ARTERY                 | (50)     | (50)     | (50)      |
| INFLAMMATION, CHRONIC            |          | 2 (4%)   | 1 (2%)    |
| DEGENERATION, NOS                |          | 1 (2%)   |           |
| *PULMONARY VEIN                  | (50)     | (50)     | (50)      |
| MINERALIZATION                   |          |          | 1 (2%)    |
| #LIVER                           | (50)     | (49)     | (50)      |
| THROMBOSIS, NOS                  | 1 (2%)   |          |           |
| *MESENTERY                       | (50)     | (50)     | (50)      |
| PERIARTERITIS                    |          |          | 1 (2%)    |
| DIGESTIVE SYSTEM                 |          |          |           |
| #SALIVARY GLAND                  | (49)     | (49)     | (47)      |
| EDEMA, NOS                       | 1 (2%)   |          |           |
| LYMPHOCYTIC INFLAMMATORY INFILTR | 1 (2%)   |          |           |
| ATROPHY, FOCAL                   |          | 1 (2%)   | 1 (2%)    |
| #LIVER                           | (50)     | (49)     | (50)      |
| MINERALIZATION                   |          | 1 (2%)   |           |
| CYST, NOS                        | 1 (2%)   |          |           |
| CONGESTION, CHRONIC PASSIVE      | 1 (2%)   | 1 (2%)   |           |
| INFLAMMATION, CHRONIC FOCAL      | 1 (2%)   | 2 (4%)   |           |
| GRANULOMA, NOS                   | 4 (8%)   | 4 (8%)   | 4 (8%)    |
| INFLAMMATION, FOCAL GRANULOMATOU | 1 (2%)   |          |           |
| DEGENERATION, NOS                | 1 (2%)   |          | 2 (4%)    |
| NECROSIS, FOCAL                  |          | 7 (14%)  |           |
| CYTOPLASMIC VACUOLIZATION        | 1 (2%)   |          | 2 (4%)    |
| BASOPHILIC CYTO CHANGE           | 30 (60%) | 40 (82%) | 38 (76%)  |
| FOCAL CELLULAR CHANGE            | 1 (2%)   | 1 (2%)   | 2 (4%)    |
| ANGIECTASIS                      |          | 1 (2%)   |           |
| #PORTAL TRACT                    | (50)     | (49)     | (50)      |
| INFLAMMATION, CHRONIC            |          |          | 1 (2%)    |

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

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

|   | CONTROL  | LOW DOSE   | HIGH DOSE   |
|---|--|--|---|
| INFLAMMATION, CHRONIC FOCAL   |  | 1 (2%)   |   |
| #LIVER/CENTRIOLOBULAR<br>CONGESTION, ACUTE<br>DEGENERATION, NOS<br>NECROSIS, NOS<br>NECROSIS, FOCAL<br>METAMORPHOSIS FATTY              | (50)<br>1 (2%)<br>2 (4%)<br>1 (2%)<br>1 (2%)<br>1 (2%) | (49)<br><br>1 (2%)                                     | (50)<br><br><br>1 (2%)                                  |
| #BILE DUCT<br>HYPERPLASIA, FOCAL<br>HYPERPLASIA, DIFFUSE  | (50)<br>4 (8%)<br>1 (2%)                               | (49)<br>1 (2%)   | (50)<br>1 (2%)  |
| #PANCREAS<br>INFLAMMATION, CHRONIC FOCAL  | (48)<br>1 (2%)   | (50)   | (50)  |
| #PANCREATIC ACINUS<br>NECROSIS, FOCAL<br>ATROPHY, NOS<br>ATROPHY, FOCAL<br>ATROPHY, DIFFUSE   | (48)<br><br>2 (4%)<br>3 (6%)                           | (50)<br><br>2 (4%)                                     | (50)<br>1 (2%)<br>4 (8%)<br>1 (2%)                      |
| #STOMACH<br>HYPERPLASIA, EPITHELIAL   | (49)<br>1 (2%)   | (49)   | (50)  |
| #COLON<br>NEMATODIASIS  | (49)<br>3 (6%)   | (49)<br>1 (2%)   | (47)  |
| URINARY SYSTEM  |  |  |   |
| #KIDNEY<br>MINERALIZATION<br>INFLAMMATION, INTERSTITIAL<br>NEPHROPATHY<br>INFARCT, FOCAL<br>PIGMENTATION, NOS<br>BASOPHILIC CYTO CHANGE | (50)<br>1 (2%)<br><br>3 (6%)<br>1 (2%)<br>1 (2%)       | (50)<br>1 (2%)<br>1 (2%)<br>4 (8%)<br>1 (2%)<br>1 (2%) | (50)<br>1 (2%)<br>2 (4%)<br>7 (14%)<br>2 (4%)<br>1 (2%) |
| #KIDNEY/CORTEX<br>CYST, NOS<br>PIGMENTATION, NOS  | (50)<br><br>   | (50)<br>1 (2%)<br>8 (16%)                              | (50)<br><br>34 (68%)                                    |
| #KIDNEY/TUBULE<br>PIGMENTATION, NOS   | (50)<br>2 (4%)   | (50)<br>1 (2%)   | (50)  |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

\* NUMBER OF ANIMALS NECROPSIED



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

|                                   | CONTROL  | LOW DOSE | HIGH DOSE |
|-----------------------------------|----------|----------|-----------|
| #KIDNEY/PELVIS                    | (50)     | (50)     | (50)      |
| MINERALIZATION                    | 2 (4%)   |          |           |
| INFLAMMATION, FOCAL GRANULOMATOUS |          |          | 1 (2%)    |
| HYPERPLASIA, EPITHELIAL           |          |          | 1 (2%)    |
| #URINARY BLADDER                  | (49)     | (48)     | (48)      |
| INFLAMMATION, ACUTE               | 1 (2%)   |          |           |
| ENDOCRINE SYSTEM                  |          |          |           |
| #PITUITARY                        | (44)     | (48)     | (49)      |
| CONGESTION, NOS                   |          |          | 1 (2%)    |
| HEMORRHAGE                        |          |          | 1 (2%)    |
| HYPERPLASIA, CHROMOPHOBE-CELL     | 9 (20%)  | 7 (15%)  | 8 (16%)   |
| ANGIECTASIS                       |          |          | 1 (2%)    |
| #ADRENAL                          | (50)     | (50)     | (50)      |
| ANGIECTASIS                       |          |          | 1 (2%)    |
| #ADRENAL CORTEX                   | (50)     | (50)     | (50)      |
| HEMORRHAGE                        | 1 (2%)   |          |           |
| NECROSIS, FOCAL                   |          | 1 (2%)   |           |
| LIPIDIDOSIS                       | 1 (2%)   | 1 (2%)   | 2 (4%)    |
| HYPERPLASIA, NODULAR              |          |          | 2 (4%)    |
| ANGIECTASIS                       |          | 2 (4%)   | 3 (6%)    |
| #ZONA FASCICULATA                 | (50)     | (50)     | (50)      |
| LIPIDIDOSIS                       | 4 (8%)   | 5 (10%)  | 2 (4%)    |
| BASOPHILIC CYTO CHANGE            |          |          | 1 (2%)    |
| HYPERPLASIA, NODULAR              | 15 (30%) | 11 (22%) | 9 (18%)   |
| HYPERPLASIA, FOCAL                |          |          | 1 (2%)    |
| ANGIECTASIS                       |          |          | 1 (2%)    |
| #ZONA RETICULARIS                 | (50)     | (50)     | (50)      |
| HYPERPLASIA, NODULAR              |          |          | 1 (2%)    |
| #ADRENAL MEDULLA                  | (50)     | (50)     | (50)      |
| HYPERPLASIA, NOS                  | 1 (2%)   | 1 (2%)   | 1 (2%)    |
| HYPERPLASIA, FOCAL                |          |          | 1 (2%)    |
| #THYROID                          | (49)     | (49)     | (50)      |
| COLLOID CYST                      | 1 (2%)   | 1 (2%)   | 2 (4%)    |
| HYPERPLASIA, C-CELL               | 10 (20%) | 12 (24%) | 10 (20%)  |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

\* NUMBER OF ANIMALS NECROPSIED

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

|                                | CONTROL        | LOW DOSE | HIGH DOSE |
|--------------------------------|----------------|----------|-----------|
| #PARATHYROID DEGENERATION, NOS | (37)<br>1 (3%) | (33)     | (39)      |
| REPRODUCTIVE SYSTEM            |                |          |           |
| *MAMMARY GLAND                 | (50)           | (50)     | (50)      |
| DILATATION/DUCTS               | 1 (2%)         |          |           |
| CYST, NOS                      | 2 (4%)         | 1 (2%)   |           |
| MULTIPLE CYSTS                 | 2 (4%)         | 1 (2%)   |           |
| FIBROSIS                       |                | 1 (2%)   |           |
| HYPERPLASIA, NODULAR           |                | 2 (4%)   | 3 (6%)    |
| HYPERPLASTIC NODULE            | 1 (2%)         |          |           |
| HYPERPLASIA, NOS               |                |          | 2 (4%)    |
| HYPERPLASIA, EPITHELIAL        |                |          | 1 (2%)    |
| HYPERPLASIA, CYSTIC            | 12 (24%)       | 12 (24%) | 5 (10%)   |
| ADENOSIS                       | 1 (2%)         |          |           |
| *MAMMARY ACINUS                | (50)           | (50)     | (50)      |
| CYST, NOS                      | 1 (2%)         |          |           |
| #UTERUS                        | (50)           | (48)     | (50)      |
| DILATATION, NOS                | 2 (4%)         | 2 (4%)   | 6 (12%)   |
| #CERVIX UTERI                  | (50)           | (48)     | (50)      |
| INFLAMMATION, CHRONIC FOCAL    |                | 1 (2%)   |           |
| HYPERPLASIA, STROMAL           |                | 1 (2%)   |           |
| #UTERUS/ENDOMETRIUM            | (50)           | (48)     | (50)      |
| FIBROSIS                       | 1 (2%)         |          |           |
| #ENDOMETRIAL GLAND             | (50)           | (48)     | (50)      |
| CYST, NOS                      | 1 (2%)         |          | 3 (6%)    |
| MULTIPLE CYSTS                 |                | 7 (15%)  | 1 (2%)    |
| INFLAMMATION, ACUTE FOCAL      | 1 (2%)         |          |           |
| HYPERPLASIA, NOS               |                | 1 (2%)   |           |
| HYPERPLASIA, EPITHELIAL        |                | 1 (2%)   |           |
| #OVARY                         | (50)           | (49)     | (50)      |
| CYST, NOS                      | 1 (2%)         |          |           |
| CORPUS LUTEUM CYST             | 1 (2%)         |          | 1 (2%)    |
| PAROVARIAN CYST                |                | 1 (2%)   |           |
| HYPERPLASIA, GRANULOSA-CELL    | 1 (2%)         |          |           |

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

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

|   | CONTROL        | LOW DOSE                                     | HIGH DOSE      |
|---|----------------|--|----------------|
| <b>NERVOUS SYSTEM</b>   |                |  |                |
| #BRAIN/MENINGES<br>INFLAMMATION, CHRONIC FOCAL  | (50)           | (50)<br>1 (2%)                               | (49)           |
| #BRAIN<br>NECROSIS, HEMORRHAGIC<br>ATROPHY, PRESSURE  | (50)           | (50)<br>1 (2%)                               | (49)<br>1 (2%) |
| #HYPOTHALAMUS<br>ATROPHY, PRESSURE  | (50)<br>2 (4%) | (50)<br>6 (12%)                              | (49)<br>2 (4%) |
| <b>SPECIAL SENSE ORGANS</b>   |                |  |                |
| *EYE/RETINA<br>ATROPHY, NOS   | (50)<br>2 (4%) | (50)   | (50)<br>4 (8%) |
| *EYE/CRYSTALLINE LENS<br>MINERALIZATION   | (50)<br>1 (2%) | (50)   | (50)<br>1 (2%) |
| *LENS CAPSULE<br>MINERALIZATION   | (50)           | (50)   | (50)<br>1 (2%) |
| <b>MUSCULOSKELETAL SYSTEM</b>   |                |  |                |
| NONE  |                |  |                |
| <b>BODY CAVITIES</b>  |                |  |                |
| *PERITONEUM<br>INFLAMMATION, FIBRINOUS  | (50)<br>1 (2%) | (50)   | (50)           |
| *MESENTERY<br>CYST, NOS<br>LYMPHOCYtic INFLAMMATORY INFILTR<br>INFLAMMATION, CHRONIC FOCAL<br>INFLAMMATION, FOCAL GRANULOMATOU<br>NECROSIS, FAT | (50)<br>2 (4%) | (50)<br>1 (2%)<br>1 (2%)<br>1 (2%)<br>1 (2%) | (50)           |
| <b>ALL OTHER SYSTEMS</b>  |                |  |                |
| *MULTIPLE ORGANS<br>INFLAMMATION, ACUTE/CHRONIC   | (50)<br>1 (2%) | (50)   | (50)           |

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

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

|  | <b>CONTROL</b> | <b>LOW DOSE</b> | <b>HIGH DOSE</b> |
|--|----------------|-----------------|------------------|
| TAIL<br>HYPERKERATOSIS                                   |                | 1               |                  |
| CRANIOBUCCAL POUCH<br>CYSTIC DUCTS                       |                | 3               |                  |
| SPECIAL MORPHOLOGY SUMMARY                               |                |                 |                  |
| AUTO/NECROPSY/HISTO PERF                                 | 1              |                 |                  |
| # NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY |                |                 |                  |
| * NUMBER OF ANIMALS NECROPSIED                           |                |                 |                  |

APPENDIX D

Summary of the Incidence of Nonneoplastic Lesions  
in Mice Fed Diets Containing C. I. Disperse Yellow 3



TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE  
FED DIETS CONTAINING C. I. DISPERSE YELLOW 3

|  | CONTROL  | LOW DOSE | HIGH DOSE |
|--|----------|----------|-----------|
| ANIMALS INITIALLY IN STUDY                               | 50       | 50       | 50        |
| ANIMALS MISSING  |          |          | 1         |
| ANIMALS NECROPSIED                                       | 50       | 49       | 49        |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY                     | 50       | 49       | 49        |
| INTEGUMENTARY SYSTEM                                     |          |          |           |
| *SKIN  | (50)     | (49)     | (49)      |
| ULCER, ACUTE   |          | 2 (4%)   |           |
| INFLAMMATION, ACUTE/CHRONIC                              |          | 1 (2%)   |           |
| INFLAMMATION, CHRONIC DIFFUSE                            |          |          | 1 (2%)    |
| FIBROSIS   | 1 (2%)   |          |           |
| FIBROSIS, FOCAL  | 2 (4%)   |          | 1 (2%)    |
| FIBROSIS, DIFFUSE  |          | 2 (4%)   |           |
| ACANTHOSIS   | 1 (2%)   |          |           |
| PARAKERATOSIS  | 1 (2%)   |          |           |
| *SUBCUT TISSUE   | (50)     | (49)     | (49)      |
| INFLAMMATION, ACUTE/CHRONIC                              | 1 (2%)   |          |           |
| INFLAMMATION, GRANULOMATOUS                              | 1 (2%)   |          |           |
| RESPIRATORY SYSTEM                                       |          |          |           |
| #LUNG/BRONCHIOLE   | (50)     | (49)     | (49)      |
| HYPERPLASIA, NOS   | 13 (26%) | 24 (49%) | 16 (33%)  |
| #LUNG  | (50)     | (49)     | (49)      |
| LYMPHOCYTIC INFLAMMATORY INFILTR                         |          |          | 1 (2%)    |
| INFLAMMATION, INTERSTITIAL                               | 5 (10%)  | 10 (20%) | 8 (16%)   |
| INFLAMMATION, FOCAL GRANULOMATOU                         |          | 2 (4%)   | 1 (2%)    |
| GRANULOMA, PYOGENIC                                      |          |          | 1 (2%)    |
| HYPERPLASIA, ALVEOLAR EPITHELIUM                         | 13 (26%) | 24 (49%) | 16 (33%)  |
| HISTIOCYTOSIS  | 2 (4%)   | 1 (2%)   | 1 (2%)    |
| HEMATOPOIETIC SYSTEM                                     |          |          |           |
| *MULTIPLE ORGANS   | (50)     | (49)     | (49)      |
| HYPERPLASIA, LYMPHOID                                    | 1 (2%)   | 1 (2%)   | 3 (6%)    |
| # NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY |          |          |           |
| * NUMBER OF ANIMALS NECROPSIED                           |          |          |           |

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

|                                  | CONTROL  | LOW DOSE | HIGH DOSE |
|----------------------------------|----------|----------|-----------|
| #BONE MARROW                     | (49)     | (48)     | (45)      |
| DEPLETION                        | 1 (2%)   | 1 (2%)   |           |
| ANGIECTASIS                      |          |          | 1 (2%)    |
| HYPERPLASIA, HEMATOPOIETIC       |          | 4 (8%)   |           |
| HYPERPLASIA, GRANULOCYTTIC       | 1 (2%)   |          | 2 (4%)    |
| #SPLEEN                          | (50)     | (49)     | (48)      |
| INFLAMMATION, FOCAL GRANULOMATOU |          | 1 (2%)   |           |
| LYMPHOID DEPLETION               | 1 (2%)   | 1 (2%)   |           |
| HYPERPLASIA, LYMPHOID            | 4 (8%)   | 1 (2%)   | 4 (8%)    |
| HEMATOPOIESIS                    |          | 2 (4%)   | 1 (2%)    |
| #SPLENIC RED PULP                | (50)     | (49)     | (48)      |
| HEMATOPOIESIS                    | 4 (8%)   | 5 (10%)  | 5 (10%)   |
| #MANDIBULAR L. NODE              | (37)     | (39)     | (36)      |
| HYPERPLASIA, LYMPHOID            |          |          | 2 (6%)    |
| #MESENTERIC L. NODE              | (37)     | (39)     | (36)      |
| HYPERPLASIA, LYMPHOID            |          |          | 1 (3%)    |
| HEMATOPOIESIS                    | 12 (32%) | 3 (8%)   | 3 (8%)    |
| #LUNG                            | (50)     | (49)     | (49)      |
| HYPERPLASIA, LYMPHOID            | 9 (18%)  | 3 (6%)   | 5 (10%)   |
| #SALIVARY GLAND                  | (50)     | (49)     | (49)      |
| HYPERPLASIA, LYMPHOID            | 8 (16%)  | 7 (14%)  | 4 (8%)    |
| #LIVER                           | (50)     | (49)     | (49)      |
| LEUKEMOID REACTION               | 1 (2%)   |          |           |
| HYPERPLASIA, LYMPHOID            | 1 (2%)   |          |           |
| HEMATOPOIESIS                    | 1 (2%)   | 2 (4%)   |           |
| *MUCOSA OF GALLBLADDE            | (50)     | (49)     | (49)      |
| HYPERPLASIA, LYMPHOID            |          | 1 (2%)   |           |
| #BILE DUCT                       | (50)     | (49)     | (49)      |
| HYPERPLASIA, LYMPHOID            | 1 (2%)   |          |           |
| #PEYER'S PATCH                   | (47)     | (49)     | (46)      |
| HYPERPLASIA, LYMPHOID            |          | 1 (2%)   | 3 (7%)    |
| #KIDNEY                          | (50)     | (49)     | (49)      |
| LEUKEMOID REACTION               | 1 (2%)   |          |           |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

\* NUMBER OF ANIMALS NECROPSIED



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

|  | CONTROL        | LOW DOSE        | HIGH DOSE       |
|--|----------------|-----------------|-----------------|
| HYPERPLASIA, LYMPHOID                          | 30 (60%)       | 28 (57%)        | 35 (71%)        |
| #U. BLADDER/SUBMUCOSA<br>HYPERPLASIA, LYMPHOID | (48)<br>4 (8%) | (49)<br>5 (10%) | (49)            |
| *URETHRA<br>HYPERPLASIA, LYMPHOID              | (50)           | (49)<br>1 (2%)  | (49)            |
| #THYMIC CORTEX<br>LYMPHOID DEPLETION           | (35)           | (29)<br>1 (3%)  | (38)<br>2 (5%)  |
| CIRCULATORY SYSTEM                             |                |                 |                 |
| #SPLEEN<br>THROMBOSIS, NOS                     | (50)           | (49)<br>1 (2%)  | (48)            |
| #MESENTERIC L. NODE<br>LYMPHANGIECTASIS        | (37)           | (39)<br>1 (3%)  | (36)<br>2 (6%)  |
| #LUNG<br>PERIVASCULITIS                        | (50)<br>1 (2%) | (49)<br>1 (2%)  | (49)            |
| #MYOCARDIUM<br>INFLAMMATION, CHRONIC FOCAL     | (50)           | (49)<br>1 (2%)  | (49)<br>1 (2%)  |
| #CARDIAC VALVE<br>HEMOSIDEROSIS                | (50)           | (49)<br>2 (4%)  | (49)<br>6 (12%) |
| *RENAL VEIN<br>CONGESTION, NOS                 | (50)           | (49)<br>1 (2%)  | (49)            |
| #U. BLADDER/SUBMUCOSA<br>PERIARTERITIS         | (48)           | (49)            | (49)<br>1 (2%)  |
| DIGESTIVE SYSTEM                               |                |                 |                 |
| #LIVER<br>HEMORRHAGIC CYST                     | (50)           | (49)            | (49)<br>1 (2%)  |
| INFLAMMATION, ACUTE/CHRONIC                    |                | 1 (2%)          | 1 (2%)          |
| INFLAMMATION, FOCAL GRANULOMATOUS              | 4 (8%)         | 1 (2%)          |                 |
| INFLAMMATION, PYOGRANULOMATOUS                 |                |                 | 1 (2%)          |
| NECROSIS, FOCAL                                | 1 (2%)         | 2 (4%)          |                 |
| NECROSIS, ISCHEMIC                             |                | 2 (4%)          | 2 (4%)          |

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

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

|   | CONTROL        | LOW DOSE       | HIGH DOSE      |
|---|----------------|----------------|----------------|
| BASOPHILIC CYTO CHANGE                                    | 1 (2%)         |                |                |
| FOCAL CELLULAR CHANGE                                     | 4 (8%)         |                | 4 (8%)         |
| ANGIECTASIS   |                | 1 (2%)         |                |
| #LIVER/CENTRIOLOBULAR<br>LYMPHOCYTIC INFLAMMATORY INFILTR | (50)<br>1 (2%) | (49)           | (49)           |
| *GALLBLADDER<br>INFLAMMATION, MULTIFOCAL                  | (50)           | (49)<br>1 (2%) | (49)           |
| INFLAMMATION, ACUTE                                       |                | 1 (2%)         |                |
| #BILE DUCT  | (50)           | (49)           | (49)           |
| DILATATION, NOS   | 1 (2%)         |                |                |
| CYST, NOS   |                |                | 2 (4%)         |
| HYPERPLASIA, NOS  |                | 1 (2%)         |                |
| HYPERPLASIA, CYSTIC                                       |                | 1 (2%)         |                |
| #PANCREAS   | (50)           | (48)           | (47)           |
| CYST, NOS   |                |                | 1 (2%)         |
| FIBROSIS, DIFFUSE   | 1 (2%)         |                |                |
| NECROSIS, NOS   | 1 (2%)         |                |                |
| #PANCREATIC ACINUS  | (50)           | (48)           | (47)           |
| ATROPHY, NOS  | 2 (4%)         |                | 1 (2%)         |
| ATROPHY, FOCAL  | 1 (2%)         |                |                |
| ATROPHY, DIFFUSE  | 1 (2%)         |                |                |
| #STOMACH  | (50)           | (47)           | (46)           |
| INFLAMMATION, ACUTE FOCAL                                 |                |                | 1 (2%)         |
| #GASTRIC FUNDAL GLAND<br>POLYP                            | (50)           | (47)           | (46)<br>1 (2%) |
| #GASTRIC SUBMUCOSA<br>INFLAMMATION, ACUTE FOCAL           | (50)           | (47)           | (46)<br>2 (4%) |
| #PEYER'S PATCH  | (47)           | (49)           | (46)           |
| HYPERPLASIA, NOS  | 1 (2%)         |                |                |
| #COLON  | (47)           | (44)           | (46)           |
| NEMATODIASIS  | 1 (2%)         |                |                |
| URINARY SYSTEM  |                |                |                |
| #KIDNEY   | (50)           | (49)           | (49)           |
| MINERALIZATION  |                | 1 (2%)         |                |

# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY

\* NUMBER OF ANIMALS NECROPSIED

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

|                               | CONTROL  | LOW DOSE | HIGH DOSE |
|-------------------------------|----------|----------|-----------|
| INFLAMMATION, INTERSTITIAL    | 1 (2%)   |          |           |
| NEPHROPATHY                   | 1 (2%)   |          | 2 (4%)    |
| NEPHROSIS, NOS                | 1 (2%)   | 3 (6%)   |           |
| METAPLASIA, OSSEOUS           |          | 1 (2%)   |           |
| #KIDNEY/CORTEX                | (50)     | (49)     | (49)      |
| INFLAMMATION, INTERSTITIAL    | 3 (6%)   |          | 1 (2%)    |
| NEPHROPATHY                   | 1 (2%)   |          | 3 (6%)    |
| NEPHROSIS, NOS                |          | 8 (16%)  |           |
| METAPLASIA, OSSEOUS           | 1 (2%)   |          |           |
| #KIDNEY/TUBULE                | (50)     | (49)     | (49)      |
| CYST, NOS                     | 2 (4%)   |          |           |
| NEPHROPATHY                   | 1 (2%)   |          |           |
| REGENERATION, NOS             | 18 (36%) | 27 (55%) | 30 (61%)  |
| #URETHRA                      | (50)     | (49)     | (49)      |
| ANGIECTASIS                   |          |          | 1 (2%)    |
| IDOCRINE SYSTEM               |          |          |           |
| #PITUITARY                    | (43)     | (34)     | (32)      |
| CYST, NOS                     | 1 (2%)   |          |           |
| HYPERPLASIA, CHROMOPHOBE-CELL |          | 1 (3%)   |           |
| #ADRENAL/CAPSULE              | (50)     | (47)     | (47)      |
| HYPERPLASIA, FOCAL            |          | 1 (2%)   |           |
| #ADRENAL CORTEX               | (50)     | (47)     | (47)      |
| CYST, NOS                     |          |          | 1 (2%)    |
| HEMORRHAGIC CYST              | 1 (2%)   |          |           |
| FOCAL CELLULAR CHANGE         |          |          | 2 (4%)    |
| HYPERPLASIA, NODULAR          |          |          | 1 (2%)    |
| THYROID                       | (49)     | (48)     | (47)      |
| FOLLICULAR CYST, NOS          | 1 (2%)   | 4 (8%)   | 2 (4%)    |
| THYROID FOLLICLE              | (49)     | (48)     | (47)      |
| DEGENERATION, NOS             |          | 1 (2%)   |           |
| DEGENERATION, CYSTIC          |          | 1 (2%)   |           |
| HYPERPLASIA, CYSTIC           |          | 1 (2%)   |           |
| PANCREATIC ISLETS             | (50)     | (48)     | (47)      |
| HYPERPLASIA, FOCAL            | 2 (4%)   |          |           |

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY  
NUMBER OF ANIMALS NECROPSIED

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

|   | CONTROL                  | LOW DOSE                 | HIGH DOSE        |
|---|--------------------------|--------------------------|------------------|
| <b>REPRODUCTIVE SYSTEM</b>  |                          |                          |                  |
| *PREPUTIAL GLAND<br>INFLAMMATION, GRANULOMATOUS<br>INFLAMMATION, PYOGRANULOMATOUS | (50)<br>1 (2%)           | (49)<br>1 (2%)           | (49)             |
| #TESTIS<br>MINERALIZATION<br>HYPERPLASIA, INTERSTITIAL CELL                       | (49)<br>1 (2%)           | (49)<br>1 (2%)           | (49)             |
| #TESTIS/TUBULE<br>MINERALIZATION<br>DEGENERATION, NOS                             | (49)<br>4 (8%)<br>1 (2%) | (49)<br>1 (2%)<br>2 (4%) | (49)<br>2 (4%)   |
| *EPIDIDYMIS<br>INFLAMMATION, ACUTE/CHRONIC<br>INFLAMMATION, FOCAL GRANULOMATOUS   | (50)<br>2 (4%)           | (49)                     | (49)<br>1 (2%)   |
| <b>NERVOUS SYSTEM</b>   |                          |                          |                  |
| #CEREBRUM<br>MINERALIZATION   | (50)<br>19 (38%)         | (48)<br>9 (19%)          | (48)<br>17 (35%) |
| #BRAIN<br>HEMORRHAGE<br>ATROPHY, PRESSURE   | (50)<br>1 (2%)           | (48)<br>1 (2%)           | (48)             |
| <b>SPECIAL SENSE ORGANS</b>   |                          |                          |                  |
| NONE  |                          |                          |                  |
| <b>MUSCULOSKELETAL SYSTEM</b>   |                          |                          |                  |
| NONE  |                          |                          |                  |
| <b>BODY CAVITIES</b>  |                          |                          |                  |
| *MEDIASTINUM<br>HEMORRHAGE  | (50)<br>1 (2%)           | (49)                     | (49)             |
| *MESENTERY<br>INFLAMMATION, FOCAL GRANULOMATOUS                                   | (50)                     | (49)                     | (49)<br>1 (2%)   |

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

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

|  | CONTROL | LOW DOSE | HIGH DOSE |
|--|---------|----------|-----------|
| ALL OTHER SYSTEMS  |         |          |           |
| NONE   |         |          |           |
| SPECIAL MORPHOLOGY SUMMARY                               |         |          |           |
| ANIMAL MISSING/NO NECROPSY                               |         |          | 1         |
| AUTO/NECROPSY/HISTO PERF                                 |         |          | 1         |
| AUTOLYSIS/NO NECROPSY                                    |         | 1        |           |
| # NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY |         |          |           |
| * NUMBER OF ANIMALS NECROPSIED                           |         |          |           |

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE  
 FED DIETS CONTAINING C. I. DISPERSE YELLOW 3

|                                      | CONTROL  | LOW DOSE | HIGH DOSE |
|--------------------------------------|----------|----------|-----------|
| ANIMALS INITIALLY IN STUDY           | 50       | 50       | 50        |
| ANIMALS NECROPSIED                   | 50       | 50       | 50        |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50       | 50       | 50        |
| INTEGUMENTARY SYSTEM                 |          |          |           |
| *SKIN                                | (50)     | (50)     | (50)      |
| HYPERPLASIA, FOCAL                   |          | 1 (2%)   |           |
| *SUBCUT TISSUE                       | (50)     | (50)     | (50)      |
| EPIDERMAL INCLUSION CYST             |          | 1 (2%)   |           |
| RESPIRATORY SYSTEM                   |          |          |           |
| #LUNG/BRONCHIOLE                     | (50)     | (50)     | (50)      |
| HYPERPLASIA, NOS                     | 1 (2%)   | 11 (22%) | 8 (16%)   |
| #LUNG                                | (50)     | (50)     | (50)      |
| CONGESTION, PASSIVE                  |          | 1 (2%)   |           |
| LYMPHOCYtic INFLAMMATORY INFILTR     | 1 (2%)   |          |           |
| INFLAMMATION, INTERSTITIAL           | 1 (2%)   | 3 (6%)   | 4 (8%)    |
| HYPERPLASIA, ALVEOLAR EPITHELIUM     | 1 (2%)   | 11 (22%) | 8 (16%)   |
| HISTIOCYTOSIS                        |          |          | 1 (2%)    |
| HEMATOPOIETIC SYSTEM                 |          |          |           |
| *MULTIPLE ORGANS                     | (50)     | (50)     | (50)      |
| HYPERPLASIA, LYMPHOID                | 13 (26%) | 10 (20%) | 10 (20%)  |
| #BONE MARROW                         | (49)     | (49)     | (48)      |
| HYPERPLASIA, GRANULOCYtic            | 4 (8%)   | 2 (4%)   | 2 (4%)    |
| HYPERPLASIA, RETICULUM CELL          | 2 (4%)   |          |           |
| #SPLEEN                              | (50)     | (50)     | (49)      |
| FIBROSIS, FOCAL                      |          |          | 1 (2%)    |
| LYMPHOID DEPLETION                   | 1 (2%)   |          |           |
| HYPERPLASIA, LYMPHOID                | 7 (14%)  | 2 (4%)   | 6 (12%)   |

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

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

|  | CONTROL                   | LOW DOSE                 | HIGH DOSE        |
|--|---------------------------|--------------------------|------------------|
| #SPLENIC RED PULP<br>HEMATOPOIESIS   | (50)<br>9 (18%)           | (50)<br>2 (4%)           | (49)<br>2 (4%)   |
| #LYMPH NODE<br>INFLAMMATION, GRANULOMATOUS   | (40)<br>1 (3%)            | (43)                     | (42)             |
| #PANCREATIC L.NODE<br>HYPERPLASIA, NOS   | (40)<br>1 (3%)            | (43)                     | (42)             |
| #MESENTERIC L. NODE<br>HEMATOPOIESIS   | (40)<br>1 (3%)            | (43)                     | (42)             |
| #LUNG<br>HYPERPLASIA, LYMPHOID   | (50)<br>3 (6%)            | (50)<br>13 (26%)         | (50)<br>11 (22%) |
| #SALIVARY GLAND<br>HYPERPLASIA, LYMPHOID   | (48)<br>2 (4%)            | (49)<br>7 (14%)          | (47)<br>3 (6%)   |
| #LIVER<br>HYPERPLASIA, LYMPHOID<br>HEMATOPOIESIS   | (50)<br>5 (10%)<br>2 (4%) | (50)                     | (50)<br>2 (4%)   |
| #PANCREAS<br>HYPERPLASIA, LYMPHOID   | (50)<br>2 (4%)            | (47)                     | (50)             |
| #KIDNEY<br>HYPERPLASIA, LYMPHOID   | (50)<br>22 (44%)          | (50)<br>20 (40%)         | (50)<br>26 (52%) |
| #URINARY BLADDER<br>HYPERPLASIA, LYMPHOID  | (50)<br>1 (2%)            | (46)                     | (49)             |
| #U.BLADDER/SUBMUCOSA<br>HYPERPLASIA, LYMPHOID  | (50)<br>17 (34%)          | (46)<br>14 (30%)         | (49)<br>18 (37%) |
| #THYMUS<br>HYPERPLASIA, EPITHELIAL<br>HYPERPLASIA, RETICULUM CELL<br>HYPERPLASIA, LYMPHOID | (41)<br><br>1 (2%)        | (43)<br>2 (5%)<br>1 (2%) | (42)             |
| #THYMIC CORTEX<br>ATROPHY, NOS   | (41)<br>1 (2%)            | (43)                     | (42)             |
| #THYMIC MEDULLA<br>HYPERPLASIA, FOCAL  | (41)                      | (43)<br>1 (2%)           | (42)             |

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

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

|   | CONTROL                   | LOW DOSE                 | HIGH DOSE                             |
|---|---------------------------|--------------------------|---------------------------------------|
| <b>CIRCULATORY SYSTEM</b>   |                           |                          |                                       |
| #LUNG<br>PERIVASCULITIS   | (50)<br>1 (2%)            | (50)<br>1 (2%)           | (50)                                  |
| #HEART<br>MINERALIZATION<br>PERIARTERITIS   | (50)                      | (50)<br>1 (2%)           | (50)<br>1 (2%)                        |
| #LEFT VENTRICLE<br>PERIARTERITIS  | (50)<br>1 (2%)            | (50)                     | (50)                                  |
| #MYOCARDIUM<br>INFLAMMATION, ACUTE/CHRONIC  | (50)                      | (50)<br>1 (2%)           | (50)                                  |
| #CARDIAC VALVE<br>HEMOSIDEROSIS   | (50)<br>4 (8%)            | (50)<br>4 (8%)           | (50)<br>3 (6%)                        |
| #KIDNEY/MEDULLA<br>PERIARTERITIS  | (50)                      | (50)                     | (50)<br>1 (2%)                        |
| #THYROID<br>PERIARTERITIS   | (50)<br>1 (2%)            | (49)                     | (49)                                  |
| <b>DIGESTIVE SYSTEM</b>   |                           |                          |                                       |
| #LIVER<br>INFLAMMATION, FOCAL GRANULOMATOUS<br>NECROSIS, FOCAL<br>FOCAL CELLULAR CHANGE | (50)<br>9 (18%)<br>1 (2%) | (50)<br>2 (4%)<br>2 (4%) | (50)<br>10 (20%)<br>2 (4%)<br>7 (14%) |
| #LIVER/CENTRIOLOBULAR<br>NECROSIS, FOCAL<br>CYTOPLASMIC VACUOLIZATION                   | (50)                      | (50)                     | (50)<br>1 (2%)<br>1 (2%)              |
| #LIVER/KUPFFER CELL<br>HYPERPLASIA, DIFFUSE   | (50)<br>1 (2%)            | (50)                     | (50)                                  |
| *GALLBLADDER<br>INFLAMMATION, ACUTE/CHRONIC   | (50)<br>1 (2%)            | (50)                     | (50)                                  |
| *MUCOSA OF GALLBLADDER<br>CYST, NOS   | (50)                      | (50)                     | (50)<br>1 (2%)                        |

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



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

|                             | CONTROL | LOW DOSE | HIGH DOSE |
|-----------------------------|---------|----------|-----------|
| #BILE DUCT                  | (50)    | (50)     | (50)      |
| DILATATION, NOS             | 1 (2%)  |          | 2 (4%)    |
| CYST, NOS                   |         |          | 2 (4%)    |
| #PANCREAS                   | (50)    | (47)     | (50)      |
| DILATATION/DUCTS            | 1 (2%)  | 2 (4%)   |           |
| CYSTIC DUCTS                | 1 (2%)  | 1 (2%)   |           |
| INFLAMMATION, NOS           | 1 (2%)  |          |           |
| INFLAMMATION, FOCAL         | 1 (2%)  |          |           |
| INFLAMMATION, ACUTE/CHRONIC | 1 (2%)  |          |           |
| NECROSIS, FOCAL             |         | 1 (2%)   |           |
| NECROSIS, FAT               | 1 (2%)  |          |           |
| #PANCREATIC ACINUS          | (50)    | (47)     | (50)      |
| ATROPHY, NOS                |         | 1 (2%)   | 1 (2%)    |
| ATROPHY, FOCAL              | 2 (4%)  | 1 (2%)   |           |
| ATROPHY, DIFFUSE            | 1 (2%)  | 1 (2%)   |           |
| #STOMACH                    | (50)    | (48)     | (50)      |
| INFLAMMATION, ACUTE FOCAL   | 1 (2%)  |          |           |
| #PEYER'S PATCH              | (48)    | (46)     | (46)      |
| ULCER, NOS                  | 1 (2%)  |          |           |
| FIBROSIS                    | 1 (2%)  |          |           |
| #ILEUM                      | (48)    | (46)     | (46)      |
| INFLAMMATION, NECROTIZING   | 1 (2%)  |          |           |
| #COLON                      | (49)    | (45)     | (48)      |
| NEMATODIASIS                | 1 (2%)  | 5 (11%)  |           |
| <b>URINARY SYSTEM</b>       |         |          |           |
| #KIDNEY                     | (50)    | (50)     | (50)      |
| HYDRONEPHROSIS              | 1 (2%)  | 1 (2%)   |           |
| NEPHROSIS, NOS              | 3 (6%)  | 1 (2%)   |           |
| #KIDNEY/CORTEX              | (50)    | (50)     | (50)      |
| NEPHROSIS, NOS              | 1 (2%)  |          |           |
| #KIDNEY/GLOMERULUS          | (50)    | (50)     | (50)      |
| NEPHROSIS, NOS              |         |          | 1 (2%)    |
| #KIDNEY/TUBULE              | (50)    | (50)     | (50)      |
| DEGENERATION, NOS           |         | 1 (2%)   |           |

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

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

|   | CONTROL                  | LOW DOSE           | HIGH DOSE                 |
|---|--------------------------|--------------------|---------------------------|
| DEGENERATION, HYALINE<br>HEMOSIDEROSIS<br>REGENERATION, NOS                                 | 1 (2%)<br>11 (22%)       | 1 (2%)<br>13 (26%) | 1 (2%)<br>18 (36%)        |
| #URINARY BLADDER<br>INFLAMMATION, CHRONIC SUPPURATIV<br>HYPERPLASIA, EPITHELIAL             | (50)<br>1 (2%)           | (46)               | (49)<br>1 (2%)            |
| <b>ENDOCRINE SYSTEM</b>   |                          |                    |                           |
| #PITUITARY<br>HYPERPLASIA, CHROMOPHOBE-CELL   | (38)<br>4 (11%)          | (30)               | (42)                      |
| #ADRENAL<br>METAMORPHOSIS FATTY   | (46)                     | (47)               | (49)<br>1 (2%)            |
| #ADRENAL CORTEX<br>CYST, NOS  | (46)                     | (47)<br>1 (2%)     | (49)                      |
| #ADRENAL MEDULLA<br>HYPERPLASIA, NOS<br>HYPERPLASIA, FOCAL                                  | (46)<br>3 (7%)<br>1 (2%) | (47)               | (49)                      |
| #THYROID<br>CYSTIC FOLLICLES<br>FOLLICULAR CYST, NOS<br>HYPERPLASIA, FOLLICULAR-CELL        | (50)<br>4 (8%)<br>1 (2%) | (49)<br>6 (12%)    | (49)<br>1 (2%)<br>5 (10%) |
| #THYROID FOLLICLE<br>MULTILOCLAR CYST<br>DEGENERATION, NOS                                  | (50)<br>1 (2%)<br>1 (2%) | (49)<br>1 (2%)     | (49)                      |
| <b>REPRODUCTIVE SYSTEM</b>  |                          |                    |                           |
| #UTERUS<br>DILATATION, NOS<br>ANGIECTASIS   | (50)<br>1 (2%)<br>3 (6%) | (50)<br>1 (2%)     | (50)<br>4 (8%)<br>1 (2%)  |
| #UTERUS/ENDOMETRIUM<br>HEMORRHAGE<br>INFLAMMATION, SUPPURATIVE<br>CYTOPLASMIC VACUOLIZATION | (50)<br>1 (2%)           | (50)<br>1 (2%)     | (50)<br>1 (2%)            |
| #ENDOMETRIAL GLAND<br>CYST, NOS   | (50)<br>1 (2%)           | (50)               | (50)<br>1 (2%)            |

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

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

|   | CONTROL            | LOW DOSE           | HIGH DOSE |
|---|--------------------|--------------------|-----------|
| HYPERPLASIA, CYSTIC<br>METAPLASIA, SQUAMOUS | 41 (82%)<br>1 (2%) | 43 (86%)<br>2 (4%) | 40 (80%)  |
| #OVARY                                      | (46)               | (48)               | (47)      |
| CYST, NOS                                   | 7 (15%)            | 9 (19%)            | 7 (15%)   |
| FOLLICULAR CYST, NOS                        |                    |                    | 1 (2%)    |
| CORPUS HEMORRHAGICUM CYST                   |                    | 1 (2%)             |           |
| MULTIPLE CYSTS                              | 1 (2%)             |                    |           |
| PAROVARIAN CYST                             | 1 (2%)             |                    |           |
| HEMORRHAGIC CYST                            |                    |                    | 1 (2%)    |
| HYPERPLASIA, PAPILLARY                      | 1 (2%)             |                    |           |
| HYPERPLASIA, STROMAL                        | 1 (2%)             |                    |           |
| NERVOUS SYSTEM                              |                    |                    |           |
| #CEREBRUM                                   | (50)               | (49)               | (50)      |
| MINERALIZATION                              | 25 (50%)           | 11 (22%)           | 15 (30%)  |
| #BRAIN                                      | (50)               | (49)               | (50)      |
| INFLAMMATION, NOS                           | 1 (2%)             |                    |           |
| PERIVASCULAR CUFFING                        |                    | 1 (2%)             |           |
| SPECIAL SENSE ORGANS                        |                    |                    |           |
| NONE  |                    |                    |           |
| MUSCULOSKELETAL SYSTEM                      |                    |                    |           |
| NONE  |                    |                    |           |
| BODY CAVITIES                               |                    |                    |           |
| *EPICARDIUM                                 | (50)               | (50)               | (50)      |
| INFLAMMATION, ACUTE/CHRONIC                 | 1 (2%)             |                    |           |
| *MESENTERY                                  | (50)               | (50)               | (50)      |
| INFLAMMATION, FOCAL GRANULOMATOU            | 1 (2%)             |                    |           |
| NECROSIS, FAT                               | 1 (2%)             |                    |           |
| ALL OTHER SYSTEMS                           |                    |                    |           |
| CRANIOBUCCAL POUCH                          |                    |                    |           |
| CYST, NOS                                   |                    |                    | 1         |

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

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

|  | <b>CONTROL</b> | <b>LOW DOSE</b> | <b>HIGH DOSE</b> |
|--|----------------|-----------------|------------------|
| SPECIAL MORPHOLOGY SUMMARY                               |                |                 |                  |
| NONE   |                |                 |                  |
| # NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY |                |                 |                  |
| * NUMBER OF ANIMALS NECROPSIED                           |                |                 |                  |

APPENDIX E

Analysis of C. I. Disperse Yellow 3

(Lot No. 19-007630)

Midwest Research Institute



## Appendix E

### Analysis of C. I. Disperse Yellow 3 (Lot No. 19-007630)

Midwest Research Institute

#### A. ELEMENTAL ANALYSIS

| Element    | C              | H            | N              | Cl <sup>-</sup> | CO <sub>3</sub> <sup>=</sup> |
|------------|----------------|--------------|----------------|-----------------|------------------------------|
| Theory     | 66.90          | 5.61         | 15.60          | 0.0             | 0.0                          |
| Determined | 59.57<br>59.31 | 6.10<br>5.98 | 13.48<br>13.50 | 3.58<br>3.36    | 0.65<br>0.66                 |

#### B. WATER ANALYSIS

(Karl Fisher)

6.62 ± 0.02(δ)%

#### C. TITRATION

TiCl<sub>3</sub> reduction of azo group

87.6 ± 1.1 (δ)% (4 electrons per mole)

#### D. MELTING POINT

##### Determined

m.p. Endotherms at 57° to 65°C,  
67° to 81°C, 91° to 99°C,  
99° to 106°C, 127° to 148°C,  
170° to 180°C, 185° to 191°C;  
exotherm at 180° to 185°C  
(Dupont 900 DTA)  
m.p. 192° to 193.5°C (decomposition  
visual, capillary)

##### Literature Values

m.p. 195°C (Patterson and  
Sheldon, 1960)

#### E. THIN-LAYER CHROMATOGRAPHY

Plates: Silica Gel 60F-254  
Amount spotted: 100 and 300 μg  
Ref. standard: Methyl Red  
Visualization: UV (254 and 366 nm)

System 1: 2-Propanol

R<sub>f</sub>: 0.85 (trace)  
0.74 (major)  
0.028 (slight trace)  
Origin (trace)  
R<sub>st</sub>: 1.89, 1.64, 0.062,  
and origin

System 2: Chloroform

R<sub>f</sub>: 0.85 (trace)  
0.52 (slight trace)  
0.21 (slight trace)  
0.11 (major)  
R<sub>st</sub>: Origin (minor)  
9.34, 5.71, 2.31,  
1.21 and origin

F. HIGH PRESSURE-LIQUID CHROMATOGRAPHY

Instrument: Waters ALC202  
Detector: Ultraviolet, 254 nm  
Column: C<sup>18</sup>  $\mu$ Bondapak (300 x 4 mm ID)  
Solvent: Methanol:water (70:30) with 0.005 M tetrabutylammonium hydroxide and 1% acetic acid  
Flow: 1.5 ml/min  
Results: Major peak, one multicomponent impurity peak and two single impurity peaks

| <u>Peak 3</u>          | <u>Retention Time (min)</u> | <u>Retention Time Relative to C. I. Disperse Yellow 3</u> | <u>Area Relative to C. I. Disperse Yellow 3</u> |
|------------------------|-----------------------------|---|---|
| minor (multicomponent) | 2.5-4.4                     | 0.32-0.57   | 2.15  |
| minor                  | 6.2                         | 0.81  | 0.28  |
| major                  | 7.7                         | 1.00  | 100.00  |
| minor                  | 13.5                        | 1.75  | 0.28  |

G. SPECTRAL DATA

(1) Infrared

Instrument: Beckman IR 12  
Cell: 1% KBr pellet  
Results: See Figure 5.

Literature Values

Identical to literature spectrum  
(Sadtler Standard Spectra)

(2) Ultraviolet/Visible

Instrument: Cary 118



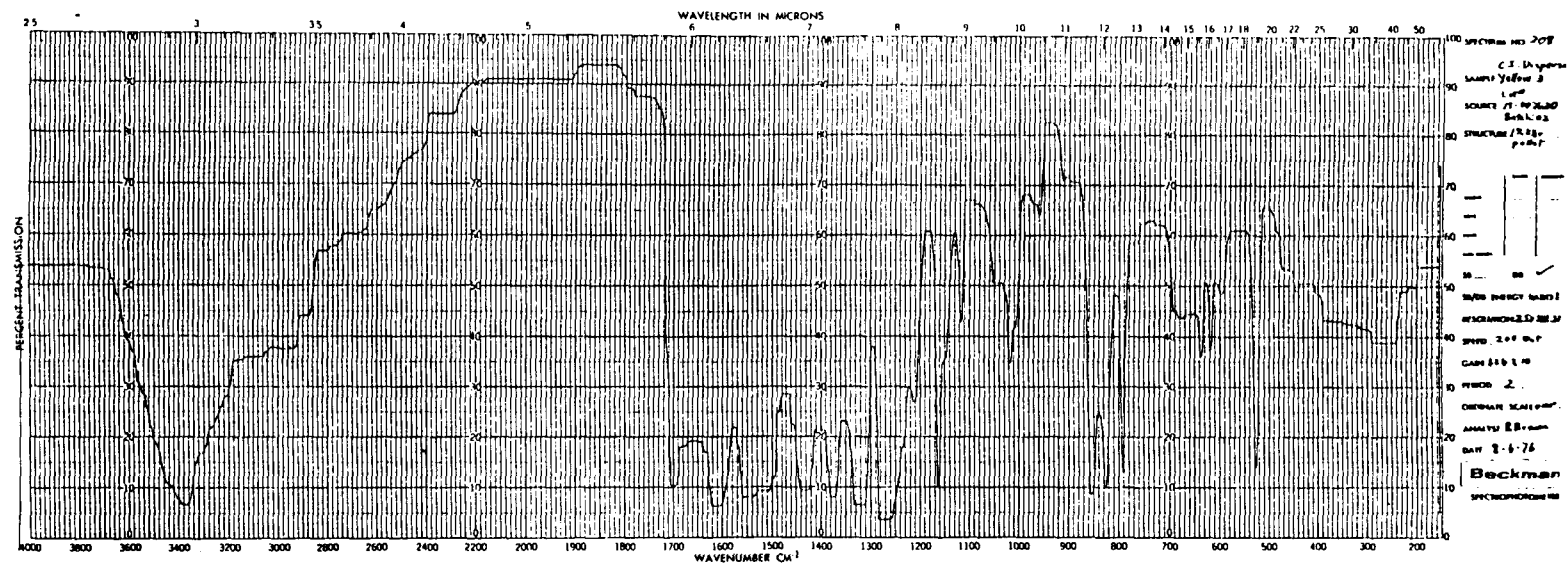


Figure 5. Infrared Absorption Spectrum of C. I. Disperse Yellow 3 (Lot No. 19-007630)

| <u><math>\lambda_{\max}</math> (nm)</u> | <u><math>\epsilon \times 10^{-2}</math></u> | <u><math>\lambda_{\max}</math> (nm)</u> | <u><math>\epsilon \times 10^{-2}</math></u> |
|---|---|---|---|
| 392                                     | 120.7 $\pm$ 0.6 ( $\delta$ )                |   |   |
| 345                                     | 169 $\pm$ 2 ( $\delta$ )                    | 360                                     | 188.50                                      |
| 249                                     | 102 $\pm$ 2 ( $\delta$ )                    |   | (Patterson and Sheldon, 1960)               |

Solvent: Methanol:  
concentrated sulfuric acid (95:5)

Solvent: 50% aqueous acetone

Determined

Literature Values

(3) Nuclear magnetic resonance

No literature reference found

Unable to obtain adequate solvent

APPENDIX F

Analysis of Formulated Diets for Stability  
of C. I. Disperse Yellow 3



## Appendix F

### Analysis of Formulated Diets For Stability of C. I. Disperse Yellow 3

#### HEAT STABILITY

##### 1. Mixing and Storage

C. I. Disperse Yellow 3 (2.500 g) and Wayne Lab Blox<sup>®</sup> Rodent Feed (22.500 g) were mixed in a mortar. Samples of the mixture were removed and stored for 2 weeks at -20°, 5°, 25°, and 45°C, respectively. These samples were then analyzed by high-pressure liquid chromatography as described below.

##### 2. Extraction

One-gram samples of each of the above stability mixtures were mixed with 50 ml of 75% aqueous methanol in an ultrasonic vibratory bath for 1 minute and then were triturated for 1 minute using a Polytron<sup>®</sup> high-speed blender. The mixture was centrifuged, and the supernatant solution was decanted into a 100-ml volumetric flask. This extraction was repeated on the feed residue, and the combined supernatant solutions were brought to volume with fresh 75% aqueous methanol.

##### 3. Analysis

Instrument: Waters ALC 202 with Model 660 Solvent Programmer

Column: C<sup>18</sup>μ Bondapak, 300 x 4 mm I.D.

Solvent: 25% A + 75% B

A - 0.005M tetrabutylammonium hydroxide and 1% acetic acid in water

B - 0.005M tetrabutylammonium hydroxide and 1% acetic acid in methanol

Detector: Ultraviolet, 254 nm

Flow rate: 1.5 ml/min

| Sample (°C) | Average Percentage<br>Compound (a) |
|-------------|------------------------------------|
| -20         | 9.9+0.6                            |
| 5           | 10.4+0.6                           |
| 25          | 9.0+0.6 (b)                        |
| 45          | 8.8+0.6 (b)                        |

(a) Corrected for a spiked recovery value of 95.2%; theoretical 100% value = 10.0%

(b) Within experimental error.

4. Conclusion

C. I. Disperse Yellow 3 mixed with feed is stable for 2 weeks at temperatures up to 45°C.

APPENDIX G

Analysis of Formulated Diets for Concentrations of

C. I. Disperse Yellow 3





## Appendix G

### Analysis of Formulated Diets for Concentrations of C. I. Disperse Yellow 3

1. For the first 18 months, samples (100 mg) of the formulated diets were extracted with 20 ml of a 1:1 acetone:water mixture. The absorbance of the extract at 473 nm was then measured in a spectrophotometer. The results of these analyses are summarized in the following table.
  2. For the final 6 months, samples (1g) of the formulated diets were extracted twice with 50 ml acidic methanol. The combined extract (100 ml) was then diluted five-fold with solvent and the absorbance at 390 nm was measured on a spectrophotometer. This second extraction method was found to give a lower feed blank absorbance value (0.062) than that obtained from the aqueous acetone extraction (0.520).
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Table G1. Analyses of Formulated Diets

| Date Mixed (a)               | Date Used               | Concentration (b) of<br>C. I. Disperse Yellow 3 in feed<br>for target concentration of |           |            |
|------------------------------|-------------------------|--|-----------|------------|
|                              |                         | 2,500 ppm  | 5,000 ppm | 10,000 ppm |
| 3/10/77                      | week of 3/14 and 3/20   |  | 5,070     | 10,750     |
| 4/17/77                      | week of 4/21 and 4/27   | 2,680  | 5,100     |            |
| 6/03/77                      | week of 6/7 and 6/13    | 2,500  | 5,260     | 9,500      |
|                              |                         |  | 5,260     | 10,010     |
| 8/24/77                      | week of 8/28 and 9/2    | 2,450  | 4,980     | 10,600     |
|                              |                         |  | 4,990     | 9,900      |
| 10/21/77                     | week of 10/24 and 10/31 | 2,530  | 4,980     | 10,400     |
|                              |                         |  | 4,740     | 10,100     |
| 1/28/78                      | week of 1/31 and 2/7    | 2,360  | 4,980     | 9,820      |
|                              |                         |  | 5,050     | 9,220      |
| 4/07/78                      | week of 4/10 and 4/17   | 2,495  | 5,010     | 10,100     |
|                              |                         |  | 4,980     | 9,980      |
| 6/21/78                      | week of 6/24 and 6/31   | 2,510  | 5,030     | 10,180     |
|                              |                         |  | 4,970     | 10,230     |
|                              |                         |  | 4,950     |            |
| 7/06/78                      | week of 7/9 and 7/16    | 2,700  | 5,000     | 9,890      |
|                              |                         |  | 5,010     | 10,800     |
|                              |                         |  | 4,800     |            |
| 9/13/78                      | week of 9/15 and 9/23   | 2,310  | 4,660     | 9,510      |
|                              |                         |  | 4,720     | 9,880      |
|                              |                         |  | 4,970     |            |
| 11/14/78                     | week of 11/17 and 11/24 | 2,480  | 5,220     | 10,100     |
|                              |                         |  | 5,040     | 9,990      |
|                              |                         |  | 4,930     |            |
| 1/22/79                      | week of 1/24 and 1/31   | 2,720  | 5,300     | 10,500     |
|                              |                         |  | 5,310     | 10,200     |
|                              |                         |  | 5,290     |            |
| 3/12/79                      | week of 3/15 and 3/22   | 2,490  | 5,180     |            |
| Mean (ppm)                   |                         | 2,519  | 5,028     | 10,079     |
| Standard deviation           |                         | 127  | 172       | 398        |
| Coefficient of Variation (%) |                         | 5  | 3         | 4          |
| Number of Samples            |                         | 12   | 28        | 21         |
| Range (ppm)                  |                         | 2,310-   | 4,660-    | 9,220-     |
|                              |                         | 2,720  | 5,310     | 10,800     |

(a) The start dates for male and for female rats were 3/10/77 and 3/23/77.

The start dates for male and for female mice were 4/8/77 and 4/13/77.

(b) The data presented are the average of duplicate analyses.

Appendix H

Feed Consumption by Rats and Mice Fed C. I. Disperse Yellow 3



Table H1. Feed Consumption by Male Rats Receiving C. I. Disperse Yellow 3

| Week   | Control                   | Low                       |                        | High                      |                         |
|--------|---------------------------|---------------------------|------------------------|---------------------------|-------------------------|
|        | GRAMS<br>FEED/<br>DAY (a) | GRAMS<br>FEED/<br>DAY (a) | LOW/<br>CONTROL<br>(b) | GRAMS<br>FEED/<br>DAY (a) | HIGH/<br>CONTROL<br>(b) |
| 5      | 19.3                      | 18.6                      | 1.0                    | 17.3                      | 0.9                     |
| 10     | 17.6                      | 17.1                      | 1.0                    | 17.7                      | 1.0                     |
| 14     | 19.1                      | 17.5                      | 0.9                    | 19.0                      | 1.0                     |
| 18     | 20.0                      | 17.9                      | 0.9                    | 21.3                      | 1.1                     |
| 22     | 18.7                      | 18.1                      | 1.0                    | 18.3                      | 1.0                     |
| 26     | 20.1                      | 19.6                      | 1.0                    | 18.9                      | 0.9                     |
| 30     | 19.7                      | 20.0                      | 1.0                    | 19.0                      | 1.0                     |
| 36     | 21.7                      | 19.4                      | 0.9                    | 20.9                      | 1.0                     |
| 41     | 18.0                      | 20.0                      | 1.1                    | 20.9                      | 1.2                     |
| 46     | 24.1                      | 22.1                      | 0.9                    | 26.1                      | 1.1                     |
| 50     | 22.6                      | 20.7                      | 0.9                    | 21.1                      | 0.9                     |
| 54     | 21.3                      | 19.7                      | 0.9                    | 23.0                      | 1.1                     |
| 58     | 22.9                      | 23.9                      | 1.0                    | 23.6                      | 1.0                     |
| 62     | 21.1                      | 18.4                      | 0.9                    | 20.3                      | 1.0                     |
| 67     | 27.4                      | 23.9                      | 0.9                    | 26.7                      | 1.0                     |
| 70     | 22.4                      | 25.9                      | 1.2                    | 25.0                      | 1.1                     |
| 75     | 19.3                      | 19.9                      | 1.0                    | 25.9                      | 1.3                     |
| 81     | 20.0                      | 18.1                      | 0.9                    | 18.1                      | 0.9                     |
| 84     | 22.4                      | 22.4                      | 1.0                    | 23.9                      | 1.1                     |
| 88     | 22.9                      | 22.6                      | 1.0                    | 24.4                      | 1.1                     |
| 92     | 18.7                      | 20.1                      | 1.1                    | 23.7                      | 1.3                     |
| 97     | 18.4                      | 18.7                      | 1.0                    | 15.3                      | 0.8                     |
| 101    | 19.7                      | 19.1                      | 1.0                    | 18.0                      | 0.9                     |
| Mean   | 20.8                      | 20.2                      | 1.0                    | 21.2                      | 1.0                     |
| SD (c) | 2.3                       | 2.3                       | 0.1                    | 3.2                       | 0.1                     |
| CV (d) | 11.1                      | 11.4                      | 10.0                   | 15.1                      | 10.0                    |

(a) Grams of feed consumed per animal per day.

(b) Ratio of feed consumed per day for the dosed group to that for the controls.

(c) Standard Deviation

(d) (Standard Deviation/Mean) x 100.

Table H2. Feed Consumption by Female Rats Receiving C. I. Disperse Yellow 3

| Week   | Control                   | Low                       |                        | High                      |                         |
|--------|---------------------------|---------------------------|------------------------|---------------------------|-------------------------|
|        | GRAMS<br>FEED/<br>DAY (a) | GRAMS<br>FEED/<br>DAY (a) | LOW/<br>CONTROL<br>(b) | GRAMS<br>FEED/<br>DAY (a) | HIGH/<br>CONTROL<br>(b) |
| 3      | 13.9                      | 15.7                      | 1.1                    | 12.3                      | 0.9                     |
| 8      | 9.0                       | 13.3                      | 1.5                    | 8.0                       | 0.9                     |
| 12     | 13.7                      | 11.6                      | 0.8                    | 11.9                      | 0.9                     |
| 16     | 14.0                      | 12.6                      | 0.9                    | 13.9                      | 1.0                     |
| 20     | 14.3                      | 13.3                      | 0.9                    | 13.3                      | 0.9                     |
| 24     | 13.4                      | 11.9                      | 0.9                    | 14.0                      | 1.0                     |
| 28     | 14.4                      | 14.9                      | 1.0                    | 15.6                      | 1.0                     |
| 34     | 13.0                      | 14.1                      | 1.1                    | 14.0                      | 1.1                     |
| 39     | 12.0                      | 12.6                      | 1.1                    | 13.9                      | 1.2                     |
| 44     | 20.6                      | 19.3                      | 0.9                    | 21.0                      | 1.0                     |
| 48     | 12.0                      | 11.7                      | 1.0                    | 13.6                      | 1.1                     |
| 52     | 15.1                      | 15.7                      | 1.0                    | 16.0                      | 1.1                     |
| 56     | 19.3                      | 20.1                      | 1.0                    | 21.6                      | 1.1                     |
| 60     | 14.1                      | 13.6                      | 1.0                    | 14.3                      | 1.0                     |
| 65     | 21.3                      | 16.4                      | 0.8                    | 19.0                      | 0.9                     |
| 68     | 14.9                      | 18.7                      | 1.3                    | 15.9                      | 1.1                     |
| 73     | 15.7                      | 15.1                      | 1.0                    | 15.0                      | 1.0                     |
| 79     | 12.1                      | 11.9                      | 1.0                    | 11.1                      | 0.9                     |
| 82     | 15.6                      | 14.9                      | 1.0                    | 14.3                      | 0.9                     |
| 86     | 16.6                      | 15.4                      | 0.9                    | 14.0                      | 0.8                     |
| 90     | 16.0                      | 14.4                      | 0.9                    | 17.1                      | 1.1                     |
| 95     | 13.0                      | 14.4                      | 1.1                    | 15.9                      | 1.2                     |
| 99     | 15.4                      | 13.1                      | 0.9                    | 15.9                      | 1.0                     |
| Mean   | 14.8                      | 14.6                      | 1.0                    | 14.8                      | 1.0                     |
| SD (c) | 2.8                       | 2.4                       | 0.1                    | 3.0                       | 0.1                     |
| CV (d) | 18.9                      | 16.4                      | 10.0                   | 20.3                      | 10.0                    |

(a) Grams of feed consumed per animal per day.

(b) Ratio of feed consumed per day for the dosed group to that for the controls.

(c) Standard Deviation.

(d) (Standard Deviation/Mean) x 100.

Table H3. Feed Consumption by Male Mice Receiving C. I. Disperse Yellow 3

| Week   | Control                   | Low                       |                        | High                      |                         |
|--------|---------------------------|---------------------------|------------------------|---------------------------|-------------------------|
|        | GRAMS<br>FEED/<br>DAY (a) | GRAMS<br>FEED/<br>DAY (a) | LOW/<br>CONTROL<br>(b) | GRAMS<br>FEED/<br>DAY (a) | HIGH/<br>CONTROL<br>(b) |
| 1      | 7.7                       | 7.7                       | 1.0                    | 8.1                       | 1.1                     |
| 5      | 7.7                       | 7.7                       | 1.0                    | 8.1                       | 1.1                     |
| 10     | 3.7                       | 3.4                       | 1.0                    | 3.4                       | 0.9                     |
| 14     | 5.9                       | 3.9                       | 0.7                    | 3.9                       | 0.7                     |
| 19     | 8.0                       | 8.4                       | 1.1                    | 8.7                       | 1.1                     |
| 23     | 8.1                       | 8.4                       | 1.1                    | 8.7                       | 1.1                     |
| 27     | 8.3                       | 8.7                       | 1.1                    | 8.9                       | 1.1                     |
| 33     | 8.1                       | 7.9                       | 1.0                    | 8.7                       | 1.1                     |
| 37     | 8.1                       | 8.3                       | 1.1                    | 8.4                       | 1.1                     |
| 42     | 8.1                       | 8.3                       | 1.0                    | 8.0                       | 1.0                     |
| 46     | 8.4                       | 8.3                       | 1.0                    | 8.6                       | 1.1                     |
| 50     | 8.3                       | 8.6                       | 1.1                    | 9.0                       | 1.1                     |
| 54     | 8.1                       | 8.4                       | 1.1                    | 9.0                       | 1.2                     |
| 58     | 7.9                       | 8.1                       | 1.1                    | 8.9                       | 1.2                     |
| 62     | 8.6                       | 8.6                       | 1.1                    | 9.3                       | 1.2                     |
| 66     | 8.3                       | 8.4                       | 1.1                    | 9.3                       | 1.1                     |
| 71     | 8.6                       | 9.0                       | 1.1                    | 10.0                      | 1.2                     |
| 76     | 8.3                       | 8.6                       | 1.1                    | 8.9                       | 1.1                     |
| 79     | 10.1                      | 10.0                      | 1.0                    | 11.9                      | 1.2                     |
| 84     | 8.4                       | 10.9                      | 1.3                    | 8.9                       | 1.1                     |
| 88     | 9.0                       | 9.4                       | 1.1                    | 10.6                      | 1.2                     |
| 92     | 9.1                       | 9.6                       | 1.2                    | 10.1                      | 1.1                     |
| 96     | 8.6                       | 9.9                       | 1.2                    | 9.9                       | 1.2                     |
| 100    | 11.0                      | 12.4                      | 1.2                    | 12.6                      | 1.2                     |
| Mean   | 8.2                       | 8.5                       | 1.0                    | 8.8                       | 1.1                     |
| SD (c) | 1.3                       | 1.8                       | 0.1                    | 1.9                       | 0.1                     |
| CV (d) | 15.9                      | 21.2                      | 10.0                   | 21.6                      | 9.1                     |

(a) Grams of feed consumed per animal per day.

(b) Ratio of feed consumed per day for the dosed group to that for the controls.

(c) Standard Deviation.

(d) (Standard Deviation/Mean) x 100.

Table H4. Feed Consumption by Female Mice Receiving C. I. Disperse Yellow 3

| Week   | Control                   | Low                       |                        | High                      |                         |
|--------|---------------------------|---------------------------|------------------------|---------------------------|-------------------------|
|        | GRAMS<br>FEED/<br>DAY (a) | GRAMS<br>FEED/<br>DAY (a) | LOW/<br>CONTROL<br>(b) | GRAMS<br>FEED/<br>DAY (a) | HIGH/<br>CONTROL<br>(b) |
| 1      | 7.0                       | 7.0                       | 0.9                    | 7.4                       | 1.0                     |
| 4      | 7.0                       | 7.0                       | 1.0                    | 7.4                       | 1.0                     |
| 9      | 2.1                       | 2.1                       | 1.0                    | 2.1                       | 1.0                     |
| 13     | 4.6                       | 2.0                       | 0.4                    | 1.7                       | 0.4                     |
| 18     | 8.0                       | 8.1                       | 1.1                    | 7.6                       | 1.0                     |
| 22     | 7.4                       | 8.4                       | 1.1                    | 7.7                       | 1.0                     |
| 26     | 7.9                       | 8.3                       | 1.1                    | 8.3                       | 1.1                     |
| 32     | 8.3                       | 7.4                       | 0.9                    | 8.4                       | 1.0                     |
| 36     | 8.1                       | 8.4                       | 1.1                    | 8.3                       | 1.1                     |
| 41     | 8.1                       | 7.9                       | 1.0                    | 7.9                       | 1.0                     |
| 45     | 8.1                       | 8.1                       | 1.1                    | 7.9                       | 1.0                     |
| 49     | 8.7                       | 8.1                       | 1.0                    | 8.4                       | 1.0                     |
| 53     | 8.0                       | 8.0                       | 1.0                    | 8.3                       | 1.1                     |
| 57     | 7.9                       | 8.7                       | 1.2                    | 6.4                       | 0.9                     |
| 61     | 8.4                       | 8.4                       | 1.1                    | 9.1                       | 1.2                     |
| 65     | 7.6                       | 8.6                       | 1.2                    | 8.9                       | 1.2                     |
| 70     | 8.7                       | 9.0                       | 1.1                    | 8.9                       | 1.0                     |
| 75     | 8.0                       | 8.4                       | 1.1                    | 8.7                       | 1.1                     |
| 78     | 10.7                      | 10.3                      | 1.0                    | 11.0                      | 1.0                     |
| 83     | 7.7                       | 8.9                       | 1.2                    | 9.1                       | 1.2                     |
| 87     | 8.6                       | 9.7                       | 1.2                    | 10.3                      | 1.2                     |
| 91     | 8.4                       | 9.0                       | 1.2                    | 9.6                       | 1.2                     |
| 95     | 8.4                       | 10.0                      | 1.3                    | 10.1                      | 1.2                     |
| 99     | 9.6                       | 11.6                      | 1.2                    | 11.0                      | 1.2                     |
| Mean   | 7.8                       | 8.1                       | 1.0                    | 8.1                       | 1.0                     |
| SD (c) | 1.6                       | 2.1                       | 0.1                    | 2.2                       | 0.2                     |
| CV (d) | 20.5                      | 25.9                      | 10.0                   | 27.2                      | 20.0                    |

- (a) Grams of feed consumed per animal per day.  
 (b) Ratio of feed consumed per day for the dosed group to that for the controls.  
 (c) Standard Deviation.  
 (d) (Standard Deviation/Mean) x 100.

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