NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 225

CARCINOGENESIS BIOASSAY OF D & C RED No. 9

(CAS NO. 5160-02-1)

IN F344 RATS AND B6C3F$_1$ 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.

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

NTP TECHNICAL REPORT

ON THE

CARCINOGENESIS BIOASSAY

OF

D & C RED No. 9

(CAS NO. 5160-02-1)

IN F344/N RATS AND B6C3F$_1$/N MICE
(FEED STUDY)

NATIONAL TOXICOLOGY PROGRAM
Research Triangle Park
Box 12233
North Carolina 27709
and
Bethesda, Maryland 20205

May 1982

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institute 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).

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

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650).

Single copies of this carcinogenesis bioassay technical report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

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ABSTRACT

A carcinogenesis bioassay of D & C Red No. 9, a pigment used in topical drugs and cosmetics, was conducted by feeding diets containing 1,000 or 3,000 ppm of the test substance (89.8% pure) to groups of 50 F344 rats of either sex for 103 weeks. Similar groups of 50 B6C3F1 mice received diets containing 1,000 or 2,000 ppm of the test substance for 103 weeks. Groups of 50 untreated rats and mice of either sex served as controls.

In a 13-week subchronic study, the spleens of most dosed rats were enlarged and pigment (unidentified) was present in the renal tubular epithelium. Lymphoreticular hyperplasia of thymic lymph nodes was found in 75-100% of females receiving 6,000-50,000 ppm D & C Red No. 9 and in 70-100% of male rats receiving 3,000-25,000 ppm. Hemosiderosis of the liver was observed at the high-dose levels in male and female rats. Mice receiving 1,250 ppm or more D & C Red No. 9 had congestion of the spleen and hemosiderin deposits. Thus, the selection of doses for the chronic study was based on the appearance of hemosiderosis and the incidences and severity of splenic lesions observed in the 91-day subchronic study.

In the chronic study, mean body weights of dosed rats of either sex and of male mice were comparable with those of controls. After week 50, the mean body weight of high-dose female mice was lower than that of the controls. No compound-related effects on survival or clinical signs were observed for rats or mice of either sex. With the possible exception of female mice, all other dosed groups of rats or mice might have tolerated higher doses, thus a clear maximum tolerated dose may not have been utilized in this study.

Splenic sarcomas (0/50, 0/50, 26/48; $P < 0.001$) and neoplastic nodules of the liver (0/50, 6/50, 7/49; $P < 0.01$) were observed in high-dose male rats at incidences significantly higher than those in the controls. Incidences of neoplastic nodules in the livers (1/50, 1/50, 5/50) of female rats showed a statistically significant ($P < 0.05$) trend. Nonneoplastic splenic lesions were also observed in dosed male and female rats.

Lymphocytic leukemia was observed in dosed male (10/50, 2/50, 2/50) and female (10/50, 2/50, 1/50) rats at statistically significant ($P < 0.05$) decreased incidences, compared with controls. Adenomas or carcinomas of the preputial gland in male rats (7/50, 2/50, 0/50) occurred with a statistically significant ($P < 0.01$) negative relationship to dose of D & C Red No. 9 ($P=0.007$).

Under the conditions of this bioassay, D & C Red No. 9 was carcinogenic for male F344 rats causing an increased incidence of sarcomas of the spleen and a dose-related increase in neoplastic nodules of the liver. D & C Red No. 9 was not considered to be carcinogenic to female F344 rats, although the increased incidence of neoplastic nodules of the liver may have been associated with administration of the test chemical. D & C Red No. 9 was not carcinogenic for B6C3F1 mice of either sex.

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 Bioassay Program. The prechronic phase of the study was started in June 1976 and finished in December 1976; the chronic study was initiated in March 1977 and completed in April 1979.

Dr. A. Peters (1) was the principal investigator for this study. Doses of the test chemical were selected by Dr. C. Cueto (2) and J. Robens (3,4). 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 (1,5), and D. Thake (1). Histopathologic evaluations were performed by Drs. G. S. Dill (mice) and R. Persing (rats). 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 (6). Statistical analyses were performed by Dr. J. R. Joiner (3) and Mr. J. Warner (3) using methods selected for the bioassay program by Dr. J. J. Gart (7). Chemical analyses were conducted at Midwest Research Institute (8). Dosage analysis was supervised by Drs. R. Freudenthal (1) and P. Leber (1,9) and by Mr. D. Emmerling (1).

This report was prepared at Tracor Jitco (3) under the direction of Dr. C. Cueto, Director of the Bioassay Program; Dr. S. S. Olin, Associate Director, Dr. M. A. Stedham, pathologist; Dr. J. E. Tomaszewski, chemist; 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 (chemical manager), Dr. Larry Hart, Dr. William V. Hartwell, Dr. Joseph Haseman, Dr. James E. Huff, Dr. Ernest E. McConnell, Dr. John A. Moore, Dr. Sherman F. Stinson, Dr. Raymond Tennant, and Dr. Jerrold M. Ward.

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(1) Battelle Columbus Laboratories, 505 King Avenue, Columbus, Ohio 43201.

(2) Formerly with NCI; now with Dynamac Corporation, 11140 Rockville Pike, Rockville, Maryland 20852.

(3) Tracor Jitco, Inc., 1776 East Jefferson Street, Rockville, Maryland 20852.

(4) Now with Bureau of Veterinary Medicine, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20857.

(5) Now with E. I. duPont de Nemours & Co., Wilmington, Delaware 19898.

(6) EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland 20852.

(7) Mathematical Statistics and Applied Mathematics Section, Biometry Branch, Field Studies and Statistics, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205.

(8) Midwest Research Institute, 425 Volker Boulevard, Kansas City, Missouri 64110.

(9) Now with PPG Industries, Inc., One Gateway Center, Pittsburgh, Pennsylvania 15222.

(10) National Toxicology Program, Bethesda, Maryland 20205 and Research Triangle Park, Box 12233, North Carolina 27709.

REVIEWERS

National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee

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Toxicology Research Laboratory
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Midland, Michigan

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Statistics
New York University Medical Center
New York, New York

James Swenberg, Ph.D.
Chief of Pathology
Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina

Gary Williams, M.D.
Chief of Experimental Pathology
American Health Foundation
Valhalla, New York

*Unable to attend February 18, 1981 meeting

SUMMARY OF PEER-REVIEW COMMENTS ON THE BIOASSAY OF D & C RED NO. 9

On February 18, 1981 this carcinogenesis bioassay report on D & C Red No. 9 was peer-reviewed and 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 31 C, National Institutes of Health, Bethesda, Maryland.

Dr. Hitchcock, as a principal reviewer for the report on the bioassay of D & C Red No. 9, agreed with the conclusion that, under the conditions of the bioassay, administration of D & C Red No. 9 in the diet is carcinogenic to male F344 rats causing sarcomas of the spleen and an increased incidence of neoplastic nodules of the liver. A carcinogenic effect could not be established in female rats or in B6C3F1 mice of either sex. Dr. Hitchcock said that the summary statement should clearly indicate that the incidence and severity of splenomegaly observed in the subchronic studies was the rationale for choosing the doses used in the chronic study. Since these effects were not seen in the chronic studies, the dose used was probably below a maximum tolerated dose. She noted that a significant positive trend occurred in the chronic study for neoplastic nodules of the liver in female rats. Thus, while she considered the study to be valid, due to the less than optimal doses, D & C Red No. 9 may be more carcinogenic than is indicated by this bioassay. She also expressed concern as to possible exposure to contaminants since rats and mice used in the study were housed in the same rooms as animals on feeding studies with C. I. Disperse Yellow 3 and C. I. Solvent Yellow 14. Both of these dyes were found to be carcinogenic. [C.I. Disperse Yellow 3 was carcinogenic for male F344 rats causing neoplastic nodules of the liver and for female BC63F1 mice producing hepatocellular adenomas; it was not carcinogenic for female F344 rats or male B6C3F1 mice (NTP 1982b). C.I. Solvent Yellow 14 was carcinogenic for male and female F344 rats causing neoplastic nodules of the liver; it was not carcinogenic for B6C3F1 mice (NTP 1982c).]

Dr. Whittemore, a second principal reviewer, was not present. Dr. Hitchcock read her review. Dr. Whittemore also agreed with the conclusion of the report but she also stressed that the negative results for the female rats and mice of both sexes could be questioned on the grounds that the animals might have tolerated higher doses.

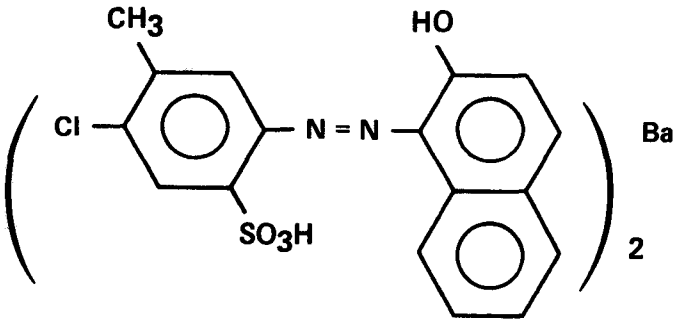
Dr. Hitchcock announced that Dr. James McNerney, Director of Toxicology for the Cosmetic, Toiletry and Fragrance Association (CTFA), had prepared to make a statement regarding CTFA sponsored toxicological studies on D & C Red No. 9 that were in progress, but had decided to defer the statement. Mr. Charles Frazier, FDA Bureau of Foods, requested that the review of the bioassay be delayed pending the completion of the CFTA studies. Dr. Hitchcock replied that the scientific review of these bioassay results and the publication of the bioassay technical report could not be delayed.

In other discussion, Dr. Swenberg suggested that the discussion on page 60, which notes that azobenzene produces neoplastic splenic lesions, should be expanded to note that aniline and para-chloroaniline also induce such lesions. Dr. Williams objected to the statement referring to hepatic neoplastic nodules in rats on page 61 which said that "The present study precludes absolute determination of the potential carcinogenicity of these lesions." He said that it should say "potential malignancy". Dr. Highland requested that in the conclusion (and abstract) there be a separate statement noting the significant positive trend for neoplastic nodules of the liver in female rats.

There was considerable discussion by the reviewers about what have been and/or what should be the criteria for determining an estimated maximum tolerated dose. The panel also gave further support for better characterization of important non-tumor lesions observed in the subchronic studies since such lesions are often the basis for setting the estimated maximum tolerated dose.

Dr. Hitchcock moved that the bioassay report on D & C Red No. 9 be accepted with the modification of the summary statement and other amendments and minor revisions proposed. Dr. Highland seconded the motion and the report was approved unanimously.

I. INTRODUCTION



D AND C RED NO. 9

C.I. Pigment Red
C.I. Pigment Red 53:1
C.I. Pigment 53, barium salt

Molecular weight = 445.5
$(C_{17}H_{13}Cl\ N_2O_4S)_2Ba$

D & C Red No. 9, 5-chloro-2-[(2-hydroxy-1-naphthalenyl)azo] -4-methyl-benzene sulfonic acid, barium salt (C. I. 15585:1, CAS No. 5160-02-1), is a bright orange pigment listed provisionally by the U.S. Food and Drug Administration for use in externally applied drugs and cosmetics, provided that the concentration of pure pigment does not exceed 6% (CFR, 1979). The orange red crystals are used in rouge and lipstick (Maruszewski, 1972; Lauffer, 1972) and in other pigments for printing inks, plastics, and rubber (Society of Dyers and Colourists, 1971). In 1978, 98,000 pounds of D & C Red No. 9 were produced in the United States (USITC, 1979). U.S. production was first reported in 1940 (IARC, 1975).

D & C Red No. 9 was not mutagenic, with or without microsomal activation, in Salmonella typhimurium TA 1535, TA 100, TA 1537, TA 1538, or TA 98 (Brown et al., 1979; Muzzall and Cook, 1979).

Groups of 25 male and 25 female Osborne-Mendel rats were fed diets containing 0, 100, 500, 2,500, or 10,000 ppm D & C Red No. 9. Relative spleen weights were more than triple those of controls in Osborne-Mendel rats of either sex fed diets containing 10,000 ppm D & C Red No. 9 for 2 years and were double those of controls in rats fed 2,500 ppm. Slight bone marrow hyperplasia was observed at both the 2,500- and 10,000-ppm dose. No

carcinogenic effects were demonstrated, but only six animals from each group were examined histopathologically (Davis and Fitzhugh, 1962; IARC, 1975).

D & C Red No. 9 was tested by the Carcinogenesis Bioassay Program because of its use in lipstick and hence potential for human exposure and because the single previous test for carcinogenicity (Davis and Fitzhugh, 1962) was considered to be inadequate due to the small number of animals examined histopathologically.

II. MATERIALS AND METHODS

A. Chemical

D & C Red No. 9 (CAS No. 5160-02-1), 5-chloro-2- [(2-hydroxy-1-naphthalenyl)azo]-4-methylbenzene sulfonic acid, barium salt (2:1), was obtained in one batch of FDA certified material (Lot No. Z-8054) from H. Kohnstamm and Company (Brooklyn, NY). The bulk compound was stored at room temperature over the course of the bioassay. Reanalysis of the bulk chemical every four months to verify the integrity of the compound indicated no decomposition occurred during the study.

Elemental analysis, melting point, thin-layer and high-pressure liquid chromatography, titration with titanous chloride, and spectral analysis including infrared and ultraviolet/visible were performed at Midwest Research Institute (Kansas City, MO). The pigment was mixed for 1 hour in a Day blender before analysis. Lot No. Z-8054 was 89.8% dye, based on titration of the diazo group with titanous chloride (Appendix E). The high elemental analysis results for barium and sulfur and the presence of sodium indicate that extraneous salts such as barium and sodium sulfates comprise the rest of this material. Five trace impurities were detected by thin-layer chromatography while high-pressure liquid chromatography indicated only a single component. The infrared, ultraviolet, and visible spectra were consistent with the structure and with literature spectra (Sadtler Standard Spectra).

B. Dietary Preparation

Formulated diets containing 100,000 ppm D & C Red No. 9 were analyzed at Midwest Research Institute and were found to be stable for 2 weeks at temperatures up to 45°C (Appendix F).

Diets were formulated by mixing weighed amounts of Purina® Laboratory Chow in the form of a meal (Table 1) and the test chemical for 15 minutes in a Patterson-Kelly® twin-shell blender equipped with an intensifier bar. Formulated diets were stored at 23°C for no longer than 10 days.

Every 8 to 10 weeks, analytical concentrations of D & C Red No. 9 were determined in blindly selected batches of formulated diets and were within ±10% of the desired concentration (Appendix G).

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). Animals were isolated and maintained in separate quarters from 12-16 days, and randomly assigned to cages. The cages were then randomly assigned to control and dosed groups.

D. Animal Maintenance

Rats and mice were housed five per cage in solid-bottom polycarbonate cages supplied with hardwood chip bedding (Table 1). 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 via an automatic watering system.

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 D & C Red No. 9 were housed in the same room as animals of the same species on feeding studies of C. I. Disperse Yellow 3 (CAS 2832-40-8) and C. I. Solvent Yellow 14 (CAS 842-07-9).

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

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

E. Single Dose and Repeated Dose Studies

Single-day dosing and 14-day repeated dose studies were conducted using 5- to 6-week-old F344 rats and B6C3F1 mice from Frederick Cancer Research Center to determine the toxicity of D & C Red No. 9 and the concentrations to be used in the 13-week subchronic studies.

In the single dose study, groups of five males and five females of each species were fed diets containing 6,000, 12,500, 25,000, 50,000, or 100,000 ppm D & C Red No. 9 for 24 hours. Purina® Laboratory Chow was available ad libitum for the rest of the study. No deaths occurred among the rats or mice and no signs of toxicity were observed. All animals were killed on day 15. The animals were not necropsied.

In the 14-day repeated dose study, groups of five males and five females of each species were fed diets containing 6,000, 12,500, 25,000, 50,000, or 100,000 ppm for 2 weeks. All animals were killed after 2 weeks (Table 2).

None of the rats died and no overt sign of toxicity was observed. In the mice, deaths occurred in 1/5 males receiving 12,500 ppm, 4/5 males and 3/5 females receiving 25,000 ppm, and in all mice fed diets containing 50,000 or 100,000 ppm. The spleens of all dosed rats and mice were dark red and enlarged, and the livers and kidneys were dark red to reddish tan. The animals were not examined histopathologically.

F. Subchronic Studies

Subchronic studies were conducted to determine toxicity of D & C Red No. 9 and to estimate the concentrations to be used in the chronic studies. Groups of 10 rats of either sex were fed diets containing 0, 3,000, 6,000, 12,500, 25,000, or 50,000 ppm D & C Red No. 9 for 91 days. Groups of 10 mice of either sex were fed diets containing 0, 600, 1,250, 2,500, 5,000 or 10,000 ppm (Tables 3 and 4). Mortality checks were made twice daily and animals were weighed weekly. Necropsies were performed on all animals and certain

Table 2. Dosage and Survival of Rats and Mice Fed Diets Containing D & C Red No. 9 for 2 Weeks

Dose (ppm)	Survival(a)	
	Male	Female
Rats		
6,000	5/5	5/5
12,500	5/5	5/5
25,000	5/5	5/5
50,000	5/5	5/5
100,000	5/5	5/5
Mice		
6,000	5/5	5/5
12,500	4/5	5/5
25,000	1/5	2/5
50,000	0/5	0/5
100,000	0/5	0/5

(a) Number surviving/number per group.

Table 3. Dosage, Survival, and Mean Body Weights of Rats Fed Diets Containing D & C Red No. 9 for 91 Days

Dose (ppm)	Survival (a)	Mean Body Weights (grams) Initial(SE)(b)	Final(SE)	Change(SE)	Weight Change Relative to Controls (c) (%)
MALE					
0	10/10	114.7(4.1)	298.1(5.0)	+183.4(5.8)	
3,000	10/10	114.9(3.3)	298.4(7.7)	+183.5(5.8)	+0.1
6,000	9/10	118.5(3.7)	317.9(4.3)	+199.4(5.0)	+8.7
12,500	10/10	107.3(4.0)	290.2(5.8)	+182.9(2.6)	-0.3
25,000	10/10	119.3(2.5)	300.7(6.1)	+181.4(5.6)	-1.1
50,000	10/10	117.5(4.9)	298.6(5.6)	+181.1(3.6)	-1.3
FEMALE					
0	10/10	103.3(3.7)	186.2(3.5)	+82.9(1.8)	
3,000	9/10	98.6(2.4)	180.6(2.7)	+82.0(2.9)	-1.1
6,000	10/10	104.9(4.8)	201.6(11.2)	+96.7(8.2)	+16.6
12,500	10/10	95.9(2.2)	186.0(2.7)	+90.1(3.2)	+8.7
25,000	10/10	101.8(2.8)	186.8(2.4)	+85.0(3.0)	+2.5
50,000	10/10	100.4(1.9)	182.5(2.7)	+82.1(2.8)	-1.0

(a) Number surviving/number per group.
(b) Standard error.
(c) Weight Change Relative to Controls =

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

Table 4. Dosage, Survival, and Mean Body Weights of Mice Fed Diets Containing D & C Red No. 9 for 91 Days

Dose (ppm)	Survival (a)	Mean Body Weights (grams) Initial(SE)(b)	Final(SE)	Change(SE)	Weight Change Relative to Controls (c) (%)
MALE					
0	10/10	23.8(0.65)	32.1(0.97)	+8.3(0.70)	
600	10/10	23.6(0.40)	32.6(0.64)	+9.0(0.54)	+8.4
1,250	10/10	24.3(0.47)	32.9(0.41)	+8.6(0.34)	+3.6
2,500	10/10	24.8(0.61)	32.5(0.76)	+7.7(0.37)	-7.2
5,000	10/10	23.4(0.40)	32.9(0.53)	+9.5(0.67)	+14.5
10,000	10/10	22.6(0.54)	31.4(0.50)	+8.8(0.49)	+6.0
FEMALE					
0	10/10	18.6(0.45)	24.2(0.74)	+5.6(0.43)	
600	10/10	18.5(0.43)	23.5(0.64)	+5.0(0.39)	-10.7
1,250	10/10	18.2(0.44)	23.6(0.37)	+5.4(0.31)	-3.6
2,500	10/10	18.2(0.20)	24.4(0.48)	+6.2(0.39)	+10.7
5,000	10/10	18.8(0.33)	24.4(0.65)	+5.6(0.48)	+3.0
10,000	10/10	18.7(0.37)	24.6(0.54)	+5.9(0.48)	+5.4

(a) Number surviving/number per group.
(b) Standard error.
(c) Weight Change relative to Controls =

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

tissues (see Section H) from the control groups and the highest dose groups (50,000 ppm for rats and 10,000 ppm for mice) were trimmed for histopathologic analysis.

Rats: One male rat receiving 6,000 ppm and one female rat receiving 3,000 ppm died. Mean body weight gains were comparable among all groups of male or female rats.

The spleens of all dosed animals were dark and were enlarged 2 to 5 times the normal size. Pigment deposition in the renal tubular epithelium was observed in all dosed rats. Congestion and lymphoreticular hyperplasia were found in the spleens of all dosed female rats, in all male rats receiving 6,000 ppm or more, and in 8 of 10 male rats receiving 3,000 ppm (the lowest dose). Lymphoreticular hyperplasia of the thymic lymph nodes was found in 75%-100% of the female rats in each dosed group, except for the group receiving 3,000 ppm (in which the group incidence was 0/10). This condition was seen in 70%-100% of the male rats in each dosed group, except for the group receiving 50,000 ppm (in which the incidence was 3/7).

Hemosiderosis of the liver was found in all dosed female rats and in 9/10 males receiving 12,500 ppm, 6/10 receiving 6,000 ppm, and 3/10 receiving 3,000 ppm. None of these tissue changes were detected in control animals.

Hemosiderosis of the liver, dose related in incidence and severity, was the major consideration in setting doses for the chronic study. Hemosiderosis of the liver was rated as mild at 3,000 ppm; thus doses of 1,000 and 3,000 ppm D & C Red No. 9 in feed were selected for rats in the chronic study.

Mice: None of the mice died. Mean body weights were comparable among all groups of male and female mice. Histologically, congestion of the spleen was observed in 55 of 60 mice receiving 2,500 ppm or more. Deposits of hemosiderin were present to a greater extent in all dosed animals than in controls with the exception of females receiving 600 or 1,250 ppm and males receiving 600 ppm. The occurrence of these lesions, hemosiderosis, and

congestion was not considered life threatening per se; however, it was considered indicative of potentially severe toxicity in a chronic study. Doses of 1,000 and 2,000 ppm D & C Red No. 9 in feed were selected for mice in the chronic study to avoid possible toxic effects.

G. Chronic Studies

The number of animals per group, doses administered, and durations of the chronic studies are shown in Table 5.

H. Clinical Examinations and Pathology

All animals were observed twice daily to discern sickness or morbidity. 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 those 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, 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

Table 5. Experimental Design of Chronic Feeding Studies with D & C Red No. 9 in Rats and Mice

Test Group	Initial No. of Animals	D & C Red No. 9 (ppm)	Weeks on Study	
			Dosed(a)	Not Dosed
Male Rats				
Control (b)	50	0	0	104
Low-Dose	50	1,000	103	1
High-Dose	50	3,000	103	1
Female Rats				
Control (b)	50	0	0	104
Low-Dose	50	1,000	103	1
High-Dose	50	3,000	103	1
Male Mice				
Control (b)	50	0	0	104
Low-Dose	50	1,000	103	2
High-Dose	50	2,000	103	2
Female Mice				
Control (b)	50	0	0	105
Low-Dose	50	1,000	103	2
High-Dose	50	2,000	103	2

(a) The start dates were March 10, and March 23, 1977 for male and female rats and April 8, and April 17, 1977 for male and female mice.

(b) Control and dose groups were of the same strain, sex, and age range and from the same source and shipment. All animals of the same species 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 II.C.

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 animals 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 for 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

Throughout the bioassay, mean body weights of dosed and control rats were comparable (Figure 1 and Table 6). No compound-related clinical signs were observed. Feed consumption by dosed rats of either sex was comparable with that of the corresponding controls (Appendix H).

B. Survival

Estimates of the probabilities of survival of male and female rats administered D & C Red No. 9 in the diet at the concentrations of this bioassay, together with those of the control group, are shown by the Kaplan and Meier curves in Figure 2. The low-dose male rats had a significantly greater rate of survival than either the high-dose group or controls. No significant differences were observed between the high-dose and control male rats or between any group of females.

In male rats, 32/50 (64%) of the controls, 44/50 (88%) of the low-dose, and 30/50 (60%) of the high-dose group lived to the end of the study at 104 weeks. In female rats, 38/50 (76%) of the controls, 40/50 (80%) of the low-dose, and 41/50 (82%) of the high-dose group lived to the end of the study at 104 weeks.

A sufficient number of rats were at risk for the development of late appearing tumors.

C. Pathology

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, respectively. Findings on nonneoplastic lesions are summarized in Appendix C, Tables C1 and C2.

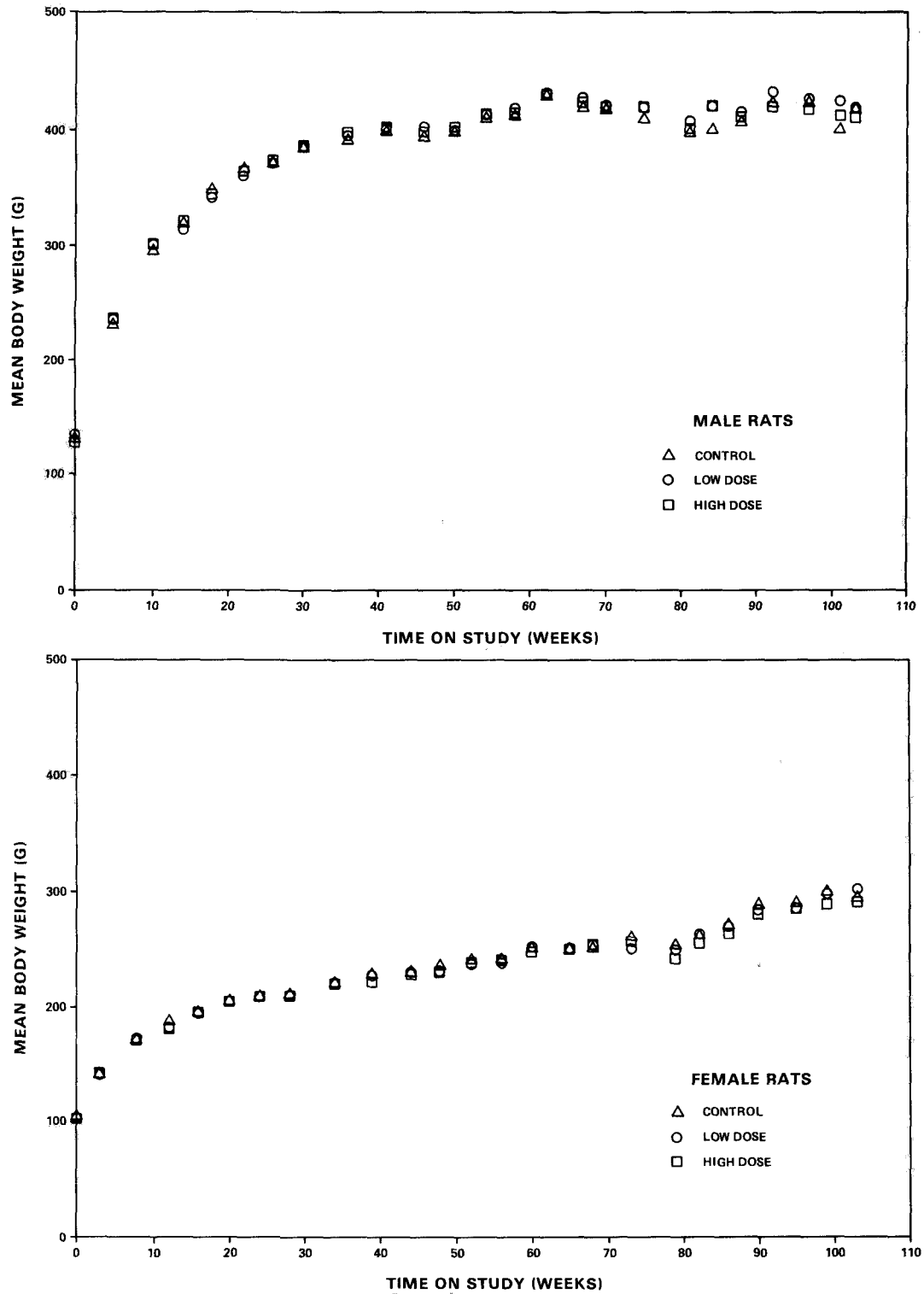


Figure 1. Growth Curves for Rats Fed Diets Containing D and C Red No. 9

Table 6. Mean Body Weight Change (Relative to Controls) of Rats Fed Diets Containing D & C Red No. 9 for 103 Weeks

	Week No.	Cumulative Mean Body Weight Change (grams)			Weight Change (%) Relative to Controls (a)	
		Controls	Low Dose	High Dose	Low Dose	High Dose
Male Rats	0	131(b)	134(b)	127(b)		
	5	101	101	109	0	+8
	26	240	236	245	-2	+2
	46	263	269	270	+2	+3
	67	289	293	297	+1	+3
	88	277	288	285	+4	+3
	103	286	283	283	-1	-1
Female Rats	0	105(b)	103(b)	102(b)		
	3	36	37	38	+3	+6
	24	103	104	105	+1	+2
	44	125	126	125	+1	0
	65	146	148	148	+1	+1
	86	168	166	162	-1	-4
	103	189	200	188	+6	-1

(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) Initial weight.

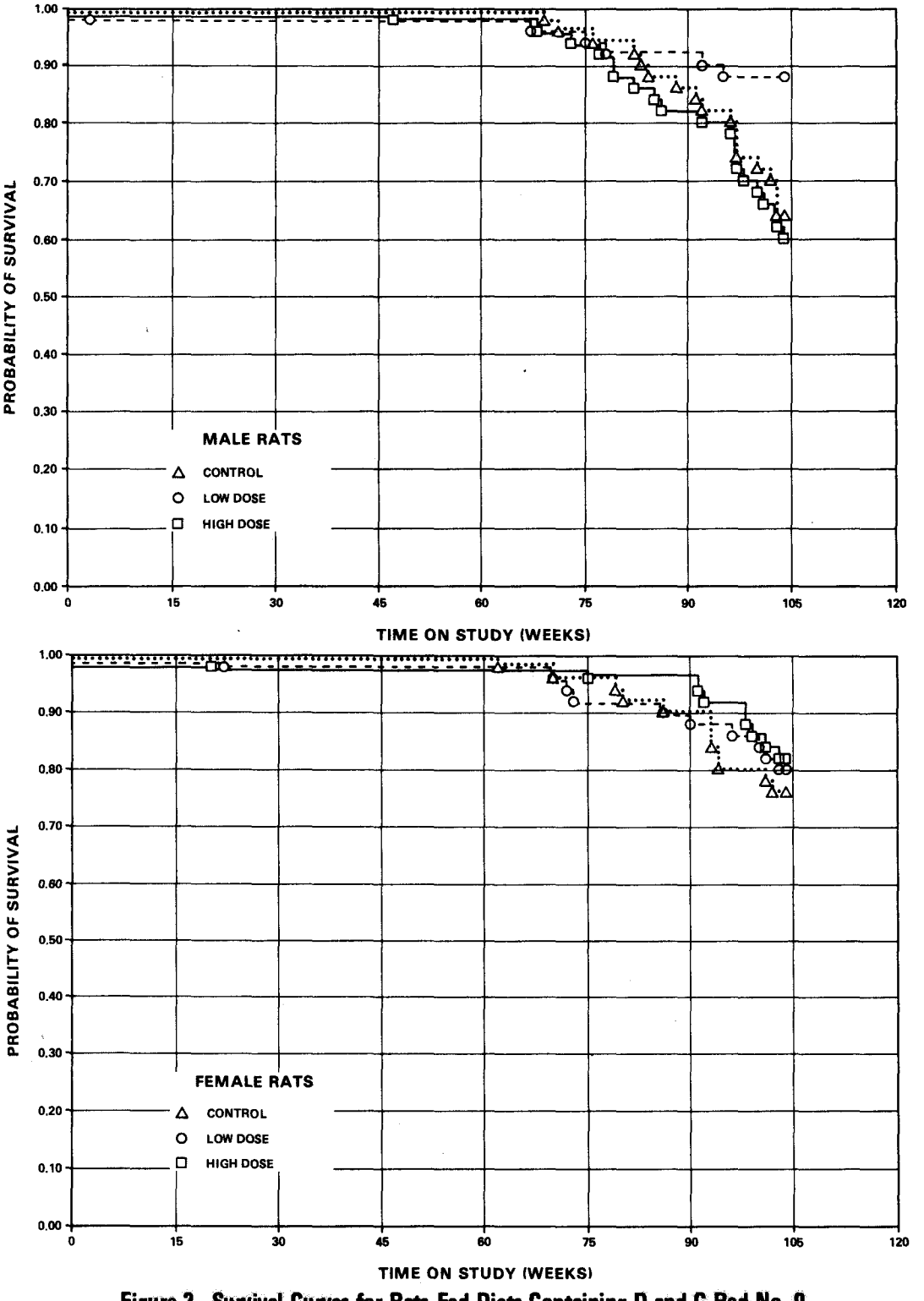


Figure 2. Survival Curves for Rats Fed Diets Containing D and C Red No. 9

The tumors represented have been encountered previously as spontaneous lesions in the rat, but several tumors of the spleen, observed with an increased incidence in the dosed animals, were not found in the corresponding control animals (Table 7). Fibrosarcomas, apparently arising from the red pulp or capsule of the spleen, were found in 17 of 48 high-dose (3,000 ppm) male rats. In high-dose male rats, one animal had a leiomyosarcoma and five had splenic osteosarcoma. A fibroma was found in one low-dose male rat. Eleven of the splenic tumors metastasized to peritoneal tissues. The two sarcomas of multiple organs in high-dose males may have originated in the spleen.

Nonneoplastic splenic lesions were observed in high-dose male rats. Fourteen of 48 males had congestion of the splenic parenchyma, 23 had focal or multifocal areas of fibrosis, 3 had diffuse fibrosis, and 13 had areas of fatty metamorphosis in the spleen. Twenty-five high-dose females had multifocal, diffuse, or focal fibrosis. Areas of fibrosis were present in two control male rats.

The splenic lesions in dosed male and female rats ranged from multifocal areas of fibroblastic proliferation in the red pulp to areas of proliferation of pleomorphic spindle cells with an oval to round, open-faced nucleus, and generally, an indistinct nucleolus. In some areas, these cells produced large amounts of collagen-like material. Areas of the neoplastic tissue were often vascular in nature, and at time osteoid was produced by the malignant cells. Many variations were found in the patterns taken by these pleomorphic fibroblast-type cells in the spleen. In some cases the neoplastic cells were through the capsule, and occasionally they were metastatic to other organs.

Large areas of pigment were occasionally seen in the fibrous areas in the splenic capsule and parenchyma. The pigment appeared different from the hemosiderin seen in spleens of aging F344 rats.

Hepatic neoplastic nodules were seen in 0/50 control males, 6/50 low-dose males, and 7/49 high dose males. Almost all of these nodules were relatively small and composed of hepatocytes with basophilic or eosinophilic cytoplasm. Hepatocellular carcinoma was seen in 1/50 control males.

Table 7. Numbers of Rats with Neoplastic and Nonneoplastic Lesions in the Spleen

	MALES			FEMALES		
	Control	Low-Dose	High Dose	Control	Low-Dose	High-Dose
Number of Spleens Examined	50	50	48	50	50	50
Spleen Lesions:						
Fibroma	0	1	0	0	0	0
Fibrosarcoma	0	0	17	0	0	0
Leimyosarcoma	0	0	1	0	0	0
Osteosarcoma	0	0	5	0	0	0
Congestion, NOS or passive	1	0	14	0	6	26
Fibrosis, Focal or Multifocal	1	0	23	0	2	15
Fibrosis, Diffuse	1	0	3	0	0	10
Necrosis, Focal	0	0	2	0	0	0
Fatty Metamorphosis	0	0	13	0	0	0
Hemosiderosis	2	1	2	1	0	0
Splenic Capsule:						
Sarcoma	0	0	1	0	0	0
Fibrosarcoma	0	0	1	0	0	0
Splenic Red Pulp:						
Fibrosarcoma	0	0	1	0	0	0

The results of histopathologic examination indicated that D & C Red No. 9 was carcinogenic in male F344 rats, inducing splenic sarcomas and hepatic neoplastic nodules.

D. Statistical Analyses of Results

Tables 8 and 9 contain the statistical analyses of those primary tumors that met both of the following criteria: (1) At least two animals in one group had the tumor, and (2) The incidence in one or more groups was at least 5%.

Fibrosarcomas of the spleen in male rats were observed in a statistically significant positive association (0/50, 0% in the controls; 0/50, 0% in the low-dose; 17/48, 35% in the high-dose). The Fisher exact test between the high-dose group and the control group was significant (P less than 0.001). The historical records of this laboratory indicate that no fibrosarcomas of the spleen were observed in 140 male rats, and the historical records for the entire bioassay program reported an incidence of 3/2,960 (0.1%). Combined sarcomas of all types in the spleen, splenic capsule, or splenic pulp of male rats totaled 0/50 (0%) in the controls, 0/50 (0%) in the low-dose, and 26/48 (54%) in the high-dose group. The Cochran-Armitage test for linear trend was significant (P less than 0.001), and the Fisher exact test between the high-dose group and the controls was significant (P less than 0.001). No such sarcomas were observed in any groups of female rats.

Neoplastic nodules of the liver in male rats were observed in a statistically significant dose-related positive relation in the dosed groups compared with the control group (0/50, 0% in the controls; 6/50, 12% in the low-dose; 7/49, 14% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant in the positive direction (P=0.020). The Fisher exact test between the control group and either of the dosed groups was significant (P=0.006 in the high-dose and P=0.013 in the low-dose). In female rats, this tumor was observed in a statistically

significant trend (P=0.039) and occurred in 5/50 (10%) of the high-dose group compared with 1/50 (2%) in the control group. The historical record at this laboratory indicates that the incidence of either male or female rats with neoplastic nodules in the liver is 5/140 (3.6%). When the incidence of male rats with either carcinomas or nodules of the liver was considered, a significant trend (P=0.045) was observed in the incidence of male rats with either carcinoma of the liver or neoplastic nodules. The Fisher exact test between the high-dose group and the controls had a probability level of P=0.028.

Lymphocytic leukemia of the hematopoietic system occurred in decreased incidence in the dosed groups of male rats compared with the control group. The Cochran-Armitage test for linear trend was statistically significant in the negative direction (P=0.015). The P values of the Fisher exact tests were P=0.014 in both the low- and high-dose groups. When the incidence of male rats with either lymphoma or leukemia was analyzed, the test for trend was significant (P=0.013) in the negative direction and the Fisher exact test between the high-dose and the control group had a probability level of P=0.011 in the negative direction. The incidence of lymphocytic leukemia was also significantly reduced in the dosed groups of female rats. The Cochran-Armitage test for linear trend was statistically significant in the negative direction (P=0.004). The P values of the Fisher exact tests were P=0.014 and P=0.004 in the low- and high-dose groups, respectively. Leukemia or lymphomas of the hematopoietic system in female rats were observed in a statistically significant negative relation in the dosed groups compared with the control group (11/50, 22% in the controls; 5/50, 10% 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=0.021), and the Fisher exact test between the control group and the high-dose group was significant (P=0.020).

Tumors of the preputial gland in male rats were observed in a statistically significant negative relation (7/50, 14% 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=0.007). The Fisher exact test between the high-dose group and the control group was significant (P=0.006). 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. Only two male and two female rats died before 52 weeks on study, so time-adjusted analyses eliminating those animals that died before week 52 did not alter the results.

Life table analyses, using the week during which an animal died naturally or was killed as a time point, did not materially change the results.

The conclusion based on statistical analysis of the data is that sarcomas of the spleen were found at a significantly higher incidence in high-dose male rats than in controls. In addition, neoplastic nodules of the liver occurred in a dose-related incidence in male rats.

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing D & C Red No. 9 (a)

Topography: Morphology	Control	Low Dose	High Dose
Subcutaneous Tissue: Fibroma (b)	4/50(8)	1/50(2)	1/50(2)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.250	0.250
Lower Limit		0.005	0.005
Upper Limit		2.411	2.411
Weeks to First Observed Tumor	102	75	82
Hematopoietic System: Lymphocytic Leukemia (b)	10/50(20)	2/50(4)	2/50(4)
P Values (c),(d)	P=0.015(N)	P=0.014(N)	P=0.014(N)
Departure from Linear Trend (f)			
Relative Risk (Control) (e)		0.200	0.200
Lower Limit		0.022	0.022
Upper Limit		0.877	0.877
Weeks to First Observed Tumor	69	3	79
Hematopoietic System: Leukemia (b)	10/50(20)	3/50(6)	3/50(6)
P Values (c),(d)	P=0.039(N)	P=0.036(N)	P=0.036(N)
Relative Risk (Control) (e)		0.300	0.300
Lower Limit		0.056	0.056
Upper Limit		1.083	1.083
Weeks to First Observed Tumor	69	3	79

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing D & C Red No. 9 (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia (b)	12/50(24)	4/50(8)	3/50(6)
P Values (c),(d)	P=0.013(N)	P=0.027(N)	P=0.011(N)
Relative Risk (Control) (e)		0.333	0.250
Lower Limit		0.084	0.048
Upper Limit		1.014	0.858
Weeks to First Observed Tumor	69	3	79
Spleen: Fibrosarcoma (b)	0/50(0)	0/50(0)	17/48(35)
P Values (c),(d)	P less than 0.001	N.S.	P less than 0.001
Departure from Linear Trend (f)	P less than 0.001		
Relative Risk (Control) (e)		--	Infinite
Lower Limit		--	5.638
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	68
Spleen: Osteosarcoma (b)	0/50(0)	0/50(0)	5/48(10)
P Values (c),(d)	P=0.003	N.S.	P=0.025
Relative Risk (Control) (e)		--	Infinite
Lower Limit		--	1.314
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	100

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing D & C Red No. 9 (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Spleen, Splenic Capsule, or Splenic Pulp: All Sarcoma (b)	0/50(0)	0/50(0)	26/48(54)
P Values (c),(d)	P less than 0.001	N.S.	P less than 0.001
Departure from Linear Trend (f)	P=0.006		
Relative Risk (Control) (e)		--	Infinite
Lower Limit		--	8.950
Upper Limit		--	Infinite
Weeks to First Observed Tumor	--	--	68
Liver: Neoplastic Nodule (b)	0/50(0)	6/50(12)	7/49(14)
P Values (c),(d)	P=0.020	P=0.013	P=0.006
Relative Risk (Control) (e)		Infinite	Infinite
Lower Limit		1.600	1.981
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	104	97
Liver: Neoplastic Nodule or Carcinoma (b)	1/50(2)	6/50(12)	7/49(14)
P Values (c),(d)	P=0.045	N.S.	P=0.028
Relative Risk (Control) (e)		6.000	7.143
Lower Limit		0.768	0.970
Upper Limit		269.891	314.496
Weeks to First Observed Tumor	104	104	97

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing D & C Red No. 9 (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma (b)	7/44(16)	7/44(16)	5/44(11)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.000	0.714
Lower Limit		0.327	0.193
Upper Limit		3.061	2.409
Weeks to First Observed Tumor	76	104	86
Adrenal: Pheochromocytoma, Malignant (b)	0/48(0)	2/50(4)	3/48(6)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		Infinite	Infinite
Lower Limit		0.284	0.602
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	104	97
Adrenal: Pheochromocytoma (b)	17/48(35)	12/50(24)	11/48(23)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.678	0.647
Lower Limit		0.333	0.309
Upper Limit		1.338	1.301
Weeks to First Observed Tumor	84	75	86

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing D & C Red No. 9 (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Thyroid: C-Cell Carcinoma (b)	2/50(4)	4/50(8)	3/47(6)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		2.000	1.596
Lower Limit		0.301	0.191
Upper Limit		21.316	18.399
Weeks to First Observed Tumor	76	104	104
Thyroid: C-Cell Adenoma (b)	3/50(6)	2/50(4)	0/47(0)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.667	0.000
Lower Limit		0.058	0.000
Upper Limit		5.570	1.766
Weeks to First Observed Tumor	97	104	--
Thyroid: C-Cell Adenoma or Carcinoma (b)	5/50(10)	6/50(12)	3/47(6)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.200	0.638
Lower Limit		0.326	0.104
Upper Limit		4.660	3.088
Weeks to First Observed Tumor	76	104	104

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing D & C Red No. 9 (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Pancreatic Islets: Islet-Cell Carcinoma (b)	0/47(0)	4/49(8)	1/39(3)
P Values (c),(d)	N.S.	N.S.	N.S.
Departure from Linear Trend (f)	P=0.032		
Relative Risk (Control) (e)		Infinite	Infinite
Lower Limit		0.891	0.065
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	104	104
Pancreatic Islets: Islet-Cell Adenoma or Carcinoma (b)	1/47(2)	4/49(8)	1/39(3)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		3.837	1.205
Lower Limit		0.399	0.016
Upper Limit		184.905	92.192
Weeks to First Observed Tumor	102	104	104
Preputial Gland: Carcinoma, NOS (b)	3/50(6)	1/50(2)	0/50(0)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.333	0.000
Lower Limit		0.006	0.000
Upper Limit		3.983	1.663
Weeks to First Observed Tumor	102	104	--

Table 8. Analyses of the Incidence of Primary Tumors in Male Rats Fed Diets Containing D & C Red No. 9 (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Preputial Gland: All tumors	7/50(14)	2/50(4)	0/50(0)
P Values (c),(d)	P=0.007(N)	N.S.	P=0.006(N)
Relative Risk (Control) (e)		0.286	0.000
Lower Limit		0.030	0.000
Upper Limit		1.411	0.515
Weeks to First Observed Tumor	102	104	--
Testis: Interstitial-Cell Tumor (b)	49/50(98)	48/50(96)	47/48(98)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.980	0.999
Lower Limit		0.941	0.959
Upper Limit		1.051	1.041
Weeks to First Observed Tumor	69	67	68

(a) Dosed groups received doses of 1,000 or 3,000 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 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing D & C Red No. 9 (a)

Topography: Morphology	Control	Low Dose	High Dose
Hematopoietic System:			
Lymphocytic Leukemia (b)	10/50(20)	2/50(4)	1/50(2)
P Values (c),(d)	P=0.004(N)	P=0.014(N)	P=0.004(N)
Relative Risk (Control) (e)		0.200	0.100
Lower Limit		0.022	0.002
Upper Limit		0.877	0.662
Weeks to First Observed Tumor	62	100	98
Hematopoietic System:			
Leukemia (b)	10/50(20)	3/50(6)	1/50(2)
P Values (c),(d)	P=0.004(N)	P=0.036(N)	P=0.004(N)
Relative Risk (Control) (e)		0.300	0.100
Lower Limit		0.056	0.002
Upper Limit		1.083	0.662
Weeks to First Observed Tumor	62	90	98
Hematopoietic System:			
Lymphoma or Leukemia (b)	11/50(22)	5/50(10)	3/50(6)
P Values (c),(d)	P=0.021(N)	N.S.	P=0.020(N)
Relative Risk (Control) (e)		0.455	0.273
Lower Limit		0.133	0.052
Upper Limit		1.306	0.958
Weeks to First Observed Tumor	62	22	20

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing D & C Red No. 9 (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Liver: Neoplastic Nodule (b)	1/50(2)	1/50(2)	5/50(10)
P Values (c),(d)	P=0.039	N.S.	N.S.
Relative Risk (Control) (e)		1.000	5.000
Lower Limit		0.013	0.588
Upper Limit		76.970	231.346
Weeks to First Observed Tumor	104	104	104
Pituitary: Adenoma, NOS (b)	5/43(12)	2/46(4)	2/47(4)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.374	0.366
Lower Limit		0.037	0.036
Upper Limit		2.149	2.105
Weeks to First Observed Tumor	104	104	104
Pituitary: Chromophobe Adenoma (b)	16/43(37)	15/46(33)	20/47(43)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.876	1.144
Lower Limit		0.465	0.656
Upper Limit		1.650	2.030
Weeks to First Observed Tumor	102	70	91

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing D & C Red No. 9 (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma or Carcinoma (b)	18/43(42)	16/46(35)	20/47(43)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.831	1.017
Lower Limit		0.462	0.599
Upper Limit		1.492	1.745
Weeks to First Observed Tumor	93	70	91
Adrenal: Cortical Adenoma (b)	3/48(6)	3/49(6)	4/50(8)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.980	1.280
Lower Limit		0.138	0.229
Upper Limit		6.979	8.332
Weeks to First Observed Tumor	104	104	104
Adrenal: Pheochromocytoma (b)	3/48(6)	3/49(6)	4/50(8)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.980	1.280
Lower Limit		0.138	0.229
Upper Limit		6.979	8.332
Weeks to First Observed Tumor	86	104	104

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing D & C Red No. 9 (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant (b)	3/48(6)	4/49(8)	5/50(10)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.306	1.600
Lower Limit		0.233	0.330
Upper Limit		8.495	9.811
Weeks to First Observed Tumor	86	72	104
Thyroid: C-Cell Adenoma (b)	2/47(4)	3/50(6)	0/50(0)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.410	0.000
Lower Limit		0.169	0.000
Upper Limit		16.282	3.177
Weeks to First Observed Tumor	104	104	--
Thyroid: C-Cell Carcinoma (b)	3/47(6)	4/50(8)	2/50(4)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.253	0.627
Lower Limit		0.224	0.054
Upper Limit		8.156	5.232
Weeks to First Observed Tumor	104	104	104

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing D & C Red No. 9 (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Thyroid: C-Cell Adenoma or Carcinoma (b)	5/47(11)	7/50(14)	2/50(4)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.316	0.376
Lower Limit		0.387	0.037
Upper Limit		4.915	2.172
Weeks to First Observed Tumor	104	104	104
Mammary Gland: Fibroadenoma (b)	10/50(20)	7/50(14)	8/50(16)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.700	0.800
Lower Limit		0.246	0.299
Upper Limit		1.869	2.060
Weeks to First Observed Tumor	79	104	98
Uterus: Endometrial Stromal Polyp (b)	11/50(22)	13/49(27)	10/50(20)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.206	0.909
Lower Limit		0.554	0.381
Upper Limit		2.675	2.140
Weeks to First Observed Tumor	93	96	104

Table 9. Analyses of the Incidence of Primary Tumors in Female Rats Fed Diets Containing D & C Red No. 9 (a)

(Continued)

(a) Dosed groups received doses of 1,000 or 3,000 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.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs

Throughout the study, mean body weights of dosed and control male mice were comparable (Figure 3 and Table 10). After week 50, the mean body weight of high-dose female mice was slightly lower than that of the controls. No compound-related clinical signs were observed. Feed consumption by dosed mice of either sex was comparable with that of the corresponding controls (Appendix H).

B. Survival

Estimates of the probabilities of survival of male and female mice administered D & C Red No. 9 in the diet at the concentrations of this bioassay, together with those of the control group, are shown by the Kaplan and Meier curves in Figure 4. No significant differences were observed in the survival of any group of either sex of mice.

In male mice, 42/50 (84%) of the controls, 40/50 (80%) of the low-dose, and 39/50 (78%) of the high-dose group lived to the end of the study at 104-105 weeks. In female mice, 40/50 (80%) of the controls, 40/50 (80%) of the low-dose, and 41/50 (82%) of the high-dose group lived to the end of the study at 105 weeks.

A sufficient number of mice were at risk for the development of late appearing tumors.

C. Pathology

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 each individual animal in the male and female mice studies, respectively. Findings on nonneoplastic lesions are summarized in Appendix D, Tables D1 and D2.

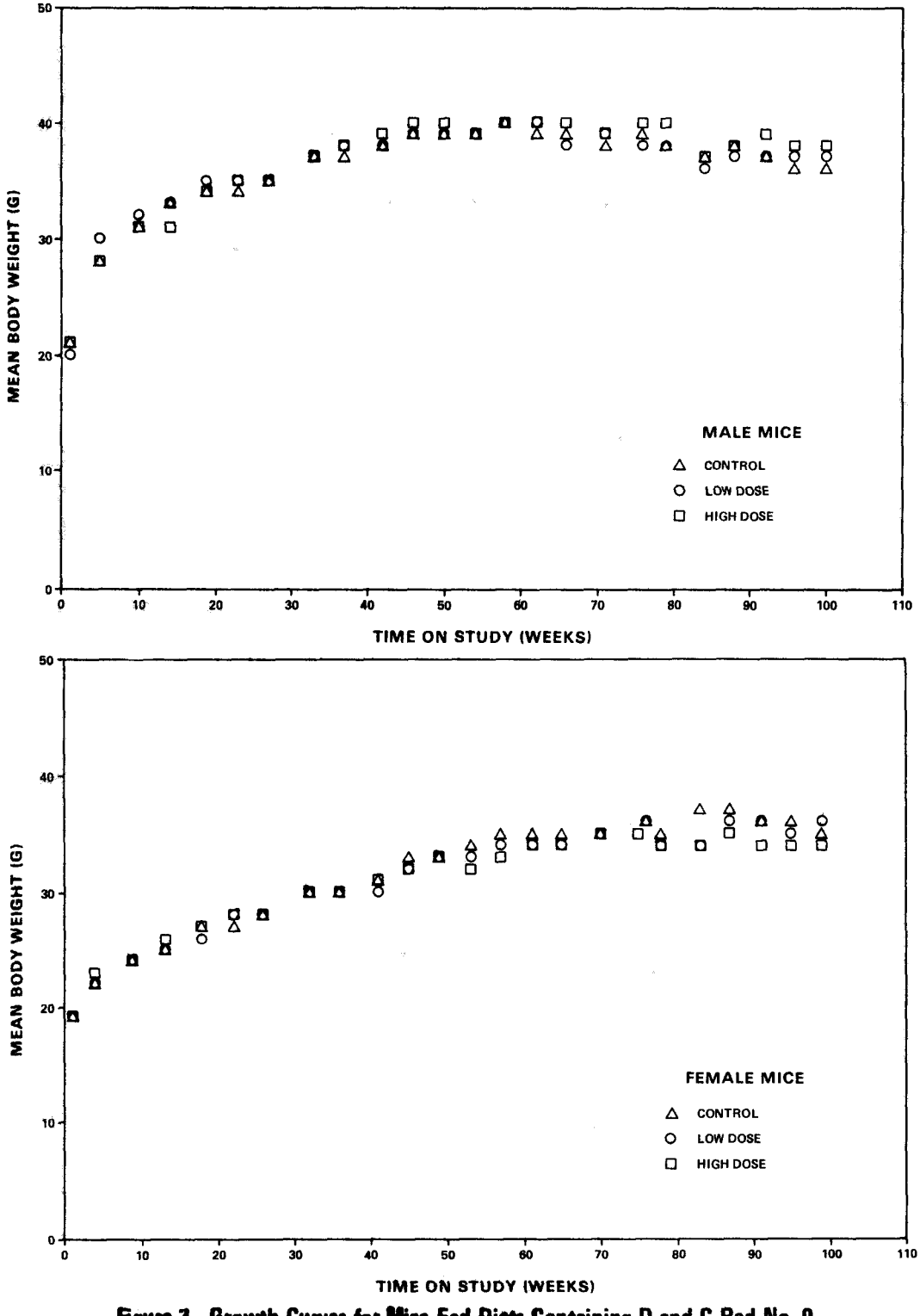


Figure 3. Growth Curves for Mice Fed Diets Containing D and C Red No. 9

Table 10. Mean Body Weight Change (Relative to Controls) of Mice Fed Diets Containing D and C Red No. 9

Week No.	Cumulative Mean Body Weight Change (grams)			Weight Change (%) Relative to Controls (a)	
	Controls	Low Dose	High Dose	Low Dose	High Dose
Males					
0	21 (b)	20 (b)	21 (b)		
5	7	10	7	+43	0
27	14	15	14	+ 7	0
46	18	19	19	+6	+ 6
66	18	18	19	0	+ 6
88	17	17	17	0	0
100	15	17	17	+13	+13
Females					
0	19 (b)	19 (b)	19 (b)		
4	3	3	4	0	+33
26	9	9	9	0	0
45	14	13	13	- 7	- 7
65	16	15	15	- 6	- 6
87	18	17	16	- 6	-11
99	16	17	15	+ 6	- 6

(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) Initial weight.

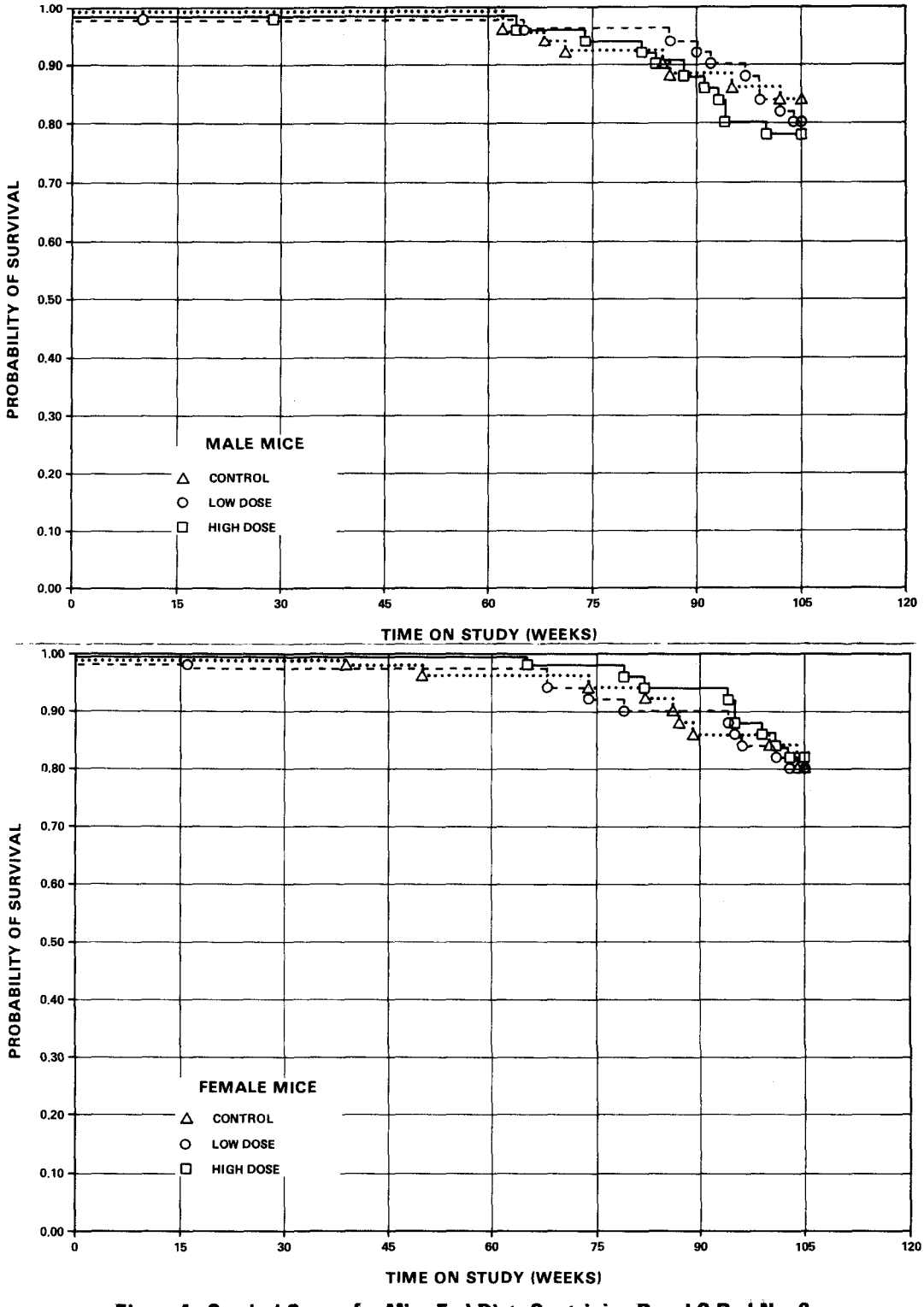


Figure 4. Survival Curves for Mice Fed Diets Containing D and C Red No. 9

Each type of neoplasm represented has been encountered previously as a spontaneous lesion in the mouse. Undifferentiated sarcomas arising in the skin or subcutaneous tissues, usually of the back, were found in six low-dose male mice. This type of anaplastic sarcoma is not unusual in male mice. This tumor type was observed in 12% of the low-dose males compared with 2% in the controls; however, no similar neoplasms were observed in high-dose males.

A variety of nonneoplastic lesions is represented among both control and dosed animals. The lesions are considered to be spontaneous in these animals. Such lesions have been encountered previously as spontaneous occurrences in aging laboratory mice.

In conclusion, histopathologic examination provided no evidence for the carcinogenicity of D & C Red No. 9 in B6C3F1 mice.

D. Statistical Analyses of Results

Tables 11 and 12 contain the statistical analyses of those primary tumors that met both of the following criteria: (1) At least two animals in one group had the tumor, and (2) The incidence in one or more groups was at least 5%.

Sarcomas of the skin in male mice were observed in increased incidence in the low-dose group compared with the other two groups (0/50, 0% in the controls; 5/50, 10% in the low-dose; 0/50, 0% in the high-dose). The Cochran-Armitage test for linear trend was not significant, and there was a departure from linear trend (P=0.002) due to the sharp increase of incidence in the low-dose group compared with the other two groups. The Fisher exact test between the low-dose group and the control group was significant (P=0.028), but this value is greater than 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. Statistical tests of the combined incidences of male mice with sarcomas and fibrosarcomas of the skin and subcutaneous tissue were not statistically significant (2/50, 4% in the controls; 6/50, 12% in the low-dose; 0/50, 0% in the high-dose), although there was a departure from linear trend (P=0.010) due to the increased incidence in the low-dose group. No significant incidence was observed in the high-dose group. This tumor type was not observed in female mice in a statistically significant incidence.

Hepatocellular carcinomas of the liver in male mice were observed in increased incidence in the dosed groups compared with the control group (4/50, 8% in the controls; 9/50, 18% in the low-dose; 11/50, 22% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant in the positive direction (P=0.038). The Fisher exact test between the high-dose group and the matched control group indicates a value of P=0.045. This value 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 record at this laboratory of male mice with hepatocellular carcinomas is 65/297 (22%). This tumor was not observed in female mice in statistically significant proportions.

Malignant lymphomas (mixed type) of the hematopoietic system in female mice were observed in increased incidence in the high-dose group (2/50, 4% in the controls; 2/50, 4% in the low-dose; 7/49, 14% in the high-dose). The Cochran-Armitage test for linear trend was statistically significant in the positive direction (P=0.040). The Fisher exact tests were not significant. The combined incidence of female mice with any type of lymphoma was not significant, and no significant results were found for this type of tumor in male mice.

Only two male and two female mice died before 52 weeks on study; therefore, time-adjusted tests eliminating those animals that died before week 52 did not alter the results.

Life table analyses, using the week in which an animal died naturally or was killed as a time point, did not materially change the results reported above.

In conclusion, there is no site in mice of either sex at which an increase in tumor incidence could be associated unequivocally with the administration of the chemical.

Table 11. Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing D & C Red No. 9 (a)

Topography: Morphology	Control	Low Dose	High Dose
Skin: Sarcoma, NOS (b)	0/50(0)	5/50(10)	0/50(0)
P Values (c),(d)	N.S.	P=0.028	N.S.
Departure from Linear Trend (e)	P=0.002		
Relative Risk (Control) (f)		Infinite	--
Lower Limit		1.261	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	65	--
Skin or Subcutaneous Tissue: Fibrosarcoma or Sarcoma, NOS (b)	2/50(4)	6/50(12)	0/50(0)
P Values (c),(d)	N.S.	N.S.	N.S.
Departure from Linear Trend (e)	P=0.010		
Relative Risk (Control) (f)		3.000	0.000
Lower Limit		0.569	0.000
Upper Limit		29.254	3.381
Weeks to First Observed Tumor	95	65	--
Lung: Alveolar/Bronchiolar Adenoma (b)	2/50(4)	3/50(6)	1/50(2)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Matched Control) (f)		1.500	0.500
Lower Limit		0.180	0.009
Upper Limit		17.329	9.290
Weeks to First Observed Tumor	104	105	105

Table 11. Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing D & C Red No. 9 (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma (b)	2/50(4)	1/50(2)	4/50(8)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (f)		0.500	2.000
Lower Limit		0.009	0.301
Upper Limit		9.290	21.316
Weeks to First Observed Tumor	85	105	74
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma (b)	4/50(8)	4/50(8)	5/50(10)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (f)		1.000	1.250
Lower Limit		0.197	0.286
Upper Limit		5.083	5.954
Weeks to First Observed Tumor	85	105	74
Hematopoietic System: Malignant Lymphoma, Histiocytic Type (b)	4/50(8)	2/50(4)	3/50(6)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (f)		0.500	0.750
Lower Limit		0.047	0.115
Upper Limit		3.318	4.206
Weeks to First Observed Tumor	102	86	82

Table 11. Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing D & C Red No. 9 (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Hematopoietic System: All Malignant Lymphomas (b)	5/50(10)	4/50(8)	4/50(8)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (f)		0.800	0.800
Lower Limit		0.168	0.168
Upper Limit		3.499	3.499
Weeks to First Observed Tumor	102	86	29
Liver: Hepatocellular Adenoma (b)	4/50(8)	4/50(8)	4/50(8)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (f)		1.000	1.000
Lower Limit		0.197	0.197
Upper Limit		5.083	5.083
Weeks to First Observed Tumor	104	105	105
Liver: Hepatocellular Carcinoma (b)	4/50(8)	9/50(18)	11/50(22)
P Values (c),(d)	P=0.038	N.S.	P=0.045
Relative Risk (Control) (f)		2.250	2.750
Lower Limit		0.676	0.882
Upper Limit		9.394	11.094
Weeks to First Observed Tumor	68	65	74

Table 11. Analyses of the Incidence of Primary Tumors in Male Mice Fed Diets Containing D & C Red No. 9 (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Liver: Hepatocellular Adenoma or Carcinoma (b)	8/50(16)	13/50(26)	15/50(30)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (f)		1.625	1.875
Lower Limit		0.688	0.825
Upper Limit		4.120	4.631
Weeks to First Observed Tumor	68	65	74
Eye/Lacrimal Gland: Adenoma, NOS (b)	1/50(2)	3/50(6)	1/50(2)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (f)		3.000	1.000
Lower Limit		0.251	0.013
Upper Limit		154.270	76.970
Weeks to First Observed Tumor	104	105	105

(a) Dosed groups received doses of 1,000 or 2,000 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 probability level for departure from linear trend is given when P is less than 0.05 for any comparison.
(f) The 95 percent confidence interval of the relative risk between each dosed group and the control group.

Table 12. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing D & C Red No. 9 (a)

Topography: Morphology	Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	2/50(4)	1/50(2)	3/49(6)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.500	1.531
Lower Limit		0.009	0.183
Upper Limit		9.290	17.671
Weeks to First Observed Tumor	105	105	105
Hematopoietic System: Malignant Lymphoma, Histiocytic Type (b)	5/50(10)	11/50(22)	4/49(8)
P Values (c),(d)	N.S.	N.S.	N.S.
Departure from Linear Trend (f)	P=0.029		
Relative Risk (Control) (e)		2.200	0.816
Lower Limit		0.765	0.171
Upper Limit		7.508	3.567
Weeks to First Observed Tumor	74	94	79
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type (b)	4/50(8)	4/50(8)	1/49(2)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.000	0.255
Lower Limit		0.197	0.005
Upper Limit		5.083	2.459
Weeks to First Observed Tumor	39	68	105

Table 12. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing D & C Red No. 9 (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Hematopoietic System:			
Malignant Lymphoma,			
Mixed Type (b)	2/50(4)	2/50(4)	7/49(14)
P Values (c),(d)	P=0.040	N.S.	N.S.
Relative Risk (Control) (e)		1.000	3.571
Lower Limit		0.075	0.723
Upper Limit		13.326	33.856
Weeks to First Observed Tumor	105	96	105
Hematopoietic System:			
All Malignant Lymphomas (b)	11/50(22)	17/50(34)	12/49(24)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.545	1.113
Lower Limit		0.765	0.498
Upper Limit		3.257	2.511
Weeks to First Observed Tumor	39	68	79
Liver: Hepatocellular Adenoma (b)	1/50(2)	1/50(2)	4/49(8)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		1.000	4.082
Lower Limit		0.013	0.423
Upper Limit		76.970	196.665
Weeks to First Observed Tumor	105	105	105

Table 12. Analyses of the Incidence of Primary Tumors in Female Mice Fed Diets Containing D & C Red No. 9 (a)

(Continued)

Topography: Morphology	Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	4/50(8)	2/50(4)	2/49(4)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.500	0.510
Lower Limit		0.047	0.048
Upper Limit		3.318	3.383
Weeks to First Observed Tumor	105	79	105
Liver: Hepatocellular Adenoma or Carcinoma (b)	5/50(10)	3/50(6)	6/49(12)
P Values (c),(d)	N.S.	N.S.	N.S.
Relative Risk (Control) (e)		0.600	1.224
Lower Limit		0.098	0.333
Upper Limit		2.910	4.751
Weeks to First Observed Tumor	105	79	105

(a) Dosed groups received doses of 1,000 or 2,000 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.

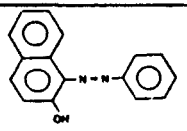
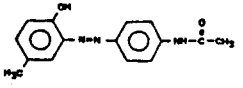
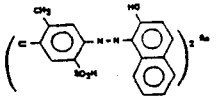
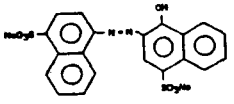
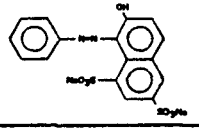
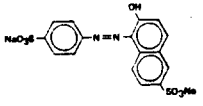
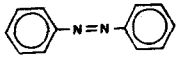
V. DISCUSSION

In subchronic studies with D & C Red No. 9, conducted to determine the toxic effects of administering the material for 13 weeks, several results of note were detected. The spleens of dosed rats were dark and enlarged two to five times when compared with controls. Pigment deposition (not further characterized) was observed in renal tubular epithelial cells and hemosiderosis was observed in livers from all dosed female rats and the majority of males receiving more than 6,000 ppm test material in the diet. These findings are consistent with those of Davis and Fitzhugh (1962) who observed splenomegaly and hepatomegaly in Osborne-Mendel rats of both sexes fed diets containing up to 20,000 ppm D & C Red No. 9 in a 20-week study. Similar findings were detected in male and female mice in the present study, particularly splenic congestion and hemosiderin deposition. In the absence of compound-related changes in body weight gain in either sex of both species, the dietary concentrations of D & C Red No. 9 selected for the chronic study (1,000 or 3,000 ppm for rats and 1,000 or 2,000 ppm for mice) were based on the histopathologic observations in the subchronic study.

Mean body weights of dosed and control rats of both sexes and of male mice were comparable throughout the chronic (2-year) study. After the 50th week, mean body weights of high-dose female mice were slightly lower than those of controls. The absence of compound-related effects on survival, weight gain, or clinical observations in rats and mice suggests that both species may have been able to tolerate higher doses of the test material.

In this bioassay, fibrosarcomas of the spleen were detected at significantly higher incidences in high-dose male rats when compared with concurrent controls. No splenic fibrosarcomas have been observed in 140 male F344 historical control rats at this laboratory. Thus, D & C Red No. 9 most likely caused the neoplastic splenic lesions observed in the present study. In reports on the bioassay of aniline (NCI, 1978), azobenzene (NCI, 1979), and p-chloroaniline (NCI, 1979a) the spleen was also the site of neoplastic lesions. Structural comparisons of these and other monoazo dyes are shown

Table 13. Comparison of Results of Chronic Feeding Studies of Water-Soluble and Water-Insoluble Monoazo Dyes and Related Compounds

Test Substance	Structure	Species	Sex	Dose (ppm)	Duration (Weeks)	Site and Type of Lesion Observed: Liver	Site and Type of Lesion Observed: Spleen
C. I. Solvent (a) Yellow 14 (NTP, 1982c) Water Insoluble		Rat (F344)	M	500	103	N (b)	
			F	500	103	N	
		Mouse (B6C3F1)	M	1,000	103		
			F	1,000	103		
C. I. Disperse (a) Yellow No. 3 (NTP, 1982b) Water Insoluble		Rat (F344)	M	10,000	103	N	
			F	10,000	103		
		Mouse (B6C3F1)	M	5,000	103		
			F	5,000	103	N	
D and C Red No. 9 (a) Water Insoluble		Rat (F344)	M	3,000	103	N	N
			F	3,000	103		
		Mouse (B6C3F1)	M	2,000	103		
			F	2,000	103		
C. I. Acid Red 14 (c) (NTP, 1982a) Water Soluble		Rat (F344)	M	12,500	103		
			F	25,500	103		
		Mouse (B6C3F1)	M	6,000	103		
			F	6,000	103		
C. I. Acid Orange 10 (c) (NTP, 1982) Water Soluble		Rat (F344)	M	3,000 (d)	103	D (e)	
			F	3,000 (d)	103		
		Mouse (B6C3F1)	M	6,000 (d)	103		
			F	6,000 (d)	103		
FD and C Yellow (c) No. 6 (NTP, 1981) Water Soluble		Rat (F344)	M	25,000	103		
			F	25,000	103		
		Mouse (B6C3F1)	M	25,000	103		
			F	25,000	103		
Azobenzene (NCI, 1979) Water Insoluble		Rat (F344)	M	400	105-106		N
			F	400	105-106		N
		Mouse (B6C3F1)	M	400	105-106		
			F	545	105-106		
Aniline Hydrochloride (NCI, 1978) Water Soluble		Rat (F344)	M	6,000	103		N
			F	6,000	103		N
		Mouse (B6C3F1)	M	12,000	103		
			F	12,000	103		

(a) C. I. Solvent Yellow 14, D & C Red No. 9, and C. I. Disperse Yellow No. 3 were on test in the same room.
(b) N = Neoplastic lesion.
(c) C. I. Acid Red 14, C. I. Acid Orange 10, and FD & C Yellow No. 6 were on test in the same room.
(d) May not be maximum tolerated dose.
(e) D = Neoplastic lesion occurred only with significant dose related trend. Results of the Fisher exact test were not significant.

in Table 13. Induction of splenic sarcomas in each of these previous positive studies was dose related, as was the increase of this type of sarcoma in male rats in the current bioassay.

Evidence of nonneoplastic toxic effects of D & C Red No. 9 is provided by the detection of splenic congestion in 14 of 48 male rats from the high-dose group. Either focal or diffuse fibrosis was found in the spleens of both high-dose males and females. These lesions ranged from multifocal areas of fibroblastic proliferation in the red pulp to areas of proliferation of pleomorphic spindle cells. The association between administration of D & C Red No. 9 in the diet and splenic neoplasia in male rats and splenic toxicity in rats of both sexes is unequivocal.

In their 2-year chronic bioassay of D & C Red No. 9 in Osborne-Mendel rats, Davis and Fitzhugh (1962) noted splenic enlargement and slight bone marrow hyperplasia at doses similar to those employed in the current study. Hemosiderosis of the spleen and renal tubular pigmentation was described in the former study at dose levels substantially higher than those in this bioassay. Davis and Fitzhugh found no carcinogenic effects in Osborne-Mendel rats attributable to their D & C Red No. 9 preparation, although the dose levels administered were substantially higher than those utilized in this study.

Significantly increased incidences of neoplastic nodules in the liver were detected in both dosed groups of male rats and a significant positive trend was found in female rats. The interpretation of these findings remains the subject of considerable scientific debate, since the absolute determination of the potential malignancy of these lesions has not yet been clearly defined. However, Hirota and Williams (1979) have confirmed the neoplastic nature of this type of nodule by observing continued growth after cessation of administration of N-2-fluorenylacetamide. These authors used well defined criteria for nodules in livers of F344 rats. Moreover, these nodules are considered to be true neoplasms by other investigators and are

indicative of a potential carcinogenic risk to humans (Squire and Levitt, 1975; National Academy of Sciences, 1980; IARC, 1980). Therefore, the increased incidence of neoplastic nodules observed in the current study can be considered to be indicative of a carcinogenic effect of D & C Red No. 9.

A compound-related decrease in lymphocytic leukemia was observed in male and female rats. Although the interpretation of this finding is unclear, administration of four other monoazo compounds (C.I. Solvent Yellow 14, C.I. Disperse Yellow 3, C.I. Acid Red 14 and C.I. Acid Orange 10) in other studies in the Bioassay Program has also been associated with decreased incidences of lymphocytic leukemia in F344 rats. In contrast to the results in rats, malignant lymphomas of the mixed type were increased in high-dose female mice in the present study; however, this increase was not statistically significant.

Statistically significant increased incidences of hepatocellular carcinomas were found in male mice after administration of D and C Red No. 9 in the diet. However, an absolute conclusion of carcinogenicity due to administration of the test material is precluded since the incidences of hepatocellular carcinomas in the high-dose and low-dose mice (11/50, 22% and 9/50, 18%) are similar to the historical control rate for male mice in this laboratory (65/297, 22%). Also, when the hepatocellular carcinomas are combined with the incidences of hepatocellular adenomas (total tumors: 8/50, 13/50, 15/50) the differences are not statistically significant. The increased incidences of anaplastic sarcomas of the skin in the low-dose male mice were also ruled out as carcinogenic effects of the test material because of the absence of these sarcomas in the high-dose group.

Azo dyes can be reduced by intestinal bacteria (Childs et al., 1967; Radomski, 1961; and Ryan et al., 1968). The relative toxicity of these dyes can be correlated with the lipid solubility of their metabolites after reductive cleavage of the azo bond (Radomski, 1974). Lipid soluble compounds are more readily absorbed across the gastrointestinal tract than water soluble compounds (Doull et al., 1980). The presence or absence of carcinogenic effects from the azo dyes studied in the Bioassay Program (Table 13)

might be correlated with the extent of absorption of the dyes and their metabolites -- absorption is greater for water insoluble dyes which yield lipid soluble metabolites and is less for water soluble dyes which yield lipid insoluble metabolites.

D & C Red No. 9 is a barium-containing pigment. Barium and its salts are known to be toxic to muscle and nervous tissue (Venugopal and Luckey, 1978). Although the toxicity of this metal is limited due to the insolubility of barium salts, a potential for barium toxicity must be recognized. However, it is unlikely that the splenic and hepatic findings in this study are due to the toxic effects of barium salts in the D & C Red No. 9 administered to the test animals.

VI. CONCLUSIONS

Under the conditions of this bioassay, D & C Red No. 9 was carcinogenic for male F344 rats causing an increased incidence of sarcomas of the spleen and a dose-related increase in neoplastic nodules of the liver. D & C Red No. 9 was not considered to be carcinogenic to female F344 rats, although the increased incidence of neoplastic nodules of the liver may have been associated with administration of the test chemical. D & C Red No. 9 was not carcinogenic for B6C3F1 mice of either sex.

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APPENDIX A

Summary of the Incidence of Neoplasms in Rats Fed Diets Containing D and C Red No. 9

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS FED DIETS CONTAINING D AND C RED NO. 9

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
FIBROUS HISTIOCYTOMA, MALIGNANT	1 (2%)		
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)
SQUAMOUS CELL CARCINOMA	1 (2%)		1 (2%)
SEBACEOUS ADENOMA	1 (2%)		
FIBROSARCOMA		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
KERATOACANTHOMA	1 (2%)		
FIBROMA	4 (8%)	1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA			1 (2%)
OSTEOSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)	1 (2%)	
LEUKEMIA,NOS		1 (2%)	1 (2%)
LYMPHOCYTIC LEUKEMIA	10 (20%)	2 (4%)	2 (4%)
#SPLEEN	(50)	(50)	(48)
FIBROMA		1 (2%)	
FIBROSARCOMA			17 (35%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
LEIOMYOSARCOMA			1 (2%)
OSTEOSARCOMA			5 (10%)
#SPLENIC CAPSULE	(50)	(50)	(48)
SARCOMA, NOS			1 (2%)
FIBROSARCOMA			1 (2%)
#SPLENIC RED PULP	(50)	(50)	(48)
FIBROSARCOMA			1 (2%)
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(50)	(48)
ANGIOSARCOMA			1 (2%)
HEMANGIOPERICYTOMA, NOS			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(49)
NEOPLASTIC NODULE		6 (12%)	7 (14%)
HEPATOCELLULAR CARCINOMA	1 (2%)		
FIBROSARCOMA, METASTATIC			2 (4%)
#PANCREAS	(47)	(49)	(39)
FIBROSARCOMA, INVASIVE			1 (3%)
#CECUM	(48)	(46)	(44)
ADENOMATOUS POLYP, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY/CORTEX	(50)	(50)	(49)
TUBULAR-CELL ADENOMA			1 (2%)
#KIDNEY/MEDULLA	(50)	(50)	(49)
TRANSITIONAL-CELL CARCINOMA	1 (2%)		
#URINARY BLADDER	(46)	(49)	(44)
TRANSITIONAL-CELL PAPILLOMA			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(44)	(44)	(44)
ADENOMA, NOS		1 (2%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CHROMOPHOBE ADENOMA	7 (16%)	7 (16%)	5 (11%)
CHROMOPHOBE CARCINOMA	1 (2%)	1 (2%)	
#ADRENAL	(48)	(50)	(48)
PHEOCHROMOCYTOMA	17 (35%)	12 (24%)	11 (23%)
PHEOCHROMOCYTOMA, MALIGNANT		2 (4%)	3 (6%)
GANGLIONEUROMA	1 (2%)	1 (2%)	1 (2%)
#THYROID	(50)	(50)	(47)
FOLLICULAR-CELL ADENOMA	2 (4%)	1 (2%)	2 (4%)
C-CELL ADENOMA	3 (6%)	2 (4%)	
C-CELL CARCINOMA	2 (4%)	4 (8%)	3 (6%)
#PARATHYROID	(41)	(41)	(37)
ADENOMA, NOS	1 (2%)	1 (2%)	
#PANCREATIC ISLETS	(47)	(49)	(39)
ISLET-CELL ADENOMA	1 (2%)		
ISLET-CELL CARCINOMA		4 (8%)	1 (3%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
FIBROMA	1 (2%)		
FIBROADENOMA	1 (2%)	1 (2%)	
*PREPUCE	(50)	(50)	(50)
KERATOACANTHOMA		1 (2%)	
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS	3 (6%)	1 (2%)	
ADENOMA, NOS	1 (2%)		
ADENOCARCINOMA, NOS	1 (2%)		
PAPILLARY ADENOMA	1 (2%)		
SEBACEOUS ADENOCARCINOMA		1 (2%)	
CYSTADENOMA, NOS	1 (2%)		
#TESTIS	(50)	(50)	(48)
INTERSTITIAL-CELL TUMOR	49 (98%)	48 (96%)	47 (98%)
NERVOUS SYSTEM			
#FOURTH VENTRICLE	(50)	(50)	(48)
OLIGODENDROGLIOMA		1 (2%)	

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#BRAIN	(50)	(50)	(48)
SQUAMOUS CELL CARCINOMA, METASTA	1 (2%)		
#CEREBRAL CORTEX	(50)	(50)	(48)
ASTROCYTOMA			1 (2%)
*SPINAL CORD	(50)	(50)	(50)
OSTEOSARCOMA, INVASIVE	1 (2%)		
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*VERTEBRAL COLUMN	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)		
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
FIBROSARCOMA			1 (2%)
MESOTHELIOMA, NOS	1 (2%)		
*MESENTERY	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
*TUNICA VAGINALIS	(50)	(50)	(50)
MESOTHELIOMA, NOS	1 (2%)	1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
FIBROSARCOMA			1 (2%)
FIBROSARCOMA, METASTATIC			8 (16%)
OSTEOSARCOMA			1 (2%)
OSTEOSARCOMA, METASTATIC			3 (6%)

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

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	11	6	20
MORIBUND SACRIFICE	7		
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	32	44	30
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	50	49	49
TOTAL PRIMARY TUMORS	119	104	122
TOTAL ANIMALS WITH BENIGN TUMORS	50	48	47
TOTAL BENIGN TUMORS	92	77	72
TOTAL ANIMALS WITH MALIGNANT TUMORS	24	16	35
TOTAL MALIGNANT TUMORS	25	20	42
TOTAL ANIMALS WITH SECONDARY TUMORS#	3		13
TOTAL SECONDARY TUMORS	4		14
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	2	7	7
TOTAL UNCERTAIN TUMORS	2	7	8
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS .			

@ INCLUDES AUTOLYZED ANIMALS

* 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 D AND C RED NO. 9

	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%)		
*SUBCUT TISSUE	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		
FIBROMA	1 (2%)	1 (2%)	1 (2%)
FIBROSARCOMA	1 (2%)		
CARCINOSARCOMA			1 (2%)
OSTEOSARCOMA	2 (4%)		
RESPIRATORY SYSTEM			
NONE			
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	2 (4%)
LEUKEMIA,NOS		1 (2%)	
LYMPHOCYTIC LEUKEMIA	10 (20%)	2 (4%)	1 (2%)
*SUBCUT TISSUE	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	
#THYMUS	(47)	(41)	(42)
CARCINOMA,NOS		1 (2%)	
CIRCULATORY SYSTEM			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE	1 (2%)	1 (2%)	5 (10%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
TUBULAR-CELL ADENOMA	1 (2%)		
TUBULAR-CELL ADENOCARCINOMA			1 (2%)
#U. BLADDER/MUCOSA	(49)	(47)	(48)
PAPILLOMA, NOS			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(43)	(46)	(47)
ADENOMA, NOS	5 (12%)	2 (4%)	2 (4%)
CHROMOPHOBE ADENOMA	16 (37%)	15 (33%)	20 (43%)
CHROMOPHOBE CARCINOMA	2 (5%)	1 (2%)	
#ADRENAL	(48)	(49)	(50)
CORTICAL ADENOMA	3 (6%)	3 (6%)	4 (8%)
PHEOCHROMOCYTOMA	3 (6%)	3 (6%)	4 (8%)
PHEOCHROMOCYTOMA, MALIGNANT		1 (2%)	1 (2%)
GANGLIONEUROMA		1 (2%)	
#THYROID	(47)	(50)	(50)
C-CELL ADENOMA	2 (4%)	3 (6%)	
C-CELL CARCINOMA	3 (6%)	4 (8%)	2 (4%)
#THYROID FOLLICLE	(47)	(50)	(50)
PAPILLARY CARCINOMA	1 (2%)		
#PARATHYROID	(33)	(40)	(38)
ADENOMA, NOS			2 (5%)
#PANCREATIC ISLETS	(49)	(49)	(49)
ISLET-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)	1 (2%)	2 (4%)

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
PAPILLARY ADENOMA			1 (2%)
PAPILLARY ADENOCARCINOMA	1 (2%)		
FIBROADENOMA	10 (20%)	7 (14%)	8 (16%)
*CLITORAL GLAND	(50)	(50)	(50)
CARCINOMA,NOS		1 (2%)	
ADENOMA, NOS		1 (2%)	
ADENOCARCINOMA, NOS			1 (2%)
#UTERUS	(50)	(49)	(50)
ADENOCARCINOMA, NOS	1 (2%)		
ENDOMETRIAL STROMAL POLYP	11 (22%)	13 (27%)	10 (20%)
NERVOUS SYSTEM			
#BRAIN	(50)	(48)	(49)
CHROMOPHOBE CARCINOMA, INVASIVE		1 (2%)	
#CEREBRAL HEMISPHERE	(50)	(48)	(49)
GLIOMA, NOS	1 (2%)		
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

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

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATHa	10	9	7
MORIBUND SACRIFICE	2	1	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	38	40	41
ANIMAL MISSING			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	44	42	40
TOTAL PRIMARY TUMORS	79	65	70
TOTAL ANIMALS WITH BENIGN TUMORS	35	35	36
TOTAL BENIGN TUMORS	53	51	55
TOTAL ANIMALS WITH MALIGNANT TUMORS	22	12	9
TOTAL MALIGNANT TUMORS	25	13	10
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	1	1	5
TOTAL UNCERTAIN TUMORS	1	1	5
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

a INCLUDES AUTOLYZED ANIMALS

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

TABLE A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF D & C RED NO. 9

CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	100	104	103	104	104	104	104	104	103	076	102	082	104	104	071	104	104	104	091	097	104	092	084	096	104
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA																				X					
SEBACEOUS ADENOMA												X													
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
KERATOACANTHOMA																									
FIBROMA											X							X							X
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT																								X	
OSTEOSARCOMA, METASTATIC																			X						
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	-	+	+
THYMUS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	-	-	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA				X																					
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRANSITIONAL-CELL CARCINOMA				X																					
URINARY BLADDER	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	+	+
CHROMOPHOBE ADENOMA										X															
CHROMOPHOBE CARCINOMA																									
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA	X		X	X				X										X				X		X	
GANGLIONEUROMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA			X																			X			
C-CELL ADENOMA			X																						
C-CELL CARCINOMA										X															
PARATHYROID	+	-	+	-	+	-	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	-	+	+	+
ADENOMA, NOS	X																								
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	+	+	+	N	N	N	+	N	N	+	N	N	N	+	+	N	N	+	N	N
FIBROMA								X																	
FIBROADENOMA																								X	
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS		X									X														
ADENOMA, NOS																									
ADENOCARCINOMA, NOS					X																				
PAPILLARY ADENOMA																		X							
CYSTADENOMA, NOS																						X			
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT																				X					
SPINAL CORD	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N
OSTEOSARCOMA, INVASIVE																			X						
SPECIAL SENSE ORGANS																									
ZYMBAL'S 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
SQUAMOUS CELL CARCINOMA																								X	
MUSCULOSKELETAL SYSTEM																									
BONE	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
OSTEOSARCOMA																			X						
BODY CAVITIES																									
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA, NOS									X																
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MESOTHELIOMA, NOS																							X		
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROUS HISTIOCYTOMA, MALIGNANT																									
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																						X			
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									X
LYMPHOCYTIC LEUKEMIA	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 A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	097	104	104	104	104	104	104	104	104	104	104	103	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SQUAMOUS CELL CARCINOMA																										1
SEBACEOUS ADENOMA																										1
SUBCUTANEOUS TISSUE	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
KERATOACANTHOMA											X															1
FIBROMA															X											4
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT																										1
OSTEOSARCOMA, METASTATIC																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	44
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
PANCREAS	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LARGE INTESTINE	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRANSITIONAL-CELL CARCINOMA																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	44
CHROMOPHOBE ADENOMA							X			X					X			X				X	X		7
CHROMOPHOBE CARCINOMA			X																							1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
PHEOCHROMOCYTOMA		X	X			X			X		X	X			X		X					X			X	17
GANGLIONEUROMA				X																						1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA																										2
C-CELL ADENOMA													X										X			3
C-CELL CARCINOMA									X																	2
PARATHYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	–	+	+	+	+	+	41
ADENOMA, NOS																										1
PANCREATIC ISLETS	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ISLET-CELL ADENOMA										X																1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	+	N	N	N	N	N	N	N	N	N	+	+	N	+	N	+	N	N	N	N	N	N	N	+	50M
FIBROMA																										1
FIBROADENOMA																										1
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	49
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N	X	N	N	N	50M
CARCINOMA, NOS																										3
ADENOMA, NOS																										1
ADENOCARCINOMA, NOS																										1
PAPILLARY ADENOMA																										1
CYSTADENOMA, NOS																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT																										1
SPINAL CORD	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	50M
OSTEOSARCOMA, INVASIVE																										1
SPECIAL SENSE ORGANS																										
ZYMBAL'S 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	50M
SQUAMOUS CELL CARCINOMA																										1
MUSCULOSKELETAL SYSTEM																										
BONE	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	50M
OSTEOSARCOMA																										1
BODY CAVITIES																										
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
MESOTHELIOMA, NOS																										1
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
MESOTHELIOMA, NOS																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N	N	N	50M
FIBROUS HISTIOCYTOMA, MALIGNANT																										1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
LYMPHOCYTIC LEUKEMIA	X							X					X					X		X			X	X		10

* 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 A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF D & C RED NO. 9

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	104	104	104	103	067	104	104	104	104	104	078	104	092	104	104	104	104	104	104	104	104	095	104	104
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA				X																					
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																									X
LYMPH NODES	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
THYMUS	+	+	+	+	+	-	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE		X		X																					
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	+	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	-	-	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS								X					X												
CHROMOPHOBE ADENOMA																			X						
CHROMOPHOBE CARCINOMA																				X					
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA	X		X	X	X					X									X						
PHEOCHROMOCYTOMA, MALIGNANT																				X					
GANGLIONEUROMA																						X			
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA	X																								
C-CELL ADENOMA			X																						
C-CELL CARCINOMA				X						X															
PARATHYROID	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	M	+	+	+	-	+	+	-	+	-
ADENOMA, NOS																			X						
PANCREATIC ISLETS	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL CARCINOMA			X							X	X														
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	+	N	N	N	N	+	N	+	N	N	+	N	+	N	+	N	N	N	N	N	+	N
FIBROADENOMA				X																					
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
PENIS	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
KERATOACANTHOMA																									
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS					X																				
SEBACEOUS ADENOCARCINOMA																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
OLIGODENDROGLIOMA								X																	
BODY CAVITIES																									
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MESOTHELIOMA, NOS																									
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS																				X					
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, HISTIOCYTIC TYPE														X									X		
LEUKEMIA,NOS																									
LYMPHOCYTIC LEUKEMIA						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 A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	026	027	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	50M
FIBROSARCOMA																									1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	50M
FIBROMA																							X		1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROMA																									1
LYMPH NODES	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	43
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+		46
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE							X								X				X			X			6
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	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	48
LARGE INTESTINE	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																									
PITUITARY	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
ADENOMA, NOS																		+							1
CHROMOPHOBE ADENOMA			X										X	X				X			X				7
CHROMOPHOBE CARCINOMA																									1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA							X			X		X							X				X		12
PHEOCHROMOCYTOMA, MALIGNANT		X																							2
GANGLIONEUROMA																	X								1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA																									1
C-CELL ADENOMA										X															2
C-CELL CARCINOMA		X																	X						4
PARATHYROID	+	-	+	+	+	+	-	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	-	+	41
ADENOMA, NOS																									1
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL CARCINOMA				X																					4
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	+	N	N	N	+	N	N	N	+	+	N	+	+	N	+	+	+	N	50M
FIBROADENOMA																									1
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	48
PROSTATE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
PENIS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
KERATOACANTHOMA																					X				1
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
CARCINOMA,NOS																									1
SEBACEOUS ADENOCARCINOMA			X																						1
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
OLIGODENDROGLIOMA																									1
BODY CAVITIES																									
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
MESOTHELIOMA, NOS					X																				1
MESENTERY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
SARCOMA, NOS																									1
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									1
LEUKEMIA,NOS																									1
LYMPHOCYTIC LEUKEMIA																									2

M 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 A3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE 2-YEAR STUDY OF D & C RED NO. 9

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	097	104	104	098	104	047	041	041	041	041	041	041	041	082	041	085	101	104	103	104	104	097	097	086	104
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
SQUAMOUS CELL CARCINOMA	X																								
SUBCUTANEOUS TISSUE	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+
FIBROMA														X											
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA							X																		
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																								X	
FIBROSARCOMA			X	X	X				X		X			X	X			X	X			X	X		
LEIOMYOSARCOMA																									
ANGIOSARCOMA																X									
HEMANGIOPERICYTOMA, NOS																									
OSTEOSARCOMA		X																		X					X
LYMPH NODES	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+
THYMUS	-	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE												+										+			
FIBROSARCOMA, METASTATIC												X										X			
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	-	+	+	+	-	+	+	+	-	+	-	+	+	+	+	-	+	+	+	+	-	+	-	+
FIBROSARCOMA, INVASIVE														X											
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMATOUS POLYP, NOS		X																							
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOMA									X																
URINARY BLADDER	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
TRANSITIONAL-CELL PAPILLOMA									X																
ENDOCRINE SYSTEM																									
PITUITARY	-	+	+	+	+	+	-	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
CHROMOPHOBE ADENOMA																							X	X	
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA		X			X		X	X	X						X					X	X			X	
PHEOCHROMOCYTOMA, MALIGNANT																							X		
GANGLIONEUROMA													X												
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
FOLLICULAR-CELL ADENOMA								X																	
C-CELL CARCINOMA											X	X													
PARATHYROID	+	+	-	+	+	-	+	-	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
PANCREATIC ISLETS	+	-	+	+	+	-	+	+	+	-	+	-	+	+	+	+	-	+	+	+	-	+	-	+	
ISLET-CELL CARCINOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	+	N	N	N	N	N	+	+	+	+	N	N	+	N	N	N	N	+	N	N	N	N	+
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
PROSTATE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ASTROCYTOMA						X																			
BODY CAVITIES																									
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROSARCOMA																						X			
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROSARCOMA																							X		
FIBROSARCOMA, METASTATIC				X									X	X			X					X			
OSTEOSARCOMA																			X						
OSTEOSARCOMA, METASTATIC		X																		X					
LEUKEMIA,NOS																									
LYMPHOCYTIC LEUKEMIA											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 A3. MALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	110	101	106	107	101	104	104	107	104	104	104	104	073	092	107	096	084	103	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	50M
SQUAMOUS CELL PAPILLOMA																			X							1
SQUAMOUS CELL CARCINOMA																										1
SUBCUTANEOUS TISSUE	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	50M
FIBROMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	49
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	48
SARCOMA, NOS																										1
FIBROSARCOMA			X			X	X			X			X				X	X						X		10
LEIOMYOSARCOMA																							X			1
ANGIOSARCOMA																										1
HEMANGIOPERICYTOMA, NOS												X														1
OSTEOSARCOMA		X																						X		3
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	A	+	+	+	+	+	44
THYMUS	+	+	-	-	+	+	+	+	-	+	+	+	-	-	+	-	+	-	+	A	+	+	-	+	-	35
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	49
NEOPLASTIC NODULE						X						X											X	X		7
FIBROSARCOMA, METASTATIC							X											X								2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
PANCREAS	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	A	+	-	+	-	+	39
FIBROSARCOMA, INVASIVE																										1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	49
STOMACH	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	48
SMALL INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	A	+	+	+	+	+	45
LARGE INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	A	-	-	+	+	+	44
ADENOMATOUS POLYP, NOS																										1
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	49
TUBULAR-CELL ADENOMA																										1
URINARY BLADDER	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	44
TRANSITIONAL-CELL PAPILLOMA																										1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	44
CHROMOPHOBE ADENOMA											X							X			X					5
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	48
PHEOCHROMOCYTOMA						X							X										X			11
PHEOCHROMOCYTOMA, MALIGNANT																		X								3
GANGLIONEUROMA																										1
THYROID	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	47
FOLLICULAR-CELL ADENOMA	X																									2
C-CELL CARCINOMA							X																			3
PARATHYROID	-	+	-	-	-	-	+	+	+	+	-	+	+	+	+	+	+	+	+	A	-	+	+	+	+	37
PANCREATIC ISLETS	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	A	+	-	+	-	+	39
ISLET-CELL CARCINOMA					X																					1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	N	+	+	N	+	N	N	N	N	+	N	+	+	N	+	+	N	N	N	N	+	+	N	50M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	48
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	47
PROSTATE	+	+	-	+	+	+	-	+	-	+	+	+	+	+	+	+	+	-	+	A	+	+	+	+	+	42
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	48
ASTROCYTOMA																										1
BODY CAVITIES																										
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
FIBROSARCOMA																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
FIBROSARCOMA																										1
FIBROSARCOMA, METASTATIC			X						X				X													8
OSTEOSARCOMA																										1
OSTEOSARCOMA, METASTATIC		X																								3
LEUKEMIA,NOS																						X				1
LYMPHOCYTIC LEUKEMIA				X																						2

M ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

1: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE A4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE 2-YEAR STUDY OF D & C RED NO. 9

CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	062	104	104	104	104	104	093	104	104	104	104	104	104	104	104	104	104	104	104	101	093	104	104	102	104
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA																									
FIBROMA																									
FIBROSARCOMA																					X				
OSTEOSARCOMA																					X				
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE			X																						
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOMA																									
URINARY BLADDER	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS														X		X									X
CHROMOPHOBE ADENOMA			X	X	X								X		X			X				X		X	
CHROMOPHOBE CARCINOMA																					X				
ADRENAL	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA		X																		X					
PHEOCHROMOCYTOMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+
PAPILLARY CARCINOMA																									
C-CELL ADENOMA									X						X										
C-CELL CARCINOMA				X																					
PARATHYROID	+	-	+	+	-	+	+	+	+	+	+	-	+	-	+	+	-	+	+	+	+	+	+	-	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	N	+	+	+	+
ADENOMA, NOS																									
PAPILLARY ADENOCARCINOMA																									X
FIBROADENOMA						X						X		X											
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									
ENDOMETRIAL STROMAL POLYP					X	X			X	X			X										X		X
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GLIOMA, NOS																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE										X															
LYMPHOCYTIC LEUKEMIA	X			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. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	089	104	104	104	104	093	086	104	105	079	094	104	070	080	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SQUAMOUS CELL CARCINOMA									X																	1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SQUAMOUS CELL CARCINOMA														X												1
FIBROMA								X																		1
FIBROSARCOMA																										1
OSTEOSARCOMA	X																									2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	47
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
PANCREAS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOMA		X																								1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	-	+	-	+	+	+	+	-	+	+	-	+	-	+	-	+	+	+	+	-	+	43
ADENOMA, NOS		X																					X			5
CHROMOPHOBE ADENOMA	X			X		X					X							X			X	X			X	16
CHROMOPHOBE CARCINOMA														X												2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	48
CORTICAL ADENOMA																				X						3
PHEOCHROMOCYTOMA						X		X	X																	3
THYROID	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	47
PAPILLARY CARCINOMA				X																						1
C-CELL ADENOMA																										2
C-CELL CARCINOMA										X													X			3
PARATHYROID	-	+	+	+	+	-	-	-	+	+	-	-	-	-	-	+	+	-	-	+	+	+	+	+	+	33
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	50M
ADENOMA, NOS				X																						1
PAPILLARY ADENOCARCINOMA																										1
FIBROADENOMA		X		X	X						X	X									X		X			10
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS																			X							1
ENDOMETRIAL STROMAL POLYP			X	X				X		X																11
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GLIOMA, NOS			X																							1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
LYMPHOCYTIC LEUKEMIA							X	X							X	X										10

M 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 OF FEMALE RATS IN THE 2-YEAR STUDY OF D & C RED NO. 9

LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	103	104	104	101	104	104	104
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																									
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																			X						
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	-	+	+	+	+
THYMUS	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+
CARCINOMA,NOS																									
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
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
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS										X															
CHROMOPHOBE ADENOMA		X				X		X					X	X	X					X	X			X	
CHROMOPHOBE CARCINOMA							X																		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA									X		X														
PHEOCHROMOCYTOMA					X					X															
PHEOCHROMOCYTOMA, MALIGNANT													X												
GANGLIONEUROMA																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA												X													
C-CELL CARCINOMA		X		X																				X	
PARATHYROID	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	+	-	+	+	+	+	-	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS																									
FIBROADENOMA			X											X									X	X	
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS																				X					
ADENOMA, NOS																		X							
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP			X		X			X	X											X		X			
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CHROMOPHOBE CARCINOMA, INVASIVE							X																		
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
LEUKEMIA,NOS																									
LYMPHOCYTIC LEUKEMIA											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. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER / WEEKS ON STUDY	026 104	027 104	028 104	029 080	030 104	031 073	032 104	033 104	034 104	035 104	036 096	037 104	038 086	039 104	040 104	041 104	042 022	043 104	044 104	045 104	046 104	047 104	048 104	049 078	050 072	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
FIBROMA													X													1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	45
THYMUS	+	+	+	+	+	–	+	+	+	–	–	+	+	+	–	+	–	+	+	+	+	+	+	+	–	41
CARCINOMA,NOS												X														1
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE												X														1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	48
SMALL INTESTINE	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	47
LARGE INTESTINE	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	–	+	47
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	46
ADENOMA, NOS					X																					2
CHROMOPHOBE ADENOMA	X													X					X		X		X		X	15
CHROMOPHOBE CARCINOMA																										1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	49
CORTICAL ADENOMA			X																							3
PHEOCHROMOCYTOMA																		X								3
PHEOCHROMOCYTOMA, MALIGNANT																								X		1
GANGLIONEUROMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-CELL ADENOMA														X								X				3
C-CELL CARCINOMA								X																		4
PARATHYROID	–	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	40
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA			X																							1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	50M
ADENOMA, NOS							X																			1
FIBROADENOMA												X				X		X								7
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
CARCINOMA,NOS																										1
ADENOMA, NOS																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	49
ENDOMETRIAL STROMAL POLYP		X			X			X			X	X				X				X						13
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	48
CHROMOPHOBE CARCINOMA, INVASIVE																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																	X									1
LEUKEMIA,NOS				X																						1
LYMPHOCYTIC LEUKEMIA																										2

M 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 OF FEMALE RATS IN THE 2-YEAR STUDY OF D & C RED NO. 9

HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	098	104	098	103	104	104	104	104	104	104	104	075	020	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																									
CARCINOSARCOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE		X												X											
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOCARCINOMA				X																					
URINARY BLADDER	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLOMA, NOS	X																								
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS								X																	
CHROMOPHOBE ADENOMA		X		X	X	X	X			X							X					X			X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																	X	X							X
PHEOCHROMOCYTOMA											X													X	
PHEOCHROMOCYTOMA, MALIGNANT																									
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL CARCINOMA								X	X																
PARATHYROID	-	+	+	+	-	+	+	-	+	+	+	+	-	+	+	+	+	+	+	-	+	+	-	-	+
ADENOMA, NOS																	X								
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	N	+	+	N	+	+	+	+	+	N	N	+	N	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS														X											
PAPILLARY ADENOMA					X																				
FIBROADENOMA			X					X	X								X					X	X		
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOCARCINOMA, NOS																			X						
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP							X	X										X	X	X				X	
OVARY	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
ZYMBAL'S 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
SQUAMOUS CELL CARCINOMA								X																	
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, HISTIOCYTIC TYPE													X												
LYMPHOCYTIC LEUKEMIA	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. FEMALE RATS: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER / WEEKS ON STUDY	026 110	027 105	028 108	029 104	030 104	031 104	032 104	033 104	034 104	035 101	036 104	037 104	038 104	039 104	040 104	041 104	042 104	043 109	044 092	045 104	046 104	047 091	048 104	049 104	050 104	TOTAL TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	50*
FIBROMA					X																					1
CARCINOSARCOMA																			X							1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
THYMUS	-	+	+	-	+	-	+	+	+	+	+	+	+	+	+	-	+	+	-	-	+	+	+	+	+	42
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE						X															X		X			5
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOCARCINOMA																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
PAPILLOMA, NOS																										1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	47
ADENOMA, NOS			X																							2
CHROMOPHOBE ADENOMA				X	X				X		X	X				X	X	X		X		X		X		20
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																				X						4
PHEOCHROMOCYTOMA				X							X															4
PHEOCHROMOCYTOMA, MALIGNANT												X														1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-CELL CARCINOMA																										2
PARATHYROID	-	+	-	+	+	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
ADENOMA, NOS								X																		2
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	50*
ADENOMA, NOS								X																		2
PAPILLARY ADENOMA																										1
FIBROADENOMA																							X	X		8
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*
ADENOCARCINOMA, NOS																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL POLYP				X		X											X							X		10
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
ZYMBAL'S 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*
SQUAMOUS CELL CARCINOMA																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50*
MALIG.LYMPHOMA, HISTIOCYTIC TYPE										X																2
LYMPHOCYTIC LEUKEMIA																										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

APPENDIX B

Summary of the Incidence of Neoplasms
in Mice Fed Diets Containing D and C Red No. 9

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE FED DIETS CONTAINING D AND C RED NO. 9

	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)
SARCOMA, NOS		5 (10%)	
FIBROSARCOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)	1 (2%)	
FIBROMA		1 (2%)	
LEIOMYOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)	3 (6%)	2 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	3 (6%)	1 (2%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	1 (2%)	4 (8%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	4 (8%)	2 (4%)	2 (4%)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
#JEJUNUM	(48)	(46)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#THYMUS	(33)	(28)	(34)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (3%)		
MALIGNANT LYMPHOMA, MIXED TYPE		1 (4%)	
CIRCULATORY SYSTEM			
#SPLEEN	(49)	(50)	(50)
HEMANGIOSARCOMA		1 (2%)	

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)	2 (4%)	1 (2%)
#TESTIS	(50)	(50)	(50)
HEMANGIOMA			1 (2%)
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
#SALIVARY GLAND	(50)	(50)	(50)
LEIOMYOSARCOMA, INVASIVE		1 (2%)	
#LIVER	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA	4 (8%)	4 (8%)	4 (8%)
HEPATOCELLULAR CARCINOMA	4 (8%)	9 (18%)	11 (22%)
#JEJUNUM	(48)	(46)	(47)
PAPILLOMA, NOS	1 (2%)		
ADENOCARCINOMA, NOS		1 (2%)	1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#ADRENAL	(49)	(48)	(48)
CORTICAL ADENOMA	1 (2%)		
CORTICAL CARCINOMA	2 (4%)		
REPRODUCTIVE SYSTEM			
#TESTIS	(50)	(50)	(50)
INTERSTITIAL-CELL TUMOR		1 (2%)	
NERVOUS SYSTEM			
NONE			

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)	3 (6%)	1 (2%)
ADENOCARCINOMA, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST			1 (2%)
*ABDOMINAL CAVITY	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)		
*PERICARDIUM	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR CA, INVASIV			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
SARCOMA, NOS	1 (2%)		
SARCOMA, NOS, METASTATIC	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATHa	6	8	10
MORIBUND SACRIFICE	2	2	1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	42	40	39
ANIMAL MISSING			

a INCLUDES AUTOLYZED ANIMALS

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

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	23	28	24
TOTAL PRIMARY TUMORS	29	37	28
TOTAL ANIMALS WITH BENIGN TUMORS	9	10	7
TOTAL BENIGN TUMORS	10	12	7
TOTAL ANIMALS WITH MALIGNANT TUMORS	18	20	17
TOTAL MALIGNANT TUMORS	19	25	21
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	4	3
TOTAL SECONDARY TUMORS	2	4	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE FED DIETS CONTAINING D AND C RED NO. 9

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA	1 (2%)		
SARCOMA, NOS	1 (2%)		
FIBROSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (4%)	1 (2%)	3 (6%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	4 (8%)	4 (8%)	
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	4 (8%)	9 (18%)	2 (4%)
MALIGNANT LYMPHOMA, MIXED TYPE	2 (4%)	2 (4%)	5 (10%)
*MEDIASTINUM	(50)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
#SPLEEN	(49)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
#LYMPH NODE	(42)	(45)	(41)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		1 (2%)	
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
#PANCREAS	(48)	(48)	(47)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#PEYER'S PATCH	(46)	(47)	(49)
MALIGNANT LYMPHOMA, MIXED 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
#KIDNEY	(50)	(50)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
#CERVIX UTERI	(47)	(49)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(49)
HEMANGIOSARCOMA		1 (2%)	1 (2%)
*SUBCUT TISSUE	(50)	(50)	(49)
HEMANGIOSARCOMA	1 (2%)		
#SPLEEN	(49)	(50)	(49)
HEMANGIOMA			1 (2%)
HEMANGIOSARCOMA	1 (2%)		
#MANDIBULAR L. NODE	(42)	(45)	(41)
HEMANGIOSARCOMA, METASTATIC			1 (2%)
#LUNG	(50)	(50)	(49)
HEMANGIOSARCOMA, METASTATIC			1 (2%)
#LIVER	(50)	(50)	(49)
HEMANGIOSARCOMA	1 (2%)		
#UTERUS	(47)	(49)	(48)
HEMANGIOSARCOMA			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(49)
HEPATOCELLULAR ADENOMA	1 (2%)	1 (2%)	4 (8%)
HEPATOCELLULAR CARCINOMA	4 (8%)	2 (4%)	2 (4%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(49)
TUBULAR-CELL ADENOCARCINOMA		1 (2%)	

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(46)	(41)
CHROMOPHOBE ADENOMA	2 (4%)	1 (2%)	2 (5%)
#ADRENAL	(50)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA	1 (2%)		
CORTICAL CARCINOMA	1 (2%)		
PHEOCHROMOCYTOMA			2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(49)
ADENOCARCINOMA, NOS			1 (2%)
ACINAR-CELL CARCINOMA		1 (2%)	
#UTERUS	(47)	(49)	(48)
ADENOCARCINOMA, NOS	1 (2%)		
FIBROMA			1 (2%)
LEIOMYOMA	1 (2%)		
LEIOMYOSARCOMA			1 (2%)
ENDOMETRIAL STROMAL POLYP		1 (2%)	
#CERVIX UTERI	(47)	(49)	(48)
FIBROMA			1 (2%)
#OVARY	(44)	(47)	(46)
PAPILLARY CYSTADENOMA, NOS		1 (2%)	
GRANULOSA-CELL TUMOR		1 (2%)	1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(50)	(50)	(49)
ADENOMA, NOS	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*ABDOMINAL WALL	(50)	(50)	(49)
FIBROSARCOMA		1 (2%)	
*PELVIS	(50)	(50)	(49)
OSTEOSARCOMA	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(49)
FIBROSARCOMA, METASTATIC		1 (2%)	
OSTEOSARCOMA, METASTATIC	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	9	9	8
MORIBUND SACRIFICE	1	1	1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	40	40	41
ANIMAL MISSING			

@ 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*	26	25	27
TOTAL PRIMARY TUMORS	30	29	35
TOTAL ANIMALS WITH BENIGN TUMORS	7	5	13
TOTAL BENIGN TUMORS	7	5	15
TOTAL ANIMALS WITH MALIGNANT TUMORS	21	21	19
TOTAL MALIGNANT TUMORS	23	23	19
TOTAL ANIMALS WITH SECONDARY TUMORS#	2	1	1
TOTAL SECONDARY TUMORS	3	1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	1
TOTAL UNCERTAIN TUMORS		1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

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

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF D & C RED NO. 9

CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	104	051	104	104	051	104	104	051	104	071	021	104	086	051	104	104	104	104	104	095	104	102	104	104
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA																					X				
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS																					X				
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA					X																				
ALVEOLAR/BRONCHIOLAR ADENOMA																		X							
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	-	A	-	+	+	+	+	-	+	+	+	+	+	+	-
THYMUS	+	-	-	+	-	+	-	+	+	-	-	+	+	-	-	+	+	+	+	+	-	+	-	+	+
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
ORAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL PAPILLOMA													X												
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																		X						X	
HEPATOCELLULAR CARCINOMA					X									X											
HEMANGIOSARCOMA									X																
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	+	+	N	+	+	+	N	N	N	N	+	+	+	+	+	+	+	+	N	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	A	+	-	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	-	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLOMA, NOS																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	A	-	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	-	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	-	+	+	+	+	+	+	+	+	+	A	+	+	+	-	+	+	+	+	+	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																									
CORTICAL CARCINOMA																								X	
THYROID	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	-	+	-	-	-	-	-	-	-	-	-	A	+	+	-	+	-	-	-	-	+	+	-	+	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
LACRIMAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																									
ADENOCARCINOMA, NOS										X															
BODY CAVITIES																									
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OSTEOSARCOMA																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS																					X				
SARCOMA, NOS, METASTATIC								X					X												
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 / WEEKS ON STUDY	TOTAL TISSUES / TUMORS
INTEGUMENTARY SYSTEM	
SKIN	50M
FIBROSARCOMA	1
SUBCUTANEOUS TISSUE	50M
SARCOMA, NOS	1
RESPIRATORY SYSTEM	
LUNGS AND BRONCHI	50
HEPATOCELLULAR CARCINOMA, METASTA	1
ALVEOLAR/BRONCHIOLAR ADENOMA	2
ALVEOLAR/BRONCHIOLAR CARCINOMA	2
TRACHEA	49
HEMATOPOIETIC SYSTEM	
BONE MARROW	47
SPLEEN	49
LYMPH NODES	41
THYMUS	33
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1
CIRCULATORY SYSTEM	
HEART	50
DIGESTIVE SYSTEM	
ORAL CAVITY	50M
SQUAMOUS CELL PAPILLOMA	1
SALIVARY GLAND	50
LIVER	50
HEPATOCELLULAR ADENOMA	4
HEPATOCELLULAR CARCINOMA	4
HEMANGIOSARCOMA	1
BILE DUCT	50
GALLBLADDER & COMMON BILE DUCT	50M
PANCREAS	48
ESOPHAGUS	50
STOMACH	47
SMALL INTESTINE	48
PAPILLOMA, NOS	1
LARGE INTESTINE	48
URINARY SYSTEM	
KIDNEY	50
URINARY BLADDER	48
ENDOCRINE SYSTEM	
PITUITARY	45
ADRENAL	49
CORTICAL ADENOMA	1
CORTICAL CARCINOMA	2
THYROID	49
PARATHYROID	20
REPRODUCTIVE SYSTEM	
MAMMARY GLAND	50M
TESTIS	50
PROSTATE	48
SPECIAL SENSE ORGANS	
LACRIMAL GLAND	50M
ADENOMA, NOS	1
ADENOCARCINOMA, NOS	1
BODY CAVITIES	
PERITONEUM	50M
OSTEOSARCOMA	1
ALL OTHER SYSTEMS	
MULTIPLE ORGANS NOS	50M
SARCOMA, NOS	1
SARCOMA, NOS, METASTATIC	1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	4

M 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 OF MALE MICE IN THE 2-YEAR STUDY OF D & C RED NO. 9

LOW DOSE

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	086	105	090	105	105	105	101	089	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	50
SARCOMA, NOS																				X						5
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	50
SARCOMA, NOS																										1
FIBROMA																										1
LEIOMYOSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METASTA														X		X										3
ALVEOLAR/BRONCHIOLAR ADENOMA			X																	X						3
ALVEOLAR/BRONCHIOLAR CARCINOMA		X																								1
TRACHEA	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA																										1
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	47
THYMUS	+	+	+	-	+	+	+	-	-	+	+	-	-	+	-	-	+	-	-	-	+	+	-	+	-	28
MALIGNANT LYMPHOMA, MIXED TYPE																										1
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LEIOMYOSARCOMA, INVASIVE																										1
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA					X																					4
HEPATOCELLULAR CARCINOMA				X										X		X				X					X	9
HEMANGIOSARCOMA																										2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	N	N	+	N	+	+	N	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	50
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	46
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	46
ADENOCARCINOMA, NOS							X																			1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	-	40
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	48
THYROID	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	47
PARATHYROID	-	-	-	-	-	+	-	+	-	+	-	+	+	-	-	-	+	-	-	-	-	-	+	+	-	24
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR																										1
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	47
SPECIAL SENSE ORGANS																										
LACRIMAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
ADENOMA, NOS									X										X							3
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50
MALIG.LYMPHOMA, HISTIOCYTIC TYPE												X														2
MALIGNANT LYMPHOMA, MIXED TYPE																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 B3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0110	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	11 05	11 05	11 05	11 05	11 05	11 05	11 05	11 05	11 05	10 92	11 05	11 05	11 05	11 05	09 71	11 05	09 99	11 05	11 02	11 05	11 05	10 65	11 05	11 05	11 05
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	N	+
SARCOMA, NOS															X				X			X		X	
SUBCUTANEOUS TISSUE *	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	N	+
SARCOMA, NOS			X																						
FIBROMA																									X
LEIOMYOSARCOMA					X																				
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA																									
ALVEOLAR/BRONCHIOLAR ADENOMA		X						X																	
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA		X																							
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
THYMUS	+	+	–	+	–	–	+	+	+	–	+	+	+	–	+	+	–	+	–	–	+	–	–	+	+
MALIGNANT LYMPHOMA, MIXED TYPE	X																								
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LEIOMYOSARCOMA, INVASIVE					X																				
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA		X						X															X		
HEPATOCELLULAR CARCINOMA													X		X										
HEMANGIOSARCOMA		X								X										X		X			
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	N	N	+	+	+	+	N	+	+	N	+	+	+	+	+	+	N	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+
ADENOCARCINOMA, NOS																									
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	–	–	+	+	+	+	+	+	+	–	+	–	+	–	+	+	+	–	+	+	+	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	+	+	–	–	–	–	+	+	+	+	–	–	–	–	+	+	+	+	+	+	+	–	+	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X																								
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
SPECIAL SENSE ORGANS																									
LACRIMAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS											X														
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																	X								
MALIGNANT LYMPHOMA, MIXED TYPE																									

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

TABLE B3.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF D & C RED NO. 9

HIGH DOSE

ANIMAL NUMBER	00011	00022	00031	00041	00052	00061	00072	00081	00092	00101	00111	00121	00131	00141	00151	00161	00171	00181	00191	00202	00212	00222	00232	00242	00252
WEEKS ON STUDY	05	03	05	05	05	05	05	05	05	04	05	05	02	05	05	05	05	05	01	05	05	05	02	04	05
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA	X																								
ALVEOLAR/BRONCHIOLAR ADENOMA					X																				
ALVEOLAR/BRONCHIOLAR CARCINOMA				X								X													
TRACHEA	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	-	A	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	+	+	-	-	-	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																		X							
HEPATOCELLULAR CARCINOMA	X									X			X			X			X				·	X
HEMANGIOSARCOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ADENOCARCINOMA, NOS																									X
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
LARGE INTESTINE	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	A	+	-	+	+	+	+	-	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+
THYROID	+	A	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+
PARATHYROID	-	A	+	+	-	-	+	-	+	-	-	+	-	+	+	-	+	-	+	+	-	+	+	-	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA						X																			
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
LACRIMAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																									
BODY CAVITIES																									
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
HEPATOCELLULAR CARCINOMA, METASTA																									
PERICARDIUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ALVEOLAR/BRONCHIOLAR CA, INVASIVE																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE													X												
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) HIGH DOSE

ANIMAL NUMBER	0 2 6	0 2 7	0 2 8	0 2 9	0 3 0	0 3 1	0 3 2	0 3 3	0 3 4	0 3 5	0 3 6	0 3 7	0 3 8	0 3 9	0 4 0	0 4 1	0 4 2	0 4 3	0 4 4	0 4 5	0 4 6	0 4 7	0 4 8	0 4 9	0 5 0	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	0 9 4	1 0 5	1 0 5	0 8 8	1 0 5	1 0 5	0 7 4	1 0 0	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	0 9 4	1 0 5	1 0 5	1 0 5	
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METASTA										X																2
ALVEOLAR/BRONCHIOLAR ADENOMA																										1
ALVEOLAR/BRONCHIOLAR CARCINOMA							X						X													4
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	-	+	-	+	-	+	A	+	+	-	-	+	+	+	+	+	+	+	42
THYMUS	+	+	+	+	+	+	-	+	+	-	+	+	-	A	+	+	+	+	-	+	+	-	+	+	+	34
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA	X				X										X											4
HEPATOCELLULAR CARCINOMA			X				X			X			X							X						11
HEMANGIOSARCOMA																				X						1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	47
ADENOCARCINOMA, NOS																										1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				X																						1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	-	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	-	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	43
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	46
PARATHYROID	+	+	-	-	+	+	-	+	+	+	-	-	+	A	+	+	-	-	-	+	-	-	-	-		23
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOMA																										1
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
LACRIMAL 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	50M
ADENOMA, NOS																X										1
BODY CAVITIES																										
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
HEPATOCELLULAR CARCINOMA, METASTA										X																1
PERICARDIUM	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	50M
ALVEOLAR/BRONCHIOLAR CA, INVASIVE							X																			1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																						X				2

M ANIMALS NECROPSIED

A: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF D & C RED NO. 9

CONTROL

ANIMAL NUMBER	0010	0020	0030	0040	0050	0060	0070	0080	0090	0100	0110	0120	0130	0140	0150	0160	0170	0180	0190	0200	0210	0220	0230	0240	0250
WEEKS ON STUDY	105	105	104	105	105	105	105	105	105	087	105	105	105	100	082	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA																									
SARCOMA, NOS										X															
HEMANGIOSARCOMA													X												
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT																									
ALVEOLAR/BRONCHIOLAR ADENOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA													X												
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
LYMPH NODES	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–
THYMUS	+	+	–	+	+	–	+	+	+	–	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																			X		X				X
HEPATOCELLULAR CARCINOMA																							X		
HEMANGIOSARCOMA																									
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	N	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+
CHROMOPHOBE ADENOMA														X											
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA, METASTAT																									
CORTICAL CARCINOMA																								X	
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	–	+	+	–	–	–	–	–	+	–	–	+	+	+	–	–	+	+	–	+	+	–	+	–	–
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	+	+	N	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	N
UTERUS	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS		X																							
LEIOMYOMA				X																					
OVARY	+	+	+	+	–	+	+	+	+	–	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
LACRIMAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																					X				
BODY CAVITIES																									
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OSTEOSARCOMA																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OSTEOSARCOMA, METASTATIC																									
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE															X										
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			X											X										X	
MALIGNANT LYMPHOMA, MIXED TYPE																									

+: 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. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) CONTROL

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	089	105	105	105	104	105	105	105	105	105	105	105	105	105	105	105	105	103	074	105	105	086	105	105	050	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	M	+	+	+	+	+	+	50M
SQUAMOUS CELL CARCINOMA	X																									1
SARCOMA, NOS																										1
HEMANGIOSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT	X																									1
ALVEOLAR/BRONCHIOLAR ADENOMA							X				X															2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	49
HEMANGIOSARCOMA																					X					1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
LYMPH NODES	+	+	+	-	+	+	-	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	-	42
THYMUS	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	-	-	-	-	+	+	38
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA			X																							1
HEPATOCELLULAR CARCINOMA																X										4
HEMANGIOSARCOMA																										1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	N	50M
PANCREAS	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	49
SMALL INTESTINE	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	-	46
LARGE INTESTINE	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	47
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	47
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	45
CHROMOPHOBE ADENOMA														X												2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA, METASTAT	X																									1
CORTICAL CARCINOMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PARATHYROID	-	+	+	+	-	+	+	-	+	+	-	-	-	-	-	+	+	+	-	-	+	+	+	-	+	25
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	N	+	+	+	+	N	N	50M
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	47
ADENOCARCINOMA, NOS																										1
LEIOMYOMA																										1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	44
SPECIAL SENSE ORGANS																										
LACRIMAL 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	50M
ADENOMA, NOS																										1
BODY CAVITIES																										
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
OSTEOSARCOMA																									X	1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
OSTEOSARCOMA, METASTATIC																									X	1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE					X													X				X				4
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																			X							4
MALIGNANT LYMPHOMA, MIXED TYPE														X						X						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 B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF D & C RED NO. 9

LOW DOSE

ANIMAL NUMBER	00112	00125	00134	00135	00136	00137	00138	00139	00141	00142	00143	00144	00145	00146	00147	00148	00149	00150	00151	00152	00153	00154	00155
WEEKS ON STUDY	105	105	079	105	096	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	074	105	105
RESPIRATORY SYSTEM																							
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																							
TRACHEA	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																							
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				X																			
THYMUS	+	+	+	+	+	-	+	-	+	+	-	+	+	+	-	+	+	+	+	A	+	+	-
CIRCULATORY SYSTEM																							
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																							
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																				X			
HEPATOCELLULAR CARCINOMA			X									X											
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																							
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOCARCINOMA																		X					
URINARY BLADDER	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																							
PITUITARY	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	A	+	+	+
CHROMOPHOBE ADENOMA																							
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	+	+	-	-	-	-	-	-	+	+	-	-	+	+	+	-	-	+	-	-	-	A	-	+	+
REPRODUCTIVE SYSTEM																							
MAMMARY GLAND	+	+	N	+	+	+	N	+	+	+	+	N	+	+	N	+	+	+	+	+	N	+	+	N	+
ACINAR-CELL CARCINOMA										X															
UTERUS	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP			X																						
OVARY	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PAPILLARY CYSTADENOMA, NOS																									
GRANULOSA-CELL TUMOR																									
BODY CAVITIES																							
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROSARCOMA																									
ALL OTHER SYSTEMS																							
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
FIBROSARCOMA, METASTATIC																									
HEMANGIOSARCOMA																									X
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE			X		X				X																
MALIG.LYMPHOMA, HISTIOCYTIC TYPE								X																	
MALIGNANT LYMPHOMA, MIXED TYPE						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 B4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

ANIMAL NUMBER	02616	02705	02805	02905	03105	03205	03405	03605	03905	04105	04305	04405	04505	04605	04705	04805	04905	05105	05205	05305	05405	05505	05605	TOTAL TISSUES TUMORS
WEEKS ON STUDY	10 5	10 5	06 8	09 5	09 4	11 5	08 6	09 5	10 5	10 3	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	11 5	11 5	10 5	
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																								1
TRACHEA	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	46
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	+	+	-	+	+	45
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																								1
THYMUS	+	+	+	-	-	-	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	39
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA																								1
HEPATOCELLULAR CARCINOMA																								2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50N
PANCREAS	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	47
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOCARCINOMA																								1
URINARY BLADDER	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																								
PITUITARY	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
CHROMOPHOBE ADENOMA																		X						1
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
THYROID	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
PARATHYROID	-	-	-	-	+	-	-	-	+	-	-	-	+	+	-	-	-	-	+	+	-	+	-	17
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	+	N	+	N	N	+	+	+	+	+	N	N	+	+	+	+	+	+	N	N	+	+	+	50N
ACINAR-CELL CARCINOMA																								1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOMETRIAL STROMAL POLYP																								1
OVARY	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	47
PAPILLARY CYSTADENOMA, NOS																			X					1
GRANULOSA-CELL TUMOR							X																	1
BODY CAVITIES																								
MEDIASTINUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50N
MALIG.LYMPHOMA, HISTIOCYTIC TYPE													X											1
PERITONEUM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50N
FIBROSARCOMA								X																1
ALL OTHER SYSTEMS																								
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50N
FIBROSARCOMA, METASTATIC								X																1
HEMANGIOSARCOMA																								1
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE				X																				4
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		X			X	X					X					X		X		X	X			9
MALIGNANT LYMPHOMA, MIXED TYPE																								2

N ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: *REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY*
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

1: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

TABLE B4.

INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE 2-YEAR STUDY OF D & C RED NO. 9

HIGH DOSE

ANIMAL NUMBER	0 0 1 5	0 0 2 5	0 0 3 5	0 0 4 5	0 0 5 5	0 0 6 5	0 0 7 5	0 0 8 5	0 0 9 5	0 1 0 5	0 1 1 5	0 1 2 5	0 1 3 5	0 1 4 5	0 1 5 5	0 1 6 5	0 1 7 5	0 1 8 5	0 1 9 5	0 2 0 5	0 2 1 5	0 2 2 5	0 2 3 5	0 2 4 5	0 2 5 5
WEEKS ON STUDY	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	0 8 2	0 9 5	1 0 5	1 0 5	1 0 5	0 9 5	1 0 5	1 0 5	1 0 5	1 0 5	0 9 9	0 6 5	0 7 9	1 0 5
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE FIBROSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA HEMANGIOSARCOMA, METASTATIC	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	A	+	+
SPLEEN HEMANGIOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	A	+	+
LYMPH NODES HEMANGIOSARCOMA, METASTATIC MALIGNANT LYMPHOMA, MIXED TYPE	+	+	+	–	+	+	+	+ X	+	–	+	+	+	–	+	+	+	+	+	+	+	+	A	+	–
THYMUS	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	–	+	+	+	+	–	A	–	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+	A	+	+
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	A	N	+
PANCREAS MALIG.LYMPHOMA, HISTIOCYTIC TYPE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	–	+	+	+	+	A	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
SMALL INTESTINE MALIGNANT LYMPHOMA, MIXED TYPE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
URINARY SYSTEM																									
KIDNEY MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+ X
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
ENDOCRINE SYSTEM																									
PITUITARY CHROMOPHOBE ADENOMA	+	–	+ X	+	+	+	–	+	+	+	–	+	+	+	+	+	–	+	+	–	+	+	A	–	+
ADRENAL PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	A	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
PARATHYROID	–	+	–	–	–	–	–	+	+	–	–	–	–	–	+	–	–	+	+	+	+	+	A	–	–
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND ADENOCARCINOMA, NOS	+	+	+	N	+	+	+	+	+	N	N	+	N	N	+	N	+	N	+	N	+	N X	A	+	+
UTERUS FIBROMA LEIOMYOSARCOMA HEMANGIOSARCOMA MALIG.LYMPHOMA, HISTIOCYTIC TYPE	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	A	–	+
OVARY GRANULOSA-CELL TUMOR	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+ X	–	+	+	A	+	+
SPECIAL SENSE ORGANS																									
LACRIMAL GLAND ADENOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N X	N	N	N	N	N	N	N	A	N	N
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS HEMANGIOSARCOMA MALIG.LYMPHOMA, HISTIOCYTIC TYPE MALIGNANT LYMPHOMA, MIXED TYPE	N	N	N X	N	N	N	N	N	N	N	N X	N	N	N	N	N	N	N	N	N	N	N	A	N X	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. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

ANIMAL NUMBER	02461	02705	02805	02905	03005	03105	03205	03305	03405	03505	03605	03705	03805	03905	04005	04105	04205	04305	04405	04505	04605	04705	04805	04905	05001	TOTAL TISSUES
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	094	105	105	105	105	105	105	105	105	101	TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	49M
FIBROSARCOMA											X															1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALVEOLAR/BRONCHIOLAR ADENOMA										X													X			3
HEMANGIOSARCOMA, METASTATIC																									X	1
TRACHEA	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOMA																										1
LYMPH NODES	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	41
HEMANGIOSARCOMA, METASTATIC																									X	1
MALIGNANT LYMPHOMA, MIXED TYPE																										1
THYMUS	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	-		40
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEPATOCELLULAR ADENOMA				X							X							X								4
HEPATOCELLULAR CARCINOMA			X						X																	2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM (CONT)																										
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	49M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	47
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MALIGNANT LYMPHOMA, MIXED TYPE		X																								1
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
CHROMOPHOBE ADENOMA															X											2
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA									X																	2
THYROID	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
PARATHYROID	-	+	+	-	+	+	-	+	-	+	-	+	+	+	-	+	+	-	-	-	+	-	+	-	+	23
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	+	+	+	+	+	N	+	N	+	N	N	+	N	+	N	+	N	+	+	+	+	+	+	N	49M
ADENOCARCINOMA, NOS																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
FIBROMA							X				X															2
LEIOMYOSARCOMA																										1
HEMANGIOSARCOMA																										1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																		X								1
OVARY	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
GRANULOSA-CELL TUMOR																										1
SPECIAL SENSE ORGANS																										
LACRIMAL 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	49M
ADENOMA, NOS																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	49M
HEMANGIOSARCOMA																									X	1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										2
MALIGNANT LYMPHOMA, MIXED TYPE							X	X									X				X					5

M 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

APPENDIX C

Summary of the Incidence of Nonneoplastic Lesions in Rats Fed Diets Containing D and C Red No. 9

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS FED DIETS CONTAINING D AND C RED NO. 9

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST	1 (2%)		
RESPIRATORY SYSTEM			
#TRACHEA	(49)	(50)	(49)
INFLAMMATION, FOCAL	1 (2%)	1 (2%)	
INFLAMMATION, MULTIFOCAL	1 (2%)	1 (2%)	2 (4%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		1 (2%)
#LUNG/BRONCHIOLE	(50)	(50)	(49)
HYPERPLASIA, NOS	1 (2%)	2 (4%)	1 (2%)
HYPERPLASIA, EPITHELIAL			1 (2%)
#LUNG	(50)	(50)	(49)
CONGESTION, NOS	1 (2%)		2 (4%)
CONGESTION, PASSIVE			2 (4%)
EDEMA, NOS	2 (4%)	2 (4%)	1 (2%)
BRONCHOPNEUMONIA, FOCAL			1 (2%)
PNEUMONIA INTERSTITIAL CHRONIC			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)	2 (4%)	2 (4%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(47)	(47)	(47)
METAMORPHOSIS FATTY	1 (2%)		
HYPOPLASIA, NOS		1 (2%)	
HYPERPLASIA, GRANULOCYTIC	1 (2%)	1 (2%)	
HYPERPLASIA, RETICULUM CELL		1 (2%)	1 (2%)
#SPLEEN	(50)	(50)	(48)
CONGESTION, NOS			14 (29%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CONGESTION, PASSIVE	1 (2%)		
FIBROSIS			1 (2%)
FIBROSIS, FOCAL	1 (2%)		15 (31%)
FIBROSIS, MULTIFOCAL			8 (17%)
FIBROSIS, DIFFUSE	1 (2%)		3 (6%)
NECROSIS, FOCAL			2 (4%)
METAMORPHOSIS FATTY			13 (27%)
HEMOSIDEROSIS	2 (4%)	1 (2%)	2 (4%)
LYMPHOID DEPLETION	6 (12%)	2 (4%)	3 (6%)
HEMATOPOIESIS		1 (2%)	
#SPLENIC CAPSULE	(50)	(50)	(48)
HYPERPLASIA, MESOTHELIAL			1 (2%)
#SPLENIC RED PULP	(50)	(50)	(48)
CONGESTION, NOS		1 (2%)	2 (4%)
FIBROSIS, MULTIFOCAL			4 (8%)
METAMORPHOSIS FATTY			1 (2%)
PIGMENTATION, NOS			1 (2%)
HEMOSIDEROSIS	2 (4%)		
LYMPHOID DEPLETION			1 (2%)
HEMATOPOIESIS	2 (4%)	5 (10%)	2 (4%)
#LYMPH NODE	(44)	(43)	(44)
INFLAMMATION, NOS			2 (5%)
PIGMENTATION, NOS			1 (2%)
#MANDIBULAR L. NODE	(44)	(43)	(44)
HEMORRHAGE	1 (2%)		
HYPERPLASIA, LYMPHOID	1 (2%)		
#BRONCHIAL LYMPH NODE	(44)	(43)	(44)
HEMOSIDEROSIS			1 (2%)
#TRACHEAL LYMPH NODE	(44)	(43)	(44)
HEMORRHAGE			1 (2%)
#MESENTERIC L. NODE	(44)	(43)	(44)
HEMORRHAGE	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
FIBROSIS			1 (2%)
DEGENERATION, NOS			1 (2%)
LYMPHOID DEPLETION	1 (2%)		
#LUNG/BRONCHUS	(50)	(50)	(49)
HYPERPLASIA, LYMPHOID			1 (2%)

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LUNG/BRONCHIOLE	(50)	(50)	(49)
HYPERPLASIA, LYMPHOID			1 (2%)
#LUNG	(50)	(50)	(49)
HYPERPLASIA, LYMPHOID	2 (4%)	12 (24%)	5 (10%)
#GASTRIC SUBMUCOSA	(50)	(50)	(48)
HYPERPLASIA, LYMPHOID	1 (2%)		
#U.BLADDER/SUBMUCOSA	(46)	(49)	(44)
HYPERPLASIA, LYMPHOID		1 (2%)	
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(50)	(48)
THROMBOSIS, NOS			1 (2%)
#LUNG	(50)	(50)	(49)
THROMBOSIS, NOS		1 (2%)	
PERIVASCULITIS			1 (2%)
#HEART	(50)	(50)	(49)
DEGENERATION, NOS	44 (88%)	45 (90%)	40 (82%)
#HEART/ATRIUM	(50)	(50)	(49)
THROMBOSIS, NOS	2 (4%)	2 (4%)	
THROMBUS, MURAL			1 (2%)
#LEFT ATRIUM	(50)	(50)	(49)
THROMBOSIS, NOS	2 (4%)	1 (2%)	
#LEFT VENTRICLE	(50)	(50)	(49)
ENDOCARDIOSIS	1 (2%)		
#MYOCARDIUM	(50)	(50)	(49)
DEGENERATION, NOS	2 (4%)		2 (4%)
#CARDIAC VALVE	(50)	(50)	(49)
FIBROSIS	1 (2%)		
FIBROSIS, FOCAL			1 (2%)
FIBROSIS, MULTIFOCAL	4 (8%)	8 (16%)	1 (2%)
*AORTIC TUNICA MEDIA	(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
*CENTRAL VEINS/LIVER	(50)	(50)	(50)
FIBROSIS	1 (2%)		
FIBROSIS, MULTIFOCAL	2 (4%)		
#HEPATIC SINUSOID	(50)	(50)	(49)
CONGESTION, NOS		1 (2%)	1 (2%)
#PANCREAS	(47)	(49)	(39)
PERIARTERITIS		1 (2%)	
*MESENTERY	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(49)
CONGESTION, PASSIVE	1 (2%)		1 (2%)
CONGESTION, CHRONIC PASSIVE	1 (2%)		
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)	10 (20%)	4 (8%)
DEGENERATION, HYALINE			1 (2%)
BASOPHILIC CYTO CHANGE	8 (16%)	28 (56%)	22 (45%)
FOCAL CELLULAR CHANGE	1 (2%)	2 (4%)	3 (6%)
#PORTAL TRACT	(50)	(50)	(49)
FIBROSIS	1 (2%)		
FIBROSIS, MULTIFOCAL	1 (2%)		
#LIVER/CENTRILOBULAR	(50)	(50)	(49)
CONGESTION, NOS		2 (4%)	1 (2%)
CONGESTION, ACUTE		2 (4%)	
DEGENERATION, NOS		2 (4%)	1 (2%)
NECROSIS, NOS		1 (2%)	
NECROSIS, FOCAL	1 (2%)	2 (4%)	7 (14%)
NECROSIS, DIFFUSE	1 (2%)	1 (2%)	
CYTOLOGIC DEGENERATION	4 (8%)		
#LIVER/HEPATOCYTES	(50)	(50)	(49)
DEGENERATION, NOS	1 (2%)		
NECROSIS, FOCAL	1 (2%)		
#BILE DUCT	(50)	(50)	(49)
DILATATION, NOS	1 (2%)		
HYPERPLASIA, NOS	1 (2%)		2 (4%)

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	35 (70%)	46 (92%)	39 (80%)
#PANCREAS	(47)	(49)	(39)
EMBRYONAL REST	1 (2%)		
DILATATION/DUCTS		1 (2%)	2 (5%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		1 (3%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)	1 (2%)	
#PANCREATIC ACINUS	(47)	(49)	(39)
ATROPHY, FOCAL	13 (28%)	18 (37%)	9 (23%)
ATROPHY, DIFFUSE		2 (4%)	2 (5%)
#STOMACH	(50)	(50)	(48)
MINERALIZATION	1 (2%)		
ULCER, FOCAL	2 (4%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		3 (6%)
#GASTRIC MUSCULARIS	(50)	(50)	(48)
NECROSIS, NOS	1 (2%)		
#GASTRIC FUNDUS	(50)	(50)	(48)
INFLAMMATION, NECRO GRAN	1 (2%)		
#ILEUM	(47)	(48)	(45)
INTUSSUSCEPTION		1 (2%)	
INFLAMMATION, NECRO GRAN		1 (2%)	
HYPERPLASIA, EPITHELIAL		1 (2%)	
#COLON	(48)	(46)	(44)
NEMATODIASIS	1 (2%)		1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(49)
MINERALIZATION		1 (2%)	
NEPHROPATHY	42 (84%)	49 (98%)	44 (90%)
NEPHROSIS, NOS	3 (6%)		1 (2%)
PIGMENTATION, NOS		1 (2%)	
#KIDNEY/CORTEX	(50)	(50)	(49)
CYST, NOS			1 (2%)
PIGMENTATION, NOS	37 (74%)	37 (74%)	49 (100%)
#KIDNEY/TUBULE	(50)	(50)	(49)
MULTILOCULAR CYST			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
#KIDNEY/PELVIS	(50)	(50)	(49)
MINERALIZATION		1 (2%)	
#URINARY BLADDER	(46)	(49)	(44)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(44)	(44)	(44)
HEMORRHAGE	1 (2%)		
HYPERPLASIA, CHROMOPHOBE-CELL	1 (2%)	3 (7%)	3 (7%)
#ADRENAL	(48)	(50)	(48)
METAMORPHOSIS FATTY	1 (2%)		
HEMOSIDEROSIS			2 (4%)
ANGIECTASIS		1 (2%)	1 (2%)
#ADRENAL CORTEX	(48)	(50)	(48)
FOCAL CELLULAR CHANGE	1 (2%)		
CYTOLOGIC DEGENERATION			1 (2%)
HYPERPLASIA, NODULAR		3 (6%)	
HYPERPLASTIC NODULE			1 (2%)
HYPERPLASIA, FOCAL			1 (2%)
#ADRENAL MEDULLA	(48)	(50)	(48)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, FOCAL			1 (2%)
#THYROID	(50)	(50)	(47)
HYPERPLASIA, C-CELL	24 (48%)	34 (68%)	26 (55%)
#THYROID FOLLICLE	(50)	(50)	(47)
MULTILOCULAR CYST	1 (2%)	1 (2%)	
#PARATHYROID	(41)	(41)	(37)
HYPERPLASIA, NOS	2 (5%)		
HYPERPLASIA, FOCAL		2 (5%)	
#PANCREATIC ISLETS	(47)	(49)	(39)
HYPERPLASIA, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
DILATATION/DUCTS	2 (4%)	2 (4%)	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			1 (2%)
*MAMMARY ACINUS	(50)	(50)	(50)
HYPERPLASIA, FOCAL		2 (4%)	
*PREPUTIAL GLAND	(50)	(50)	(50)
ABSCESS, NOS			1 (2%)
#PROSTATE	(48)	(48)	(42)
INFLAMMATION, MULTIFOCAL	6 (13%)	18 (38%)	8 (19%)
INFLAMMATION, ACUTE FOCAL	2 (4%)		
INFLAMMATION ACTIVE CHRONIC			1 (2%)
INFLAMMATION, ACUTE/CHRONIC	5 (10%)		
INFLAMMATION, CHRONIC NECROTIZIN	1 (2%)		
*SEMINAL VESICLE	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL	3 (6%)		
#TESTIS	(50)	(50)	(48)
MINERALIZATION	1 (2%)		
DEGENERATION, NOS	1 (2%)		1 (2%)
ATROPHY, NOS	10 (20%)	11 (22%)	14 (29%)
ATROPHY, DIFFUSE	1 (2%)		1 (2%)
HYPERPLASIA, INTERSTITIAL CELL	1 (2%)		
#TESTIS/TUBULE	(50)	(50)	(48)
DEGENERATION, NOS	3 (6%)	5 (10%)	11 (23%)
*EPIDIDYMIS	(50)	(50)	(50)
MINERALIZATION			2 (4%)
INFLAMMATION, SUPPURATIVE			1 (2%)
*DUCT OF EPIDIDYMIS	(50)	(50)	(50)
MINERALIZATION			1 (2%)
NERVOUS SYSTEM			
*NEURON	(50)	(50)	(50)
NECROSIS, FOCAL	1 (2%)		
#BRAIN	(50)	(50)	(48)
HYDROCEPHALUS, NOS	2 (4%)		1 (2%)
HEMORRHAGE	1 (2%)		
NECROSIS, HEMORRHAGIC			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
ATROPHY, PRESSURE	1 (2%)		
#VENTRAL THALAMUS	(50)	(50)	(48)
ATROPHY, PRESSURE	1 (2%)		
#HYPOTHALAMUS	(50)	(50)	(48)
ATROPHY, PRESSURE			1 (2%)
#MEDULLA OBLONGATA	(50)	(50)	(48)
HEMATOMA, NOS	1 (2%)		
SPECIAL SENSE ORGANS			
*EYE/CORNEA	(50)	(50)	(50)
ULCER, NOS	1 (2%)		
*EYE/IRIS	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)		
INFLAMMATION, NOS	1 (2%)		
*EYE/RETINA	(50)	(50)	(50)
DEGENERATION, NOS	1 (2%)		
*LENS CAPSULE	(50)	(50)	(50)
CYTOLOGIC DEGENERATION	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*FEMUR	(50)	(50)	(50)
HEALED FRACTURE			1 (2%)
HYPERPLASIA, FOCAL			1 (2%)
*SKELETAL MUSCLE	(50)	(50)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
BODY CAVITIES			
*PARIETAL PERITONEUM	(50)	(50)	(50)
HYPERPLASIA, MESOTHELIAL			1 (2%)
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, GRANULOMATOUS	2 (4%)		

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

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
INFLAMMATION, FOCAL GRANULOMATOU		5 (10%)	1 (2%)
ALL OTHER SYSTEMS			
CRANIOBUCCAL POUCH			
EMBRYONAL REST	1		
SPECIAL MORPHOLOGY SUMMARY			
AUTO/NECROPSY/NO HISTO			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 D AND C RED NO. 9

	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)
KERATIN-PEARL FORMATION	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
INFLAMMATION, NECROTIZING		1 (2%)	
RESPIRATORY SYSTEM			
#TRACHEA	(50)	(49)	(48)
INFLAMMATION, MULTIFOCAL		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC	2 (4%)	2 (4%)	2 (4%)
#TRACHEAL GLAND	(50)	(49)	(48)
DILATATION, NOS		1 (2%)	
#LUNG/BRONCHIOLE	(49)	(50)	(50)
HYPERPLASIA, NOS	3 (6%)	3 (6%)	2 (4%)
#LUNG	(49)	(50)	(50)
CONGESTION, NOS	1 (2%)		1 (2%)
CONGESTION, PASSIVE	1 (2%)		
EDEMA, NOS	1 (2%)		3 (6%)
INFLAMMATION, INTERSTITIAL			2 (4%)
PNEUMONIA, ASPIRATION	1 (2%)	1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
GRANULOMA, NOS		1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM	3 (6%)	3 (6%)	3 (6%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(50)	(50)
FIBROSIS, MULTIFOCAL			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
HYPERPLASIA, GRANULOCYTIC	1 (2%)	2 (4%)	2 (4%)
HYPERPLASIA, RETICULUM CELL	2 (4%)	3 (6%)	3 (6%)
HYPERPLASIA, LYMPHOID			2 (4%)
HYPOPLASIA, HEMATOPOIETIC	1 (2%)		
HYPOPLASIA, ERYTHROID	1 (2%)		
HYPOPLASIA, GRANULOCYTIC	1 (2%)		1 (2%)
#SPLEEN	(50)	(50)	(50)
CONGESTION, NOS		6 (12%)	26 (52%)
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)
FIBROSIS, FOCAL			1 (2%)
FIBROSIS, MULTIFOCAL		2 (4%)	14 (28%)
FIBROSIS, DIFFUSE			10 (20%)
PIGMENTATION, NOS			2 (4%)
HEMOSIDEROSIS	1 (2%)		
LYMPHOID DEPLETION	1 (2%)	1 (2%)	1 (2%)
HYPERPLASIA, RETICULUM CELL			1 (2%)
HYPERPLASIA, LYMPHOID			1 (2%)
HEMATOPOIESIS		3 (6%)	3 (6%)
#SPLENIC CAPSULE	(50)	(50)	(50)
FIBROSIS, MULTIFOCAL			1 (2%)
#SPLENIC RED PULP	(50)	(50)	(50)
FIBROSIS, FOCAL			1 (2%)
HEMATOPOIESIS	2 (4%)		
#LYMPH NODE	(44)	(45)	(47)
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)
HEMOSIDEROSIS	1 (2%)		
#BRONCHIAL LYMPH NODE	(44)	(45)	(47)
INFLAMMATION, DIFFUSE			1 (2%)
INFLAMMATION, GRANULOMATOUS			1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU			13 (28%)
#PANCREATIC L.NODE	(44)	(45)	(47)
HEMOSIDEROSIS			1 (2%)
#MESENTERIC L. NODE	(44)	(45)	(47)
CYST, NOS			1 (2%)
CONGESTION, PASSIVE		1 (2%)	
REACTION, FOREIGN BODY		1 (2%)	
PIGMENTATION, NOS			1 (2%)
#LUNG	(49)	(50)	(50)
HYPERPLASIA, LYMPHOID	17 (35%)	27 (54%)	24 (48%)

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)		
#KIDNEY	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	
#THYMUS	(47)	(41)	(42)
HEMORRHAGE		2 (5%)	
MYELOPROLIFERATIVE DISORDER			1 (2%)
HYPERPLASIA, RETICULUM CELL	1 (2%)		
CIRCULATORY SYSTEM			
#LUNG	(49)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
#HEART	(50)	(50)	(50)
DEGENERATION, NOS	45 (90%)	46 (92%)	48 (96%)
#HEART/ATRIUM	(50)	(50)	(50)
THROMBUS, MURAL	1 (2%)		
#LEFT ATRIUM	(50)	(50)	(50)
THROMBUS, MURAL		1 (2%)	2 (4%)
#CARDIAC VALVE	(50)	(50)	(50)
FIBROSIS, FOCAL	2 (4%)		1 (2%)
FIBROSIS, MULTIFOCAL	4 (8%)	8 (16%)	4 (8%)
#HEPATIC SINUSOID	(50)	(50)	(50)
CONGESTION, NOS	2 (4%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(47)	(50)	(50)
EDEMA, NOS	1 (2%)		
HYPERPLASIA, FOCAL		1 (2%)	
#LIVER	(50)	(50)	(50)
INFLAMMATION, CHRONIC NECROTIZIN	1 (2%)		
INFLAMMATION, FOCAL GRANULOMATOU	25 (50%)	32 (64%)	23 (46%)
DEGENERATION, 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
NECROSIS, FOCAL		1 (2%)	
CYTOPLASMIC VACUOLIZATION	1 (2%)		
BASOPHILIC CYTO CHANGE	33 (66%)	40 (80%)	41 (82%)
FOCAL CELLULAR CHANGE	2 (4%)	1 (2%)	1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
CONGESTION, NOS			1 (2%)
DEGENERATION, NOS	5 (10%)		4 (8%)
NECROSIS, NOS	2 (4%)		
NECROSIS, FOCAL		1 (2%)	
NECROSIS, DIFFUSE	2 (4%)		1 (2%)
#LIVER/HEPATOCYTES	(50)	(50)	(50)
CYTOLOGIC DEGENERATION		1 (2%)	
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, FOCAL	27 (54%)	27 (54%)	27 (54%)
#PANCREAS	(49)	(49)	(49)
DILATATION/DUCTS		1 (2%)	1 (2%)
#PANCREATIC ACINUS	(49)	(49)	(49)
ATROPHY, FOCAL	7 (14%)	10 (20%)	10 (20%)
ATROPHY, DIFFUSE			1 (2%)
#STOMACH	(50)	(48)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
#CARDIAC STOMACH	(50)	(48)	(50)
ULCER, FOCAL	1 (2%)		
#GASTRIC FUNDUS	(50)	(48)	(50)
DILATATION, NOS			1 (2%)
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
#JEJUNUM	(48)	(47)	(48)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
#COLON	(50)	(47)	(49)
ULCER, NOS			1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)
NEMATODIASIS	2 (4%)		1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
MINERALIZATION	2 (4%)		

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CONGESTION, PASSIVE	1 (2%)		
INFLAMMATION, MULTIFOCAL	1 (2%)		
INFLAMMATION, INTERSTITIAL	1 (2%)		
INFLAMMATION, HEMORRHAGIC	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	2 (4%)		
NEPHROPATHY	5 (10%)	15 (30%)	7 (14%)
INFECTION, BACTERIAL	1 (2%)		
NEPHROSIS, NOS	2 (4%)		
PIGMENTATION, NOS	1 (2%)		
#KIDNEY/CORTEX	(50)	(50)	(50)
INFLAMMATION, INTERSTITIAL		1 (2%)	
GLOMERULOSCLEROSIS, NOS	1 (2%)		
PIGMENTATION, NOS	30 (60%)	36 (72%)	48 (96%)
#KIDNEY/TUBULE	(50)	(50)	(50)
MULTIPLE CYSTS			1 (2%)
PIGMENTATION, NOS		1 (2%)	1 (2%)
REGENERATION, NOS	4 (8%)	14 (28%)	14 (28%)
#KIDNEY/PELVIS	(50)	(50)	(50)
MINERALIZATION		2 (4%)	
#URINARY BLADDER	(49)	(47)	(48)
HYPERPLASIA, EPITHELIAL			2 (4%)
#U. BLADDER/MUCOSA	(49)	(47)	(48)
MINERALIZATION		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(43)	(46)	(47)
HEMORRHAGE			2 (4%)
HYPERPLASIA, NOS			2 (4%)
HYPERPLASIA, FOCAL			1 (2%)
HYPERPLASIA, CHROMOPHOBE-CELL	3 (7%)	4 (9%)	4 (9%)
#ADRENAL	(48)	(49)	(50)
NECROSIS, CORTICAL	1 (2%)		
METAMORPHOSIS FATTY		2 (4%)	
ANGIECTASIS	2 (4%)		
#ADRENAL CORTEX	(48)	(49)	(50)
INFLAMMATION, ACUTE/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
METAMORPHOSIS FATTY	1 (2%)	3 (6%)	3 (6%)
LIPOIDOSIS			1 (2%)
CYTOPLASMIC VACUOLIZATION			2 (4%)
BASOPHILIC CYTO CHANGE			1 (2%)
FOCAL CELLULAR CHANGE	1 (2%)		
HYPERPLASIA, NODULAR	2 (4%)	2 (4%)	
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL	2 (4%)	4 (8%)	5 (10%)
ANGIECTASIS	3 (6%)	2 (4%)	1 (2%)
#ADRENAL MEDULLA	(48)	(49)	(50)
HYPERPLASIA, FOCAL			1 (2%)
#THYROID	(47)	(50)	(50)
HYPERPLASIA, FOCAL		1 (2%)	
HYPERPLASIA, C-CELL	38 (81%)	35 (70%)	40 (80%)
#PANCREATIC ISLETS	(49)	(49)	(49)
HYPERPLASIA, FOCAL			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
DILATATION/DUCTS	19 (38%)	23 (46%)	26 (52%)
HYPERPLASIA, NOS	1 (2%)		
*MAMMARY ACINUS	(50)	(50)	(50)
DILATATION, NOS	1 (2%)	14 (28%)	17 (34%)
HYPERPLASIA, FOCAL	2 (4%)		4 (8%)
*VAGINA	(50)	(50)	(50)
PROLAPSE	1 (2%)		
INTUSSUSCEPTION	1 (2%)		
INFLAMMATION, NECROTIZING	1 (2%)		
#UTERUS	(50)	(49)	(50)
DILATATION, NOS	2 (4%)	4 (8%)	6 (12%)
NECROSIS, NOS			1 (2%)
INVOLUTION, NOS	1 (2%)		
#UTERINE SUBSEROSA	(50)	(49)	(50)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
#UTERUS/ENDOMETRIUM	(50)	(49)	(50)
INFLAMMATION, 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
INFLAMMATION, DIFFUSE	1 (2%)		
INFLAMMATION, SUPPURATIVE			1 (2%)
#ENDOMETRIAL GLAND	(50)	(49)	(50)
DILATATION, NOS		2 (4%)	2 (4%)
HYPERPLASIA, CYSTIC	3 (6%)		1 (2%)
#OVARY	(50)	(49)	(49)
CYST, NOS	1 (2%)	2 (4%)	
CORPUS LUTEUM CYST	1 (2%)		1 (2%)
PAROVARIAN CYST	2 (4%)		
NERVOUS SYSTEM			
*CHOROID PLEXUS	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
#CEREBRUM	(50)	(48)	(49)
COMPRESSION	1 (2%)	1 (2%)	
HYDROCEPHALUS, NOS	1 (2%)		
HEMORRHAGE		1 (2%)	
ATROPHY, PRESSURE		1 (2%)	
#BRAIN	(50)	(48)	(49)
NECROSIS, NOS	1 (2%)		
ATROPHY, PRESSURE		1 (2%)	
#CEREBELLUM	(50)	(48)	(49)
HEMORRHAGE			1 (2%)
HEMATOMA, NOS	1 (2%)		
SPECIAL SENSE ORGANS			
*EYE/RETINA	(50)	(50)	(50)
DEGENERATION, NOS		1 (2%)	1 (2%)
*LENS CAPSULE	(50)	(50)	(50)
MINERALIZATION			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			

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

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, GRANULOMATOUS		1 (2%)	
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)
ALL OTHER SYSTEMS			
CRANIOBUCCAL POUCH			
CYST, NOS		1	
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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 D and C Red No. 9

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE FED DIETS CONTAINING D AND C RED NO. 9

	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%)
ULCER, ACUTE	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)		
FIBROSIS, FOCAL	1 (2%)	1 (2%)	
FIBROSIS, DIFFUSE			1 (2%)
HYPERPLASIA, BASAL CELL		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROSIS		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(50)	(50)	(50)
HYPERPLASIA, NOS	4 (8%)	5 (10%)	4 (8%)
#LUNG	(50)	(50)	(50)
CONGESTION, ACUTE		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (2%)		
INFLAMMATION, INTERSTITIAL	3 (6%)		3 (6%)
PNEUMONIA INTERSTITIAL CHRONIC	6 (12%)	17 (34%)	12 (24%)
GRANULOMA, FOREIGN BODY		1 (2%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM	4 (8%)	5 (10%)	4 (8%)
HISTIOCYTOSIS		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(47)	(50)	(50)
ANGIECTASIS			1 (2%)
HYPERPLASIA, HEMATOPOIETIC	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
#SPLEEN	(49)	(50)	(50)
INFLAMMATION ACUTE AND CHRONIC		1 (2%)	
FIBROSIS, FOCAL			1 (2%)
FIBROSIS, DIFFUSE		1 (2%)	
HYPERPLASIA, RETICULUM CELL		4 (8%)	
HYPERPLASIA, LYMPHOID	2 (4%)		1 (2%)
HEMATOPOIESIS	1 (2%)	4 (8%)	1 (2%)
#LYMPH NODE	(41)	(47)	(42)
PLASMACYTOSIS		1 (2%)	
HYPERPLASIA, LYMPHOID			1 (2%)
#MANDIBULAR L. NODE	(41)	(47)	(42)
PLASMACYTOSIS	1 (2%)		
HYPERPLASIA, RETICULUM CELL	1 (2%)		
#PANCREATIC L.NODE	(41)	(47)	(42)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
#MESENTERIC L. NODE	(41)	(47)	(42)
HEMORRHAGE	2 (5%)		
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, GRANULOMATOUS			1 (2%)
PLASMACYTOSIS	1 (2%)		
HYPERPLASIA, RETICULUM CELL		1 (2%)	1 (2%)
HYPERPLASIA, LYMPHOID	1 (2%)		1 (2%)
#PEYER'S PATCH	(48)	(46)	(47)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	2 (4%)
#JEJUNUM	(48)	(46)	(47)
HYPERPLASIA, LYMPHOID			2 (4%)
#KIDNEY	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID	5 (10%)		
#KIDNEY/CORTEX	(50)	(50)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)
#THYMIC MEDULLA	(33)	(28)	(34)
HYPERPLASIA, RETICULUM CELL		1 (4%)	
CIRCULATORY SYSTEM			
#BONE MARROW	(47)	(50)	(50)
THROMBOSIS, NOS			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
#HEART	(50)	(50)	(49)
MINERALIZATION	1 (2%)		
INFLAMMATION, CHRONIC FOCAL			1 (2%)
#HEART/ATRIUM	(50)	(50)	(49)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
*PULMONARY VEIN	(50)	(50)	(50)
THROMBUS, ORGANIZED			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(50)	(50)
CYSTIC DUCTS		1 (2%)	
#LIVER	(50)	(50)	(50)
CYST, NOS			1 (2%)
MULTIPLE CYSTS			1 (2%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)	
INFLAMMATION, NECRO GRAN		1 (2%)	
DEGENERATION, CYSTIC		1 (2%)	
NECROSIS, FOCAL		1 (2%)	
NECROSIS, ISCHEMIC		1 (2%)	1 (2%)
BASOPHILIC CYTO CHANGE		2 (4%)	
FOCAL CELLULAR CHANGE		2 (4%)	1 (2%)
ANGIECTASIS		1 (2%)	1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
NECROSIS, FOCAL		2 (4%)	
#LIVER/HEPATOCYTES	(50)	(50)	(50)
DEGENERATION, NOS	1 (2%)		
NECROSIS, FOCAL	2 (4%)		2 (4%)
CYTOPLASMIC VACUOLIZATION	1 (2%)		
#BILE DUCT	(50)	(50)	(50)
CYST, NOS		3 (6%)	
MULTILOCULAR CYST			1 (2%)
HYPERPLASIA, FOCAL		1 (2%)	1 (2%)
#PANCREAS	(48)	(46)	(49)
FIBROSIS, DIFFUSE		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
#PANCREATIC ACINUS	(48)	(46)	(49)
ATROPHY, NOS	1 (2%)		
ATROPHY, FOCAL	2 (4%)		
#CARDIAC STOMACH	(47)	(50)	(49)
ULCER, FOCAL	1 (2%)		
#COLON	(48)	(49)	(49)
NEMATODIASIS	1 (2%)	2 (4%)	3 (6%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
INFLAMMATION, CHRONIC DIFFUSE	1 (2%)		
#KIDNEY/CORTEX	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
DEGENERATION, NOS		1 (2%)	
METAPLASIA, OSSEOUS	1 (2%)		
REGENERATION, NOS	1 (2%)		
#KIDNEY/TUBULE	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL		1 (2%)	
PIGMENTATION, NOS			1 (2%)
REGENERATION, NOS	8 (16%)	9 (18%)	5 (10%)
#URINARY BLADDER	(48)	(50)	(47)
INFLAMMATION, ACUTE NECROTIZING		1 (2%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)
*URETHRA	(50)	(50)	(50)
INFLAMMATION, ACUTE DIFFUSE		1 (2%)	
*PROSTATIC URETHRA	(50)	(50)	(50)
INFLAMMATION, ACUTE DIFFUSE	1 (2%)		
ENDOCRINE SYSTEM			
#ADRENAL	(49)	(48)	(48)
FOCAL CELLULAR CHANGE			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
#ADRENAL CORTEX	(49)	(48)	(48)
FOCAL CELLULAR CHANGE	1 (2%)	5 (10%)	1 (2%)
#ZONA FASCICULATA	(49)	(48)	(48)
FOCAL CELLULAR CHANGE	1 (2%)	2 (4%)	1 (2%)
HYPERPLASIA, NODULAR	1 (2%)		
#ZONA RETICULARIS	(49)	(48)	(48)
FOCAL CELLULAR CHANGE			2 (4%)
#THYROID	(49)	(47)	(46)
HYPERPLASIA, FOLLICULAR-CELL		1 (2%)	
#PARATHYROID	(20)	(24)	(23)
THYROGLOSSAL DUCT CYST		1 (4%)	
#PANCREATIC ISLETS	(48)	(46)	(49)
HYPERPLASIA, FOCAL	2 (4%)		1 (2%)
REPRODUCTIVE SYSTEM			
*PENIS	(50)	(50)	(50)
NECROSIS, FOCAL		1 (2%)	
*PREPUTIAL GLAND	(50)	(50)	(50)
INFLAMMATION, NECROTIZING			1 (2%)
INFLAMMATION ACUTE AND CHRONIC		2 (4%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)
ABSCESS, CHRONIC	2 (4%)		
#PROSTATE	(48)	(47)	(49)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
INFLAMMATION ACTIVE CHRONIC			1 (2%)
*SEMINAL VESICLE	(50)	(50)	(50)
INFLAMMATION, ACUTE			1 (2%)
#TESTIS	(50)	(50)	(50)
MINERALIZATION			1 (2%)
ATROPHY, FOCAL	1 (2%)		
ATROPHY, DIFFUSE		3 (6%)	
*EPIDIDYMIS	(50)	(50)	(50)
INFLAMMATION, ACUTE/CHRONIC		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
GRANULOMA, NOS		1 (2%)	
GRANULOMA, SPERMATIC		1 (2%)	
NERVOUS SYSTEM			
#CEREBRUM	(49)	(50)	(50)
PERIVASCULAR CUFFING	1 (2%)		
#BRAIN	(49)	(50)	(50)
DEGENERATION, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE/CORNEA	(50)	(50)	(50)
ULCER, FOCAL	1 (2%)		
INFLAMMATION ACUTE AND CHRONIC	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
ANGIECTASIS		1 (2%)	
*MESENTERY	(50)	(50)	(50)
INFLAMMATION, PYOGRANULOMATOUS		1 (2%)	
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
INFLAMMATION, GRANULOMATOUS		1	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	5	3	6
AUTO/NECROPSY/HISTO PERF	1		2

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 D AND C RED NO. 9

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(49)
INFLAMMATION, FOCAL GRANULOMATOU			1 (2%)
GRANULOMA, FOREIGN BODY		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(49)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(50)	(50)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
#LUNG/BRONCHIOLE	(50)	(50)	(49)
HYPERPLASIA, NOS	4 (8%)	1 (2%)	1 (2%)
#LUNG	(50)	(50)	(49)
HEMORRHAGE		1 (2%)	
INFLAMMATION, INTERSTITIAL		2 (4%)	
INFLAMMATION ACUTE AND CHRONIC		1 (2%)	
PNEUMONIA INTERSTITIAL CHRONIC	8 (16%)	7 (14%)	10 (20%)
HEMOSIDEROSIS			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	4 (8%)	1 (2%)	1 (2%)
HISTIOCYTOSIS	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(49)
LEUKOCYTOSIS, NEUTROPHILIC		1 (2%)	
HYPERPLASIA, LYMPHOID	1 (2%)		
#BONE MARROW	(47)	(46)	(46)
HYPERPLASIA, GRANULOCYTIC	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
#SPLEEN	(49)	(50)	(49)
INFLAMMATION, ACUTE DIFFUSE			1 (2%)
HISTIOCYTOSIS	1 (2%)		
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	2 (4%)
HEMATOPOIESIS			1 (2%)
#SPLENIC RED PULP	(49)	(50)	(49)
HISTIOCYTOSIS	1 (2%)		
#LYMPH NODE	(42)	(45)	(41)
HYPERPLASIA, LYMPHOID			1 (2%)
#MANDIBULAR L. NODE	(42)	(45)	(41)
HEMORRHAGIC CYST	1 (2%)		
HYPERPLASIA, LYMPHOID			1 (2%)
#MESENTERIC L. NODE	(42)	(45)	(41)
NECROSIS, DIFFUSE			1 (2%)
LYMPHOID DEPLETION		1 (2%)	
ANGIECTASIS			1 (2%)
#PEYER'S PATCH	(46)	(47)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
*MESENTERY	(50)	(50)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	
#KIDNEY	(50)	(50)	(49)
HYPERPLASIA, LYMPHOID	1 (2%)		1 (2%)
#THYMUS	(38)	(39)	(40)
NECROSIS, NOS			1 (3%)
HYPERPLASIA, LYMPHOID	1 (3%)		
#THYMIC MEDULLA	(38)	(39)	(40)
HYPERPLASIA, EPITHELIAL	1 (3%)		
CIRCULATORY SYSTEM			
#LUNG	(50)	(50)	(49)
PERIVASCULITIS	1 (2%)		2 (4%)
#HEART	(50)	(50)	(49)
PERIVASCULITIS			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
#MYOCARDIUM	(50)	(50)	(49)
PIGMENTATION, NOS			1 (2%)
*CORONARY ARTERY	(50)	(50)	(49)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
*VAGINA	(50)	(50)	(49)
PERIVASCULITIS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(49)
CYST, NOS		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
INFLAMMATION, ACUTE FOCAL	3 (6%)	1 (2%)	1 (2%)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)		
NECROSIS, FOCAL			1 (2%)
BASOPHILIC CYTO CHANGE		2 (4%)	
FOCAL CELLULAR CHANGE			1 (2%)
NODULAR REGENERATION		1 (2%)	
#LIVER/HEPATOCYTES	(50)	(50)	(49)
DEGENERATION, NOS		1 (2%)	
NECROSIS, FOCAL		2 (4%)	2 (4%)
*GALLBLADDER	(50)	(50)	(49)
INFLAMMATION, CHRONIC			1 (2%)
#BILE DUCT	(50)	(50)	(49)
DILATATION, NOS		1 (2%)	
#PANCREAS	(48)	(48)	(47)
MULTIPLE CYSTS			1 (2%)
CYSTIC DUCTS	1 (2%)	2 (4%)	
INFLAMMATION, GRANULOMATOUS			1 (2%)
#PANCREATIC DUCT	(48)	(48)	(47)
MULTIPLE CYSTS		2 (4%)	2 (4%)
#PANCREATIC ACINUS	(48)	(48)	(47)
ATROPHY, NOS		2 (4%)	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ATROPHY, FOCAL			2 (4%)
ATROPHY, DIFFUSE		1 (2%)	
#GASTRIC SUBMUCOSA	(49)	(50)	(49)
INFLAMMATION, ACUTE FOCAL			1 (2%)
#COLON	(47)	(50)	(49)
NEMATODIASIS	3 (6%)	2 (4%)	2 (4%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
INFLAMMATION, FOCAL GRANULOMATOU	1 (2%)		
#KIDNEY/CAPSULE	(50)	(50)	(49)
GLOMERULOSCLEROSIS, NOS		1 (2%)	
#KIDNEY/CORTEX	(50)	(50)	(49)
METAPLASIA, OSSEOUS			1 (2%)
#KIDNEY/GLOMERULUS	(50)	(50)	(49)
AMYLOIDOSIS		1 (2%)	1 (2%)
#KIDNEY/TUBULE	(50)	(50)	(49)
DILATATION, NOS	1 (2%)		
INFLAMMATION, CHRONIC FOCAL			1 (2%)
DEGENERATION, NOS	2 (4%)		
REGENERATION, NOS	2 (4%)		
ENDOCRINE SYSTEM			
#PITUITARY	(45)	(46)	(41)
HYPERPLASIA, FOCAL	1 (2%)		
HYPERPLASIA, CHROMOPHOBE-CELL	2 (4%)	5 (11%)	
#ADRENAL	(50)	(50)	(49)
INFLAMMATION, ACUTE DIFFUSE			1 (2%)
#ADRENAL CORTEX	(50)	(50)	(49)
CYST, NOS	1 (2%)	1 (2%)	
HEMORRHAGE		1 (2%)	
FOCAL CELLULAR CHANGE	2 (4%)		

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#ZONA GLOMERULOSA	(50)	(50)	(49)
CYTOPLASMIC VACUOLIZATION			1 (2%)
#ZONA FASCICULATA	(50)	(50)	(49)
INFLAMMATION ACUTE AND CHRONIC		1 (2%)	
FOCAL CELLULAR CHANGE			2 (4%)
CYTOMEGALY	1 (2%)		
#ZONA RETICULARIS	(50)	(50)	(49)
FOCAL CELLULAR CHANGE	1 (2%)		
#ADRENAL MEDULLA	(50)	(50)	(49)
HYPERPLASIA, FOCAL	1 (2%)		
#THYROID	(50)	(47)	(47)
FOLLICULAR CYST, NOS	4 (8%)		3 (6%)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
HYPERPLASIA, FOLLICULAR-CELL			2 (4%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(49)
CYST, NOS	1 (2%)		
HYPERPLASIA, CYSTIC	2 (4%)		1 (2%)
#UTERUS	(47)	(49)	(48)
DILATATION, NOS		1 (2%)	
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
ANGIECTASIS		1 (2%)	
#UTERUS/ENDOMETRIUM	(47)	(49)	(48)
INFLAMMATION ACUTE AND CHRONIC		1 (2%)	
HYPERPLASIA, STROMAL			1 (2%)
#ENDOMETRIAL GLAND	(47)	(49)	(48)
MULTIPLE CYSTS	1 (2%)	9 (18%)	3 (6%)
HYPERPLASIA, CYSTIC	33 (70%)	33 (67%)	38 (79%)
#OVARY	(44)	(47)	(46)
FOLLICULAR CYST, NOS	8 (18%)	8 (17%)	10 (22%)
CORPUS HEMORRHAGICUM CYST	1 (2%)		
CORPUS LUTEUM CYST	2 (5%)		
HEMORRHAGIC CYST			2 (4%)

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
GRANULOMA, NOS		1 (2%)	
#MESOVARIUM	(44)	(47)	(46)
LYMPHOCYTIC INFLAMMATORY INFILTR	2 (5%)		
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(49)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR			3 (6%)
#HYPOTHALAMUS	(50)	(49)	(49)
ATROPHY, PRESSURE	1 (2%)		1 (2%)
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(50)	(50)	(49)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
INFLAMMATION CHRONIC CYSTIC	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL WALL	(50)	(50)	(49)
ABSCESS, CHRONIC			1 (2%)
*PERITONEUM	(50)	(50)	(49)
INFLAMMATION, ACUTE FIBRINOUS			1 (2%)
INFLAMMATION ACUTE AND CHRONIC			1 (2%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	1	

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

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
AUTO/NECROPSY/HISTO PERF		1	
AUTOLYSIS/NO NECROPSY			1

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

APPENDIX E

Analysis of D and C Red No. 9
(Lot No. Z-8054)
Midwest Research Institute

APPENDIX E

Analysis of D & C Red No. 9

(Lot No. Z-8054)

A. Elemental Analysis

Element	C	H	N	Ba	S	Na	Cl
Theory (100% compound)	45.93	2.72	6.30	15.45	7.21	-	-
Theory (89.8% compound; 1.58% water)	41.25	2.44	5.65	13.87	6.47	-	-
Determined	40.97	2.45	5.36	15.61	7.32	0.85	7.30
	40.85	2.50	5.33	15.61	7.41	0.93	7.40

B. Water Analysis

(Karl Fisher) 1.58 ± 0.040%

C. Titration with Titanous Chloride

89.8 ± 0.5 (δ)%

D. Melting Point

Determined	Literature Values
m.p. 343°-345°C, dec. (visual, capillary)	No literature values found
m.p. 356°-392°C, dec. (Du Pont 900 DTA	

E. Thin-layer Chromatography

Plates: (System 1) Alumina Type E F254; activated 1 hr at 140°C
(System 2) Silica Gel 60 F254

Ref. Standard: Methyl Red

Visualization: Self-visualization, UV (254 and 366 nm)

Amount Spotted: 100 and 300 μg

System 1: n-Butanol:Ethanol: Sulfuric Acid:Water (40:35:5:20)

System 2: Ethyl acetate: acetate:isopropanol: Water:tetrabutyl-ammonium hydroxide (25% in methanol) (35:35:20:10)

R_f: 0.97 (trace); 0.79 (major) 0.26 (trace); origin (trace)	R_f: 0.98 (trace); 0.85 (trace); 0.81 (trace); 0.65 (trace); 0.57 (trace); origin (major)
R_{st}: 6.47; 5.27; 1.73; origin	R_{st}: 1.15; 1.00; 0.95; 0.76; 0.67; origin

F. High-Pressure Liquid Chromatography

Instrument: Waters ALC 202 with Model 660 Solvent Programmer
Column: C_{18} μ-Bondapak, 300 x 4 mm I.D.
Detector: Ultraviolet, 254 nm
Solvent: 75% B + 25% A
A: 0.005 M tetrabutyl ammonium hydroxide and 1% acetic acid in water.
B: 0.005 M tetrabutyl ammonium hydroxide and 1% acetic acid in methanol.
Flow: 1.5 ml/min
Results: Single compound peak
Retention time: 9.8 min

G. Spectral Data

(1) Infrared:

Instrument: Beckman IR-12
Cell: 2% potassium bromide pellet
Results: See Figure 5.

Consistent with literature spectrum (Sadtler Standard Spectra)

(2) Ultraviolet/Visible:

Instrument: Cary 118

λ max (nm)	$\epsilon \times 10^{-3}$
492	10.7 ± 0.4 (δ)
415s	5.8 ± 0.2 (δ)
307	5.2 ± 0.9 (δ)
277	6.1 ± 0.9 (δ)
267	6.8 ± 0.9 (δ)
227	1.6 ± 0.1 (δ)

Solvent: Distilled water

No literature reference found

(3) Nuclear Magnetic Resonance: Compound not sufficiently soluble for spectral analysis.

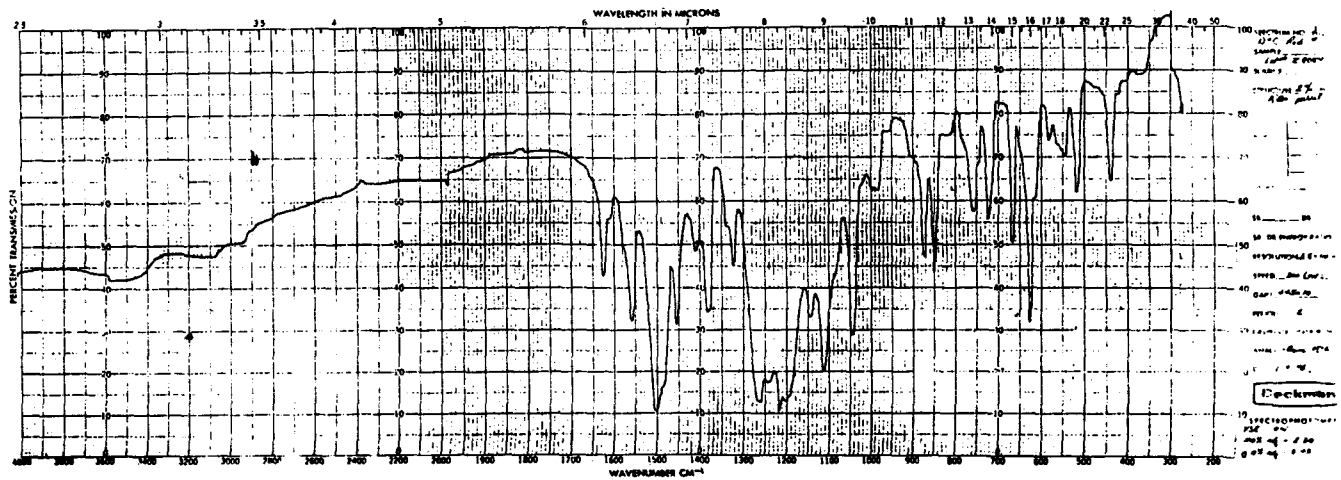

Figure 5. Infrared Absorption Spectrum of D and C Red No. 9 (Lot No. Z-8054)

APPENDIX F

Analysis of Formulated Diets for Stability of D & C Red No. 9

APPENDIX F

Analysis of Formulated Diets for Stability of D & C Red No. 9

1. MIXING AND STORAGE

D & C Red No. 9 (2.476 g) and Wayne Lab-Blox® Rodent Feed (23.462 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.

2. EXTRACTION

One-gram samples of the above mixtures were mixed with 50 ml of 0.005 M aqueous tetrabutyl-ammonium hydroxide and 50 ml of chloroform (to solubilize the dye and extract the resulting tetrabutylammonium-dye salt). This mixture was placed in an ultrasonic vibratory bath for 30 seconds and then tritiated in a Polytron® high-speed blender for 1 minute. The feed residue was separated by centrifugation and the liquid phases were decanted into a separatory funnel. The chloroform phase was remixed with the feed residue and fresh chloroform. The above extraction was repeated. All the chloroform phases were combined and made up to a volume of 100 ml. Two milliliters of this solution were diluted to 100 ml with fresh chloroform, and this constituted the test solution. The absorption at 490 nm in the ultraviolet region of the spectrum was measured to determine the tetrabutylammonium-dye salt concentration.

3. RESULTS

Sample (°C)	Average %(a) Compound
-20	8.9 ± 0.8
5	9.8 ± 0.8
25	8.5 ± 0.8
45	9.2 ± 0.8

(a) Corrected for a spiked recovery yield of 100.8% ± 1.0%. Theoretical yield, 9.54%

4. CONCLUSION

D & C Red No. 9 mixed with feed is stable for 2 weeks at temperatures up to 45°C.

APPENDIX G

Analysis of Formulated Diets for Concentrations of D & C Red No. 9

APPENDIX G

Analysis of Formulated Diets for Concentrations of D & C Red No. 9

A 100-mg sample of the dye-feed mixture was mixed with 10 ml of 2% H_2SO_4 in ethanol and vortexed for 30 seconds. Mixing times greater than 30 seconds were required when levels of D & C Red No. 9 exceeded 150 μg of dye per 100 mg of feed sample and a volume of 10 ml of solvent was used. Concentrations of 15 μg/ml could be achieved quite rapidly (in 30 seconds or less). For higher concentrations, progressively longer mixing times were required. The suspension was centrifuged at room temperature for 5 minutes at 2,000 rpm. An appropriate volume of supernatant was removed and diluted to achieve a final concentration in the linear portion of the standard curve. Internal standards were prepared using control powdered feed and assayed in the same manner. All samples and standards were run in triplicate. The absorbance was determined at 490 nm in a Gilford 2400-S spectrophotometer. The spectrophotometer was blanked with a 100-mg feed sample treated in the same manner as the samples. The standard curve developed with feed-eye standards (triplicate) automatically incorporates a correction for recovery. The concentration of dye in a feed sample could be read directly from the curve without any further adjustment for recovery.

The results of the analyses are presented in Table G1.

Table G-1. Analyses of Formulated Diets

Date Mixed (a)	Date Used	Concentration (b) of D & C Red No. 9 in feed for target concentration of 1,000 ppm	2,000 ppm	3,000 ppm
3/10/77	Week of 3/14/77	940		2,880
3/23/77	Week of 3/27/77	980		2,850
4/16/77	Week of 4/20/77	980	2,040	
6/3/77	Week of 6/7/77	1,000		3,110
		1,010	1,960	2,840
8/30/77	Week of 9/2/77	980	1,970	2,890
		950		2,920
10/21/77	Week of 10/24/77	1,010	1,920	2,980
		1,000		2,950
1/31/78	Week of 2/3/77	1,000	2,010	2,990
4/13/78	Week of 4/17/77	1,085	2,105	3,030
				3,030
6/22/78	Week of 6/26/78	995	2,040	2,940
		995		2,920
7/13/78	Week of 7/17/78	1,040	2,070	2,920
		1,010		2,960
11/13/78	Week of 11/17/78	1,060	2,000	2,910
		990		2,880
1/22/79	Week of 1/26/79	1,000	1,990	2,850
		950		2,790
Mean (ppm)		999	2,010	2,931
Standard Deviation		35	55	78
Coefficient of Variation (%)		3.5	2.7	2.7
Range (ppm)		940-1,085	1,920-2,105	2,790-3,110
Number of Samples		19	10	19

(a) 4/8/77 was the start date for mice and 3/10/77 was the start date for rats.

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

APPENDIX H

Feed Consumption by Rats and Mice Receiving D & C Red No. 9

Table H1. Feed Consumption by Male Rats Receiving D & C Red No. 9

Week	Control GRAMS FEED/ DAY(a)	Low GRAMS FEED/ DAY(a)	Low LOW/ CONTROL (b)	High GRAMS FEED/ DAY(a)	High HIGH/ CONTROL (b)
5	19.4	20.3	1.0	18.6	1.0
10	16.1	15.9	1.0	18.7	1.2
14	17.3	17.9	1.0	17.9	1.0
18	19.7	19.7	1.0	18.4	0.9
22	17.9	18.4	1.0	18.9	1.1
26	14.4	19.0	1.3	14.7	1.0
30	19.0	19.1	1.0	20.0	1.1
36	20.3	20.7	1.0	19.6	1.0
41	19.1	19.7	1.0	18.4	1.0
46	24.0	25.3	1.1	24.4	1.0
50	20.9	23.0	1.1	19.3	0.9
54	20.3	21.4	1.1	20.3	1.0
58	19.7	26.3	1.3	24.7	1.3
62	21.7	18.9	0.9	18.3	0.8
67	26.4	24.9	0.9	22.9	0.9
70	25.0	24.3	1.0	24.0	1.0
75	18.3	18.0	1.0	18.4	1.0
81	20.9	17.0	0.8	16.9	0.8
84	22.3	23.3	1.0	22.9	1.0
88	20.3	22.6	1.1	23.9	1.2
92	19.7	19.7	1.0	21.3	1.1
97	17.6	17.6	1.0	22.0	1.3
101	18.9	18.9	1.0	21.7	1.1
Mean	20.0	20.5	1.0	20.3	1.0
SD (c)	2.7	3.0	0.1	2.7	0.1
CV (d)	13.5	14.8	10.0	13.3	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 H2. Feed Consumption by Female Rats Receiving D & C Red No. 9

Week	Control GRAMS FEED/ DAY(a)	Low GRAMS FEED/ DAY(a)	Low LOW/ CONTROL (b)	High GRAMS FEED/ DAY(a)	High HIGH/ CONTROL (b)
3	13.1	13.3	1.0	14.0	1.1
8	8.3	11.6	1.4	13.6	1.6
12	13.7	10.6	0.8	10.4	0.8
16	14.1	12.4	0.9	13.7	1.0
20	12.6	13.1	1.0	14.4	1.1
24	13.1	12.6	1.0	12.4	0.9
28	13.0	14.9	1.1	14.1	1.1
34	12.7	13.1	1.0	14.0	1.1
39	12.0	13.3	1.1	13.3	1.1
44	19.4	19.9	1.0	20.7	1.1
48	12.6	11.6	0.9	12.7	1.0
52	13.3	16.4	1.2	15.1	1.1
56	22.0	22.6	1.0	20.4	0.9
60	12.6	13.3	1.1	11.6	0.9
65	17.0	17.1	1.0	17.1	1.0
68	13.1	20.1	1.5	18.4	1.4
73	14.0	14.4	1.0	13.0	0.9
79	12.7	12.9	1.0	11.3	0.9
82	14.6	14.3	1.0	14.4	1.0
86	15.0	18.3	1.2	14.9	1.0
90	14.0	16.3	1.2	15.0	1.1
95	13.1	15.3	1.2	14.6	1.1
99	14.3	12.9	0.9	13.7	1.0
Mean	13.9	14.8	1.1	14.5	1.1
SD (c)	2.6	3.1	0.2	2.6	0.2
CV (d)	18.7	20.9	18.2	17.9	18.2

(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 D & C Red No. 9

Week	Control GRAMS FEED/ DAY(a)	Low GRAMS FEED/ DAY(a)	Low LOW/ CONTROL (b)	High GRAMS FEED/ DAY(a)	High HIGH/ CONTROL (b)
1	7.4	7.6	1.0	7.7	1.0
5	7.9	7.6	1.0	7.7	1.0
10	3.1	3.6	1.2	3.3	1.1
14	5.6	3.7	0.7	3.6	0.6
19	7.9	8.0	1.0	8.0	1.0
23	7.9	8.4	1.1	8.3	1.1
27	8.0	8.9	1.1	8.4	1.1
33	8.1	8.3	1.0	7.7	1.0
37	8.3	8.3	1.0	8.1	1.0
42	8.3	8.3	1.0	8.6	1.0
46	8.4	8.1	1.0	8.3	1.0
50	8.3	8.6	1.0	8.9	1.1
54	8.4	8.4	1.0	8.7	1.0
58	8.1	8.6	1.1	8.1	1.0
62	8.6	8.6	1.0	8.7	1.0
66	8.6	8.4	1.0	8.6	1.0
71	9.0	8.7	1.0	8.7	1.0
76	9.0	8.1	0.9	8.6	1.0
79	10.4	10.6	1.0	10.1	1.0
84	8.7	8.1	0.9	8.6	1.0
88	9.1	9.6	1.1	9.0	1.0
92	9.7	8.9	0.9	9.3	1.0
96	9.9	9.4	0.9	10.1	1.0
100	11.4	10.4	0.9	11.4	1.0
Mean	8.3	8.2	1.0	8.3	1.0
SD (c)	1.6	1.6	0.1	1.7	0.1
CV (d)	19.3	19.5	10.0	20.5	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 H4. Feed Consumption by Female Mice Receiving D & C Red No. 9

Week	Control GRAMS FEED/ DAY(a)	Low GRAMS FEED/ DAY(a)	Low LOW/ CONTROL (b)	High GRAMS FEED/ DAY(a)	High HIGH/ CONTROL (b)
1	7.7	7.0	0.9	7.3	0.9
4	7.7	7.3	0.9	7.4	1.0
9	1.6	1.9	1.2	1.4	0.9
13	1.9	1.7	0.9	1.3	0.7
18	8.3	8.1	1.0	7.7	0.9
22	8.1	8.4	1.0	7.9	1.0
26	8.1	8.7	1.1	8.0	1.0
31	8.7	8.4	1.0	7.7	0.9
36	8.4	8.6	1.0	8.1	1.0
41	8.0	8.1	1.0	8.3	1.0
45	8.4	8.4	1.0	7.7	0.9
49	8.3	9.0	1.1	8.1	1.0
53	8.0	8.4	1.1	8.0	1.0
57	8.6	8.0	1.0	7.6	0.9
61	9.3	9.1	1.0	8.9	1.0
65	9.0	9.0	1.0	9.0	1.0
70	9.0	9.1	1.0	8.3	0.9
75	8.6	9.1	1.1	8.0	0.9
76	8.3	9.0	1.1	9.4	1.1
78	10.7	10.3	1.0	10.7	1.0
83	9.0	9.1	1.0	8.0	0.9
87	9.6	9.3	1.0	9.0	0.9
91	9.4	9.4	1.0	8.3	0.9
95	8.6	8.3	1.0	8.0	0.9
99	10.0	11.0	1.1	10.0	1.0
Mean	8.1	8.2	1.0	7.8	0.9
SD (c)	2.1	2.1	0.1	2.1	0.1
CV (d)	25.9	25.6	10.0	26.9	11.1

(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.

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