NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 407

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

C.I. PIGMENT RED 3

(CAS NO. 2425-85-6)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies 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.

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge while supplies last from the NTP Central Data Management, NIEHS, P.O. Box 12233, MD A0-01, Research Triangle Park, NC 27709 (919-541-1371).

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF C.I. PIGMENT RED 3

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IN F344/N RATS AND B6C3F$_1$ MICE

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NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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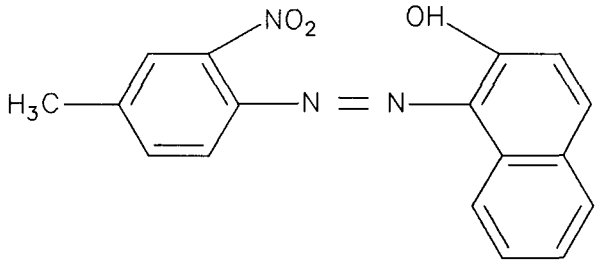
ABSTRACT



C.I. PIGMENT RED 3

CAS No. 2425-85-6

Chemical Formula: $C_{17}H_{13}N_3O_3$ Molecular Weight: 307.31

Synonyms: 2-Naphthalenol, 1-((4-methyl-2-nitrophenyl)azo)-; Calcotone Toluidine Red YP; Fast Red A; Pigment Scarlet R; Recolite Fast Red RBL; Sengale Light Red B

C.I. Pigment Red 3, a yellowish red solid, is widely used for coloring paints, inks, plastics, and rubber, and in textile printing. It is used in a wide range of consumer items such as wallpaper, typewriter ribbons, carbon paper, and art materials. Toxicology and carcinogenicity studies were conducted by feeding groups of F344/N rats and B6C3F$_1$ mice of each sex diets containing C.I. Pigment Red 3 (97% pure) for 2 weeks, 13 weeks, and 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and cultured Chinese hamster ovary cells.

2-Week Studies: Groups of five rats and five mice of each sex were given feed containing 0, 6,000, 12,500, 25,000, 50,000, or 100,000 ppm C.I. Pigment Red 3 for 2 weeks. No chemical-related deaths occurred in rats or mice. Final mean body weights of exposed rats and male mice were lower than controls; female mice that received 6,000 and 50,000 ppm had significantly increased final mean body weights compared to that of the controls. The feed consumption of treated rats and mice was slightly greater than that of the controls, suggesting that C.I. Pigment Red 3 had no adverse effects on the feed palatability. Dose-related decreases in erythrocyte counts and hematocrit values and an increase in reticulocyte counts were observed in rats. Changes in these parameters were observed in mice, but there were no clear, dose-related trends.

13-Week Studies: Groups of ten rats and ten mice of each sex were given feed containing 0, 3,000, 6,000, 12,500, 25,000, or 50,000 ppm C.I. Pigment Red 3 for 13 weeks. No chemical-related deaths were observed in rats or mice. The final mean body weights of exposed female rats were significantly lower than that of the controls; the final mean body weights of exposed male rats and exposed mice were similar to controls. There were significant increases in relative liver and kidney weights of exposed male rats. Increases in the relative liver weights in mice did not occur with a dose-related trend and thus they were not considered related to chemical administration. Sites for the toxicity of C.I. Pigment Red 3 were the bone marrow, kidney, liver, and spleen in rats. Lesions observed in rats included bone marrow hyperplasia, congestion and hematopoietic cell proliferation of the spleen, and iron-positive pigmentation of the spleen, kidney, and liver. Sites for the toxicity of C.I. Pigment Red 3 in mice were the liver, kidney, and spleen in males and the liver and spleen in females. Lesions noted among mice in the spleen were hematopoietic cell

proliferation and iron-positive pigmentation. In the liver, there was hematopoietic cell proliferation in male and female mice. Cytomegaly occurred in the renal tubule epithelium of the male mouse kidney.

2-Year Studies: Doses selected for the 2-year feed studies were 0, 6,000, 12,500, and 25,000 ppm for rats and 0, 12,500, 25,000, and 50,000 ppm for mice. The dose selection for rats was based on body weight changes observed for females that received 50,000 ppm; the dose selection for mice was based on the lack of body weight depression or death at the doses tested during the 13-week studies. Concentrations higher than 50,000 ppm in the feed were not used because higher levels might have adversely affected the nutritional value of the diet during the 2-year studies.

Body Weight, Feed Consumption, Clinical Findings, and Survival in the 2-Year Studies: Final mean body weights for male rats that received 25,000 ppm, female rats that received 12,500 and 25,000 ppm, and male and female mice that received 50,000 ppm were more than 10% lower than those of the controls. Feed consumption of exposed rats and mice was similar to that of the controls. No clinical findings indicative of toxicity were observed in rats or mice. The survival of low-dose male rats was greater than that of the controls (0 ppm, 28/50; 6,000 ppm, 40/50; 12,500 ppm, 28/50; 25,000 ppm, 20/50). Survival of exposed female rats and exposed male mice was similar to the controls; the survival of high-dose female mice was significantly decreased compared to that of the controls (39/50, 37/50, 31/50, 25/50). The reduced survival in this dose group may have been due to the increased incidence of ovarian abscesses.

Neoplasms and Nonneoplastic Lesions in the 2-Year Studies: Benign adrenal pheochromocytomas were significantly increased in the 12,500 and 25,000 ppm groups of male rats compared to the controls (22/50, 29/50, 35/50, 34/50). However, malignant neoplasms were not increased in incidence (6/50, 7/50, 10/50, 4/50). The incidence of adrenal pheochromocytomas in dosed groups exceeded the range for NTP historical controls for feed studies (22%-48%), and the increased incidence of this neoplasm was attributed to C.I. Pigment Red 3 administration.

Squamous cell papillomas of the skin occurred with a positive trend in male rats (0/50, 4/50, 2/50, 6/50), and the incidence in the high-dose group was significantly greater than that of the controls. A poorly differentiated squamous cell carcinoma (diagnosed as carcinoma) was observed in a control male. The historical control rate for squamous cell papillomas in NTP feed studies is low (16/800 or 2%, range 0%-4%), and the higher incidence of this tumor in male rats may have been caused by the administration of C.I. Pigment Red 3.

Hepatocellular adenomas occurred with a positive trend in female rats, with a significantly greater incidence in the high-dose group than in the control group (0/50, 0/50, 1/50, 10/50). This neoplasm has occurred in only one historical control group in NTP feed studies (3/800, range 0%-6%), and the increase in hepatocellular adenomas in female rats was attributed to chemical administration.

Chemical-related nonneoplastic lesions observed in the livers of male and female rats included eosinophilic or mixed type foci of cellular alteration. Foci were often accompanied by angiectasis and cystic degeneration in males and by granulomas and cholesterol pigmentation in females. Chronic nephropathy occurred with increased severity in exposed male and female rats. The lesions were more severe in males than in females. Other lesions considered secondary to renal disease included parathyroid gland hyperplasia, fibrous osteodystrophy of the bone, and mineralization of various organs (stomach, intestine, heart, and blood vessels). The increased incidence of hyperplasia of the transitional epithelium of the renal papilla observed in treated rats was considered to be part of the chronic nephropathy.

Zymbal's gland carcinoma incidences were marginally increased in the mid- and high-dose male rats (0/50, 0/50, 2/50, 3/50). The incidence in the high-dose group was outside the NTP historical control range (0%-4%), and the Zymbal's gland carcinomas may have been related to C.I. Pigment Red 3 administration.

Mononuclear cell leukemias, mammary gland fibroadenomas, and preputial gland/clitoral gland adenomas occurred at lower incidences in exposed male and female rats. The decrease in mononuclear cell leukemia was attributed to the direct effect of C.I. Pigment Red 3 or its metabolites on the mechanism responsible for inducing leukemias in aging rats, while the decreased incidence of mammary gland fibroadenomas might be attributed to

decreased body weights in female rats. The cause of the decreased incidences of preputial and clitoral gland tumors is unknown.

Tubule adenomas of the renal cortex occurred at a significantly higher incidence in high-dose male mice than in controls (0 ppm, 0/50; 12,500 ppm, 0/50; 25,000 ppm, 0/50; 50,000 ppm, 6/50). Because this tumor occurred only in exposed males and was outside the range for NTP historical controls in feed studies (0%-2%), renal cortical tubule adenomas in male mice were considered to be related to the administration of C.I. Pigment Red 3.

Follicular cell adenoma of the thyroid gland occurred with a positive trend in male mice (0/50, 0/49, 1/50, 5/50). The incidence in the high-dose group was significantly greater than that in the controls. This chemical-related effect is supported by the increased incidence of follicular cell hyperplasia. Because the incidence of this tumor exceeded the range of the historical controls from NTP feed studies (0%-4%), the increase of follicular cell adenoma was attributed to chemical administration. Female mice receiving C.I. Pigment Red 3 had a significant increase in follicular cell hyperplasia but showed no increase in tumor incidence at this site.

Focal renal tubule hyperplasia and cystic hyperplasia occurred in exposed male mice but not in the controls. Cytomegaly (karyomegaly) of the renal tubule epithelium was seen in all treated male mice. The severity of the accompanying chronic nephropathy was increased in both male and female mice.

Genetic Toxicology: C.I. Pigment Red 3 was mutagenic in *Salmonella typhimurium* strains TA100 and TA98 in the presence of exogenous metabolic activation (S9); no increases in gene mutation were observed in strains TA1535 and TA1537, with or without S9. C.I. Pigment Red 3 did not induce sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells in either the presence or the absence of S9.

Conclusions: Under the conditions of these 2-year feed studies, there was *some evidence of carcinogenic activity** of C.I. Pigment Red 3 in male F344/N rats as exhibited by increased incidences of benign pheochromocytomas of the adrenal gland. The marginal increase in the incidences of squamous cell papillomas of the skin and Zymbal's gland carcinomas may have been related to C.I. Pigment Red 3 administration. There was *some evidence of carcinogenic activity* of C.I. Pigment Red 3 in female F344/N rats as indicated by the increased incidence of hepatocellular adenomas. There was *some evidence of carcinogenic activity* of C.I. Pigment Red 3 in male B6C3F_1 mice as exhibited by the increased incidences of tubule adenomas of the renal cortex and follicular cell adenomas of the thyroid gland. There was *no evidence of carcinogenic activity* of C.I. Pigment Red 3 in female B6C3F_1 mice that received 12,500, 25,000, or 50,000 ppm.

The incidences of mononuclear cell leukemia and preputial gland tumors in male rats and mononuclear cell leukemia, mammary gland fibroadenoma, and clitoral gland tumors in female rats were lower in the exposed groups. The incidences of liver foci were markedly increased in exposed male and female rats. The severity of chronic nephropathy was increased in male rats and to a lesser extent in female rats given C.I. Pigment Red 3. An increase in the severity of nephropathy was observed in male and female mice; cytomegaly (karyomegaly) of renal tubule epithelium was observed in male mice. Thyroid follicular cell hyperplasia occurred with an increased incidence in male and female mice receiving C.I. Pigment Red 3.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

Summary of the 2-Year Carcinogenicity and Genetic Toxicology Studies of C.I. Pigment Red 3

Variable	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Exposure concentrations	0, 6,000, 12,500, and 25,000 ppm in feed	0, 6,000, 12,500, and 25,000 ppm in feed	0, 12,500, 25,000, and 50,000 ppm in feed	0, 12,500, 25,000, and 50,000 ppm in feed
Body weights	Dosed groups lower than controls	Dosed groups lower than controls	High-dose group lower than controls	Mid- and high-dose groups lower than controls
Feed consumption	Dosed groups similar to controls	Dosed groups similar to controls	Dosed groups similar to controls	Dosed groups similar to controls
2-Year survival rates	28/50, 40/50, 28/50, 20/50	32/50, 41/50, 39/50, 40/50	33/50, 28/50, 31/50, 33/50	39/50, 37/50, 31/50, 25/50
Nonneoplastic effects	Liver: eosinophilic foci (6/50, 37/50, 36/50, 41/50); mixed cell foci (2/50, 24/50, 21/50 15/50); cystic degeneration (9/50, 36/50, 40/50, 36/50) Kidney: chronic nephropathy (severity grades: 2.4, 3.1, 3.6, 3.8)	Liver: eosinophilic foci (1/50, 7/50, 18/50, 16/50); mixed cell foci (4/50, 16/50, 30/50 40/50); biliary tract proliferation (18/50, 12/50, 18/50, 29/50) Kidney: chronic nephropathy (severity grades: 1.7, 2.2, 2.4, 2.8)	Kidney: chronic nephropathy (severity grades: 0.8, 1.0, 1.2, 1.6); cytomegaly of the renal tubule epithelium (0/50, 40/50, 47/50, 46/50) Thyroid gland: follicular cell hyperplasia (2/50, 10/49, 24/48, 41/50)	Kidney: chronic nephropathy (severity grades: 0.7, 1.2, 1.2, 1.6) Thyroid gland: follicular cell hyperplasia (11/50, (11/50, 24/49, 38/50)
Neoplastic effects	Adrenal medulla: pheochromocytomas (24/50, 32/50, 37/50, 36/50)	Liver: hepatocellular adenomas (0/50, 0/50, 1/50, 10/50)	Kidney (cortex): tubule adenomas (0/50, 0/50, 0/50, 6/50) Thyroid gland: follicular cell adenomas (0/50, 0/49, 1/50, 5/50)	None
Uncertain findings	Skin: squamous cell papillomas (0/50, 4/50, 2/50, 6/50) Zymbal's gland: carcinoma (0/50, 0/50, 2/50, 3/50)	None	None	None

Summary of the 2-Year Carcinogenicity and Genetic Toxicology Studies of C.I. Pigment Red 3 (continued)

Variable	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Other findings	Mononuclear cell leukemia (22/50, 6/50, 2/50, 1/50) Preputial gland: neoplasms (7/49, 0/13, 1/25, 1/50)	Mononuclear cell leukemia (10/50, 1/50, 0/50, 2/50) Clitoral gland: adenoma (9/47, 1/14, 0/14, 1/50) Mammary gland: fibroadenoma (23/50, 16/50, 20/49, 12/50)	None	None
Level of evidence of carcinogenic activity	Some evidence	Some evidence	Some evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutation:	Positive with S9 in strains TA100 and TA98 Negative with and without S9 in strains TA1535 and TA1537			
Sister chromatid exchange Chinese hamster ovary cells *in vitro*:	Negative with and without S9			
Chromosomal aberrations Chinese hamster ovary cells *in vitro*:	Negative with and without S9			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

- **Clear evidence of carcinogenic activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence of carcinogenic activity** is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence of carcinogenic activity** describes studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence of carcinogenic activity** is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study of carcinogenic activity** is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on C.I. Pigment Red 3 on July 9, 1991, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, panel members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On July 9, 1991, the draft Technical Report on the toxicology and carcinogenesis studies of C.I. Pigment Red 3 received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.D. Irwin, NIEHS, introduced the toxicology and carcinogenesis studies of C.I. Pigment Red 3 by discussing the uses and rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplastic and nonneoplastic lesions in rats and mice. The proposed conclusions were *some evidence of carcinogenic activity* of C.I. Pigment Red 3 in male and female rats and in male mice, and *no evidence of carcinogenic activity* of C.I. Pigment Red 3 in female mice.

Dr. Davis, a principal reviewer, agreed with the proposed conclusions. He asked for clarification of why 50,000 ppm was the upper limit in a feed study, and why, in view of the chemical's uses, the dermal route of exposure was not chosen. Dr. Irwin said there was a long-standing NTP policy that dietary levels exceeding 5% (50,000 ppm) might compromise the nutritional status of the animal. Dr. Davis commented on the inclusion of statements that there were no clinical findings indicative of toxicity and asked how this could be reconciled with reductions in body weight gain of more than 10%. Dr. Irwin agreed that reduced body weight gain could be an indicator of toxicity but was not classified as a clinical finding.

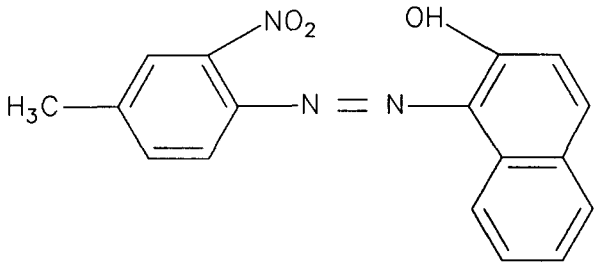
Dr. Klaassen, the second principal reviewer, agreed with the proposed conclusions.

Dr. Bailey, the third principal reviewer, agreed with the conclusions. He also questioned whether dermal exposure might have been appropriate, and thought percutaneous absorption data might have been useful. Dr. Irwin explained that pigments have to be dissolved in an organic solvent for dermal administration and often a residue of the pigment remains on the skin. A variable amount of the residual chemical will be ingested by the animal through natural grooming. Thus, the oral study is likely to be more quantitative and should provide a better measure of carcinogenic potential.

Dr. McKnight suggested that for Zymbal's gland tumors in male rats, a statistically significant trend test and a high-dose group incidence that exceeded that in any historical control group supported these tumors being considered *some evidence of carcinogenic activity.* These tumors were in the conclusion as "may have been related to chemical administration."

Dr. Davis moved that the Technical Report on C.I. Pigment Red 3 be accepted with the revisions discussed and with the conclusions as written for male and female rats and male mice, *some evidence of carcinogenic activity,* and for female mice, *no evidence of carcinogenic activity.* Dr. Goodman seconded the motion. Dr. McKnight offered an amendment that Zymbal's gland carcinomas be included as supporting *some evidence of carcinogenic activity* in male rats. Dr. Zeise seconded the amendment, which was defeated eight votes to two (Drs. McKnight and Zeise). The original motion was then accepted unanimously with ten votes.

INTRODUCTION



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Synonyms: 2-Naphthalenol, 1-((4-methyl-2-nitrophenyl)azo)-; Calcotone Toluidine Red YP; Fast Red A; Pigment Scarlet R; Recolite Fast Red RBL; Sengale Light Red B

PHYSICAL AND CHEMICAL PROPERTIES

C.I. Pigment Red 3 is a yellowish red solid with a melting point of 278° C. It is insoluble in water, slightly soluble in ethanol and xylene, and poorly soluble in esters and ketones (*Colour Index*, 1971). Manufacturers couple 2-nitro-4-methylaniline with 2-naphthol to produce this pigment (*Kirk-Othmer*, 1978).

PRODUCTION, USE, AND HUMAN EXPOSURE

United States production of C.I. Pigment Red 3 in 1986 was 440,000 kg (USITC, 1987). The United States imported 3,600 kg of C.I. Pigment Red 3 in 1983 (USITC, 1984). Its low cost, bright scarlet hue, high tinctorial strength, and acid-fast, alkaline-fast, and lightfast properties cause C.I. Pigment Red 3 to be one of the most widely used red pigments (*Colour Index*, 1971). The pigment is used for coloring paints, inks, plastics, rubber, and in textile printing (Gosselin *et al.*, 1976). From a survey conducted from 1981-1983, NIOSH estimated that 51,931 workers, including 11,615 women, have been exposed to C.I. Pigment Red 3 (NIOSH, 1990).

METABOLISM AND DISPOSITION

Disposition studies in which 7- to 8-week-old, male Fischer 344/N rats were given a single dose of C.I. Pigment Red 3 (11.8 mg/kg) by gavage in corn oil demonstrated that 72.4% of the dose was excreted in the feces. Only tissues in contact with C.I. Pigment Red 3 contained detectable amounts of the pigment. The pigment was not detected in samples of blood, plasma, liver, kidney, or lung, even after the administration of doses 10 times as large as the original dose. Recovery in urine was 4% at 24 and 48 hours after dosing (El Dareer *et al.*, 1984). Based on its recovery in urine, it was concluded that C.I. Pigment Red 3 or its microbial breakdown products were absorbed in the intestine and metabolized by the rats. The study did not attempt to identify these metabolites and breakdown products. No other information on the metabolism and disposition of C.I. Pigment Red 3 was found in the literature.

TOXICITY AND CARCINOGENICITY

Human

The literature provided no data or epidemiological reports on the toxicity or carcinogenicity of C.I. Pigment Red 3 in humans.

Animal

No reports of toxicity studies on C.I. Pigment Red 3 previous to the 2-week and 13-week studies conducted by the NTP were found in the literature (Morgan *et al.*, 1989). In the NTP studies, F344/N rats and B6C3F$_1$ mice fed diets containing 0.3% to 10% of the pigment showed hematologic changes (reduced erythrocyte and hematocrit values, and hemoglobin concentrations) consistent with hemolytic anemia. Methemoglobin concentrations were not determined in these studies. Histopathological evaluation of tissues obtained after 90 days of treatment revealed that the spleen, liver, and kidney of rats and mice, as well as the bone marrow of rats, were the sites of chemical toxicity. The spleen of treated rats showed an increase in hematopoietic cell proliferation, iron-positive pigment, congestion of the red pulp, and inflammation of the splenic capsule. Hematopoietic cell proliferation was observed in the liver and bone marrow of treated rats. In treated mice, there were increases in hematopoietic cell proliferation of the liver and in iron-positive pigment of the spleen. Mild cytomegaly of the renal tubule epithelium was also observed in treated mice.

No animal carcinogenicity study results were found in the literature.

GENETIC TOXICOLOGY

C.I. Pigment Red 3 contains an azo bond, considered to be a structural alert for genotoxic activity by virtue of the potential for azo reduction, releasing aromatic amine products; the aromatic nitro group is also considered to be an alert for potential genotoxicity (Ashby *et al.*, 1989). However, experimental data for this compound are sparse. C.I. Pigment Red 3 was weakly mutagenic in *Salmonella typhimurium* strains TA100 and TA98 in the presence of induced hamster S9 (Mortelmans *et al.*, 1986). An earlier study had reported negative results in a *S. typhimurium* assay (Miyagoshi *et al.*, 1983), but the lower concentrations used in this test may not have allowed detection of a weak response.

There are no additional published data on the mutagenicity of C.I. Pigment Red 3 or any of its metabolites, but some structural analogs of C.I. Pigment Red 3 have been tested for genotoxicity. 1-[(2-Methylphenyl)azo]-2-naphthalenol was reported to be negative for induction of DNA damage in *Bacillus subtilis* (Kada *et al.*, 1972) and induction of gene reversion in *S. typhimurium* (Miyagoshi *et al.*, 1983). C.I. Solvent Yellow 14 was reported to be negative in two *S. typhimurium* gene mutation tests (Garner and Nutman, 1977; Brown *et al.*, 1978) and weakly positive in two other studies which employed higher doses and different sources of S9 activation enzymes (Cameron *et al.*, 1987; Zeiger *et al.*, 1988). A positive response was reported for C.I. Solvent Yellow 14 in the mouse lymphoma assay for induction of trifluorothymidine resistance in L5178Y cells (Cameron *et al.*, 1987) and the compound gave an equivocal response in the *in vivo/in vitro* rat hepatocyte assay for induction of unscheduled DNA synthesis (Kornbrust and Barfknecht, 1984). No induction of chromosomal aberrations was observed in Chinese hamster ovary cells exposed to C.I. Solvent Yellow 14, but sister chromatid exchanges were induced in Chinese hamster ovary cells with and without induced S9 (Ivett *et al.*, 1989). Another structural analog, C.I. Solvent Red 1, was negative for induction of gene mutations in several strains of *S. typhimurium*, negative in a Chinese hamster ovary cell chromosomal aberration test, and positive for induction of sister chromatid exchanges in Chinese hamster ovary cells (Brooks *et al.*, 1989).

STUDY RATIONALE

C.I. Pigment Red 3 was nominated by the National Cancer Institute for testing due to the lack of information on its toxicity and because of its widespread use and high potential for human exposure. In addition, C.I. Pigment Red 3, a nitrophenylazonaphthol, is structurally similar to known phenylazonaphthol carcinogens such as Ponceau 3R, Oil Orange SS, and Citrus Red 2 (IARC, 1975). The oral route was chosen to ensure systemic exposure.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF C.I. PIGMENT RED 3

C.I. Pigment Red 3 was obtained from American Cyanamid Company (Wayne, NJ; lot G-1292) and Sun Chemical Company (New York, NY; lot S051783). Lot G-1292 was used throughout the 2-week and 13-week studies and in a portion of the 2-year studies. Lot S051783 was used throughout the remainder of the 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO), and confirmed by the study laboratory (Appendix H).

Both lots of the study chemical, a red powder, were identified as C.I. Pigment Red 3 by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of both lots was found to be greater than 97% by weight loss on drying, elemental analyses, thin-layer chromatography, and high-performance liquid chromatography (HPLC). Stability studies indicated that C.I. Pigment Red 3 was stable as a bulk chemical for 2 weeks at temperatures up to 60° C when stored protected from light. The stability of the bulk chemical was monitored periodically at the study laboratory with ultraviolet spectroscopy and HPLC analysis methods. No change in purity was observed.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by mixing appropriate amounts of C.I. Pigment Red 3 and feed in a blender (Table H1). Studies to determine homogeneity and stability of the dosed feed preparations were conducted by the analytical chemistry laboratory. Homogeneity was confirmed using an ultraviolet spectroscopic method for sample analysis. The stability of the dose formulations stored for 2 weeks at 45° C and protected from light was confirmed using an HPLC method.

Periodic analyses of the dose formulations of C.I. Pigment Red 3 were conducted at the study laboratory and the analytical chemistry laboratory using ultraviolet spectroscopy. During the 2-week studies, the dose formulations were analyzed at the beginning of the studies (Table H2). During the 13-week studies, the dose formulations were analyzed at the initiation and the midpoint of the studies (Table H3). During the 2-year studies, the dose formulations were analyzed at least once every 8 weeks (Table H4). All dose formulations were within 10% of the target concentrations. Results of periodic referee analyses performed by the analytical chemistry laboratory were in agreement with the results obtained by the study laboratory (Table H5).

2-WEEK STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Center (Frederick, MD). At receipt, the rats had an average age of 29 days, and the mice had an average age of 36 days. The rats and mice were quarantined for 19 days before dosing began.

Groups of five rats and five mice of each sex were fed diets containing 0, 6,000, 12,500, 25,000, 50,000, or 100,000 ppm C.I. Pigment Red 3. The appropriate feed was supplied weekly and was available *ad libitum* for 15 or 16 days for rats and for 15 to 17 days for mice. Animals were housed five to a cage with water available *ad libitum*. Clinical findings were recorded twice daily. The animals were weighed at study initiation, weekly, and at study termination. Details of study design and animal maintenance are summarized in Table 1.

At study termination, blood samples were collected from all animals for hematology and clinical chemistry studies. For rats, blood was obtained from the inferior vena cava; for mice, blood samples were collected by cardiac puncture. The clinical pathology parameters measured are listed in Table 1.

A necropsy was performed on all animals. The brain, heart, right kidney, liver, lung, and thymus of all animals were weighed at necropsy. Tissues for microscopic examination were embedded in paraffin,

sectioned to a thickness of 4 to 6 μm, and stained with hematoxylin and eosin. Histopathology was performed on the 0 and 100,000 ppm dose groups. Table 1 lists those tissues and organs examined microscopically.

13-WEEK STUDIES

13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to C.I. Pigment Red 3 and to determine the appropriate doses for the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Center. At receipt, the average age of the rats was 43 days, and the average age of the mice was 39 days. The animals were quarantined for 19 days prior to study initiation. Five animals of each species and sex were randomly selected and sacrificed for parasite evaluation and gross observation for evidence of disease prior to study initiation. At study termination, serologic analyses were performed on the serum of five control animals of each species and sex in accordance with the protocols of the NTP Sentinel Animal Program (Appendix K).

Groups of 10 rats and 10 mice of each sex were fed diets containing 0, 3,000, 6,000, 12,500, 25,000, or 50,000 ppm C.I. Pigment Red 3. Beginning on day 2, the appropriate feed was available *ad libitum* for 91 to 94 consecutive days to rats and for 92 to 94 consecutive days to mice.

Animals were housed five per cage. Water was available *ad libitum*. Animals were observed twice daily. Animals were weighed at study initiation, weekly, and at termination. Clinical observations were recorded weekly and at study termination.

At study termination, blood samples were collected by cardiac puncture for measurement of hematology and clinical chemistry parameters. Urine samples were collected by tapping into the bladder for urinalysis. Table 1 contains the complete list of the analyses performed on animals in the 13-week studies of C.I. Pigment Red 3.

During necropsy, the organs and tissues of all animals were examined for visible lesions. Organ weights were recorded for the brain, heart, right kidney, liver, lung, and thymus of all animals, and the right testis of all males. Tissues for microscopic examination were embedded in paraffin, sectioned to a thickness of 4 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all animals. Table 1 lists the tissues and organs examined microscopically.

2-YEAR STUDIES

Groups of 60 rats of each sex were fed diets containing 0, 6,000, 12,500, or 25,000 ppm C.I. Pigment Red 3. Groups of 60 mice of each sex were fed diets containing 0, 12,500, 25,000, or 50,000 ppm C.I. Pigment Red 3. The appropriate feed was supplied weekly and available *ad libitum* for 103 weeks. Up to 10 rats and 10 mice per dose group were designated for interim evaluations (organ weights, hematology, clinical chemistry, and histopathology) after 15 months of chemical administration. An additional five rats and five mice from a separate special study were also evaluated at 15 months. The results from the analyses of these special study animals were incorporated with the results of the 15-month interim evaluations of the 2-year study animals.

Source and Specification of Animals

The F344/N rats and B6C3F$_1$ mice used in these studies were obtained from Frederick Cancer Research Facility. All animals were quarantined for 12 days, then five rats and five mice of each sex were randomly selected and sacrificed for parasite evaluation and gross observation of evidence of disease. The average age of the animals was 42 days when dosing began. Animal health was monitored by serologic analyses during the course of the studies in accordance with the protocols of the NTP Sentinel Animal Program.

Animal Maintenance

Rats were housed five per cage throughout the studies. Mice were housed five per cage for 14 months, then individually until study termination. Cages were rotated vertically (top to bottom) within dose groups, and racks were rotated counterclockwise every 2 weeks during rack change. Drinking water was available *ad libitum*. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical observations were recorded every 4 weeks. Individual body weights were obtained weekly

through week 13 and monthly thereafter. After 15 months, 10 rats and 10 mice from each dose group were evaluated. Blood samples were collected from the inferior vena cava in rats and by cardiac puncture in mice for measurement of hematology and clinical chemistry parameters. Urine samples were collected in metabolism cages for urinalysis. Organ weights were recorded for the brain, right kidney, liver, and spleen of all animals killed at 15 months. Table 1 contains the complete list of the analyses performed on animals in the 2-year studies of C.I. Pigment Red 3.

A necropsy was performed on all animals. During necropsy, all organs and tissues were examined for visible lesions. Tissues for microscopic examination were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned to a thickness of 4 to 6 μm, and stained with hematoxylin and eosin. The 15-month interim evaluations included a complete histopathology on all control and high-dose animals and all animals that died early. For the interim evaluation animals that received lower doses, all gross lesions (excluding red skin and hair), the bone marrow and liver in rats, the kidney in rats and mice, and the spleen in rats and mice were examined. A complete histopathologic examination was performed on all control and high-dose animals that survived to study termination and on all animals that died or were killed moribund after 15 months. For rats that received lower doses, organs examined included all gross lesions (excluding red skin and hair); the bone marrow, liver, lung, lymph nodes (mandibular, mediastinal, and mesenteric), kidney, pancreas, and spleen in male and female rats; the adrenal gland in male rats; and the mammary gland in female rats. Organs examined for mice at lower doses included all gross lesions (excluding red skin and hair); liver, kidney, spleen, and thyroid gland in males and females; and bone marrow and ovary in females.

Microscopic evaluations were completed by the study laboratory pathologist and the pathology data were entered into the Toxicology Data Management System (TDMS). The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. A quality assessment pathologist reviewed selected tissues for accuracy and consistency of lesion diagnosis.

For rats this review included all diagnoses in the kidney, liver, and pancreas in both sexes, the adrenal medulla in males, and all neoplasms in any tissue. In addition, sections of the spleen and mesenteric lymph node from both sexes were reviewed to confirm the incidence of selected nonneoplastic lesions (including pigmentation, cholesterol in the mesenteric nodes) and the incidence of mononuclear cell leukemia in the spleen. Sections of the femoral and turbinate bones from all animals and the cranial bone from a few females were reviewed to confirm the presence of osteopetrosis. Sections of the bone marrow from all control and high-dose males were reviewed to confirm the incidence of hyperplasia. For mice this review included all diagnoses in the kidney, liver, spleen, and thyroid gland in each sex, the ovary in females, and neoplasms in any tissue.

The quality assessment report and slides were submitted to the Pathology Working Group (PWG) chair, who reviewed tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. The PWG chair also reviewed all diagnoses in the kidney, liver, and pancreas in rats of each sex; the adrenal medulla in male rats; the kidney, liver, spleen, and thyroid gland in mice of each sex; and the ovary in female mice. Representative histopathology slides containing examples of lesions related to disagreements between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chair to the PWG for review. The PWG included the quality assessment pathologist as well as other pathologists experienced in rodent toxicologic pathology, who examined these tissues without knowledge of dose group or previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the final diagnosis was changed to reflect the opinion of the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the results section of this report. Animals were censored from the survival analyses at the time they were found dead from other than natural causes; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table tests to identify dose-related trends. All reported P values for the survival analysis are two sided.

Calculation of Incidence

The incidence of neoplasms or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) before tissue sampling for histopathology, or when lesions could have appeared at multiple sites (e.g., mononuclear cell leukemia), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence

The majority of tumors in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was logistic regression analysis, which assumed that the diagnosed tumors were discovered as the result of death from an unrelated cause and did not affect the risk of death. In this approach, tumor prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When tumors are incidental, this comparison of the time-specific tumor prevalences also provides a comparison of the time-specific tumor incidences (McKnight and Crowley, 1984).

In addition to logistic regression, alternative methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal tumors, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of tumor-bearing animals.

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

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of tumor incidence. Consequently, control tumor incidences from the NTP historical control database (Haseman *et al.*, 1984, 1985) are included in the NTP reports for tumors appearing to show compound-related effects.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between dosed and control groups in the analysis of continuous variables. Organ and body weight data that had approximately normal distributions were analyzed using the parametric multiple comparison procedures of Williams (1971, 1972) and Dunnett (1955). Organ and body weight and clinical pathology data that had skewed distributions were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-response trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-response trend (Dunnett's or Dunn's test). Average nephropathy severity values for the 2-year studies

were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

Quality Assurance Methods

The 13-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as study records were submitted to the NTP Archives, they were audited by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary review draft of this NTP Technical Report were conducted. Audit procedures are presented in the reports, which are on file at the NIEHS. The audit findings were reviewed and assessed by the NTP staff so that all discrepancies had been resolved or were otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

The genetic toxicity of C.I. Pigment Red 3 was assessed by testing its ability to induce mutations in *Salmonella typhimurium* and sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells. The protocols and results for these studies are given in Appendix E.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of C.I. Pigment Red 3

2-Week Studies	13-Week Studies	2-Year Studies
Study Laboratory Southern Research Institute (Birmingham, AL)	Same as 2-week studies	Same as 2-week studies
Strain and Species Rats: F344/N Mice: $B6C3F_1$	Same as 2-week studies	Same as 2-week studies
Animal Source Frederick Cancer Research Facility (Frederick, MD)	Same as 2-week studies	Same as 2-week studies
Time Held Before Studies 19 days	19 days	12 days
Average Age When Placed on Studies Rats: 48 days Mice: 55 days	Rats: 62 days Mice: 58 days	Rats: 41 days Mice: 41 days
Date of First Dose Rats: 1 June 1981 Mice: 8 June 1981	Rats: 17 November 1981 Mice: 24 November 1981	Rats: 15 March 1983 Mice: 12 April 1983
Duration of Dosing Day 1 to day of sacrifice (15-17 days), dosed feed available *ad libitum*	Day 2 to day of sacrifice (days 93-96), dosed feed available *ad libitum*	Day 1 to day 721, dosed feed available *ad libitum* (except during urine collection)
Date of Last Dose Rats: 15-16 June 1981 Mice: 22-24 June 1981	Rats: 16-19 February 1982 Mice: 23-26 February 1982	Rats: 4 March 1985 Mice: 1 April 1985
Average Age When Killed Rats: 63 days Mice: 70 days	Male rats: 163 days Female rats: 149 days Mice: 152 days	Rats: Interim - 492 or 499 days Terminal - 773 days Mice: Interim - 498 or 499 days Terminal - 773 days
Method of Sacrifice Thoracotomy under chloroform anesthesia	Thoracotomy under ether anesthesia	Interim - thoracotomy under ether anesthesia Terminal - CO_2 asphyxiation
Size of Study Groups 5 males and 5 females	10 males and 10 females	60 males and 60 females
Method of Animal Distribution Animals were grouped by weight intervals. The animals were then assigned to treatment groups using a table of random numbers.	Same as 2-week studies	Same as 2-week studies
Animals per Cage 5 animals	5 animals	5 animals; mice were housed individually after 11 June 1984

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of C.I. Pigment Red 3 (continued)

2-Week Studies	13-Week Studies	2-Year Studies
Method of Animal Identification		
Earmark	Same as 2-week studies	Earmark and/or toe clip
Diet		
NIH-07 open formula mash diet (Zeigler Bros., Gardners, PA), available *ad libitum*	Same as 2-wwek studies	Same as 2-week studies
Maximum Storage Time for Feed		
90 days from milling	Same as 2-week studies	90 days from milling until July 1984, when storage time changed to 120 days from milling
Water		
Birmingham Water Works (Birmingham, AL), available *ad libitum*	Same as 2-week studies	Same as 2-week studies
Cages		
Polycarbonate (Lab Products, Inc., Garfield, NJ), changed twice weekly	Same as 2-week studies	Same as 2-week studies
Bedding		
BetaChips®, hardwood laboratory bedding (Northeastern Products, Warrensburg, NY), changed twice weekly	Same as 2-week studies	Same as 2-week studies
Cage Filters		
Reemay spun-bonded polyester (Snow Filtration, Cincinnati, OH), changed once every 2 weeks	Same as 2-week studies	Same as 2-week studies
Racks		
Stainless steel (Lab Products, Inc., Garfield, NJ), changed once every 2 weeks for rats and once weekly for mice	Stainless steel (Lab Products, Inc., Garfield, NJ), changed once every 2 weeks	Same as 13-week studies
Animal Room Environment		
Rats: Temperature: 22°-23° C Relative humidity: 44%-59% Fluorescent light: 12 hours/day Room air changes: minimum of 15 changes/hour Mice: Temperature: 22°-24° C Relative humidity: 43%-57% Fluorescent light: 12 hours/day Room air changes: minimum of 15 changes/hour	Rats: Temperature: 22°-26° C Relative humidity: 30%-66% Fluorescent light: 12 hours/day Room air changes: minimum of 15 changes/hour Mice: Temperature: 22°-25° C Relative humidity: 30%-66% Fluorescent light: 12 hours/day Room air changes: minimum of 15 changes/hour	Rats: Temperature: 19°-26° C Relative humidity: 10%-78% Fluorescent light: 12 hours/day Room air changes: minimum of 15 changes/hour Mice: Temperature: 19°-27° C Relative humidity: 20%-85% Fluorescent light: 12 hours/day Room air changes: minimum of 15 changes/hour

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of C.I. Pigment Red 3 (continued)

2-Week Studies	13-Week Studies	2-Year Studies
Doses 0, 6,000, 12,500, 25,000, 50,000, or 100,000 ppm in feed	0, 3,000, 6,000, 12,500, 25,000, or 50,000 ppm in feed	Rats: 0, 6,000, 12,500, or 25,000 ppm in feed Mice: 0, 12,500, 25,000, or 50,000 ppm in feed
Type and Frequency of Observation Observed twice daily; weighed initially, weekly, and at termination; clinical observations recorded twice daily	Observed twice daily; weighed initially, weekly throughout the studies, and at termination; clinical observations recorded weekly and at study termination.	Observed twice daily; weighed initially, weekly through week 13, monthly thereafter, and at scheduled sacrifice or death; clinical observations recorded monthly.
Necropsy Necropsy and tissue collection performed on all animals. Organ weights recorded for the brain, heart, right kidney, liver, lung, and thymus of all animals.	Necropsy and tissue collection performed on all animals. Organ weights recorded for the brain, heart, right kidney, liver, lung, and thymus of all animals, and the right testis of all males.	Necropsy performed on all animals. Organ weights recorded for the brain, right kidney, liver, and spleen of all animals evaluated at 15 months.
Clinical Pathology Blood samples were collected from all animals ***Hematology:*** hematocrit, hemoglobin, erythrocytes, platelets, reticulocytes, and leukocyte count and differential ***Clinical chemistry:*** urea nitrogen, creatinine (rats), sodium (rats), potassium (rats), chloride, calcium (rats), phosphorus (rats), total protein (rats and male mice), albumin (rats and male mice), albumin/globulin ratio (rats and male mice), total bilirubin, alanine aminotransferase (rats), aspartate aminotransferase, lactate dehydrogenase, sorbitol dehydrogenase (rats), cholinesterase (rats), and pH	Blood and urine samples were collected from all animals ***Hematology:*** hematocrit, hemoglobin, erythrocytes, platelets, reticulocytes, and leukocyte count and differential ***Clinical chemistry:*** urea nitrogen, creatinine (rats), sodium, potassium, chloride, partial carbon dioxide, calcium (rats), phosphorus (rats), total protein (rats), albumin (rats), albumin/globulin ratio (rats), total bilirubin (rats), alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, sorbitol dehydrogenase, cholinesterase (rats), and pH ***Urinalysis:*** urine total bilirubin	Blood and urine samples were collected from animals evaluated at the 15-month interim evaluation ***Hematology:*** hematocrit, hemoglobin, erythrocytes, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelets, and leukocytes ***Clinical chemistry:*** total bilirubin and methemoglobin ***Urinalysis:*** urine total bilirubin

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of C.I. Pigment Red 3 (continued)

2-Week Studies	13-Week Studies	2-Year Studies
Histopathology Histopathologic examinations were performed on all control and 100,000 ppm animals. In addition to tissue masses, gross lesions, and associated lymph nodes, tissues examined included: adrenal gland, bone (femur including marrow), brain, bronchi, clitoral gland (rats), colon, esophagus, gallbladder (mice), heart, kidney, liver, lung, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity, nasal turbinates, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, small intestine, spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.	Complete histopathologic examinations were performed on all animals. In addition to tissue masses, gross lesions, and associated lymph nodes, the tissues examined included: adrenal gland, bone (femur including marrow), brain, bronchi, clitoral gland (rats), colon, epididymis, esophagus, gallbladder (mice), heart, kidney, liver, lung, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity, nasal turbinates, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, skin (rats), small intestine, spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.	At the 15-month interim evaluation, complete histopathology was performed on all control and high-dose animals and all animals that died early. For interim evaluation animals receiving lower doses, all gross lesions (excluding red skin and hair), bone marrow and liver (rats), kidneys (rats and mice), and spleen (rats and mice) were examined. At terminal sacrifice, a complete histopathology was performed on all control and high-dose animals and animals that died early. For rats receiving lower doses, organs examined included all gross lesions (excluding red skin and hair); bone marrow, liver, lung, lymph nodes (mandibular, mediastinal, and mesenteric), kidney, pancreas, and spleen in male and female rats; adrenal gland in male rats; and mammary gland in female rats. For mice receiving lower doses, all gross lesions (excluding red skin and hair); liver, kidney, spleen, and thyroid gland in males and females; and bone marrow and ovary in females were examined at terminal sacrifice. In addition to tissue masses, gross lesions, and associated regional lymph nodes, the following organs and/or tissues were included in complete histopathologic examinations: adrenal gland, aorta, bone (femur including marrow), brain, clitoral gland (rats), epididymis, esophagus, gallbladder (mice), heart, kidneys, large intestine (cecum, colon, rectum), liver, lung, mammary gland, mesenteric lymph node, nasal cavity, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, skin, small intestine (duodenum, jejunum, ileum), spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.

RESULTS

RATS

2-Week Studies

All rats lived to the end of the studies (Table 2). The final mean body weights and body weight gains of male rats that received C.I. Pigment Red 3 were similar to those of the controls. The final mean body weight of female rats that received 100,000 ppm was significantly lower than that of the controls; all exposed female rats had significantly reduced mean body weight gains compared to that of the controls. Average feed consumption by dosed groups was similar to consumption by the control groups.

There were no clinical findings indicative of chemical toxicity. Red-stained extremities, feces, and fur were due to contact with C.I. Pigment Red 3 and were not indicative of toxicity.

All dosed male groups showed significant increases in relative liver weights compared to that of the controls (Table F1). Significantly increased relative heart weights were noted for male rats that received 50,000 and 100,000 ppm. No other significant differences in organ weights were observed in exposed male rats; there were no significant changes in organ weights in exposed female rats.

TABLE 2
Survival, Mean Body Weights, and Feed Consumption of Rats in the 2-Week Feed Studies of C.I. Pigment Red 3

Concentration (ppm)	Survival[a]	Mean Body Weights[b] (g) Initial	Final	Change	Final Weight Relative to Control (%)	Feed Consumption[c]
Male						
0	5/5	143 ± 8	203 ± 8	60 ± 3		15.9
6,000	5/5	144 ± 5	206 ± 8	62 ± 5	102	15.8
12,500	5/5	146 ± 5	200 ± 3	54 ± 4	98	15.2
25,000	5/5	143 ± 7	194 ± 7	51 ± 4	96	15.3
50,000	5/5	142 ± 5	185 ± 3	43 ± 5	91	15.5
100,000	5/5	142 ± 4	194 ± 8	52 ± 5	96	15.2
Female						
0	5/5	128 ± 3	155 ± 4	27 ± 2		12.3
6,000	5/5	132 ± 2	152 ± 3	20 ± 1*	98	12.8
12,500	5/5	129 ± 4	151 ± 4	22 ± 1*	97	13.0
25,000	5/5	128 ± 2	147 ± 2	19 ± 1**	95	11.9
50,000	5/5	131 ± 3	149 ± 5	18 ± 2**	96	11.5
100,000	5/5	130 ± 3	144 ± 3*	14 ± 3**	93	10.9

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving/number of animals initially in group
[b] Weights and weight changes given as mean ± standard error
[c] Grams per animal per day, based on average consumption data per group per day for days 1 through 13.

Male rats that received doses of 12,500 ppm or greater had significantly decreased erythrocyte counts (Table G1). Males that received 25,000 ppm or greater had significantly increased reticulocyte counts and significantly decreased hemoglobin and hematocrit values. Male rats that received 100,000 ppm showed significantly increased values for total serum bilirubin, alanine aminotransferase (ALT), and cholinesterase. All dosed female rat groups had significantly increased ALT values and significantly decreased hemoglobin values and erythrocyte counts. Female rats that received 25,000 ppm or greater had significantly increased reticulocyte counts and sorbitol dehydrogenase values and significantly decreased hematocrit and cholinesterase levels. Female rats that received 50,000 ppm or greater had significantly increased total serum bilirubin levels. There were no other biologically significant changes in hematology and clinical chemistry parameters for exposed rats.

There were no gross or microscopic lesions attributable to C.I. Pigment Red 3 administration.

13-Week Studies

All rats lived to the end of the studies (Table 3). The final mean body weights of all exposed female groups were significantly less than that of the controls. Mean body weight gains of females that received 6,000 ppm or greater were significantly lower than that of the controls. Average feed consumption by exposed and control groups was similar (Table 4).

There were no clinical findings indicative of chemical toxicity. Red-stained extremities, feces, and fur were due to contact with C.I. Pigment Red 3 and were not indicative of toxicity.

Relative liver weights were significantly increased for all exposed groups compared to those of the controls (Table F2). Relative kidney weights were increased for all male groups except the 6,000 ppm group. Relative lung weights were increased for male groups that received 25,000 or 50,000 ppm and for all exposed female groups. No other biologically significant differences in organ weights were observed in rats.

TABLE 3
Survival and Mean Body Weights of Rats in the 13-Week Feed Studies of C.I. Pigment Red 3

Concentration (ppm)	Survival[a]	Mean Body Weights[b] (g)			Final Weight Relative to Control (%)
		Initial	Final	Change	
Male					
0	10/10	168 ± 5	370 ± 5	202 ± 3	
3,000	10/10	172 ± 5	367 ± 8	195 ± 8	99
6,000	10/10	169 ± 4	370 ± 9	201 ± 7	100
12,500	10/10	169 ± 4	380 ± 11	211 ± 8	103
25,000	10/10	172 ± 6	374 ± 8	202 ± 6	101
50,000	10/10	161 ± 4	354 ± 6	193 ± 4	96
Female					
0	10/10	127 ± 2	210 ± 3	83 ± 2	
3,000	10/10	123 ± 2	200 ± 3*	76 ± 2	95
6,000	10/10	120 ± 3	195 ± 3**	75 ± 3*	93
12,500	10/10	121 ± 2	196 ± 3**	75 ± 3*	94
25,000	10/10	122 ± 4	194 ± 5**	71 ± 3**	92
50,000	10/10	122 ± 2	189 ± 3**	67 ± 3**	90

* Significantly different ($P \leq 0.05$) from the control group by Dunn's test
** $P \leq 0.01$
[a] Number of animals surviving/number of animals initially in group
[b] Weights and weight changes given as mean ± standard error

TABLE 4
Mean Feed Consumption by Rats in the 13-Week Feed Studies of C.I. Pigment Red 3[a]

Week on Study	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male						
1	135	85	89	84	85	84
2	82	83	49	85	81	87
3	76	80	68	73	71	72
4	72	88	66	66	67	67
5	39	60	65	64	60	63
6	64	49	54	58	50	68
7	56	56	59	58	60	66
8	50	51	56	52	53	54
9	54	55	55	56	53	61
10	52	51	57	53	52	55
11	47	48	49	54	49	54
12	46	49	48	46	47	54
13	41	43	45	44	43	47
Mean ± SD	63 ± 26	61 ± 16	58 ± 12	61 ± 13	59 ± 13	64 ± 12
Female						
1	148	95	115	142	92	93
2	87	87	137	115	87	90
3	81	81	73	85	80	84
4	88	75	70	81	70	85
5	75	72	71	62	67	100
6	116	91	136	61	63	67
7	65	63	65	58	66	76
8	61	64	60	55	68	74
9	67	70	73	73	72	75
10	57	61	55	58	58	60
11	61	92	73	56	53	61
12	57	58	55	67	61	52
13	52	62	59	58	55	60
Mean ± SD	78 ± 27	75 ± 13	80 ± 29	73 ± 27	67 ± 12	75 ± 15

[a] Grams of feed consumed per kilogram body weight per day

Reticulocyte counts and albumin, total serum bilirubin, and cholinesterase values in exposed males and potassium, total serum bilirubin, and sorbitol dehydrogenase values in exposed females were significantly increased, but not in a dose-related manner (Table G2). Hematocrit levels were significantly decreased in all males except for those that received 25,000 ppm; the hematocrit level for this group was significantly increased compared to the controls. Males and females that received 6,000 ppm or greater had significantly decreased erythrocyte counts. Female rats that received 6,000 ppm or greater had significantly increased reticulocyte counts and albumin levels. Total serum protein was significantly increased for all males except for those that received 6,000 ppm. Significant decreases in hemoglobin concentration in males and urea nitrogen and lactate dehydrogenase in females that received 25,000 or 50,000 ppm were detected. High-dose males had a significantly increased platelet count and serum phosphorus value and significantly decreased alanine aminotransferase and aspartate aminotransferase values. High-dose females had significantly increased creatinine and

phosphorus values and a significantly decreased hematocrit value. No other clinically significant changes in hematology, clinical chemistry, and urinalysis parameters were noted for exposed rats.

The most significant histopathologic alterations in exposed rats occurred in the bone marrow, liver, spleen, and kidney (Tables 5 and 6). These lesions were of greater severity and/or occurred with an increased frequency in the higher dose groups. Most of the changes were considered secondary to the anemia. These secondary changes included hematopoietic cell proliferation within the bone marrow, spleen, and liver, and the presence of pigment within the kidney, liver, and spleen which was interpreted as hemosiderin. The slightly increased incidence of renal protein casts in male rats suggests a possible exacerbation of the progression of chronic glomerulonephropathy commonly seen in aging F344/N rats, particularly males.

TABLE 5
Histopathologic Diagnoses in Male Rats in the 13-Week Feed Study of C.I. Pigment Red 3[a]

	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Bone Marrow: Hyperplasia						
Overall rates[b]	0/10	10/10**	10/10**	10/10**	10/10**	10/10**
Average severity[c]		1.1	1.7	2.0	1.9	1.9
Kidney: Pigment						
Overall rates	0/10	0/10	1/10	10/10**	10/10**	10/10**
Average severity			1.0	1.0	1.5	2.0
Kidney: Protein Casts						
Overall rates	0/10	3/10	5/10*	10/10**	10/10**	9/10**
Average severity		1.0	1.0	1.0	1.0	1.0
Liver: Hematopoietic Cell Proliferation						
Overall rates	0/10	0/10	2/10	8/10**	10/10**	10/10**
Average severity			1.0	1.0	1.7	1.9
Liver: Pigment						
Overall rates	0/10	0/10	0/10	3/10	6/10**	10/10**
Average severity				1.0	1.0	1.0
Spleen: Congestion						
Overall rates	0/10	10/10**	10/10**	10/10**	10/10**	10/10**
Average severity		1.0	1.7	2.0	1.9	2.0
Spleen: Hematopoietic Cell Proliferation						
Overall rates	0/10	10/10**	10/10**	10/10**	10/10**	10/10**
Average severity		1.0	1.7	2.0	2.0	2.0
Spleen: Pigment						
Overall rates	0/10	10/10**	10/10**	10/10**	10/10**	10/10**
Average severity		1.0	1.7	2.0	2.0	2.0

* Significantly different (P≤0.05) from the control group by Fisher's exact test
** P≤0.01
[a] Cited in Morgan *et al.*, 1989
[b] Number of lesion-bearing animals/number of animals necropsied or number of animals with tissues examined microscopically
[c] Severity of lesion: 1 = minimal, 2 = mild

Dose Selection Rationale: Exposure concentrations for rats in the 2-year studies were based on the body weight changes observed in rats that received 50,000 ppm in the 13-week studies. The final mean body weight of female rats that received 50,000 ppm was 10% less than that of the controls; therefore, the next highest dose, 25,000 ppm, was chosen as the highest dose for use in the 2-year study of female rats. Based on the 2-week and 13-week studies, males may have tolerated 50,000 ppm, but for consistency, 25,000 ppm was also used as the highest dose for male rats.

TABLE 6
Histopathologic Diagnoses in Female Rats in the 13-Week Feed Study of C.I. Pigment Red 3[a]

	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Bone Marrow: Hyperplasia						
Overall rates[b]	0/10	8/10**	10/10**	10/10**	10/10**	10/10**
Average severity[c]		1.0	1.8	2.0	1.9	2.0
Kidney: Pigment						
Overall rates	0/10	0/10	0/10	4/10*	10/10**	10/10**
Average severity				1.0	1.0	2.0
Liver: Hematopoietic Cell Proliferation						
Overall rates	0/10	0/10	6/10**	10/10**	10/10**	10/10**
Average severity			1.0	1.2	1.6	1.8
Liver: Pigment						
Overall rates	0/10	0/10	0/10	9/10**	10/10**	10/10**
Average severity				1.0	1.0	1.0
Spleen: Congestion						
Overall rates	0/10	9/10**	10/10**	10/10**	10/10**	10/10**
Average severity		1.0	1.7	2.0	2.0	2.0
Spleen: Hematopoietic Cell Proliferation						
Overall rates	0/10	9/10**	10/10**	10/10**	10/10**	10/10**
Average severity		1.0	2.0	2.0	2.0	2.0
Spleen: Pigment						
Overall rates	0/10	10/10**	10/10**	10/10**	10/10**	10/10**
Average severity		1.0	2.0	2.0	2.0	2.0

* Significantly different ($P \leq 0.05$) from the control group by Fisher's exact test
** $P \leq 0.01$
[a] Cited in Morgan *et al.*, 1989
[b] Number of lesion-bearing animals/number of animals necropsied or number of animals with tissues examined microscopically
[c] Severity of lesion: 1 = minimal, 2 = mild

2-Year Studies

15-Month Interim Evaluations

Ten male and ten female rats from each study group were evaluated after 15 months. Five rats of each sex receiving the same doses as rats in the 2-year studies were taken from a special study of C.I. Pigment Red 3* and evaluated at 15 months as well. The results of the analyses from animals taken from the special study were incorporated with those from rats used for the interim evaluations of the 2-year studies.

Rats were stained with red dye, due to contact with the chemical rather than to chemical toxicity. The absolute and relative weights of the liver and spleen were significantly increased in a dose-related manner as a result of increased hematopoietic activity and congestion in the spleen (Table F3). There were marginal dose-dependent decreases in hematocrit, hemoglobin, and erythrocyte counts and increases in total serum bilirubin concentrations (Table G3).

The administration of C.I. Pigment Red 3 was associated with histologic changes in bone marrow, kidney, liver, and spleen (Table 7). Liver changes in male rats consisted of cystic degeneration (spongiosis hepatis) which was often associated with foci of cellular change. Foci of cellular change were increased in a dose-related manner and were morphologically similar to the eosinophilic and mixed cell foci described in the results of the 2-year study. Three of these foci were relatively advanced in development. There was a marginal increase in the incidence and severity of bile duct epithelial hyperplasia. The degree of hematopoietic activity present in the bone marrow and spleen was greater in dosed groups than in the controls. Focal splenic subcapsular fibrosis occurred in six exposed males (Table 7). These lesions were small fibrotic areas with increased deposition of pigment (hemosiderin). The severity of chronic nephropathy was slightly increased in exposed rats; the increase in severity was more obvious in females than in males. There were no significant differences in the incidences of neoplasms at any site among groups (Table 8).

* A special study was conducted to investigate whether the apparent increase in urinary bilirubin concentrations observed in the 13-week studies (Appendix G) was due to contamination with C.I. Pigment Red 3. The results of the special study showed that the increased concentrations were due to C.I. Pigment Red 3.

TABLE 7
Nonneoplastic Diagnoses in Rats in the 15-Month Interim Evaluations in the 2-Year Feed Studies of C.I. Pigment Red 3[a]

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Male				
Liver: Cystic Degeneration				
Overall rates[a]	0/15	8/16**	10/15**	13/15**
Liver: Focal Cellular Change				
Overall rates	0/15	5/16*	11/15**	9/15**
Liver: Biliary Tract Proliferation				
Overall rates	5/15	14/16**	15/15**	15/15**
Spleen: Hematopoietic Cell Proliferation				
Overall rates	6/15	13/16*	13/15*	14/15**
Spleen: Hemosiderin Pigment				
Overall rates	6/15	13/16*	13/15*	14/15**
Spleen: Fibrosis				
Overall rates	0/15	1/16	4/15*	1/15
Bone Marrow: Hyperplasia				
Overall rates	0/15	6/16*	7/15**	11/15**
Kidney: Chronic Nephropathy				
None	0/15	2/16	1/15	0/15
Minimal	4/15	3/16	1/15	0/15
Mild	11/15	11/16	11/15	14/15
Moderate	0/15	0/16	2/15	1/15
Average severity grade[b]	1.73 ± 0.46	1.56 ± 0.72	1.93 ± 0.70	2.07 ± 0.26*
Female				
Liver: Focal Cellular Change				
Overall rates	0/17	2/16	9/16**	16/16**
Liver: Biliary Tract Proliferation				
Overall rates	0/17	4/16*	6/16**	13/16**
Spleen: Hematopoietic Cell Proliferation				
Overall rates	0/17	15/16**	16/16**	16/16**
Spleen: Hemosiderin Pigmentation				
Overall rates	0/17	16/16**	16/16**	16/16**
Bone Marrow: Hyperplasia				
Overall rates	0/17	2/16	6/16**	12/16**
Kidney: Chronic Nephropathy				
None	14/17	2/16	0/16	1/16
Minimal	3/17	10/16	7/16	4/16
Mild	0/17	3/16	8/16	11/16
Moderate	0/17	1/16	1/16	0/16
Average severity grade	0.18 ± 0.39	1.19 ± 0.75**	1.63 ± 0.62**	1.63 ± 0.62**

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test or the Mann-Whitney U test (nephropathy severity)
** $P \leq 0.01$
[a] Number of lesion-bearing animals/number of animals necropsied or number of animals with tissues examined microscopically
[b] Average severity grade is expressed as the mean ± standard deviation. 0 = none, 1 = minimal, 2 = mild, 3 = moderate

TABLE 8
Incidence of Neoplasms in Rats at the 15-Month Interim Evaluations in the 2-Year Feed Studies of C.I. Pigment Red 3

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Male				
Adrenal Gland: Malignant Pheochromocytoma				
Overall rates	0/15	–[a]	1/1[b]	0/15
Intestine (Jejunum): Adenocarcinoma				
Overall rates	0/15	0/16	1/15	0/15
Mesentery: Mesothelioma				
Overall rates	0/15	0/16	0/15	1/15
Preputial Gland: Adenoma				
Overall rates	0/15	1/1[b]	–	0/15
Skin (Ear): Schwannoma				
Overall rates	1/15	0/16	0/15	0/15
Testicle: Interstitial Cell Adenoma				
Overall rates	14/15	5/5[b]	4/4[b]	13/15
Thyroid Gland (C-cell): Adenoma				
Overall rates	1/15	–	–	0/15
Female				
Brain: Malignant Ependymoma				
Overall rates	0/17	–	1/1[b]	0/16
Mammary Gland: Fibroadenoma				
Overall rates	0/17	0/16	1/16	1/16
Mammary Gland: Adenocarcinoma				
Overall rates	1/17	1/16	0/16	0/16
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	3/17	1/1[b]	1/1[b]	1/16
Skin: Basal Cell Adenoma				
Overall rates	0/17	1/16	0/16	0/16
Uterus: Adenocarcinoma				
Overall rates	1/17	0/16	0/16	0/16
Uterus: Fibrous Histiocytoma				
Overall rates	1/17	0/16	0/16	0/16
Uterus: Stromal Polyp				
Overall rates	1/17	2/16	3/16	2/16
Uterus: Stromal Sarcoma				
Overall rates	0/17	1/16	0/16	0/16

[a] Not examined microscopically
[b] Only those animals noted to have gross lesions were examined microscopically.

Body Weight, Feed Consumption, and Clinical Findings

Mean body weights of low- and mid-dose male rats were within 10% of the control weights throughout the study (Table 9 and Figure 1). From week 82 to the end of the studies, the mean body weights of the high-dose males were over 10% lower than those of controls. The mean body weights of exposed females were more than 10% lower than those of the controls from week 82 for the low-dose group, week 66 for the mid-dose group, and week 42 for high-dose group (Table 10). The average daily feed consumption of exposed rats was similar to that of the controls (Tables I1 and I2). There were no clinical findings indicative of chemical toxicity. Red-stained extremities, feces, and fur were not indicative of toxicity, but were due to contact with C.I. Pigment Red 3.

TABLE 9
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3

Weeks on Study	0 ppm		6,000 ppm			12,500 ppm			25,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	116	60	119	102	60	120	103	60	117	101	60
2	162	60	164	101	60	165	102	60	162	100	60
3	202	60	204	101	60	204	101	60	202	100	60
4	234	60	234	100	60	236	101	60	232	99	60
5	256	60	256	100	60	258	101	60	252	99	60
6	274	60	274	100	60	276	101	60	270	99	60
7	290	60	287	99	60	289	100	60	285	98	60
8	304	60	300	99	60	302	99	60	298	98	60
9	318	60	314	99	60	317	100	60	312	98	60
10	327	60	324	99	60	326	100	60	319	97	60
11	339	60	333	98	60	333	98	60	327	96	60
12	346	60	339	98	60	342	99	60	334	97	60
13	356	60	346	97	60	351	99	60	337	95	60
17	380	60	372	98	60	375	99	60	363	96	60
21	405	60	396	98	60	402	99	60	390	96	60
25	419	60	409	98	60	413	99	60	397	95	60
30	435	60	422	97	60	421	97	60	407	94	60
34	449	60	433	96	60	432	96	60	418	93	60
38	459	60	442	96	60	431	94	60	427	93	60
42	462	60	448	97	60	444	96	60	433	94	60
46	471	60	446	95	60	450	96	60	440	93	60
50	480	60	465	97	60	463	96	60	448	93	60
54	487	60	463	95	60	465	95	60	454	93	60
58	495	60	468	95	59	468	95	60	456	92	60
62	492	60	468	95	58	466	95	60	456	93	60
66[a]	482	50	458	95	49	458	95	50	445	92	50
70	476	50	454	95	49	454	95	50	438	92	50
74	476	50	452	95	49	451	95	50	439	92	49
78	472	49	449	95	49	446	95	48	427	91	49
82	468	48	447	96	49	436	93	48	416	89	48
86	457	47	431	94	48	429	94	44	408	89	46
90	449	45	429	96	44	422	94	42	403	90	42
94	444	42	426	96	43	417	94	41	396	89	40
98	436	35	415	95	42	403	92	41	383	88	33
102	426	30	407	96	40	391	92	33	374	88	27
Terminal sacrifice		28			40			28			20
Mean for weeks											
1-13	271		269	99		271	100		265	98	
14-52	440		426	97		426	97		414	94	
53-102	466		444	95		439	94		423	91	

[a] Interim evaluation occurred during this week.

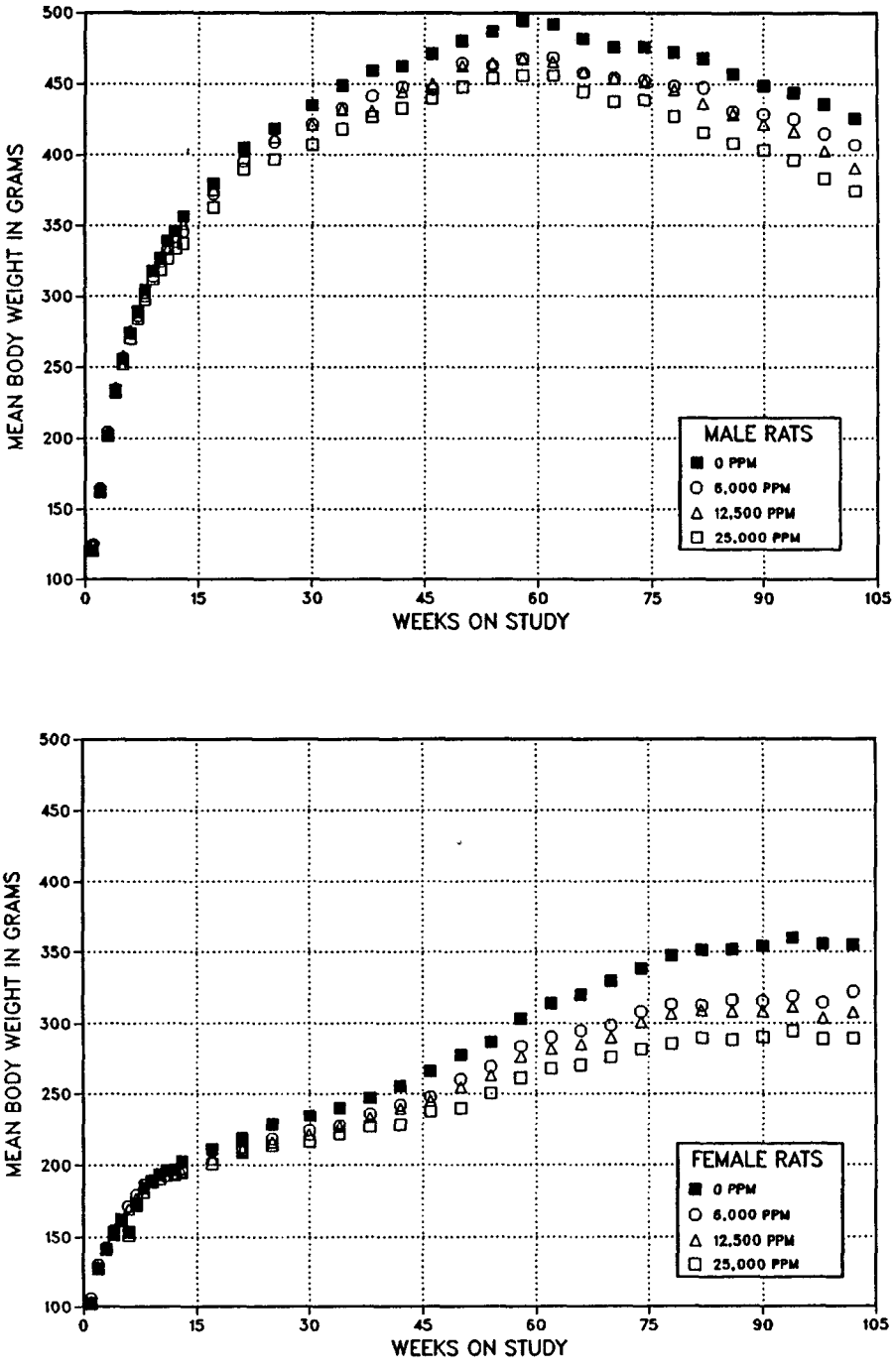


FIGURE 1
Growth Curves for Male and Female Rats Administered C.I. Pigment Red 3 in Feed for 2 Years

TABLE 10
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3

Weeks on Study	0 ppm		6,000 ppm			12,500 ppm			25,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	98	60	102	103	60	101	102	60	100	101	60
2	127	60	130	103	60	128	101	60	127	100	60
3	140	60	142	101	60	141	101	60	141	101	60
4	153	60	155	101	60	152	99	60	151	99	60
5	162	60	162	100	60	161	99	60	161	100	60
6	154	60	172	112	60	169	110	60	151	99	60
7	173	60	179	103	60	177	102	60	172	99	60
8	184	60	186	101	60	184	100	60	181	99	60
9	189	60	189	100	60	188	100	60	188	100	60
10	193	60	193	100	60	190	98	60	190	98	60
11	196	60	196	100	60	193	98	60	193	98	60
12	197	60	196	100	60	194	99	60	193	98	60
13	202	60	198	98	60	195	96	60	196	97	60
17	211	60	210	100	60	204	97	60	201	95	60
21	218	60	212	97	60	210	96	60	209	96	60
25	228	59	218	96	60	216	95	60	214	94	60
30	234	59	224	96	60	221	94	60	216	92	60
34	240	59	227	95	60	226	95	60	222	92	60
38	247	59	236	95	60	233	94	60	227	92	60
42	256	59	242	95	60	239	94	60	228	89	60
46	266	59	248	93	60	245	92	60	238	89	60
50	278	59	260	94	60	255	92	60	240	86	60
54	287	59	269	94	60	263	92	60	251	87	60
58	303	59	284	94	59	276	91	60	261	86	60
62	314	58	290	92	59	282	90	59	268	85	59
66[a]	320	58	295	92	59	285	89	59	271	85	59
70	330	48	299	91	48	290	88	49	276	84	48
74	338	48	308	91	47	301	89	48	282	83	48
78	348	47	313	90	46	307	88	48	286	82	47
82	351	47	313	89	46	309	88	47	290	82	46
86	352	47	316	90	45	308	88	47	288	82	45
90	354	45	315	89	44	308	87	45	290	82	44
94	360	44	319	89	43	311	87	44	295	82	44
98	356	43	315	88	42	304	85	42	289	81	44
102	355	36	322	91	41	308	87	39	290	82	42
Terminal sacrifice		32			41			39			40
Mean for weeks											
1-13	167		169	101		167	100		165	99	
14-52	242		231	95		228	94		222	92	
53-102	336		304	90		296	88		280	83	

[a] Interim evaluation occurred during this week.

Survival

Survival of the mid- and high-dose male rats was similar to that of the controls; survival of the low-dose male rats was slightly greater than that of the controls (Table 11 and Figure 2). In dosed female rats, there were no significant differences in survival.

Pathology and Statistical Analyses of Results

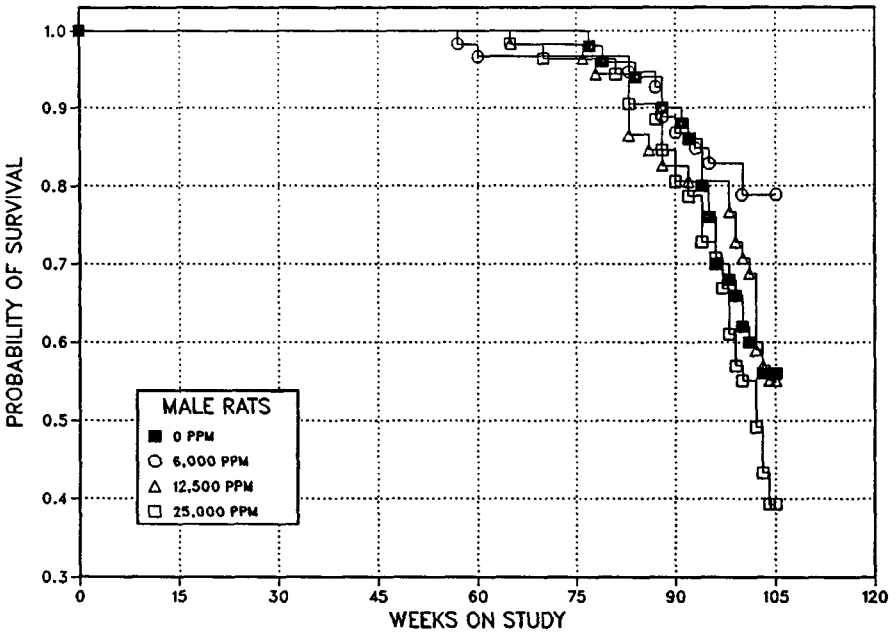
This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplastic or nonneoplastic lesions of the liver, adrenal medulla, skin, Zymbal's gland, clitoral and preputial glands, kidney, and mammary gland, as well as incidences of mononuclear cell leukemia in rats.

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

TABLE 11
Survival of Rats in the 2-Year Feed Studies of C.I. Pigment Red 3

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Male				
Animals initially in study	60	60	60	60
15-month interim evaluation[a,b]	10	10	10	10
Natural deaths	5	3	6	5
Moribund kills	17	7	16	25
Animals surviving to study termination	28	40	28	20
Percent survival at end of study[c]	56	79	55	39
Mean survival (days)[d]	656	664	656	649
Survival analysis[e]	P=0.013	P=0.047N	P=0.907	P=0.167
Female				
Animals initially in study	60	60	60	60
15-month interim evaluation[a]	10	10	10	10
Natural deaths	3	2	3	3
Moribund kills	15	7	8	7
Animals surviving to study termination	32	41[f]	39	40
Percent survival at end of study[c]	64	83	78	80
Mean survival (days)[d]	654	659	663	662
Survival analysis[e]	P=0.217N	P=0.105N	P=0.234N	P=0.145N

[a] Censored from survival analysis.
[b] Each dosed group contains one animal that died or was killed moribund prior to the interim evaluation.
[c] Kaplan-Meier determinations. Survival rates adjusted for interim evaluations.
[d] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[e] The entry in the control column is the trend test result (Tarone, 1975). Subsequent entries are the results of pairwise tests (Cox, 1972). A negative trend or lower mortality in a dose group is indicated by N.
[f] Includes one animal that died during the last week of the study



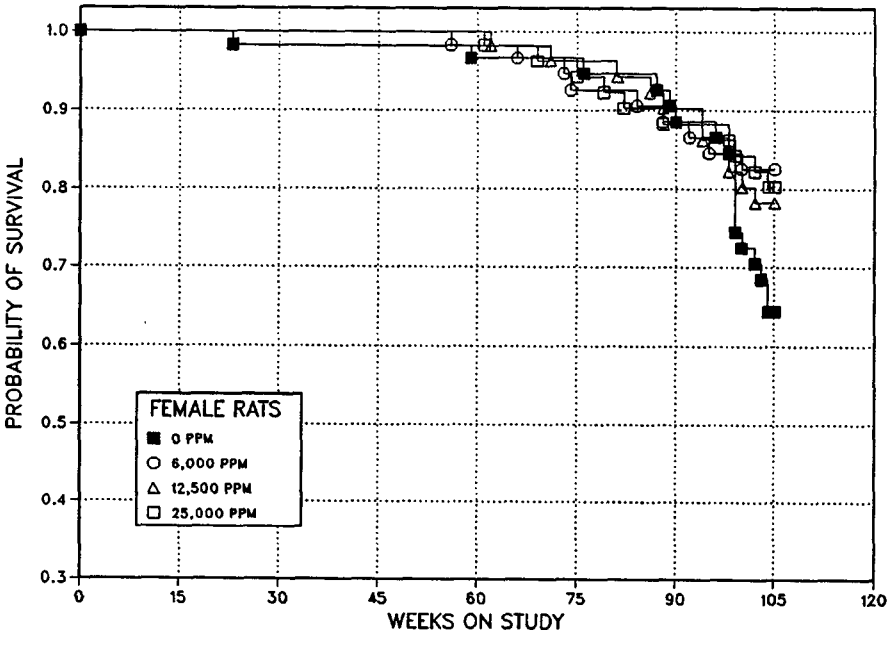


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Administered C.I. Pigment Red 3 in Feed for 2 Years

Liver: There was a marked increase in the occurrence of hepatocellular adenomas in high-dose female rats (Table 12); hepatocellular carcinomas were not observed in any dose group. These adenomas were well-demarcated, nodular proliferations which often occupied several lobules and caused compression of the surrounding parenchyma (Plate 1). There was loss of normal lobular architecture, and hepatic cords abruptly intersected those of the surrounding parenchymal tissue (Plate 2). Generally, neoplastic cells were larger and contained abundant eosinophilic or vacuolated cytoplasm as well as large round nuclei. In NTP feed study historical control groups, hepatocellular adenomas were observed in only 3/800 females (0.4%, range 0%-6%; Table B4a), and those 3 females were all in the control group of the same study.

Females also had an increased incidence of eosinophilic and mixed cell foci. Many of the foci were large and occupied several hepatic lobules but exhibited limited or no compression of the adjacent parenchymal tissue. The eosinophilic foci contained large hepatocytes resembling those described for hepatocellular adenoma. Mixed cell foci usually had a predominance of cells similar to those in the eosinophilic foci, but also included admixtures of cells that exhibited clear, vacuolated, or amphophilic cytoplasm. A dose-related increased incidence of small granulomas was seen in female groups, and the granulomas were most commonly associated with the foci of cellular alteration. These granulomas consisted of focal aggregates (50 to 250 μm in diameter) of macrophages and lesser numbers of lymphocytes. Often, minuscule clear clefts (diagnosed as pigmentation, cholesterol) were observed within the granulomas. Cholesterol clefts were also present in mesenteric lymph nodes in all study groups of each sex, but the severity was marginally increased in dosed groups. Spontaneously occurring hepatic granulomas are common in rats, but are more common in females and may occur in foci of cellular alteration (Eustis *et al.*, 1990). There was also a small increase in biliary tract proliferation in the high-dose females.

Increased incidences of eosinophilic and mixed cell foci were observed in dosed males; generally these foci were smaller than those observed in females and there was little evidence of compression of the adjacent parenchyma. Exposed males had increased incidences of cystic degeneration (spongiosis hepatis) and angiectasis (peliosis hepatis). These conditions were often associated with foci of hepatocellular alteration or hepatocellular adenoma. Cystic degeneration was characterized by variably sized cystic spaces containing proteinaceous fluid and scattered viable and degenerated erythrocytes. Spaces were not lined, or were only partially lined, by flattened cells. Microscopic examination revealed that angiectasis of the liver consisted of dilated vascular spaces filled with erythrocytes. Cystic degeneration occurs spontaneously at low incidences in aging rats, but may be quite common in younger rats following exposure to a hepatocarcinogen. Angiectasis is more common in males and can be induced by certain chemicals, particularly nitrosamines; the spontaneous occurrence of angiectasis is also common in F344/N rats (Eustis *et al.*, 1990).

Adrenal Medulla: The incidence of benign adrenal medulla pheochromocytomas (unilateral and bilateral) in dosed male rats occurred with a positive trend, and the incidences in the mid- and high-dose groups were significantly greater than that of the control group by pairwise comparisons (Table 13). The incidence of malignant pheochromocytoma in dosed groups was similar to that of the controls. The combined incidence of benign and malignant pheochromocytoma occurred with a positive trend and the incidence in the mid- and high-dose groups was significantly greater than in the control. The incidence in all dose groups exceeded the NTP historical control rate (benign 284/788, 36%, range 14%-47%; benign and malignant combined 306/788, 39%, range 22%-48%; Table A4a). The pheochromocytomas were often large, discrete masses occupying most of the medulla with the neoplastic cells arranged in packets or trabeculae. The incidence of adrenal medulla hyperplasia in high-dose males was similar to controls. However, in the present study, hyperplasias were only diagnosed when no pheochromocytomas were present in the same gland. Thus, it is probable that had both been diagnosed when present, the incidence of hyperplasias would have been higher. Also, when large adenomas occupied most of the medulla, hyperplasias would not be observed.

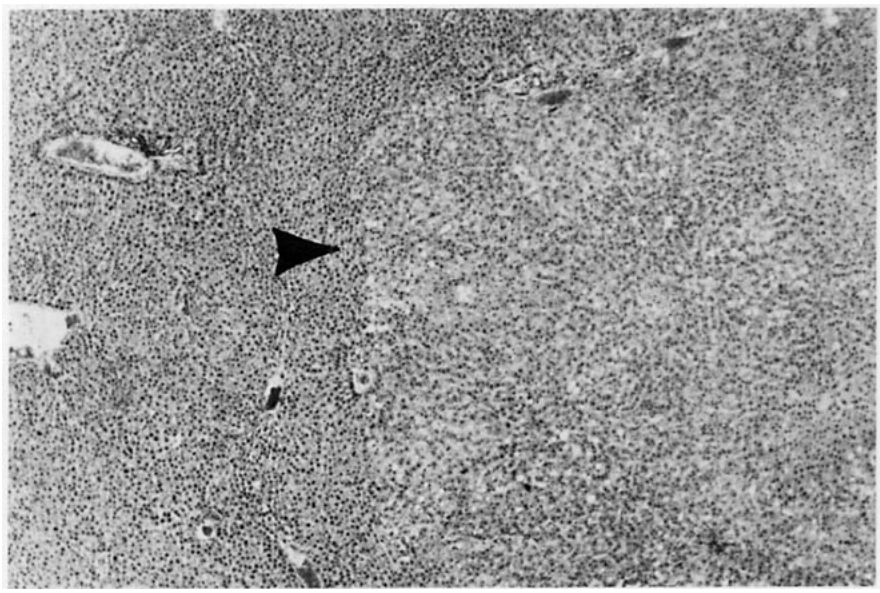


PLATE 1
Liver: Well-demarcated expansile hepatocellular adenoma with compression of the surrounding parenchyma (arrow) in a female F344/N rat administered 25,000 ppm C.I. Pigment Red 3 in feed for two years. ×30

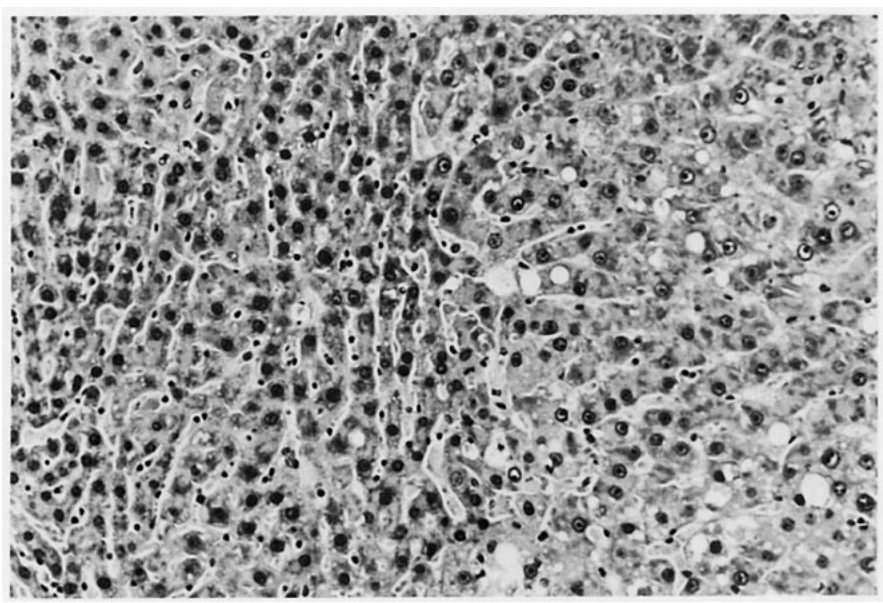


PLATE 2
Liver: Higher magnification of Plate 1 demonstrating abrupt intersection of adenoma hepatic cords with the adjacent parenchyma; adenoma on the right. ×150

TABLE 12
Liver Lesions in Rats in the 2-Year Feed Studies of C.I. Pigment Red 3

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Male				
Hepatocellular Adenoma[a]				
Overall rates[b]	0/50 (0%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rates[c]	0.0%	2.5%	10.7%	2.2%
Terminal rates[d]	0/28 (0%)	1/40 (3%)	3/28 (11%)	0/20 (0%)
First incidence (days)	-[f]	729 (T)	729 (T)	612
Logistic regression tests[e]	P=0.334	P=0.571	P=0.120	P=0.558
Eosinophilic Focus				
Overall rates	6/50 (12%)	37/50 (74%)**	36/50 (72%)**	41/50 (82%)**
Mixed Cell Focus				
Overall rates	2/50 (4%)	24/50 (48%)**	21/50 (42%)**	15/50 (30%)**
Cystic Degeneration				
Overall rates	9/50 (18%)	36/50 (72%)**	40/50 (80%)**	36/50 (72%)**
Multifocal Angiectasis				
Overall rates	3/50 (6%)	20/50 (40%)**	21/50 (42%)**	29/50 (58%)**
Female				
Hepatocellular Adenoma[g]				
Overall rates	0/50 (0%)	0/50 (0%)	1/50 (2%)	10/50 (20%)
Adjusted rates	0.0%	0.0%	2.6%	23.0%
Terminal rates	0/32 (0%)	0/41 (0%)	1/39 (3%)	7/40 (18%)
First incidence (days)	-	-	729 (T)	553
Logistic regression tests	P≤0.001	-	P=0.539	P=0.001
Eosinophilic Focus				
Overall rates	1/50 (2%)	7/50 (14%)	18/50 (36%)**	16/50 (32%)**
Mixed Cell Focus				
Overall rates	4/50 (8%)	16/50 (32%)**	30/50 (60%)**	40/50 (80%)**
Granuloma				
Overall rates	27/50 (54%)	21/50 (42%)	43/50 (86%)**	44/50 (88%)**
Cystic Degeneration				
Overall rates	0/50 (0%)	1/50 (2%)	3/50 (6%)	5/50 (10%)
Cholesterol Pigmentation				
Overall rates	0/50 (0%)	3/50 (6%)	14/50 (28%)**	41/50 (82%)**
Biliary Tract Proliferation				
Overall rates	18/50 (36%)	12/50 (24%)	18/50 (36%)	29/50 (58%)*

* Significantly different (P≤0.05) from the control group by logistic regression tests
** P≤0.01
(T)Terminal sacrifice
[a] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 19/799 (2.4% ± 2.9%); range 0%-8%
[b] Number of lesion-bearing animals/number of animals with tissues examined microscopically
[c] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard lesions in animals dying prior to terminal kill as nonfatal.
[f] Not applicable; no tumors in animal group
[g] Historical incidence: 3/800 (0.4% ± 1.5%); range 0%-6%

TABLE 13
Adrenal Medulla Lesions in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Adrenal Medulla: Hyperplasia				
Overall rates[a]	22/50 (44%)	8/50 (16%)	12/50 (24%)	26/50 (52%)
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates	22/50 (44%)	29/50 (58%)	35/50 (70%)	34/50 (68%)
Adjusted rates[b]	60.2%	65.7%	89.3%	79.9%
Terminal rates[c]	14/28 (50%)	25/40 (63%)	24/28 (86%)	12/20 (60%)
First incidence (days)	653	605	529	486
Logistic regression tests[d]	P=0.004	P=0.191	P=0.006	P=0.010
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rates	6/50 (12%)	7/50 (14%)	10/50 (20%)	4/50 (8%)
Adjusted rates	19.4%	17.0%	25.8%	11.5%
Terminal rates	4/28 (14%)	6/40 (15%)	3/28 (11%)	1/20 (5%)
First incidence (days)	666	660	529	567
Logistic regression tests	P=0.318N	P=0.588	P=0.207	P=0.358N
Adrenal Medulla: Pheochromocytoma (Benign or Malignant)[e]				
Overall rates	24/50 (48%)	32/50 (64%)	37/50 (74%)	36/50 (72%)
Adjusted rates	64.1%	71.0%	89.9%	82.8%
Terminal rates	15/28 (54%)	27/40 (68%)	24/28 (86%)	13/20 (65%)
First incidence (days)	653	605	529	486
Logistic regression tests	P=0.005	P=0.133	P=0.005	P=0.010

[a] Number of lesion-bearing animals/number of animals with tissues examined microscopically
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard lesions in animals dying prior to terminal kill as nonfatal. A negative trend or lower incidence in a dose group is indicated by N.
[e] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 306/788 (38.8% ± 8.4%); range 22%-48%

Skin: The incidence of squamous cell papillomas of the skin was increased in dosed males (0/50, 4/50, 2/50, 6/50). However, one control male had an anaplastic squamous cell carcinoma (diagnosed as carcinoma) and when combined with the papillomas (1/50, 4/50, 2/50, 6/50), only the trend test remained marginally significant. The historical control incidence of skin squamous cell papillomas in male rats in NTP studies is 16/800 (2.0%, range of 0%-4%); the historical control incidence of squamous cell papillomas and carcinomas combined in male rats in NTP studies is 20/800 (2.5%, range of 0%-4%; Table A4b). These neoplasms were located on the head, ears, feet, and tail. Microscopically, the papillomas were characterized by arborized, finger-like projections supported by a fibrovascular stromal core and covered by thickened keratinized squamous epithelium. The squamous cell carcinoma was located on the lip and was poorly differentiated with invasion of surrounding tissue by anaplastic epithelial cells. The marginal increase in squamous cell papillomas in this study may have been associated with chemical administration.

Zymbal's Gland: There was a marginal increase in the occurrence of Zymbal's gland carcinomas in male rats (0/50, 0/50, 2/50, 3/50; Table A3). The incidence in the high-dose group was greater than in the NTP historical control groups (6/800, 1%, range 0%-4%; Table A4c). Zymbal's gland neoplasms infrequently occur spontaneously but are induced by a variety of carcinogens, particularly the aromatic

amines (Copeland-Haines and Eustis, 1990). The marginal increase in carcinomas in this study may have been associated with chemical administration.

Clitoral Gland/Preputial Gland: The incidences of clitoral gland and preputial gland neoplasms were lower in exposed animals than in controls (Table 14). The NTP feed study historical control incidence is 64/800 (8%, range 2%-18%) for clitoral gland adenomas and 74/800 (9%, range 4%-22%) for preputial gland adenomas; for combined adenomas and carcinomas the historical incidences are 88/800 (11%, range 4%-20%) for clitoral gland and 112/800 (14% range 4%-28%) for preputial gland. Clitoral gland carcinomas were not observed in females; a single preputial gland carcinoma occurred in the male control group. This effect is supported by a marginal decrease in hyperplasias of these glands as well. Additionally, fewer clitoral gland duct cysts were observed in dosed females than in controls.

TABLE 14
Preputial and Clitoral Gland Lesions in Rats in the 2-Year Feed Studies of C.I. Pigment Red 3[a]

	0 ppm	25,000 ppm
Male		
Preputial Gland: Hyperplasia		
Overall rates[b]	4/49 (8%)	1/50 (2%)
Preputial Gland: Adenoma		
Overall rates	6/49 (12%)	1/50 (2%)
Preputial Gland: Adenoma or Carcinoma		
Overall rates	7/49 (14%)	1/50 (2%)*
Female		
Clitoral Gland: Hyperplasia		
Overall rates	7/47 (15%)	3/50 (6%)
Clitoral Gland: Adenoma		
Overall rates	9/47 (19%)	1/50 (2%)**

* Significantly different (P≤0.05) from the control group by logistic regression tests
** P≤0.01
[a] In the 6,000 and 12,500 ppm groups only preputial or clitoral glands observed to be abnormal at necropsy were examined microscopically; thus those groups were excluded from statistical analysis.
[b] Number of lesion-bearing animals/number of animals with tissues examined microscopically

Kidney: The severity of nephropathy was greater in dosed rats than in controls (Table 15). Severity grades were based upon the percentage of the renal parenchyma exhibiting the tissue changes. Nephropathy in dosed rats was typical of the spontaneously occurring lesions observed in aged F344/N rats. Nephropathy was characterized by varying degrees of tubule dilation and distortion with occasional cyst formation; proteinaceous tubule casts, atrophy, regeneration, and hypertrophy of tubule epithelium; thickening of tubule and glomerular basement membranes; interstitial fibrosis; scattered foci of suppurative inflammation (primarily within degenerating tubules); and various mononuclear inflammatory cells within the interstitium. Regenerating tubule epithelial cells had basophilic nuclei and scant cytoplasm and usually formed a single cell layer.

There was also an increased incidence of renal tubule hyperplasia in the high-dose male rats as well as a dose-related increased incidence of renal papillary transitional epithelium hyperplasia and renal cortical cysts (Table 16). The renal tubule hyperplasia was characterized by one or more slightly dilated tubules with the lumens partially or completely filled with tubule epithelial cells. The cells were typically small with a scant amount of cytoplasm. Hyperplasia of the renal papillary transitional epithelium was minimal to mild and consisted of focal papillary projections of the transitional epithelium lining the renal papilla.

A dose-related increase in the severity of nephropathy was observed in female rats (Table 15). However, as opposed to the males, the only associated secondary lesion was a dose-related increased incidence of renal papillary transitional epithelial hyperplasia (1/50, 5/50, 4/50, 12/49; Table B5).

TABLE 15
Nephropathy Severity in Rats in the 2-Year Feed Studies of C.I. Pigment Red 3[a]

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Male				
None	0/50	1/50	0/50	0/49
Minimal	1/50	0/50	0/50	0/49
Mild	30/50	6/50	2/50	1/49
Moderate	16/50	27/50	15/50	9/49
Marked	3/50	16/50	33/50	39/49
Average severity grade	2.4 ± 0.6	3.1 ± 0.8**	3.6 ± 0.6**	3.8 ± 0.5**
Female				
None	1/50	1/50	0/50	1/49
Minimal	21/50	2/50	3/50	2/49
Mild	21/50	32/50	26/50	13/49
Moderate	4/50	15/50	21/50	22/49
Marked	3/50	0/50	0/50	11/49
Average severity grade	1.7 ± 0.9	2.2 ± 0.6**	2.4 ± 0.6**	2.8 ± 0.9**

** Significantly different ($P \leq 0.01$) from the control group by the Mann-Whitney U test
[a] Number of animals with severity grade/number of animals examined. Average severity grade is expressed as the mean ± standard deviation. 0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

TABLE 16
Selected Lesions in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Kidney (Renal Tubule): Hyperplasia				
Overall rates[a]	2/50 (4%)	3/50 (6%)	2/50 (4%)	7/49 (14%)
Kidney (Cortex): Cyst				
Overall rates	3/50 (6%)	6/50 (12%)	13/50 (26%)**	17/49 (35%)**
Kidney (Papilla Transitional Epithelium): Hyperplasia				
Overall rates	7/50 (14%)	40/50 (80%)**	43/50 (86%)**	43/49 (88%)**
Parathyroid Gland: Hyperplasia				
Overall rates	2/48 (4%)	2/12 (17%)[b]	9/21 (43%)[b]	34/49 (69%)**
Stomach (Glandular): Mineralization				
Overall rates	1/50 (2%)	0/10 (0%)[b]	5/22 (23%)[b]	16/49 (33%)**
Bone: Fibrous Osteodystrophy				
Overall rates	1/50 (2%)	0/10 (0%)[b]	8/22 (36%)[b]	36/50 (72%)**

** Significantly different (P≤0.01) from the control group by logistic regression tests
[a] Number of lesion-bearing animals/number of animals necropsied or number of animals with tissues examined microscopically
[b] Tissues examined microscopically only when observed to be abnormal.

Mammary Gland: The incidence of mammary gland fibroadenomas was marginally decreased in the high-dose females (23/50, 16/50, 20/49, 12/50; Table B2). Fibroadenomas are the most common neoplasm of the mammary gland in female rats, occurring in 314/800 (39%, range 8%-58%) NTP feed study control animals. The lower incidence of fibroadenomas in high-dose females may be due to chemical administration or to the decreased body weights in this group.

Mononuclear Cell Leukemia: Exposure to C.I. Pigment Red 3 resulted in decreased incidences of mononuclear cell leukemia in male (22/50, 6/50, 2/50, 1/50; Table A3) and female rats (10/50, 1/50, 0/50, 2/50; Table B3). Historically, the administration of aniline and aniline-related compounds has caused significant reductions in the incidence of leukemias in F344/N rats (NCI, 1977, 1978, 1979a,b,c; NTP, 1982a,b, 1989).

Other Lesions: Male rats also had treatment-related increased incidences of parathyroid gland hyperplasia, fibrous osteodystrophy, and glandular stomach mineralization; these lesions are thought to be secondary to nephropathy (Table 16).

There was histologic evidence of treatment-related increased incidences of focal and multifocal pancreatic acinus atrophy in both males (24/50, 32/50, 39/49, 41/50; Table A5) and females (22/50, 33/50, 40/50, 36/49; Table B5). Microscopic examination revealed a loss of acinar tissue from a lobule or lobule portion. Atrophy resulted in condensation of the stromal tissue around the remaining pancreatic ducts and islets with a few lymphocytes scattered within the stroma.

The association of pancreatic acinus atrophy with chemical administration is uncertain. While the incidence was increased in dosed groups, the severity of these lesions was minimal and was similar among all groups. Pancreatic acinus atrophy is the most common spontaneous degenerative lesion of the exocrine pancreas in aging F344/N rats and occurs at a high and variable rate. The cause of naturally occurring pancreatic atrophy in the rat is unknown. It may be induced by pancreatic duct ligation, dietary copper or magnesium deficiency, and cytotoxic chemicals (Eustis *et al.*, 1990).

MICE

2-Week Studies

All mice lived to the end of the studies (Table 17). Male mice that received 100,000 ppm had 9% lower final mean body weight than the controls. All exposed females except those that received 25,000 ppm had significantly increased body weight gains relative to that of the controls. Average feed consumption by exposed groups was similar to that of the controls.

There were no clinical findings indicative of chemical toxicity. Red-stained extremities, feces, and fur were due to contact with C.I. Pigment Red 3 and were not indicative of toxicity.

Absolute and relative liver weights were significantly increased in females that received 50,000 or 100,000 ppm (Table F4). Relative brain weights were decreased for females that received 12,500 ppm or greater. No other biologically significant differences in organ weights were observed in mice.

Hemoglobin values and erythrocyte counts were significantly decreased for all mice that received 12,500, 25,000, or 50,000 ppm (Table G4). Male mice that received 100,000 ppm had significantly increased reticulocyte, leukocyte and segmented neutrophil counts and albumin/globulin ratios. Female mice that received 25,000 ppm or greater had significantly increased leukocyte counts; female mice that received 50,000 or 100,000 ppm had significantly increased lymphocyte counts. There were no other biologically significant changes in hematology and clinical chemistry parameters for exposed mice.

There were no gross or microscopic lesions attributable to C.I. Pigment Red 3 administration.

TABLE 17
Survival, Mean Body Weights, and Feed Consumption of Mice in the 2-Week Feed Studies of C.I. Pigment Red 3

Concentration (ppm)	Survival[a]	Mean Body Weights[b] (g) Initial	Final	Change	Final Weight Relative to Control (%)	Feed Consumption[c]
Male						
0	5/5	23.8 ± 0.7	28.2 ± 1.1	4.4 ± 0.4		9.6
6,000	5/5	24.0 ± 0.7	28.2 ± 0.8	4.2 ± 0.4	100	10.1
12,500	5/5	23.6 ± 0.2	29.2 ± 0.4	5.6 ± 0.2	104	9.7
25,000	5/5	22.2 ± 0.5	26.0 ± 0.6	3.8 ± 0.2	92	8.3
50,000	5/5	23.6 ± 0.5	27.8 ± 0.6	4.2 ± 0.4	99	8.7
100,000	5/5	23.0 ± 0.6	25.8 ± 0.7*	2.8 ± 0.4**	91	8.0
Female						
0	5/5	18.0 ± 0.5	20.4 ± 0.5	2.4 ± 0.2		9.9
6,000	5/5	18.2 ± 0.2	23.0 ± 0.3**	4.8 ± 0.2**	113	8.5
12,500	5/5	18.0 ± 0.3	22.0 ± 0.3	4.0 ± 0.3**	108	8.9
25,000	5/5	17.4 ± 0.2	21.0 ± 0.5	3.6 ± 0.2	103	8.5
50,000	5/5	18.0 ± 0.3	22.4 ± 0.5*	4.4 ± 0.5**	110	7.1
100,000	5/5	17.6 ± 0.4	21.6 ± 0.6	4.0 ± 0.3**	106	7.5

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving/number of animals initially in group
[b] Weights and weight changes given as mean ± standard error
[c] Grams of feed per animal per day, based on average consumption data per group per day for days 1 through 13

13-Week Studies

One male mouse that received 12,500 ppm died during week 4, and one control male mouse died during week 13 (Table 18). The final mean body weights and body weight changes of exposed mice were similar to those of the controls. Average feed consumption by exposed groups was similar to those of control groups (Table 19).

There were no clinical findings indicative of chemical toxicity. Red-stained extremities, feces, and fur were due to contact with C.I. Pigment Red 3 and were not indicative of toxicity.

Male mice that received 25,000 or 50,000 ppm had significantly increased relative liver weights (Table F5). No other biologically significant changes in organ weights were observed in mice.

There were no biologically significant changes in hematology, clinical chemistry, or urinalysis parameters for exposed mice (Table G5).

TABLE 18
Survival and Mean Body Weights of Mice in the 13-Week Feed Studies of C.I. Pigment Red 3

Concentration (ppm)	Survival[a]	Mean Body Weights[b] (g)			Final Weight Relative to Control (%)
		Initial	Final	Change	
Male					
0	9/10[c]	23.8 ± 0.4	33.0 ± 0.4	9.2 ± 0.5	
3,000	10/10	23.0 ± 0.5	32.1 ± 0.6	9.1 ± 0.4	97
6,000	10/10	22.9 ± 0.6	30.5 ± 0.9	7.6 ± 0.6	92
12,500	9/10[d]	23.8 ± 0.5	33.0 ± 0.7	9.2 ± 0.6	100
25,000	10/10	22.8 ± 0.8	30.1 ± 1.1	7.8 ± 0.6	93
50,000	10/10	23.4 ± 0.7	32.1 ± 0.6	8.7 ± 0.7	97
Female					
0	10/10	17.7 ± 0.2	24.9 ± 0.3	7.2 ± 0.4	
3,000	10/10	17.4 ± 0.3	25.8 ± 0.7	8.4 ± 0.5	104
6,000	10/10	17.1 ± 0.4	25.2 ± 1.1	8.1 ± 0.8	101
12,500	10/10	17.8 ± 0.4	26.4 ± 0.7	8.6 ± 0.6	106
25,000	10/10	17.2 ± 0.4	25.2 ± 0.5	8.0 ± 0.3	101
50,000	10/10	17.5 ± 0.5	25.0 ± 0.7	7.5 ± 0.5	100

[a] Number of animals surviving/number of animals initially in group
[b] Weights and weight changes given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies. Differences from the control group are not significant by Dunn's test.
[c] Week of death: 13
[d] Week of death: 4

TABLE 19
Mean Feed Consumption by Mice in the 13-Week Feed Studies of C.I. Pigment Red 3[a]

Week on Study	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male						
1	234	217	213	131	310	184
2	196	176	185	162	251	215
3	125	146	182	205	359	219
4	157	208	179	301	332	244
5	157	166	169	214	201	98
6	148	121	135	320	201	222
7	210	202	187	506	363	262
8	143	132	162	291	353	239
9	159	149	185	230	160	196
10	138	151	102	223	155	177
11	121	160	132	263	147	145
12	127	160	146	239	147	170
13	323	199	307	354	312	287
Female						
1	230	212	283	311	335	260
2	225	212	267	237	318	353
3	234	308	246	201	199	222
4	218	237	216	177	214	198
5	216	212	289	211	214	295
6	210	200	175	237	257	253
7	280	268	479	315	367	329
8	164	162	207	218	248	181
9	249	223	207	249	248	249
10	234	152	173	244	271	124
11	234	262	311	266	283	208
12	224	259	266	202	170	262
13	245	190	234	394	171	336

[a] Grams of feed consumed per kilogram body weight per day

The most significant histopathologic alterations occurred in the kidney, liver, and spleen of dosed males and in the liver and spleen of dosed females (Table 20). Increased incidences of hematopoietic cell proliferation in the spleen and liver and splenic pigment (hemosiderin) are probably associated with mild anemia. Renal tubule epithelial cytomegaly, although a minimal to mild change, was thought to be a toxic effect of C.I. Pigment Red 3 administration. This lesion is described in more detail in the results of the 2-year studies.

Dose Selection Rationale: Exposure concentrations for mice in the 2-year studies were based on the lack of chemical-related deaths or decreases in body weights in the 13-week studies. Doses higher than 50,000 ppm might have diluted the nutrients in feed excessively, thereby altering its nutritional value.

TABLE 20
Histopathologic Diagnoses in Mice in the 13-Week Feed Studies of C.I. Pigment Red 3[a]

	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male						
Kidney (Cortex): Cytomegaly						
Overall rates[b]	0/10	0/10	4/10*	8/10**	10/10**	10/10**
Average severity[c]			1.0	1.1	1.4	1.4
Liver: Glycogen Depletion						
Overall rates	0/10	0/10	2/10	6/10**	4/10*	8/10**
Average severity			1.0	1.0	1.0	1.1
Liver: Hematopoietic Cell Proliferation						
Overall rates	1/10	2/10	3/10	5/10	1/10	7/10**
Average severity	1.0	1.0	1.0	1.0	1.0	1.0
Spleen: Hematopoietic Cell Proliferation						
Overall rates	0/10	6/10**	6/10**	2/10	4/10*	10/10**
Average severity		1.5	2.8	1.0	1.0	2.0
Spleen: Pigment						
Overall rates	0/10	0/10	0/10	0/10	1/10	10/10**
Average severity					1.0	1.2
Female						
Liver: Hematopoietic Cell Proliferation						
Overall rates	6/10	6/10	9/10	6/10	10/10*	10/10*
Average severity	1.0	1.0	1.0	1.0	1.0	1.6
Spleen: Hematopoietic Cell Proliferation						
Overall rates	0/10	4/10*	4/10*	4/10*	8/10**	10/10**
Average severity		1.0	1.0	1.0	1.1	1.4
Spleen: Pigment						
Overall rates	0/10	0/10	0/10	3/10	7/10**	10/10**
Average severity				1.0	1.0	1.3

* Significantly different (P≤0.05) from the control group by Fisher's exact test
** P≤0.01
[a] Cited in Morgan *et al.*, 1989
[b] Number of lesion-bearing animals/number of animals necropsied or number of animals examined microscopically
[c] Severity of lesion: 1 = minimal, 2 = mild, and 3 = moderate, 4 = marked

2-Year Studies

15-Month Interim Evaluations

Ten male and ten female mice from each study group were evaluated after 15 months. Five mice of each sex receiving the same doses as mice in the 2-year studies were taken from a special study of C.I. Pigment Red 3* and evaluated at 15 months as well. The results of the analyses from animals taken from the special study were incorporated with those from animals used for the interim evaluations of the 2-year studies.

All of the animals were stained with red dye, but there were no clinical findings indicative of chemical toxicity. Absolute and relative liver weights were significantly increased in exposed male and female mice (Table F6). The high-dose female group had a significantly decreased hematocrit value and hemoglobin concentration; serum total bilirubin was significantly increased in the high-dose male and female groups (Table G6).

Significant histologic findings at 15 months were increased incidences of nephropathy in high-dose males, dose-related cytomegaly of individual renal tubule epithelial cells in males, golden brown granular pigment (hemosiderin) in the spleens of high-dose males and females (Tables 21 and 22). The nephropathy in males was characterized by regenerative tubules and eosinophilic tubular casts. Cytomegaly was characterized by multifocal renal tubule epithelial cells that had enlarged nuclei and, frequently, increased amounts of cytoplasm. Incidences of neoplasms were similar among groups (Table 23).

* A special study was conducted to investigate whether the apparent increase in urinary bilirubin concentrations observed in the 13-week studies (Appendix G) was due to contamination with C.I. Pigment Red 3. The results of the special study showed that the increased concentrations were due to C.I. Pigment Red 3.

TABLE 21
Kidney Lesions in Male Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of C.I. Pigment Red 3

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Renal Tubule Regeneration				
Overall rates[a]	1/14	1/15	1/10	5/13
Average severity[b]	2.0	1.0	1.0	1.8
Renal Tubule Cytomegaly				
Overall rates	0/14	9/15**	10/10**	13/13**
Average severity		1.0	1.0	1.9

** Significantly different ($P \leq 0.01$) from the control group by the Fisher exact test
[a] Number of lesion-bearing animals/number of animals necropsied or number of animals with tissues examined microscopically
[b] Severity of lesion: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

TABLE 22
Spleen Pigmentation in Mice at the 15-Month Interim Evaluations in the 2-Year Feed Studies of C.I. Pigment Red 3

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male				
Overall rates[a]	0/14	15/15**	9/10**	13/13**
Average severity[b]		1.0	1.0	1.9
Female				
Overall rates	0/13	15/15**	15/15**	15/15**
Average severity		1.0	1.2	2.0

** Significantly different ($P \leq 0.01$) from the control group by the Fisher exact test
[a] Number of lesion-bearing animals/number of animals necropsied or number of animals with tissues examined microscopically
[b] Severity of lesion: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

TABLE 23
Incidence of Neoplasms in Mice at the 15-Month Interim Evaluations in the 2-Year Feed Studies of C.I. Pigment Red 3

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male				
Adrenal Gland: Pheochromocytoma				
Overall rates	0/14	-	-	1/13
Liver: Hepatocellular Adenoma				
Overall rates	3/14	1/2[b]	2/3[b]	1/13
Liver: Hepatocellular Carcinoma				
Overall rates	1/14	-	-	1/13
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	2/14	-[a]	1/2[b]	0/13
Skin: Fibrosarcoma				
Overall rates	1/14	0/15	0/10	0/13
Female				
Liver: Hepatocellular Adenoma				
Overall rates	1/13	-	1/3[b]	0/15
Lymph Node: Lymphoma				
Overall rates	0/13	1/15	0/15	0/15
Uterus: Leiomyoma				
Overall rates	1/13	0/15	0/15	0/15

[a] Not examined microscopically
[b] Only those animals noted to have gross lesions were examined microscopically

Body Weight, Feed Consumption, and Clinical Findings

Mean body weights of mice that received 12,500 or 25,000 ppm were generally within 10% of those of the controls throughout the studies (Tables 24 and 25 and Figure 3). Mean body weights of high-dose mice were decreased by more than 10% from those of the controls from week 62 for males and from week 38 for females. Average feed consumption was similar among all groups (Tables I3 and I4). No clinical findings indicative of chemical toxicity were observed. Red-stained extremities, feces, and fur were due to contact with the administered chemical and were not indicative of toxicity.

TABLE 24
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	12,500 ppm Av. Wt. (g)	12,500 ppm Wt. (% of controls)	12,500 ppm No. of Survivors	25,000 ppm Av. Wt. (g)	25,000 ppm Wt. (% of controls)	25,000 ppm No. of Survivors	50,000 ppm Av. Wt. (g)	50,000 ppm Wt. (% of controls)	50,000 ppm No. of Survivors
1	23.0	60	22.4	97	60	22.5	98	60	23.0	100	60
2	25.8	60	25.6	99	60	25.3	98	60	25.3	98	60
3	26.2	60	27.1	103	60	26.8	102	60	26.6	102	60
4	28.3	60	27.2	96	60	25.8	91	60	28.0	99	60
5	29.5	60	28.5	97	60	28.4	96	60	29.0	98	60
6	30.5	60	29.9	98	60	30.5	100	60	30.2	99	60
7	30.2	60	30.8	102	60	31.2	103	60	30.9	102	60
8	31.8	60	30.8	97	60	31.7	100	60	31.5	99	60
9	32.3	60	31.9	99	59	32.1	99	60	31.9	99	60
10	32.9	60	32.9	100	59	33.0	100	60	32.7	99	60
11	33.5	60	33.1	99	59	33.6	100	60	33.0	99	60
12	34.2	60	33.9	99	59	33.9	99	60	33.6	98	60
13	34.4	60	34.0	99	59	34.4	100	59	33.7	98	59
17	37.1	60	35.6	96	59	36.3	98	59	35.4	95	59
21	37.8	60	36.7	97	59	37.0	98	59	35.5	94	59
26	37.3	59	37.2	100	59	36.9	99	59	35.3	95	59
30	37.5	59	38.3	102	58	38.4	102	59	35.6	95	59
34	37.8	59	38.4	102	57	38.8	103	58	35.7	94	57
38	38.5	58	39.6	103	57	39.5	103	58	36.0	94	57
42	39.9	57	40.5	102	56	40.6	102	57	36.1	91	55
46	40.0	57	40.5	101	54	40.4	101	56	36.7	92	53
50	40.4	56	41.8	104	52	42.1	104	56	37.0	92	50
54	40.1	56	42.1	105	52	41.6	104	55	36.5	91	50
58	40.9	56	41.9	102	50	41.6	102	55	37.0	91	50
62	40.5	55	41.9	104	50	40.9	101	54	35.7	88	50
66[a]	40.4	44	41.7	103	40	41.3	102	45	36.0	89	41
70	40.3	44	41.4	103	39	40.0	99	44	34.8	86	41
74	40.9	43	42.1	103	38	41.4	101	44	36.4	89	41
78	39.9	43	41.4	104	38[b]	41.1	103	42	35.9	90	41
82	39.8	43	41.1	103	38	40.8	103	39	35.6	89	35
86	39.4	42	40.3	102	36	39.4	100	39	35.2	89	34
90	39.0	41	39.1	100	36	39.0	100	39	34.9	90	34
94	39.3	39	40.5	103	32	38.5	98	38	35.2	90	34
98	39.1	36	39.9	102	31	38.4	98	36	35.2	90	33
102	39.7	34	39.7	100	28	37.6	95	32	34.7	87	33
Terminal sacrifice		33			28			31			33
Mean for weeks											
1-13	30.2		29.9	99		29.9	99		30.0	99	
14-52	38.5		38.7	101		38.9	101		35.9	93	
53-102	39.9		41.0	103		40.1	101		35.6	89	

[a] Interim evaluation occurred during this week.
[b] The number of animals weighed for this week is fewer than the number of animals surviving.

TABLE 25
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3

Weeks on Study	0 ppm		12,500 ppm			25,000 ppm			50,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	17.0	60	16.5	97	60	16.9	99	60	16.8	99	60
2	18.4	58	18.6	101	60	18.4	100	60	18.5	101	60
3	19.3	58	20.0	104	60	19.8	103	60	19.7	102	60
4	20.3	58	20.7	102	60	19.2	95	60	20.4	101	60
5	21.0	58	21.3	101	60	20.5	98	60	21.0	100	60
6	22.1	58	22.3	101	60	22.1	100	60	22.0	100	60
7	22.6	58	23.3	103	60	22.9	101	60	22.9	101	60
8	23.2	58	23.6	102	60	22.9	99	60	23.1	100	60
9	23.8	58	24.2	102	60	23.8	100	60	23.8	100	60
10	24.3	58	24.5	101	60	24.4	100	60	24.2	100	60
11	24.6	58	25.1	102	60	24.7	100	60	24.1	98	60
12	25.2	58	25.5	101	60	25.1	100	60	24.7	98	60
13	25.7	58	25.8	100	60	25.5	99	60	25.3	98	60
17	27.6	58	27.4	99	60	25.9	94	60	25.9	94	60
21	28.7	58	28.3	99	60	26.9	94	60	27.0	94	60
26	29.6	58	29.7	100	60	28.7	97	60	28.0	95	60
30	30.8	58	31.6	103	60	30.3	98	60	28.2	92	60
34	32.1	58	33.0	103	60	31.7	99	60	28.9	90	60
38	34.0	58	35.2	104	60	33.1	97	60	30.1	89	60
42	35.9	58	37.0	103	60	35.4	99	60	31.2	87	59
46	37.8	58	38.4	102	60	36.9	98	60	32.4	86	59
50	40.5	57	42.0	104	59	39.0	96	60	33.9	84	59
54	41.1	57	42.5	103	59	39.2	95	60	33.5	82	58
58	40.8	57	42.3	104	59	38.7	95	60	33.9	83	58
62	39.8	57	41.6	105	59	38.1	96	60	32.5	82	58
66[a]	41.0	48	41.4	101	49	39.2	96	50	33.6	82	48
70	40.9	48	41.9	102	49	38.6	94	49	33.0	81	48
74	42.3	47	44.0	104	49	39.3	93	48	34.1	81	48
78	42.8	46	42.2	99	49	38.9	91	48	33.6	79	48
82	41.5	46	41.7	101	46	38.3	92	46	33.9	82	45
86	41.5	46	42.3	102	46	37.9	91	44	33.3	80	43
90	41.5	46	41.3	100	44	36.7	88	40	32.5	78	38
94	41.6	45	42.5	102	43	38.2	92	39	32.9	79	29
98	42.1	44	42.5	101	41	37.8	90	36	33.4	79	29
102	41.0	41	40.9	100	39	38.4	94	34	32.8	80	26
Terminal sacrifice		39			37			31			25
Mean for weeks											
1-13	22.1		22.4	101		22.0	100		22.0	100	
14-52	33.0		33.6	102		32.0	97		29.5	89	
53-102	41.4		42.1	102		38.4	93		33.3	80	

[a] Interim evaluation occurred during this week.

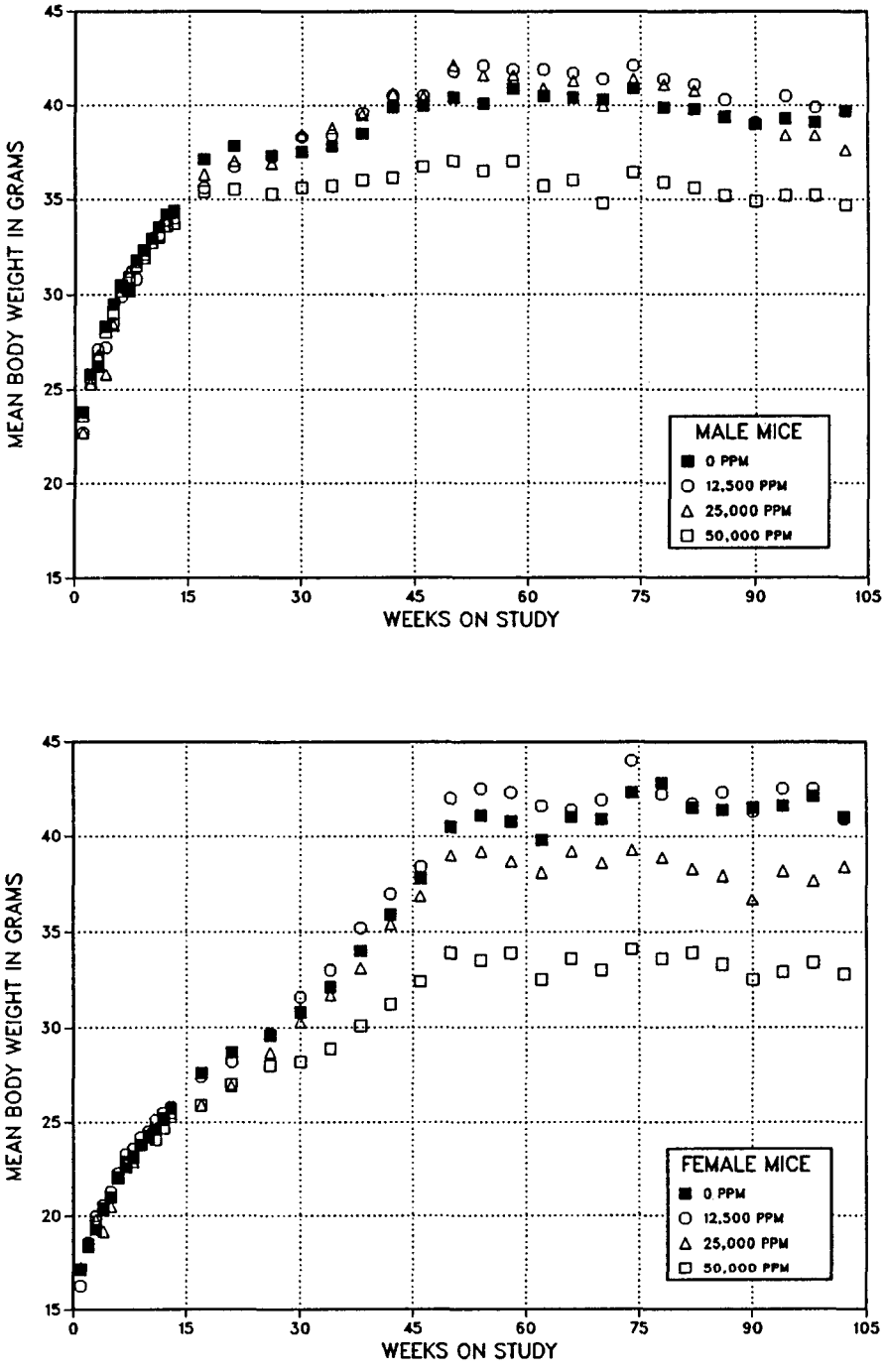


FIGURE 3
Growth Curves for Male and Female Mice Administered C.I. Pigment Red 3 in Feed for 2 Years

Survival

Survival of exposed male mice was similar to that of the controls (Table 26 and Figure 4). The survival of the high-dose females was significantly decreased due to moribund sacrifices. The moribund state of these mice may have been associated with ovarian abscesses.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in mice in the incidences of neoplastic or nonneoplastic lesions of the kidney, ovary, thyroid gland, liver, and skin.

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

TABLE 26
Survival of Mice in the 2-Year Feed Studies of C.I. Pigment Red 3

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male				
Animals initially in study	60	60	60	60
15-month interim evaluation[a,b]	10	10	10	10
Natural deaths	9	9	19	7
Moribund kills	8	13	10	10
Animals surviving to study termination	33	28	31	33
Percent survival at end of study[c]	68	58	62	66
Mean survival (days)[d]	627	589	618	590
Survival analysis[e]	P=0.817	P=0.330	P=0.684	P=0.662
Female				
Animals initially in study	60	60	60	60
15-month interim evaluation[a,f]	10	10	10	10
Natural deaths	2	4	8	5
Moribund kills	7	9	11	20
Accidental deaths[a]	2			
Animals surviving to study termination	39	37	31	25
Percent survival at end of study[c]	80	74	62	50
Mean survival (days)[d]	646	659	651	629
Survival analysis[e]	P≤0.001	P=0.637	P=0.078	P=0.002

[a] Censored from survival analyses
[b] One male receiving 25,000 ppm and two males receiving 50,000 ppm died prior to the interim evaluation.
[c] Kaplan-Meier determinations. Survival rates adjusted for interim evaluations and accidental deaths.
[d] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[e] The entry in the control column is the trend test (Tarone, 1975) result. Subsequent entries are the results of pairwise tests (Cox, 1972).
[f] One control female was killed moribund prior to the interim evaluation.

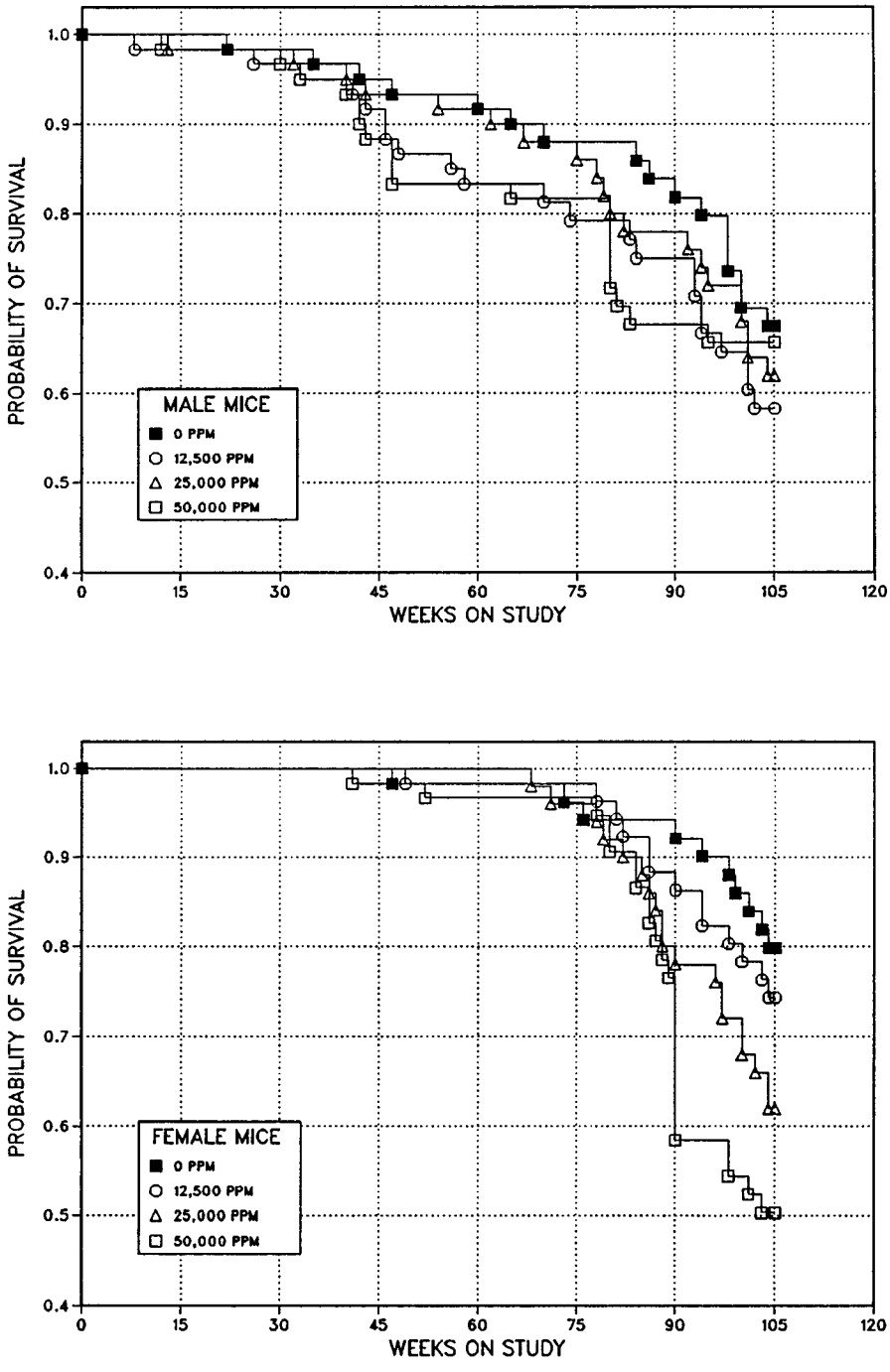


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Mice Administered C.I. Pigment Red 3 in Feed for 2 Years

Kidney: Six tubule adenomas of the renal cortex occurred among the high-dose males; none were seen in other groups (Table 27). Renal tubule adenomas have occurred in 2/865 (0.2%, range 0%-2%) male mice in NTP feed study historical controls (Table C4a). A treatment-related increase in the incidence of potentially preneoplastic renal tubule hyperplasia was also seen and was not considered to be associated with the mild nephropathy which occurred in these animals. Renal tubule cystic hyperplasias were found in four other high-dose males, but were considered to be associated with the mild nephropathy rather than preneoplastic lesions. The adenomas (Plate 3) ranged in size from 0.4-10 mm and consisted of a uniform population of large, pale, eosinophilic cells arranged in variably sized tubular or lobular structures separated by a fine fibrovascular stroma. Tubule hyperplasia typically consisted of portions of tubules lined by multiple layers of slightly enlarged epithelial cells occluding the lumen. In contrast, cystic hyperplasia consisted of a dilated tubule lined by one layer of slightly enlarged epithelial cells and an enlarged tubule lumen. There was a mild increase in the severity of nephropathy in dosed males and females (Table 28); however, the severity was significantly less than in the rats. Also, unlike the rat studies, no associated increase in the incidences of secondary lesions was seen except a marginal dose-related increase in the incidence of renal cortical cysts, which was presumed to be related to increased nephropathy severity.

Cytomegaly of the tubule epithelium consisted primarily of random enlargement of nuclei (karyomegaly) and was noted in all dosed male groups but was quite subtle in all except the high-dose group. Any association between this lesion and the development of adenomas is uncertain.

Ovary: There was a marginal positive trend (P=0.032) in the incidence of ovarian granulosa cell adenomas (0/50, 0/49, 1/50, 2/50; Table D1). These tumors are relatively uncommon (Table D4a) but were not considered related to chemical administration because the incidences were low, and incidences of 1/50 have been seen in control groups from NTP feed studies. However, interpretation of this marginal increase is made difficult by ovarian abscesses which, in several high-dose mice, were severe enough to have potentially interfered with the diagnosis of a tumor. In high-dose females, 24 of 100 ovaries were severely affected; both ovaries were affected in six of the high-dose females. Only 7 of 100 ovaries were severely affected in the mid-dose females.

The incidence of ovarian abscesses increased with dose (2/50, 2/49, 12/50, 19/50; Table D5). These abscesses were large and frequently completely replaced the ovarian tissue (Plate 4). The abscesses were often encapsulated by a variably thick fibrous band and were filled with neutrophils, erythrocytes, cell debris, and fibrin. The adjacent mesentery and occasionally the kidney capsule were involved. Other dose-related lesions included myeloid cell hyperplasia of the bone marrow, neutrophils in hepatic sinusoids, hematopoietic cell proliferation in the spleen and liver, suppurative inflammation in the abdominal cavity, and lymphoid hyperplasia of the iliac, mediastinal, and renal lymph nodes. Involvement of these tissues was probably related to the ovarian inflammatory process and reflects the increased demand for the production of neutrophils as well as an immunologic response by the area lymph nodes.

TABLE 27
Kidney Lesions in Mice in the 2-Year Feed Studies of C.I. Pigment Red 3

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male				
Cortex: Renal Tubule Adenoma[a]				
Overall rates[b]	0/50 (0%)	0/50 (0%)	0/50 (0%)	6/50 (12%)
Adjusted rates[c]	0.0%	0.0%	0.0%	18.2%
Terminal rates[d]	0/33 (0%)	0/28 (0%)	0/31 (0%)	6/33 (18%)
First incidence (days)	–[f]	–	–	729 (T)
Logistic regression test[e]	P≤0.001	–	–	P=0.017
Renal Tubule: Hyperplasia				
Overall rates	0/50 (0%)	1/50 (2%)	7/50 (14%)**	7/50 (14%)**
Renal Tubule: Hyperplasia Cystic				
Overall rates	0/50 (0%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Renal Tubule Epithelium: Cytomegaly				
Overall rates	0/50 (0%)	40/50 (80%)**	47/50 (94%)**	46/50 (92%)**
Nephropathy				
Overall rates	34/50 (68%)	39/50 (78%)*	42/50 (84%)*	45/50 (90%)*
Female				
Nephropathy				
Overall rates	33/50 (66%)	45/49 (92%)**	46/49 (96%)**	45/50 (90%)**

* Significantly different ($P \leq 0.05$) from the control group by logistic regression tests
** $P \leq 0.01$
(T)Terminal sacrifice
[a] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 2/865 (0.2% ± 0.7%); range 0%-2%
[b] Number of lesion-bearing animals/number of animals with tissues examined microscopically
[c] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard lesions in animals dying prior to terminal kill as nonfatal.
[f] Not applicable; no tumors in animal group

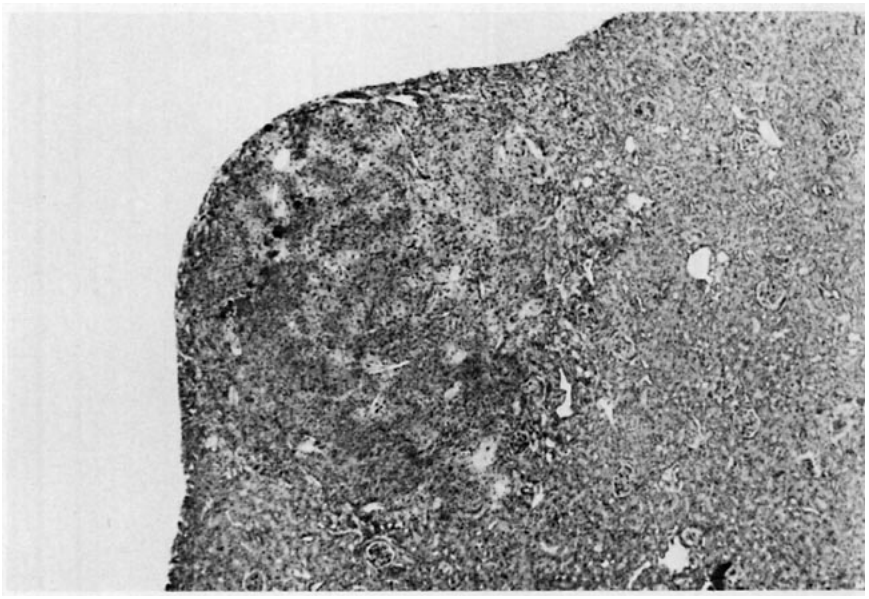


PLATE 3
Kidney: Expansile renal tubular adenoma in the kidney of a male B6C3F_1 mouse administered 50,000 ppm C.I. Pigment Red 3 in feed for two years. ×30

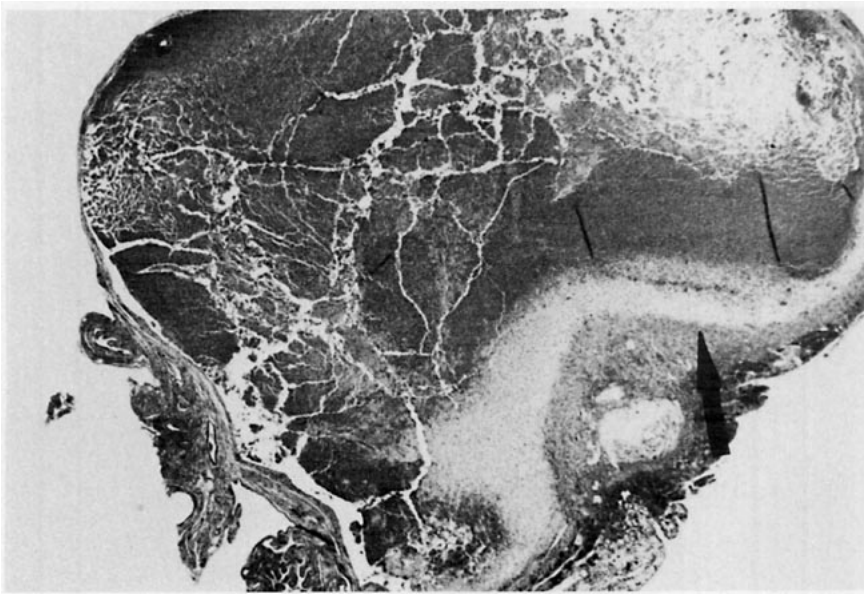


PLATE 4
Ovary: Ovarian abscess which has totally replaced the ovarian parenchyma in a female B6C3F_1 mouse administered 50,000 ppm C.I. Pigment Red 3 in feed for two years. Note the fibrous capsule (arrow) surrounding a core of neutrophils and necrotic cellular debris. ×15

TABLE 28
Nephropathy Severity in Mice in the 2-Year Feed Studies of C.I. Pigment Red 3[a]

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male				
None	16/50	11/50	8/50	5/50
Minimal	29/50	28/50	30/50	22/50
Mild	3/50	11/50	7/50	11/50
Moderate	2/50	0/50	5/50	12/50
Marked	0/50	0/50	0/50	0/50
Group average severity grade	0.8 ± 0.7	1.0 ± 0.7	1.2 ± 0.8*	1.6 ± 1.0**
Female				
None	17/50	4/49	3/49	5/50
Minimal	33/50	35/49	36/49	15/50
Mild	0/50	8/49	7/49	26/50
Moderate	0/50	2/49	3/49	4/50
Marked	0/50	0/49	0/49	0/50
Group average severity grade	0.7 ± 0.5	1.2 ± 0.6**	1.2 ± 0.6**	1.6 ± 0.8**

* Significantly different ($P \leq 0.05$) from the control group by the Mann-Whitney U test
** $P \leq 0.01$
[a] Number of animals with severity grade/number of animals examined. Average severity grade is expressed as the mean ± standard deviation. 0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

Thyroid Gland: There was a treatment-related increased incidence of thyroid gland follicular cell adenomas in males, as well as of follicular cell hyperplasia and follicular cysts (Table 29). The incidence of adenomas in the high-dose males exceeds the incidence of 14/856 (2%, range 0%-4%) in historical controls from NTP feed studies (Table C4b). Typically adenomas were partially encapsulated, well-demarcated masses which compressed surrounding parenchyma and were composed of cells forming follicles and papillary projections. Cells were well-differentiated, but varied in size. Hyperplasia consisted of focal areas with increased numbers of cuboidal to columnar follicular epithelial cells generally in a single layer. Often the cells formed rows or ribbons; papillary projections were often present and were lined by these cells. Some follicular hyperplasias were cystic; in these cases, follicles were dilated and lined by cuboidal epithelium and exhibited small papillary projections. Follicular cysts were characterized by one or more enlarged (>300 μm) follicles filled with colloid and lined by a single layer of flattened to cuboidal epithelium. In females, incidences of thyroid follicular cell hyperplasia and follicular cysts were also increased. However, the incidence of follicular cell adenomas in females was not increased and was not considered related to chemical administration.

TABLE 29
Thyroid Gland Lesions in Mice in the 2-Year Feed Studies of C.I. Pigment Red 3

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male				
Thyroid Gland (Follicular Cell): Adenoma[a]				
Overall rates[b]	0/50 (0%)	0/49 (0%)	1/50 (2%)	5/50 (10%)
Adjusted rates[c]	0.0%	0.0%	2.6%	14.3%
Terminal rates[d]	0/33 (0%)	0/28 (0%)	0/31 (0%)	4/33 (12%)
First incidence (days)	–[f]	–	658	557
Logistic regression test[e]	P=0.001	–	P=0.500	P=0.027
Thyroid Gland (Follicular Cell): Hyperplasia				
Overall rates	2/50 (4%)	10/49 (20%)**	24/48 (48%)**	41/50 (82%)**
Thyroid Gland: Follicular Cyst				
Overall rates	3/50 (6%)	4/49 (8%)	19/50 (38%)**	38/50 (76%)**
Female				
Thyroid Gland (Follicular Cell): Adenoma[g]				
Overall rates	4/50 (8%)	1/50 (2%)	0/49 (0%)	3/50 (6%)
Adjusted rates	9.9%	2.7%	0.0%	12.0%
Terminal rates	3/39 (8%)	1/37 (3%)	0/31 (0%)	3/25 (12%)
First incidence (days)	703	729 (T)	–	729 (T)
Logistic regression test	P=0.525	P-0.190N	P=0.097N	P=0.596
Thyroid Gland (Follicular Cell): Hyperplasia				
Overall rates	11/50 (22%)	11/50 (22%)	24/49 (49%)**	38/50 (76%)**
Thyroid Gland: Follicular Cyst				
Overall rates	7/50 (14%)	12/50 (24%)	11/49 (22%)	21/50 (42%)**

** Significantly different (P≤0.01) from the control group by logistic regression tests
(T)Terminal sacrifice
[a] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 14/856 (1.6% ± 1.7%); range 0%-4%
[b] Number of lesion-bearing animals/number of animals with tissues examined microscopically
[c] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard these lesions as nonfatal. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[f] Not applicable; no tumors in animal group
[g] Historical incidence: 21/850 (2.5% ± 3.2%); range 0%-9%

Liver: There was a marginal but statistically significant increase in the incidence of hepatocellular adenomas in the male mice (8/50, 12/48, 11/50, 16/49; Table C3); the combined incidence of hepatocellular adenomas and carcinomas (12/50, 16/48, 16/50, 19/49) was even less significant. All incidences of hepatocellular adenoma or carcinoma (combined) in male mice are well within the range of NTP historical controls for feed studies (10%-58%) and were not considered to be chemical related. The incidence of basophilic foci was also marginally increased in high-dose males (3/50, 2/48, 3/50, 8/49; Table C5). The adenomas in mice were similar to those described in rats. Compression of the surrounding parenchyma by adenomas was distinct as opposed to minimal or no compression by the foci. Hepatocellular carcinomas were large, often occupying most of the section or lobe, and component cells were often pleomorphic. No significant increase in the incidence of liver neoplasms was observed in female mice.

Male and female mice exhibited dose-related increased incidences of cytologic alteration, Kupffer cell pigmentation, and granulomatous inflammation (Tables C5 and D5). Cytologic alteration involved the centrilobular hepatocytes, and this general diagnosis included one or more of the following: cytomegaly, nuclear basophilia, increased cytoplasmic eosinophilia, and, occasionally, cytoplasmic vacuolation or cellular necrosis. Kupffer cells contained a green-brown pigment which was most easily recognized in the high-dose males and was variably present in other male and female groups. Generally, granulomatous inflammation was diagnosed to address an aggregate of mononuclear cells (2 to 4 cells or more) associated with the previously described green-brown pigment.

Skin: There was a marginal statistically significant decreased incidence of combined subcutaneous tissue fibroma or fibrosarcoma in male mice (15/50, 7/50, 10/50, 6/50; Table C3). The NTP feed study historical control rate for combined subcutaneous fibroma, neurofibroma, neurofibrosarcoma, fibrosarcoma, or sarcoma in male mice is 127/872 (15%, range 0%-41%). This combination is used for comparison because without further diagnostic procedures, such as electron microscopy or immunohistochemistry, the ability to distinguish the various subcutaneous malignant spindle cell tumors can be low. Though within the historical control range, the 30% incidence in the concurrent control group, as opposed to the incidences in the treatment groups, exceeds the average rate of 15%. Also, mice in these 2-year studies were initially housed in groups, and there is a suspected association between fight wounds and the development of subcutaneous sarcomas in male mice. This negative trend was not considered related to chemical administration.

GENETIC TOXICITY

C.I. Pigment Red 3 (33 to 3,333 μg/plate) was tested for induction of gene mutations in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 using a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table E1) (Mortelmans *et al.*, 1986). Positive responses were obtained with strains TA100 and TA98 in the presence of hamster S9 and an equivocal response was obtained with TA100 in the presence of rat S9; no mutagenic activity was detected in any of the four tester strains in the absence of S9.

In cytogenetic tests with Chinese hamster ovary cells, C.I. Pigment Red 3 was negative for induction of sister chromatid exchanges (Table E2) and chromosomal aberrations (Table E3) in the presence and the absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9. Doses tested were 10 to 50 μg/mL in the sister chromatid exchange test without S9 and up to 160 μg/mL in all other trials.

DISCUSSION AND CONCLUSIONS

C.I. Pigment Red 3, a yellowish red solid, is used for coloring paints, inks, plastics, rubber, and in textile printing. This chemical was nominated by the National Cancer Institute (NCI) for testing because of the lack of information on its carcinogenicity and toxicity and its structural similarity to several known phenylazonaphthol carcinogens such as Ponceau 3R, Oil Orange SS, and Citrus Red 2. The large volume of C.I. Pigment Red 3 produced annually (440,000 kg in 1986) suggests a great potential for human exposure. Carcinogenicity and toxicity studies were conducted by feeding diets containing C.I. Pigment Red 3 to groups of F344/N rats and B6C3F$_1$ mice for 2 weeks, 13 weeks, and 2 years. The dosed feed route of administration was selected to ensure systemic exposure. Genetic toxicology studies were conducted in *Salmonella typhimurium* and Chinese hamster ovary cells.

Morgan *et al.* (1989) described the results of the NTP 2-week and 13-week feed studies of C.I. Pigment Red 3. The major toxic effects observed in the 2-week studies included dose-related decreases in erythrocyte counts and hematocrit values and an increase in reticulocyte counts in rats. Changes in these hematology parameters occurred in mice, but not with a clearly dose-related trend. No chemical-related deaths occurred in rats or mice. Final mean body weights were significantly lower than controls in female rats and male mice that received 100,000 ppm and significantly increased in female mice that received 6,000 ppm and 50,000 ppm. The feed consumption of exposed rats and mice was similar to that of the controls, suggesting that C.I. Pigment Red 3 doses had no adverse effects on the feed palatability.

In the 13-week studies, male rats fed diets containing C.I. Pigment Red 3 showed a significant increase in the relative weight of the liver (all doses) and kidney (12,500 ppm and higher). There were significant decreases in the final mean body weights of all exposed female rats. No chemical-related changes in body or relative organ weights were observed in mice. The major sites of toxicity of C.I. Pigment Red 3 in the 13-week studies were the bone marrow, kidney, liver, and spleen in rats; the kidney, liver, and spleen in male mice; and the liver and spleen in female mice.

Chemical-related decreases in erythrocyte counts, hematocrit values, hemoglobin concentrations, and mean cell volumes and an increase in reticulocyte counts occurred in rats in the 13-week studies. Serum and urine bilirubin levels were also elevated in exposed rats. Although there were increases in urine bilirubin levels, no significant chemical-related changes of hematology parameters were observed in exposed mice in the 13-week studies.

In rats, histopathologic lesions attributed to C.I. Pigment Red 3 included bone marrow hyperplasia, congestion and hematopoietic cell proliferation in the spleen, and pigmentation (interpreted as hemosiderin) of the kidney, liver, and spleen. Protein casts occurred in kidneys of exposed male rats. Chemical-related histopathologic lesions seen in male and female mice included hematopoietic cell proliferation and pigmentation in the spleen and hematopoietic cell proliferation in the liver. Renal tubule epithelial cytomegaly was noted in male mice.

The appearance of these toxic effects in dosed rats and mice suggests that C.I. Pigment Red 3 or its metabolites were absorbed. Because C.I. Pigment Red 3 is insoluble in water and other solvents, it is unlikely that absorption of the chemical occurred in the gastrointestinal tract. In a preliminary disposition study in rats, it was concluded that a limited amount of C.I. Pigment Red 3 may be degraded by intestinal microflora since not all of the administered dose was recovered (El Dareer *et al.*, 1984). Based on these observations, the active agent may have been one of the more readily absorbable potential aromatic amine metabolites of this pigment. Azo reduction of C.I. Pigment Red 3 by intestinal microflora would yield 4-methyl-2-nitroaniline and 2-hydroxy-α-naphthylamine. The hematologic changes caused by C.I. Pigment Red 3 could be due to one or both of these metabolites. Structurally related aromatic amines have been reported to produce similar hematologic effects (Beard and Noe, 1981). Absorption and further metabolism of these aromatic amines may produce the *n*-hydroxy metabolites which are considered to

be responsible for the hematologic changes (Weisburger, 1983). The histopathologic lesions (hemosiderin deposition in the spleen and hematopoietic cell proliferation in the bone marrow and liver) as well as the hematologic changes observed are all indicative of hemolytic anemia. Amino and nitro aromatic compounds produce this type of anemia and also produce methemoglobinemia (Beard and Noe, 1981; Beutler, 1985). Blood methemoglobin levels were determined in rats and mice only at the 15-month interim evaluations and values were only marginally increased in dosed animals. The hemolytic anemia in rats fed C.I. Pigment Red 3 was characterized by microcytosis, indicated by the decrease in the mean cell volume.

There were chemical-related hematologic changes in rats at the end of the 2-week studies as well as at the end of the 13-week studies. There were dose-related hematologic changes in mice at the end of the 2-week studies but not at the end of the 13-week studies. This suggests that hemolytic anemia produced by C.I. Pigment Red 3 in mice is transient and indicates a species difference in susceptibility to hemolytic anemia. This species difference could be related to the differences between rat and mouse erythrocyte life span and in the rate of metabolism and clearance of C.I. Pigment Red 3 and its aromatic amine metabolites from the blood. Erythrocyte life span has been estimated at 50 to 65 days for rats and 20 to 30 days for mice (Prankerd, 1961). The shorter life span of mice erythrocytes may allow these animals to replace damaged erythrocytes faster than rats. Differences in the clearance rates of aromatic amines have been demonstrated in several species. Clearance of *p*-chloroaniline from blood in A/J mice was 10 times faster than in dogs or F344/N rats (Perry *et al.*, 1981). Similarly, aromatic amine metabolites of C.I. Pigment Red 3 may be more rapidly cleared from mouse blood, which would result in a short-lived hematologic effect in this species.

Doses of C.I. Pigment Red 3 selected for the 2-year feed studies were 0, 6,000, 12,500, and 25,000 ppm for rats and 0, 12,500, 25,000, and 50,000 ppm for mice. The dose selection was based on the body weight change observed in female rats that received 50,000 ppm and the absence of body weight depression or mortality in mice in the 13-week studies.

In the 2-year rat studies, males in the 6,000 ppm dose group had significantly higher survival than the control group (0 ppm, 28/50; 6,000 ppm, 40/50; 12,500 ppm, 28/50; 25,000 ppm, 20/50). There was no significant difference between the survival rates of female rats fed C.I. Pigment Red 3 and that of the controls (32/50, 41/50, 39/50, 40/50). The lower survival of male control rats may have been due to the high incidence of leukemia. The decreased survival of male rats that received 12,500, or 25,000 ppm was probably due to the increased severity of chronic nephropathy. However, a sufficient number of animals survived long enough to be at risk for developing tumors. Additionally, the body weights of dosed rats were lower than those of the controls, which suggests that the doses used were sufficient for testing the potential carcinogenic activity of C.I. Pigment Red 3. The depression in body weight suggests that the pigment may have been absorbed from the gastrointestinal tract.

In the 2-year studies, the survival rates of dosed mice were similar to those of the controls, except for an increased number of females killed moribund that received 50,000 ppm. The increased incidence of ovarian abscesses in this group may have contributed to the moribund state. Although the final survival rate in the 50,000 ppm female group was reduced, 78% of the animals were alive at week 90, and the study was considered adequate for determining the potential carcinogenicity of C.I. Pigment Red 3. Decreases in mean body weights occurred in male mice that received 50,000 ppm and female mice that received 25,000 or 50,000 ppm. The decreased body weights in the 50,000 ppm dose groups suggest that C.I. Pigment Red 3 or its metabolites were absorbed from the gastrointestinal tract.

A significant positive trend was observed in the incidence of benign pheochromocytoma of the adrenal medulla of male rats (22/50, 29/50, 35/50, 34/50). Pairwise comparisons between the control and dosed groups showed that the incidences in the 12,500 and 25,000 ppm dose groups were significantly greater than that in the control group. Because the incidences of benign pheochromocytoma of the adrenal medulla in dosed male groups were also greater than the historical control rate of 284/788 (36%, range 14%-47%), this increase was considered to be due to chemical administration.

Similarly, the incidence of squamous cell papilloma of the skin occurred with a positive trend and the incidence in the 25,000 ppm dose group was significantly greater than that in the control group (0/50, 4/50, 2/50, 6/50). Further, the incidence of squamous cell papillomas in each exposed group was also above the historical control rate of 16/800 (2%, range 0%-4%); the increased incidence of this neoplasm may have been caused by the administration of C.I. Pigment Red 3. Evidence of a carcinogenic effect is weakened by the uncertain biological behavior of these benign squamous cell papillomas and by the occurrence of a squamous cell carcinoma on the lip of a control male rat.

The majority of chemicals tested by the NTP which have caused neoplasms in the skin of F344/N rats have been the benzidine derivatives which were administered orally and caused an increased incidence of basal and squamous cell neoplasms mostly in males (Elwell *et al.*, 1990). Other chemicals applied to skin may result in hyperplasia of the epithelium of the epidermis and adnexa. In these instances it may be appropriate to combine most or all epithelial tumors of the skin. However, in this C.I. Pigment Red 3 study it appears inappropriate to combine all epithelial neoplasms of the skin as most of the squamous cell papillomas were located on the face, ears, feet, and tail, and occurred with an increased incidence, while the other skin epithelial tumors occurred in various locations and with an incidence rate similar to that of their respective historical control groups. Data are insufficient to determine if there was an association between chemical contact with the skin and development of squamous cell papillomas. However, these less haired extremities do allow the greatest contact of dye with the skin.

Of the structurally related compounds studied via the dosed feed route by NCI and NTP, aniline hydrochloride was the only compound that caused an increase in the incidence of adrenal gland pheochromocytoma (NCI, 1978), and none of the compounds caused an increase in the incidence of squamous cell papilloma. *p*-Chloroaniline hydrochloride, administered by gavage, caused an increased incidence in pheochromocytoma in F344/N male rats (NTP, 1989).

The incidence of hepatocellular adenoma occurred with a positive trend in female rats given C.I. Pigment Red 3 (0/50, 0/50, 1/50, 10/50). Because the incidence of this neoplasm in the 25,000 ppm group was significantly greater than that in the control group and because hepatocellular adenomas are uncommon in historical controls (3/800, 0.4%, range 0%-6%; Table B4a), the increased incidence was considered to be associated with chemical administration. Increases in hepatocellular (neoplastic nodules) adenomas have been reported in the 2-year feed studies of two water insoluble pigments, C.I. Solvent Yellow 14 and D & C Red No. 9 (NTP, 1982a,b).

The marked increased incidence in hepatocellular adenomas in high-dose female rats was accompanied by an increased incidence in eosinophilic and mixed cell foci. Foci of hepatocellular alteration, hepatocellular adenoma, and hepatocellular carcinoma are thought to represent a spectrum of lesions that constitute the natural history of neoplasia. There are several morphological classifications of foci. One cannot determine with certainty which foci of cellular alteration may progress to neoplasia; however, morphological criteria used for diagnosis of an adenoma are indicative of development of autonomy of growth. Adenomas are typically larger, and, unlike foci, cause distinct compression of surrounding parenchyma with abrupt intersection of hepatic cords with the adjacent parenchyma. Generally the growth pattern of adenomas is altered and cellular atypia is greater than in foci.

In these studies, the morphology of cells within the eosinophilic and mixed cell foci was similar to cells of the adenomas, which may suggest the potential for progression of these foci to adenomas. The number of adenomas in the high-dose females was significantly increased, but in weighing the biological significance of this effect, one must consider that many of these adenomas were not advanced in their development, and there were no diagnoses of hepatocellular carcinoma. Eosinophilic and basophilic foci accompanied by angiectasis and cystic degeneration were seen in female F344/N rats given the hepatocarcinogens C.I. Solvent Yellow 14 and D & C Red No. 9. Both of these pigments, as well as C.I. Pigment Red 3, are azonaphthol compound.

The decreased incidence of clitoral gland and preputial gland neoplasms is difficult to interpret, but appears related to the administration of C.I. Pigment Red 3. Zymbal's glands, clitoral glands, and preputial glands are of similar origin (modified sebaceous glands), and in NTP studies,

chemicals which cause neoplasms in one of these glands often cause neoplasms in the others as well as in the skin. However, there are exceptions, and in the present studies, the incidence of Zymbal's gland neoplasms was slightly increased in the high-dose male rats. The clitoral or preputial glands of rodents produce pheromones or pheromone-like substances which seem to affect some aspects of sexual behavior. The decrease or absence of trophic pituitary hormones or androgens result in decreased function and atrophy of these glands. However, there was no evidence that these hormones may have been significantly decreased or absent in the dosed animals.

A significant negative trend in the incidence of mammary gland fibroadenoma was observed in female rats. Aniline hydrochloride, a structurally related compound, was reported to cause a similar negative trend (NCI, 1978). The decreased incidence of mammary tumors could be related to body weight depression in dosed females. The incidence of mammary tumors in NTP studies has been found to be positively associated with body weight. No association has been found between mammary tumor incidence and survival (Rao *et al.*, 1990).

As with other structurally related compounds, C.I. Pigment Red 3 caused a significant decrease in the incidence of mononuclear cell leukemia in male and female rats. A review of NCI and NTP studies revealed that leukemia was negatively associated with survival (Rao *et al.*, 1990). Because the incidence of mononuclear cell leukemia in F344/N rats was found to be inversely associated with survival, the reduced survival of the 25,000 ppm dose groups in the present studies cannot be attributed to mononuclear cell leukemia. The hematopoietic system and the spleen are the major sites for the toxicity of C.I. Pigment Red 3, as well as for structurally related compounds; the decreased mononuclear cell leukemia incidence may be due to the direct effect of the pigment on the mechanism responsible for the induction of mononuclear cell leukemia in aging rats. Splenectomy has been reported to greatly decrease the incidence of mononuclear cell leukemia in F344/N rats, suggesting that this neoplasm originates in the spleen (Moloney and King, 1973).

Chronic nephropathy, a disease seen in aging F344/N rats, was more severe in male and female rats given C.I. Pigment Red 3 than in the control rats. The increased severity of nephropathy appears to be associated with the administration of C.I. Pigment Red 3. In male rats there was an increase in the incidence and/or severity of a number of renal and nonrenal lesions that are commonly observed in male rats with nephropathy, and, thus are generally considered secondary to the nephropathy: renal papillary transitional epithelial hyperplasia, renal cortical cysts, parathyroid gland hyperplasia, glandular stomach mineralization, and fibrous osteodystrophy. The incidence and/or severity of these lesions increases in concert with increasing severity of the nephropathy. As the severity of nephropathy increases, the number of normal nephrons remaining decreases until the kidney loses its ability to function normally. One major adverse effect is loss of calcium, which leads to the inability of the animal to properly maintain calcium/phosphorus homeostasis. Renal secondary hyperparathyroidism often develops to increase calcium levels; this causes calcium to be removed from bones with subsequent development of fibrous osteodystrophy. The exact cause of mineralization of various tissues secondary to renal disease is uncertain, but it is thought to be associated with uremia.

Hyperplasia of the renal papillary transitional epithelium was minimal to mild. The mechanism for renal papillary transitional epithelium hyperplasia is not determined but hyperplasia is commonly increased in severity and incidence with increased severity of nephropathy.

The incidence of renal tubule hyperplasia was increased in the high-dose male rats. With progression of nephropathy, regeneration of tubule epithelium increases. Frequently, hyperplastic lesions which are potentially preneoplastic occur, and in these studies, they occurred in animals with moderate to marked nephropathy. However, a direct effect of C.I. Pigment Red 3 cannot be eliminated.

A dose-related increase in the severity of nephropathy was also observed in the females; however, as opposed to the males, the only associated secondary lesion was a dose-related increase in renal papillary transitional epithelium hyperplasia. This is not unexpected as most of the associated secondary lesions are observed only in animals in which the nephropathy is severe enough to markedly alter kidney morphology or interfere

with certain functions (thresholds may vary for specific effects). Renal nephropathy in aged female rats is generally not as severe as in males, and while there was a chemical exacerbation of the nephropathy in the females in the present study, the severity of the nephropathy in the females was much less than in the males.

Pancreatic acinar cell atrophy was observed with increased incidence in dosed rats. Because this lesion is quite common in aging rats and because the severity of these lesions was similar among all dosed groups, the increased incidence of this lesion was not considered to be related to chemical administration.

Although the spleen was a site for the toxicity of C.I. Pigment Red 3 in the 13-week studies in rats, no chemical-related effects were seen in this organ for rats given similar doses in the 2-year studies. This lack of effect suggests a possible adaptive response to the treatment.

In mice, renal cortical tubule adenoma occurred in six males that received 50,000 ppm, and none occurred in the other dosed groups or controls. Because this tumor occurred only in high-dose male mice, and because the incidence exceeds the historical rate for this tumor (2/865, 0.2%, range 0%-2%), the increased incidence of renal cortical tubule adenoma was considered to be related to chemical administration. Adenoma of the renal cortex was not seen in females. Chronic nephropathy occurred with increased severity in dosed males and females. Karyomegaly observed in dosed male mice was attributed to chemical administration; the lesion was subtle in all but the 50,000 ppm group.

Thyroid gland follicular cell adenomas were observed at a significantly increased incidence in male mice that received 50,000 ppm (0 ppm, 0/50; 12,500 ppm, 0/49; 25,000 ppm, 1/50; 50,000 ppm, 5/50). There was also a significant, dose-related follicular cell hyperplastic response. Progression from follicular cell hyperplasia to adenoma and carcinoma is common among laboratory rodents; however, removal of thyroid stimulating hormone will cause reversal of some of the proliferative lesions. Also, morphologic criteria are not always predictive of biological behavior. Generally, follicular cell adenomas have greater overall complexity and cellular atypia than focal hyperplasias. The marked hyperplastic response coupled with the low historical rate for adenomas (14/856, 2%, range 0%-4%) indicated that the increased incidence of thyroid follicular cell adenoma observed in the 50,000 ppm males was caused by C.I. Pigment Red 3 administration. However, in evaluation of the overall biological significance of this carcinogenic effect, one must consider that the adenomas were not advanced in development. Also, carcinomas were not observed in any group, and an increase in follicular cell hyperplasia was observed in females with no corresponding carcinogenic response.

The increased incidence in hepatocellular neoplasms in the high-dose male mice (12/50, 16/48, 16/50, 19/49; Table C3) was marginal but statistically significant. The discussion of the morphological and biological progression of hepatocellular proliferative lesions in rats also applies to mice. The marginal increase in hepatocellular neoplasms was not considered to be associated with C.I. Pigment Red 3 administration for the following reasons: a) the occurrence of these neoplasms in male mice was highly variable; b) the incidence in the concurrent control group (24%) is slightly below that of the historical controls (29%) in NTP feed studies while the incidences in the low-and mid-dose groups were similar to the historical controls; also, the incidence in the high-dose group (38%) is only slightly above the historical rate and well within the range (10%-58%) in historical control groups; and c) only the incidence of adenomas increased; there was no increase in the incidence of carcinomas.

Ovarian infection has been observed in other NTP studies (Rao *et al*, 1987). In these studies, most mice died or were killed in moribund condition, indicating that this is a life shortening disease of aged $B6C3F_1$ mice. The incidence of lesions ranged from less than 1% to 70% in different studies. Of those animals from which the ovarian abscesses were cultured, many were positive for *Klebsiella spp.* Cultures were not done in these C.I. Pigment Red 3 studies. These organisms are usually considered to be opportunistic pathogens for laboratory mice. The abscesses may be the result of altered microbial status or other physiological changes (maybe immunological) secondary to the chemical, rather than a direct effect.

C.I. Pigment Red 3, with its aromatic nitro group and diazo bond, is structurally alerting for DNA reactivity (Tennant and Ashby, 1991) and is

mutagenic in *Salmonella typhimurium* in the presence of S9 activation enzymes (Mortelmans *et al.*, 1986). The positive results in *S. typhimurium* are highly predictive of carcinogenicity (89% of chemicals mutagenic to *S. typhimurium* are carcinogenic in rodents) based on the detailed analysis of the NTP genetic toxicity testing database conducted by Tennant *et al.* (1987), and are in accord with the results of this bioassay, where tumor induction was noted in 3 of 4 treatment groups. C.I. Pigment Red 3 can, therefore, be considered a genotoxic carcinogen, as was predicted by Tennant *et al.* (1990) prior to the completion of the bioassay.

Conclusions: Under the conditions of these 2-year feed studies, there was *some evidence of carcinogenic activity** of C.I. Pigment Red 3 in male F344/N rats as exhibited by increased incidences of benign pheochromocytomas of the adrenal gland. The marginal increase in the incidences of squamous cell papillomas of the skin and Zymbal's gland carcinomas may have been related to C.I. Pigment Red 3 administration. There was *some evidence of carcinogenic activity* of C.I. Pigment Red 3 in female F344/N rats as indicated by the increased incidence of hepatocellular adenomas. There was *some evidence of carcinogenic activity* of C.I. Pigment Red 3 in male B6C3F$_1$ mice as exhibited by the increased incidences of tubule adenomas of the renal cortex and follicular cell adenomas of the thyroid gland. There was *no evidence of carcinogenic activity* of C.I. Pigment Red 3 in female B6C3F$_1$ mice that received 12,500, 25,000, or 50,000 ppm.

The incidences of mononuclear cell leukemia and preputial gland tumors in male rats and mononuclear cell leukemia, mammary gland fibroadenoma, and clitoral gland tumors in female rats were lower in the exposed groups. The incidences of liver foci were markedly increased in exposed male and female rats. The severity of chronic nephropathy was increased in male rats and to a lesser extent in female rats given C.I. Pigment Red 3. An increase in the severity of nephropathy was observed in male and female mice; cytomegaly (karyomegaly) of renal tubule epithelium was observed in male mice. Thyroid follicular cell hyperplasia occurred with an increased incidence in male and female mice receiving C.I. Pigment Red 3.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR FEED STUDY OF C.I. PIGMENT RED 3

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3[a]

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-month interim evaluation[b]	10	10	10	10
Early deaths				
Natural death	5	3	6	5
Moribund	17	7	16	25
Survivors				
Terminal sacrifice	28	40	28	20
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(49)	(10)	(19)	(50)
Polyp adenomatous				1 (2%)
Intestine large, colon	(50)	(10)	(22)	(50)
Osteosarcoma, metastatic, bone				1 (2%)
Polyp adenomatous			1 (5%)	
Intestine small, duodenum	(50)	(9)	(21)	(50)
Osteosarcoma, metastatic, bone				1 (2%)
Intestine small, ileum	(50)	(9)	(19)	(49)
Intestine small, jejunum	(50)	(10)	(20)	(49)
Leiomyosarcoma	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Carcinoma, metastatic, two, multiple, kidney				1 (2%)
Hepatocellular carcinoma			1 (2%)	
Hepatocellular adenoma		1 (2%)	3 (6%)	1 (2%)
Osteosarcoma, metastatic, bone				1 (2%)
Mesentery	(11)	(6)	(6)	(6)
Carcinoma, greater than five, metastatic, multiple, kidney				1 (17%)
Fibrosarcoma, metastatic, spleen	1 (9%)			
Hemangiosarcoma			1 (17%)	
Osteosarcoma, metastatic, bone				1 (17%)
Oral mucosa		(1)		
Gingival, squamous cell carcinoma		1 (100%)		
Pancreas	(50)	(50)	(49)	(50)
Carcinoma, metastatic, two, multiple, kidney				1 (2%)
Osteosarcoma, metastatic, bone				1 (2%)
Acinar cell, adenoma	1 (2%)	1 (2%)		
Salivary glands	(50)	(10)	(22)	(50)
Stomach, forestomach	(50)	(10)	(22)	(49)
Osteosarcoma, metastatic, bone				1 (2%)
Squamous cell carcinoma			1 (5%)	
Stomach, glandular	(50)	(10)	(22)	(49)
Tongue	(1)			
Papilloma squamous	1 (100%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3
(continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Cardiovascular System				
Heart	(50)	(11)	(27)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (4%)	
Carcinoma, metastatic, kidney				1 (2%)
Endocrine System				
Adrenal gland	(50)	(50)	(50)	(50)
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Adenoma		1 (2%)	1 (2%)	
Capsule, carcinoma, metastatic, two, multiple, kidney				1 (2%)
Capsule, osteosarcoma, metastatic, bone				1 (2%)
Adrenal gland, medulla	(50)	(50)	(50)	(50)
Pheochromocytoma malignant	6 (12%)	7 (14%)	9 (18%)	3 (6%)
Pheochromocytoma malignant, multiple			1 (2%)	1 (2%)
Pheochromocytoma benign	16 (32%)	11 (22%)	20 (40%)	22 (44%)
Pheochromocytoma benign, multiple	6 (12%)	18 (36%)	15 (30%)	12 (24%)
Islets, pancreatic	(50)	(50)	(49)	(50)
Adenoma	5 (10%)		2 (4%)	
Adenoma, multiple			1 (2%)	
Pituitary gland	(50)	(16)	(25)	(50)
Pars distalis, adenoma	17 (34%)	9 (56%)	8 (32%)	12 (24%)
Pars distalis, carcinoma		1 (6%)		
Pars distalis, carcinoma, metastatic, Zymbal's gland			1 (4%)	
Pars intermedia, carcinoma, metastatic, Zymbal's gland			1 (4%)	
Pars nervosa, carcinoma, metastatic, Zymbal's gland			1 (4%)	
Thyroid gland	(50)	(11)	(23)	(50)
C-cell, adenoma	4 (8%)			4 (8%)
C-cell, carcinoma	2 (4%)	1 (9%)		1 (2%)
Follicular cell, adenoma				1 (2%)
Follicular cell, adenoma, cystic	1 (2%)			
Follicular cell, adenoma, cystic, papillary			1 (4%)	
Follicular cell, carcinoma	1 (2%)		1 (4%)	2 (4%)
General Body System				
None				

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3
(continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Genital System				
Epididymis	(50)	(10)	(23)	(50)
Preputial gland	(49)	(13)	(25)	(50)
Adenoma	6 (12%)		1 (4%)	1 (2%)
Carcinoma	1 (2%)			
Prostate	(50)	(10)	(22)	(50)
Carcinoma, metastatic, kidney				1 (2%)
Seminal vesicle	(50)	(11)	(22)	(50)
Carcinoma, metastatic, kidney				1 (2%)
Osteosarcoma, metastatic, bone				1 (2%)
Testes	(50)	(49)	(48)	(50)
Interstitial cell, adenoma	6 (12%)	12 (24%)	6 (13%)	12 (24%)
Interstitial cell, adenoma, multiple	41 (82%)	35 (71%)	39 (81%)	37 (74%)
Hematopoietic System				
Bone marrow	(50)	(10)	(22)	(49)
Lymph node	(50)	(50)	(50)	(50)
Axillary, basosquamous tumor malignant, metastatic, skin			1 (2%)	
Axillary, osteosarcoma, metastatic, bone			1 (2%)	
Mediastinal, basosquamous tumor malignant, metastatic, skin			1 (2%)	
Mediastinal, carcinoma, metastatic, two, multiple, kidney				1 (2%)
Pancreatic, squamous cell carcinoma, metastatic, stomach			1 (2%)	
Lymph node, mandibular	(48)	(50)	(50)	(50)
Carcinoma, metastatic, Zymbal's gland			1 (2%)	
Spleen	(50)	(50)	(50)	(49)
Carcinoma, metastatic, two, multiple, kidney				1 (2%)
Fibrosarcoma	1 (2%)			1 (2%)
Hemangiosarcoma	1 (2%)	2 (4%)	1 (2%)	
Osteosarcoma, metastatic, bone				1 (2%)
Thymus	(44)	(10)	(19)	(49)
Epithelial cell, thymoma benign	1 (2%)			
Integumentary System				
Mammary gland	(50)	(13)	(24)	(48)
Adenocarcinoma	1 (2%)			
Fibroadenoma	2 (4%)		1 (4%)	2 (4%)
Fibroadenoma, multiple	1 (2%)			
Skin	(50)	(31)	(47)	(50)
Basal cell adenoma	1 (2%)	2 (6%)	1 (2%)	
Basosquamous tumor malignant			1 (2%)	
Carcinoma	1 (2%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Integumentary System (continued)				
Skin (continued)				
Keratoacanthoma	2 (4%)		2 (4%)	2 (4%)
Papilloma squamous		4 (13%)	2 (4%)	6 (12%)
Trichoepithelioma	1 (2%)	1 (3%)		
Subcutaneous tissue, fibroma	4 (8%)		2 (4%)	4 (8%)
Subcutaneous tissue, fibrosarcoma	2 (4%)	2 (6%)		
Subcutaneous tissue, lipoma	1 (2%)			
Subcutaneous tissue, osteosarcoma	1 (2%)		1 (2%)	
Subcutaneous tissue, sarcoma	1 (2%)			
Subcutaneous tissue, schwannoma benign				1 (2%)
Musculoskeletal System				
Bone	(50)	(10)	(22)	(50)
Osteosarcoma			1 (5%)	1 (2%)
Skeletal muscle		(1)		(1)
Diaphragm, osteosarcoma, metastatic, bone				1 (100%)
Nervous System				
Brain	(50)	(11)	(22)	(50)
Astrocytoma malignant	1 (2%)		1 (5%)	
Carcinoma, metastatic, pituitary gland		1 (9%)		
Carcinoma, greater than five, metastatic, multiple, Zymbal's gland			1 (5%)	
Glioma malignant			1 (5%)	
Meningioma malignant		1 (9%)		
Spinal cord		(1)		
Chordoma		1 (100%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		2 (4%)		2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)		1 (2%)	
Basosquamous tumor malignant, greater than five, metastatic, multiple, skin			1 (2%)	
Carcinoma, greater than five, metastatic, multiple, kidney				1 (2%)
Carcinoma, greater than five, metastatic, multiple, Zymbal's gland			1 (2%)	1 (2%)
Chordoma, metastatic		1 (2%)		
Osteosarcoma, greater than five, metastatic, multiple, bone			1 (2%)	
Pheochromocytoma malignant, greater than five, metastatic, multiple, adrenal gland			1 (2%)	
Schwannoma malignant, three, metastatic, multiple, ear		1 (2%)		
Nose	(50)	(10)	(22)	(50)
Papilloma				1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3
(continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Special Senses System				
Ear		(2)		(2)
Schwannoma benign				2 (100%)
Schwannoma malignant		1 (50%)		
Zymbal's gland			(2)	(3)
Carcinoma			2 (100%)	3 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Carcinoma	1 (2%)			
Renal tubule, adenoma		1 (2%)	1 (2%)	
Renal tubule, carcinoma				1 (2%)
Renal tubule, oncocytoma benign			1 (2%)	
Transitional epithelium, carcinoma				1 (2%)
Systemic Lesions				
Multiple organs[c]	(50)	(50)	(50)	(50)
Leukemia mononuclear	22 (44%)	6 (12%)	2 (4%)	1 (2%)
Mesothelioma malignant	3 (6%)	1 (2%)	2 (4%)	3 (6%)
Tumor Summary				
Total animals with primary neoplasms[d]	49	50	50	50
Total primary neoplasms	164	122	135	141
Total animals with benign neoplasms	49	50	50	49
Total benign neoplasms	117	98	108	123
Total animals with malignant neoplasms	32	22	22	16
Total malignant neoplasms	47	24	27	18
Total animals with secondary neoplasms[e]	1	3	5	3
Total secondary neoplasms	1	3	14	21

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Each dosed group contains one animal that died or was sacrificed moribund prior to the interim scheduled sacrifice
[c] Number of animals with any tissue examined microscopically
[d] Primary tumors: all tumors except metastatic tumors
[e] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm

Number of Days on Study	5 3 4	5 5 3	5 8 7	6 1 0	6 1 1	6 3 7	6 4 4	6 5 3	6 5 8	6 5 8	6 6 0	6 6 3	6 6 6	6 6 6	6 6 6	6 8 1	6 9 0	7 0 0	7 0 0	7 0 6	7 1 6	7 2 1	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 4 1	0 5 1	0 8 1	0 2 1	1 5 2	0 1 1	0 5 3	0 3 1	0 3 2	0 8 2	0 5 4	0 9 1	0 1 1	0 2 2	0 4 2	0 8 3	0 6 1	1 1 2	0 0 2	0 2 3	0 6 2	0 7 1	0 1 3	0 1 4	0 1 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+					+						+						+						
Fibrosarcoma, metastatic, spleen																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Papilloma squamous																									
Tooth																						+			
Cardiovascular System																									
Blood vessel											+														
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant															X							X			
Pheochromocytoma benign								X		X	X								X		X	X		X	
Pheochromocytoma benign, multiple														X			X								X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma	X			X																					
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 2 4	0 2 5	0 3 3	0 3 4	0 3 5	0 4 3	0 4 4	0 4 5	0 5 5	0 6 3	0 6 4	0 6 5	0 7 2	0 7 3	0 7 4	0 7 5	0 8 4	0 8 5	0 9 2	1 0 3	0 9 3	0 9 4	0 9 5	1 0 4	1 0 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma										X																1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery			+			+			+		+						+		+						+	11
Fibrosarcoma, metastatic, spleen																									X	1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell, adenoma															X											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue										+																1
Papilloma squamous										X																1
Tooth																										1
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant										X				X				X							X	6
Pheochromocytoma benign			X			X				X			X	X			X	X		X		X				16
Pheochromocytoma benign, multiple								X			X								X							6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X													X	X										5
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	48

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	5 3 4	5 5 3	5 8 7	6 1 0	6 1 1	6 3 7	6 4 4	6 5 3	6 5 8	6 5 8	6 6 0	6 6 3	6 6 6	6 6 6	6 6 6	6 8 1	6 9 0	7 0 0	7 0 0	7 0 6	7 1 6	7 2 1	7 2 9	7 2 9
Carcass ID Number	0 4 1	0 5 1	0 8 1	0 2 1	0 5 2	1 0 1	0 5 3	0 3 1	0 3 2	0 8 2	0 5 4	0 9 1	0 1 1	0 2 2	0 4 2	0 8 3	0 6 1	0 1 2	1 0 2	0 2 3	0 6 2	0 7 1	0 1 3	0 1 4	0 1 5
Endocrine System (continued)																								
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X		X		X		X			X				X				X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma				X										X											
C-cell, carcinoma														X											
Follicular cell, adenoma, cystic																			X						
Follicular cell, carcinoma																									X
General Body System																									
None																									
Genital System																									
Coagulating gland											+														
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X								X		X						
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma		X	X								X	X							X						
Interstitial cell, adenoma, multiple	X			X	X		X	X	X	X			X	X			X	X		X	X	X	X	X	X
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Hemangiosarcoma			X																						
Thymus	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Epithelial cell, thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Fibroadenoma																							X		
Fibroadenoma, multiple																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 2 4	0 2 5	0 3 3	0 3 4	0 3 5	0 4 3	0 4 4	0 4 5	0 5 5	0 6 3	0 6 4	0 6 5	0 7 2	0 7 3	0 7 4	0 7 5	0 8 4	0 8 5	0 9 2	1 0 3	0 9 3	0 9 4	0 9 5	1 0 4	1 0 5	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X					X			X	X		X				X	X			X			X		17
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X			X																						4
C-cell, carcinoma														X												2
Follicular cell, adenoma, cystic																										1
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X											X			X										6
Carcinoma									X																	1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma											X															6
Interstitial cell, adenoma, multiple	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	41
Hematopoietic System																										
Blood														+												1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+		+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																									X	1
Hemangiosarcoma																										1
Thymus	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Epithelial cell, thymoma benign									X																	1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																					X					1
Fibroadenoma																			X							2
Fibroadenoma, multiple														X												1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	5 3 4	5 5 3	5 8 7	6 1 0	6 1 1	6 3 7	6 4 4	6 5 3	6 5 8	6 5 8	6 6 0	6 6 3	6 6 6	6 6 6	6 6 6	6 8 1	6 9 0	7 0 0	7 0 0	7 0 6	7 1 6	7 2 1	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 4 1	0 5 1	0 8 1	0 2 1	0 5 2	1 0 1	0 5 3	0 3 1	0 3 2	0 8 2	0 5 4	0 9 1	0 1 1	0 2 2	0 4 2	0 8 3	0 6 1	1 1 2	0 0 2	0 2 3	0 6 2	0 6 1	1 9 3	1 9 4	1 9 5
Integumentary System (continued)																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																				X					
Carcinoma							X																		
Keratoacanthoma												X													
Trichoepithelioma																									
Subcutaneous tissue, fibroma								X									X								
Subcutaneous tissue, fibrosarcoma										X															
Subcutaneous tissue, lipoma																							X		
Subcutaneous tissue, osteosarcoma																	X								
Subcutaneous tissue, sarcoma																						X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye							+																		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma												X													
Urethra									+		+														
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X		X	X				X			X		X	X	X	X	X				
Mesothelioma malignant		X											X												

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	0 2 4	0 2 5	0 3 3	0 3 4	0 3 5	0 4 3	0 4 4	0 4 5	0 5 5	0 6 3	0 6 4	0 6 5	0 7 2	0 7 3	0 7 4	0 7 5	0 8 4	0 8 5	0 9 2	1 0 3	0 9 3	0 9 4	0 9 5	1 0 4	1 0 5	**Total Tissues/ Tumors**
Integumentary System (continued)																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Carcinoma																										1
Keratoacanthoma														X												2
Trichoepithelioma										X																1
Subcutaneous tissue, fibroma						X														X						4
Subcutaneous tissue, fibrosarcoma																				X						2
Subcutaneous tissue, lipoma																										1
Subcutaneous tissue, osteosarcoma																										1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant													X													1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye			+	+	+	+	+	+			+		+	+	+				+			+	+		+	15
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Urethra																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X			X	X		X	X	X	X	X		X	X	X	22
Mesothelioma malignant																			X							3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 6,000 ppm

Number of Days on Study	4 2 0	5 8 1	6 0 5	6 1 0	6 1 6	6 2 4	6 5 1	6 6 0	6 9 4	6 9 6	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	3 7 1	4 6 1	4 3 1	3 9 1	3 8 1	4 4 1	4 0 1	4 4 2	4 3 2	4 2 1	4 1 1	3 7 2	3 7 3	3 7 4	3 7 5	3 8 2	3 8 3	3 8 4	3 8 5	3 9 2	3 9 3	3 9 4	3 9 5	4 0 2	4 0 3
Alimentary System																									
Esophagus	M	+	+	+	+	+	+	+	+	+															
Intestine large	+	+	+	+	+	+	+	+	+	+															
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+															
Intestine large, colon	+	+	+	+	+	+	+	+	+	+															
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+															
Intestine small	+	+	+	+	+	+	+	+	+	+															
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+															
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+															
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+															
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery																									
Oral mucosa																									
Gingival, squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+															
Stomach	+	+	+	+	+	+	+	+	+	+															
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+															
Stomach, glandular	+	+	+	+	+	+	+	+	+	+															
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+															
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant								X					X											X	
Pheochromocytoma benign			X		X								X				X					X		X	
Pheochromocytoma benign, multiple							X		X		X	X				X			X						X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+														
Pituitary gland	M	+	+	+	+	+	+	+	+	+		+	+			+			+				+		
Pars distalis, adenoma		X			X	X				X		X	X										X		
Pars distalis, carcinoma																			X						
Thyroid gland	+	+	+	+	+	+	+	+	+	+															
C-cell, carcinoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 6,000 ppm
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	4 0 4	4 0 5	4 1 2	4 1 3	4 1 4	4 1 5	4 2 2	4 2 3	4 2 4	4 2 5	4 3 3	4 3 4	4 3 5	4 4 3	4 4 4	4 4 5	4 5 1	4 5 2	4 5 3	4 5 4	4 5 5	4 6 2	4 6 3	4 6 4	4 6 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus																										9
Intestine large																										10
Intestine large, cecum																										10
Intestine large, colon																										10
Intestine large, rectum																										10
Intestine small																										10
Intestine small, duodenum																										9
Intestine small, ileum																										9
Intestine small, jejunum																										10
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																							X			1
Mesentery			+						+						+	+	+	+								6
Oral mucosa																						+				1
Gingival, squamous cell carcinoma																						X				1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell, adenoma										X																1
Salivary glands																										10
Stomach																										10
Stomach, forestomach																										10
Stomach, glandular																										10
Cardiovascular System																										
Heart															+											11
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant							X									X							X		X	7
Pheochromocytoma benign												X				X	X				X		X			11
Pheochromocytoma benign, multiple	X	X	X	X				X	X	X	X			X	X									X		18
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland																	+									12
Pituitary gland													+						+							16
Pars distalis, adenoma													X						X							9
Pars distalis, carcinoma																										1
Thyroid gland											+															11
C-cell, carcinoma											X															1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 6,000 ppm
(continued)

Number of Days on Study	4 2 0	5 8 1	6 0 5	6 1 0	6 1 6	6 2 4	6 5 1	6 6 0	6 9 4	6 9 6	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	3 7 1	4 6 1	4 3 1	3 9 1	3 8 1	4 4 1	4 0 1	4 4 2	4 3 2	4 2 1	4 1 1	3 7 2	3 7 3	3 7 4	3 7 5	3 8 2	3 8 3	3 8 4	3 8 5	3 9 2	3 9 3	3 9 4	3 9 5	4 0 2	4 0 3
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+															
Preputial gland	+	+	+	+	+	+	+	+	+	+						+									
Prostate	+	+	+	+	+	+	+	+	+	+															
Seminal vesicle	+	+	+	+	+	+	+	+	+	+															
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma	X		X			X			X		X		X				X								
Interstitial cell, adenoma, multiple				X	X		X	X				X		X	X	X		X	X	X	X	X	X	X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+															
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X											X										
Thymus	+	+	+	+	+	+	+	+	+	+															
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+		+												+	
Skin	+	+	+	+	+	+	+	+	+	+	+			+			+	+	+		+	+	+	+	+
Basal cell adenoma																									
Papilloma squamous																					X		X		
Trichoepithelioma											X														
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+															
Skeletal muscle			+																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+								+							
Carcinoma, metastatic, pituitary gland																		X							
Meningioma malignant			X																						
Spinal cord														+											
Chordoma														X											

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 6,000 ppm
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	4 0 4	4 0 5	4 1 2	4 1 3	4 1 4	4 1 5	4 2 2	4 2 3	4 2 4	4 2 5	4 3 3	4 3 4	4 3 5	4 4 3	4 4 4	4 4 5	4 5 1	4 5 2	4 5 3	4 5 4	4 5 5	4 6 2	4 6 3	4 6 4	4 6 5	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Epididymis																										10
Preputial gland						+								+												13
Prostate																										10
Seminal vesicle														+												11
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell, adenoma	X	X												X	X				X							12
Interstitial cell, adenoma, multiple			X	X	X	X	X	X	X	X	X	X	X			X	X	X	X		X	X	X	X	X	X	35
Hematopoietic System																										
Bone marrow																										10
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Thymus																										10
Integumentary System																										
Mammary gland														+												13
Skin	+	+	+		+	+				+	+	+				+	+		+							31
Basal cell adenoma		X																	X							2
Papilloma squamous					X	X																				4
Trichoepithelioma																										1
Subcutaneous tissue, fibrosarcoma			X								X															2
Musculoskeletal System																										
Bone																										10
Skeletal muscle																										1
Nervous System																										
Brain																										11
Carcinoma, metastatic, pituitary gland																										1
Meningioma malignant																										1
Spinal cord																										1
Chordoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 6,000 ppm
(continued)

Number of Days on Study	4 2 0	5 8 1	6 0 5	6 1 0	6 1 6	6 2 4	6 5 1	6 6 0	6 9 4	6 9 6	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	3 7 1	4 6 1	4 3 1	3 9 1	3 8 1	4 4 1	4 0 1	4 4 2	4 3 2	4 2 1	4 1 1	3 7 2	3 7 3	3 7 4	3 7 5	3 8 2	3 8 3	3 8 4	3 8 5	3 9 2	3 9 3	3 9 4	3 9 5	4 0 2	4 0 3
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X																								
Chordoma, metastatic														X											
Schwannoma malignant, three, metastatic, multiple, ear										X															
Nose	+	+	+	+	+	+	+	+	+	+															
Trachea	+	+	+	+	+	+	+	+	+	+															
Special Senses System																									
Ear										+													+		
Schwannoma malignant										X															
Eye				+					+											+	+	+	+	+	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma							X																		
Urinary bladder	+	+	+	+	+	+	+	+	+	+															
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X				X	X					X													
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 6,000 ppm
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	4 0 4	4 0 5	4 1 2	4 1 3	4 1 4	4 1 5	4 2 2	4 2 3	4 2 4	4 2 5	4 3 3	4 3 4	4 3 5	4 4 3	4 4 4	4 4 5	4 5 1	4 5 2	4 5 3	4 5 4	4 5 5	4 6 2	4 6 3	4 6 4	4 6 5	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X																			2
Chordoma, metastatic																										1
Schwannoma malignant, three, metastatic, multiple, ear																										1
Nose																										10
Trachea																										10
Special Senses System																										
Ear							M																			2
Schwannoma malignant																										1
Eye	+	+															+	+	+	+	+	+	+			16
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Urinary bladder			+																							11
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																X										6
Mesothelioma malignant																		X								1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm

Number of Days on Study	5 2 9	5 4 0	5 7 5	5 7 6	5 7 6	5 7 8	5 9 8	6 1 0	6 4 1	6 8 2	6 8 2	6 8 7	6 9 0	6 9 5	7 0 7	7 0 8	7 0 8	7 1 0	7 1 0	7 1 4	7 1 8	7 2 2	7 3 0	7 3 0	7 3 0
Carcass ID Number	2 9 1	2 5 1	3 2 1	2 5 2	2 8 1	3 2 2	2 6 1	3 3 1	3 0 1	2 8 2	3 3 2	2 7 1	2 9 2	2 5 3	3 1 1	2 9 3	3 4 1	2 7 2	3 4 2	4 4 3	3 7 3	2 8 3	2 5 4	2 5 5	2 6 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	A	+	+			
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Polyp adenomatous							X																		
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	A	+	+			
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+			
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																						X			
Hepatocellular adenoma																									
Mesentery											+	+						+							
Hemangiosarcoma																									
Pancreas	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Squamous cell carcinoma														X											
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Cardiovascular System																									
Blood vessel									+						+			+	+		+				
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Alveolar/bronchiolar carcinoma, metastatic, lung							X																		
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant	X								X		X	X		X							X			X	X
Pheochromocytoma malignant, multiple																X									
Pheochromocytoma benign	X							X	X		X	X					X				X			X	X
Pheochromocytoma benign, multiple							X			X			X							X			X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 6 3	2 6 4	2 6 5	2 7 4	2 7 5	2 8 4	2 8 5	2 9 4	2 9 5	3 0 2	3 0 3	3 0 4	3 0 5	3 1 2	3 1 3	3 1 4	3 1 5	3 2 3	3 2 4	3 2 5	3 3 3	3 3 4	3 3 5	3 4 4	3 4 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus																										22
Intestine large																										22
Intestine large, cecum																										19
Intestine large, colon																										22
Polyp adenomatous																										1
Intestine large, rectum																										22
Intestine small																										22
Intestine small, duodenum																										21
Intestine small, ileum																										19
Intestine small, jejunum																										20
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Hepatocellular adenoma										X												X	X			3
Mesentery					+											+							+			6
Hemangiosarcoma					X																					1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands																										22
Stomach																										22
Stomach, forestomach																										22
Squamous cell carcinoma																										1
Stomach, glandular																										22
Cardiovascular System																										
Blood vessel																										5
Heart										+		+					+			+	+					27
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																	X									9
Pheochromocytoma malignant, multiple																										1
Pheochromocytoma benign	X		X					X	X	X		X	X			X	X							X	X	20
Pheochromocytoma benign, multiple				X		X	X				X				X			X	X	X	X	X				15

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	5 2 9	5 4 0	5 7 5	5 7 6	5 7 6	5 7 8	5 9 8	6 1 0	6 4 1	6 8 2	6 8 2	6 8 7	6 9 0	6 9 5	7 0 7	7 0 8	7 0 8	7 1 0	7 1 0	7 1 4	7 1 8	7 2 2	7 3 0	7 3 0	7 3 0
Carcass ID Number	2 9 1	2 5 1	3 2 1	2 5 2	2 8 1	3 2 2	2 6 1	3 3 1	3 0 1	2 8 2	3 3 2	2 7 1	2 9 2	2 5 3	3 1 1	2 9 3	3 4 1	2 7 2	3 4 2	3 4 3	2 7 3	2 8 3	2 5 4	2 5 5	2 6 2
Endocrine System (continued)																									
Islets, pancreatic	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X																					
Adenoma, multiple																								X	
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	M	+	+	+	+			
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	
Pars distalis, adenoma	X				X					X								X	X		X			X	
Pars distalis, carcinoma, metastatic, Zymbal's gland				X																					
Pars intermedia, carcinoma, metastatic, Zymbal's gland				X																					
Pars nervosa, carcinoma, metastatic, Zymbal's gland				X																					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Follicular cell, adenoma, cystic, papillary																									
Follicular cell, carcinoma												X													
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma									X	X								X							
Interstitial cell, adenoma, multiple		X	X			X	X	X			X	X	X	X	X	X	X		X	X	X	X	X	X	X
Hematopoietic System																									
Blood							+																		
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, basosquamous tumor malignant, metastatic, skin										X															
Axillary, osteosarcoma, metastatic, bone										X															
Mediastinal, basosquamous tumor malignant, metastatic, skin										X															
Pancreatic, squamous cell carcinoma, metastatic, stomach														X											

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 6 3	2 6 4	2 6 5	2 7 4	2 7 5	2 8 4	2 8 5	2 9 4	2 9 5	3 0 2	3 0 3	3 0 4	3 0 5	3 1 2	3 1 3	3 1 4	3 1 5	3 2 3	3 2 4	3 2 5	3 3 3	3 3 4	3 3 5	3 4 4	3 4 5	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																				X						2
Adenoma, multiple																										1
Parathyroid gland			+																							21
Pituitary gland																		+			+					25
Pars distalis, adenoma																		X								8
Pars distalis, carcinoma, metastatic, Zymbal's gland																										1
Pars intermedia, carcinoma, metastatic, Zymbal's gland																										1
Pars nervosa, carcinoma, metastatic, Zymbal's gland																										1
Thyroid gland										+																23
Follicular cell, adenoma, cystic, papillary										X																1
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Epididymis																+										23
Preputial gland		+						+							+											25
Adenoma															X											1
Prostate																										22
Seminal vesicle																										22
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+		48
Interstitial cell, adenoma		X				X												X								6
Interstitial cell, adenoma, multiple	X		X	X	X		X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	39
Hematopoietic System																										
Blood																										1
Bone marrow																										22
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Axillary, basosquamous tumor malignant, metastatic, skin																										1
Axillary, osteosarcoma, metastatic, bone																										1
Mediastinal, basosquamous tumor malignant, metastatic, skin																										1
Pancreatic, squamous cell carcinoma, metastatic, stomach																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	5 2 9	5 4 0	5 7 5	5 7 6	5 7 6	5 7 8	5 9 8	6 1 0	6 4 1	6 8 2	6 8 2	6 8 7	6 9 0	6 9 5	7 0 7	7 0 8	7 0 8	7 1 0	7 1 0	7 1 4	7 1 8	7 2 2	7 3 0	7 3 0	7 3 0
Carcass ID Number	2 9 1	2 5 1	3 2 1	2 5 2	2 8 1	3 2 2	2 6 1	3 3 1	3 0 1	2 8 2	3 3 2	2 7 1	2 9 2	2 5 3	3 1 1	2 9 3	3 4 1	2 7 2	3 4 2	3 4 3	2 7 3	2 8 3	2 5 4	2 5 5	2 6 2
Hematopoietic System (continued)																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland				X																					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+			
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Fibroadenoma																X									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Basal cell adenoma																									
Basosquamous tumor malignant										X															
Keratoacanthoma																									
Papilloma squamous									X																
Subcutaneous tissue, fibroma												X		X											
Subcutaneous tissue, osteosarcoma										X															
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Osteosarcoma							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Astrocytoma malignant													X												
Carcinoma, greater than five, metastatic, multiple, Zymbal's gland				X																					
Glioma malignant		X																							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma							X																		
Basosquamous tumor malignant, greater than five, metastatic, multiple, skin										X															
Carcinoma, greater than five, metastatic, multiple, Zymbal's gland				X																					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 6 3	2 6 4	2 6 5	2 7 4	2 7 5	2 8 4	2 8 5	2 9 4	2 9 5	3 0 2	3 0 3	3 0 4	3 0 5	3 1 2	3 1 3	3 1 4	3 1 5	3 2 3	3 2 4	3 2 5	3 3 3	3 3 4	3 3 5	3 4 4	3 4 5	**Total Tissues/ Tumors**
Hematopoietic System (continued)																										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma		X																								1
Thymus																										19
Integumentary System																										
Mammary gland						+																	+			24
Fibroadenoma																										1
Skin	+	+		+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	47
Basal cell adenoma				X																						1
Basosquamous tumor malignant																										1
Keratoacanthoma												X													X	2
Papilloma squamous															X											2
Subcutaneous tissue, fibroma																										2
Subcutaneous tissue, osteosarcoma																										1
Musculoskeletal System																										
Bone																										22
Osteosarcoma																										1
Nervous System																										
Brain																										22
Astrocytoma malignant																										1
Carcinoma, greater than five, metastatic, multiple, Zymbal's gland																										1
Glioma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Basosquamous tumor malignant, greater than five, metastatic, multiple, skin																										1
Carcinoma, greater than five, metastatic, multiple, Zymbal's gland																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	5 2 9	5 4 0	5 7 5	5 7 6	5 7 6	5 7 8	5 9 8	6 1 0	6 4 1	6 8 2	6 8 2	6 8 7	6 9 0	6 9 5	7 0 7	7 0 8	7 0 8	7 1 0	7 1 0	7 1 4	7 1 8	7 2 2	7 3 0	7 3 0	7 3 0
Carcass ID Number	2 9 1	2 5 1	3 2 1	2 5 2	2 8 1	3 2 2	2 6 1	3 3 1	3 0 1	2 8 2	3 3 2	2 7 1	2 9 2	2 5 3	3 1 1	2 9 3	3 1 1	2 4 2	3 7 2	2 4 2	3 4 3	3 7 3	2 8 3	2 5 4	2 5 5	2 6 2
Respiratory System (continued)																									
Lung (continued)																									
Osteosarcoma, greater than five, metastatic, multiple, bone							X																		
Pheochromocytoma malignant, greater than five, metastatic, multiple, adrenal gland											X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Special Senses System																									
Eye				+		+					+	+					+				+	+		+	
Zymbal's gland			+	+																					
Carcinoma			X	X																					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																					X				
Renal tubule, oncocytoma benign																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Mesothelioma malignant											X														

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 6 3	2 6 4	2 6 5	2 7 4	2 7 5	2 8 4	2 8 5	2 9 4	2 9 5	3 0 2	3 0 3	3 0 4	3 0 5	3 1 2	3 1 3	3 1 4	3 1 5	3 2 3	3 2 4	3 2 5	3 3 4	3 3 5	3 4 4	3 4 5		**Total Tissues/ Tumors**
Respiratory System (continued)																										
Lung (continued)																										
Osteosarcoma, greater than five, metastatic, multiple, bone																										1
Pheochromocytoma malignant, greater than five, metastatic, multiple, adrenal gland																										1
Nose																										22
Trachea																										22
Special Senses System																										
Eye				+	+	+	+														+	+	+			15
Zymbal's gland																										2
Carcinoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Renal tubule, oncocytoma benign													X													1
Urinary bladder																										22
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear															X											2
Mesothelioma malignant																X										2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm

Number of Days on Study	4 8 6	5 6 7	5 7 7	5 8 1	6 0 5	6 1 2	6 1 2	6 2 4	6 2 6	6 4 3	6 5 5	6 5 8	6 5 8	6 6 6	6 7 8	6 7 9	6 8 0	6 8 1	6 8 2	6 9 0	6 9 0	6 9 4	7 0 8	7 1 0	7 1 0
Carcass ID Number	1 3 1	1 8 1	1 7 1	2 0 1	2 1 1	1 7 2	2 0 2	2 0 3	1 4 1	1 8 2	1 7 3	2 0 4	2 2 1	1 9 1	2 2 2	1 8 3	1 3 2	1 7 4	1 8 4	1 4 2	1 6 1	1 2 3	2 7 5	1 3 3	1 1 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous					X																				
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone												X													
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone												X													
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, two, multiple, kidney																									
Hepatocellular adenoma						X																			
Osteosarcoma, metastatic, bone												X													
Mesentery												+								+					+
Carcinoma, greater than five, metastatic, multiple, kidney																									
Osteosarcoma, metastatic, bone												X													
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, two, multiple, kidney																									
Osteosarcoma, metastatic, bone												X													
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone												X													
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel		+	+															+	+		+			+	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	7 1 6	7 1 8	7 1 8	7 2 3	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 6 2	1 5 1	2 2 4	1 5 2	1 9 2	1 5 3	1 9 3	1 9 4	2 2 5	1 3 4	1 3 5	1 4 3	1 4 4	1 4 5	1 5 4	1 5 5	1 6 3	1 6 4	1 6 5	1 8 5	1 9 5	2 0 5	2 1 3	2 1 4	2 1 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Intestine small, ileum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, two, multiple, kidney			X																							1
Hepatocellular adenoma																										1
Osteosarcoma, metastatic, bone																										1
Mesentery			+								+					+										6
Carcinoma, greater than five, metastatic, multiple, kidney			X																							1
Osteosarcoma, metastatic, bone																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, two, multiple, kidney			X																							1
Osteosarcoma, metastatic, bone																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Osteosarcoma, metastatic, bone																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Cardiovascular System																										
Blood vessel																						+				7
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney			X																							1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	4 8 6	5 6 7	5 7 7	5 8 1	6 0 5	6 1 2	6 1 2	6 2 4	6 2 6	6 4 3	6 5 5	6 5 8	6 5 8	6 6 6	6 7 8	6 7 9	6 8 0	6 8 1	6 8 2	6 9 0	6 9 0	6 9 4	7 0 8	7 1 0	7 1 0
Carcass ID Number	1 3 1	1 8 1	1 7 1	2 0 1	2 1 1	1 7 2	2 0 2	2 0 3	1 4 1	1 8 2	1 7 3	2 0 4	2 2 1	1 9 1	2 2 2	1 8 3	1 3 2	2 7 4	1 8 4	1 4 2	1 6 1	2 2 3	1 7 5	1 3 3	2 1 2
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, carcinoma, metastatic, two, multiple, kidney																									
Capsule, osteosarcoma, metastatic, bone												X													
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant				X												X									
Pheochromocytoma malignant, multiple		X																							
Pheochromocytoma benign	X			X	X	X					X		X	X		X	X					X	X	X	
Pheochromocytoma benign, multiple							X		X						X				X		X				X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X					X	X	X	X						X					X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma							X										X								
C-cell, carcinoma																						X			
Follicular cell, adenoma																									
Follicular cell, carcinoma									X							X									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney																									
Osteosarcoma, metastatic, bone												X													
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma	X		X	X				X	X	X	X														
Interstitial cell, adenoma, multiple					X	X	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematopoietic System																									
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, carcinoma, metastatic, two, multiple, kidney																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	7 1 6	7 1 8	7 1 8	7 2 3	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 6 2	1 5 1	2 2 4	1 5 2	1 9 2	1 5 3	1 9 3	1 9 4	1 2 5	1 3 4	1 3 5	1 4 3	1 4 4	1 4 5	1 5 4	1 5 5	1 6 3	1 6 4	1 6 5	1 8 5	1 9 5	2 0 5	2 1 3	2 1 4	2 1 5	**Total Tissues/ Tumors**
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, carcinoma, metastatic, two, multiple, kidney			X																							1
Capsule, osteosarcoma, metastatic, bone																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																		X								3
Pheochromocytoma malignant, multiple																										1
Pheochromocytoma benign	X		X				X			X				X	X					X		X	X		X	22
Pheochromocytoma benign, multiple				X	X	X		X	X															X		12
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X		X					X							X		X							12
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X															X										4
C-cell, carcinoma																										1
Follicular cell, adenoma			X																							1
Follicular cell, carcinoma																										2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney			X																							1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney			X																							1
Osteosarcoma, metastatic, bone																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma	X		X						X					X								X				12
Interstitial cell, adenoma, multiple		X		X	X	X	X	X		X	X	X	X		X	X	X	X	X	X	X		X	X	X	37
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, carcinoma, metastatic, two, multiple, kidney			X																							1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	4 8 6	5 6 7	5 7 7	5 8 1	6 0 5	6 1 2	6 1 2	6 2 4	6 2 6	6 4 3	6 5 5	6 5 8	6 5 8	6 6 6	6 7 8	6 7 9	6 8 0	6 8 1	6 8 2	6 9 0	6 9 0	6 9 4	7 0 8	7 1 0	7 1 0
Carcass ID Number	1 3 1	1 8 1	1 7 1	2 0 1	2 1 1	1 7 2	2 0 2	2 0 3	1 4 1	1 8 2	1 7 3	2 0 4	2 2 1	1 9 1	2 2 2	1 8 3	1 3 2	1 7 4	1 8 4	1 4 2	1 6 1	2 2 3	1 7 5	1 3 3	2 1 2
Hematopoietic System (continued)																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, two, multiple, kidney																									
Fibrosarcoma																									
Osteosarcoma, metastatic, bone												X													
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma					X																				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Papilloma squamous																X						X			
Subcutaneous tissue, fibroma				X																X					
Subcutaneous tissue, schwannoma benign																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma												X													
Skeletal muscle												+													
Diaphragm, osteosarcoma, metastatic, bone												X													
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, greater than five, metastatic, multiple, kidney																									
Carcinoma, greater than five, metastatic, multiple, Zymbal's gland								X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	7 1 6	7 1 8	7 1 8	7 2 3	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 6 2	1 5 1	2 2 4	1 5 2	1 9 2	1 5 3	1 9 3	1 9 4	2 2 5	1 3 4	1 3 5	1 4 3	1 4 4	1 4 5	1 5 4	1 5 5	1 6 3	1 6 4	1 6 5	1 8 5	1 9 5	2 0 5	2 1 3	2 1 4	2 1 5	**Total Tissues/ Tumors**
Hematopoietic System (continued)																										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, two, multiple, kidney			X																							1
Fibrosarcoma																					X					1
Osteosarcoma, metastatic, bone																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibroadenoma																									X	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma								X														X				2
Papilloma squamous												X								X	X		X			6
Subcutaneous tissue, fibroma	X				X																					4
Subcutaneous tissue, schwannoma benign																						X				1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																										1
Diaphragm, osteosarcoma, metastatic, bone																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X	X																				2
Carcinoma, greater than five, metastatic, multiple, kidney			X																							1
Carcinoma, greater than five, metastatic, multiple, Zymbal's gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma																	X									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	4	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7	
	8	6	7	8	0	1	1	2	2	4	5	5	5	6	7	7	8	8	8	9	9	9	0	1	
	6	7	7	1	5	2	2	4	6	3	5	8	8	6	8	9	0	1	2	0	0	4	8	0	
Carcass ID Number	1	1	1	2	2	1	2	2	1	1	1	2	2	1	2	1	1	1	1	1	1	2	1	1	
	3	8	7	0	1	7	0	0	4	8	7	0	2	9	2	8	3	7	8	4	6	2	7	3	
	1	1	1	1	1	2	2	3	1	2	3	4	1	1	2	3	2	4	4	2	1	3	5	3	
Special Senses System																									
Ear																							+		
Schwannoma benign																							X		
Eye																	+	+			+				
Zymbal's gland								+														+			
Carcinoma								X														X			
Urinary System																									
Kidney	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Renal tubule, carcinoma																									
Transitional epithelium, carcinoma			X																						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear												X													
Mesothelioma malignant																				X				X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	7 1 6	7 1 8	7 1 8	7 2 3	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	1 6 2	1 5 1	2 2 4	1 5 2	1 9 2	1 5 3	1 9 3	1 9 4	2 2 5	1 3 4	1 3 5	1 4 3	1 4 4	1 4 5	1 5 4	1 5 5	1 6 3	1 6 4	1 6 5	1 8 5	1 9 5	2 0 5	2 1 3	2 1 4	2 1 5	**Total Tissues/ Tumors**
Special Senses System																										
Ear														+												2
Schwannoma benign														X												2
Eye	+	+	+	+		+									+				+					+	+	12
Zymbal's gland		+																								3
Carcinoma		X																								3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, carcinoma			X																							1
Transitional epithelium, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Mesothelioma malignant											X															3

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	22/50 (44%)	29/50 (58%)	35/50 (70%)	34/50 (68%)
Adjusted rates[b]	60.2%	65.7%	89.3%	79.9%
Terminal rates[c]	14/28 (50%)	25/40 (63%)	24/28 (86%)	12/20 (60%)
First incidence (days)	653	605	529	486
Life table tests[d]	P≤0.001	P=0.527N	P=0.019	P=0.005
Logistic regression tests[d]	P=0.004	P=0.191	P=0.006	P=0.010
Cochran-Armitage test[d]	P=0.010			
Fisher exact test[d]		P=0.115	P=0.007	P=0.013
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rates	6/50 (12%)	7/50 (14%)	10/50 (20%)	4/50 (8%)
Adjusted rates	19.4%	17.0%	25.8%	11.5%
Terminal rates	4/28 (14%)	6/40 (15%)	3/28 (11%)	1/20 (5%)
First incidence (days)	666	660	529	567
Life table tests	P=0.553N	P=0.499N	P=0.247	P=0.498N
Logistic regression tests	P=0.318N	P=0.588	P=0.207	P=0.358N
Cochran-Armitage test	P=0.325N			
Fisher exact test		P=0.500	P=0.207	P=0.370N
Adrenal Medulla: Pheochromocytoma (Benign or Malignant)				
Overall rates	24/50 (48%)	32/50 (64%)	37/50 (74%)	36/50 (72%)
Adjusted rates	64.1%	71.0%	89.9%	82.8%
Terminal rates	15/28 (54%)	27/40 (68%)	24/28 (86%)	13/20 (65%)
First incidence (days)	653	605	529	486
Life table tests	P≤0.001	P=0.555N	P=0.025	P=0.005
Logistic regression tests	P=0.005	P=0.133	P=0.005	P=0.010
Cochran-Armitage test	P=0.010			
Fisher exact test		P=0.079	P=0.007	P=0.012
Liver: Hepatocellular Adenoma				
Overall rates	0/50 (0%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rates	0.0%	2.5%	10.7%	2.2%
Terminal rates	0/28 (0%)	1/40 (3%)	3/28 (11%)	0/20 (0%)
First incidence (days)	-[e]	729 (T)	729 (T)	612
Life table tests	P=0.232	P=0.571	P=0.120	P=0.500
Logistic regression tests	P=0.334	P=0.571	P=0.120	P=0.558
Cochran-Armitage test	P=0.350			
Fisher exact test		P=0.500	P=0.121	P=0.500
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	0/50 (0%)	1/50 (2%)	4/50 (8%)	1/50 (2%)
Adjusted rates	0.0%	2.5%	14.3%	2.2%
Terminal rates	0/28 (0%)	1/40 (3%)	4/28 (14%)	0/20 (0%)
First incidence (days)	-	729 (T)	729 (T)	612
Life table tests	P=0.205	P=0.571	P=0.061	P=0.500
Logistic regression tests	P=0.310	P=0.571	P=0.061	P=0.558
Cochran-Armitage test	P=0.336			
Fisher exact test		P=0.500	P=0.059	P=0.500

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3
(continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Mammary Gland: Fibroadenoma				
Overall rates	3/50 (6%)	0/50 (0%)	1/50 (2%)	2/50 (4%)
Adjusted rates	10.7%	0.0%	2.9%	7.1%
Terminal rates	3/28 (11%)	0/40 (0%)	0/28 (0%)	1/20 (5%)
First incidence (days)	729 (T)	-	708	605
Life table tests	P=0.546	P=0.066N	P=0.292N	P=0.623N
Logistic regression tests	P=0.578N	P=0.066N	P=0.284N	P=0.520N
Cochran-Armitage test	P=0.562N			
Fisher exact test		P=0.121N	P=0.309N	P=0.500N
Mammary Gland: Fibroadenoma or Adenocarcinoma				
Overall rates	4/50 (8%)	0/50 (0%)	1/50 (2%)	2/50 (4%)
Adjusted rates	14.3%	0.0%	2.9%	7.1%
Terminal rates	4/28 (14%)	0/40 (0%)	0/28 (0%)	1/20 (5%)
First incidence (days)	729 (T)	-	708	605
Life table tests	P=0.512N	P=0.027N	P=0.171N	P=0.473N
Logistic regression tests	P=0.401N	P=0.027N	P=0.160N	P=0.364N
Cochran-Armitage test	P=0.380N			
Fisher exact test		P=0.059N	P=0.181N	P=0.339N
Pancreatic Islets: Adenoma				
Overall rates	5/50 (10%)	0/50 (0%)	3/49 (6%)	0/50 (0%)
Adjusted rates	14.4%	0.0%	9.1%	0.0%
Terminal rates	3/28 (11%)	0/40 (0%)	2/28 (7%)	0/20 (0%)
First incidence (days)	534	-	576	-
Life table tests	P=0.072N	P=0.020N	P=0.369N	P=0.057N
Logistic regression tests	P=0.039N	P=0.034N	P=0.358N	P=0.026N
Cochran-Armitage test	P=0.047N			
Fisher exact test		P=0.028N	P=0.369N	P=0.028N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	17/50 (34%)	9/16 (56%)[f]	8/25 (32%)[f]	12/50 (24%)
Adjusted rates	47.9%			35.3%
Terminal rates	11/28 (39%)			3/20 (15%)
First incidence (days)	637			577
Life table tests				P=0.419N
Logistic regression tests				P=0.195N
Fisher exact test				P=0.189N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	17/50 (34%)	10/16 (63%)[f]	8/25 (32%)[f]	12/50 (24%)
Adjusted rates	47.9%			35.3%
Terminal rates	11/28 (39%)			3/20 (15%)
First incidence (days)	637			577
Life table tests				P=0.419N
Logistic regression tests				P=0.195N
Fisher exact test				P=0.189N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3
(continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Preputial Gland: Adenoma				
Overall rates	6/49 (12%)	0/13 (0%)[f]	1/25 (4%)[f]	1/50 (2%)
Adjusted rates	18.0%			2.9%
Terminal rates	3/28 (11%)			0/20 (0%)
First incidence (days)	658			679
Life table tests				P=0.100N
Logistic regression tests				P=0.061N
Fisher exact test				P=0.053N
Preputial Gland: Adenoma or Carcinoma				
Overall rates	7/49 (14%)	0/13 (0%)[f]	1/25 (4%)[f]	1/50 (2%)
Adjusted rates	21.2%			2.9%
Terminal rates	4/28 (14%)			0/20 (0%)
First incidence (days)	658			679
Life table tests				P=0.066N
Logistic regression tests				P=0.035N
Fisher exact test				P=0.028N
Skin: Squamous Papilloma				
Overall rates	0/50 (0%)	4/50 (8%)	2/50 (4%)	6/50 (12%)
Adjusted rates	0.0%	10.0%	5.9%	25.0%
Terminal rates	0/28 (0%)	4/40 (10%)	1/28 (4%)	4/20 (20%)
First incidence (days)	-	729 (T)	641	679
Life table tests	P=0.004	P=0.117	P=0.235	P=0.008
Logistic regression tests	P=0.014	P=0.117	P=0.239	P=0.013
Cochran-Armitage test	P=0.023			
Fisher exact test		P=0.059	P=0.247	P=0.013
Skin: Squamous Papilloma and Carcinoma NOS				
Overall rates	1/50 (2%)	4/50 (8%)	2/50 (4%)	6/50 (12%)
Adjusted rates	2.3%	10.0%	5.9%	25.0%
Terminal rates	0/28 (0%)	4/40 (10%)	1/28 (4%)	4/20 (20%)
First incidence (days)	644	729 (T)	643	679
Life table tests	P=0.014	P=0.275	P=0.487	P=0.032
Logistic regression tests	P=0.044	P=0.195	P=0.509	P=0.051
Cochran-Armitage test	P=0.056			
Fisher exact test		P=0.183	P=0.500	P=0.056
Skin: Basal Cell Adenoma or Trichoepithelioma				
Overall rates	2/50 (4%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rates	6.7%	7.5%	3.6%	0.0%
Terminal rates	1/28 (4%)	3/40 (8%)	1/28 (4%)	0/20 (0%)
First incidence (days)	706	729 (T)	729 (T)	-
Life table tests	P=0.156N	P=0.650	P=0.483N	P=0.289N
Logistic regression tests	P=0.126N	P=0.592	P=0.484N	P=0.259N
Cochran-Armitage test	P=0.101N			
Fisher exact test		P=0.500	P=0.500N	P=0.247N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3
(continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Skin (Subcutaneous Tissue): Fibroma				
Overall rates	4/50 (8%)	0/50 (0%)	2/50 (4%)	4/50 (8%)
Adjusted rates	12.0%	0.0%	5.2%	13.2%
Terminal rates	2/28 (7%)	0/40 (0%)	0/28 (0%)	0/20 (0%)
First incidence (days)	653	-	687	581
Life table tests	P=0.260	P=0.040N	P=0.318N	P=0.545
Logistic regression tests	P=0.376	P=0.062N	P=0.337N	P=0.640N
Cochran-Armitage test	P=0.363			
Fisher exact test		P=0.059N	P=0.339N	P=0.643N
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rates	5/50 (10%)	2/50 (4%)	2/50 (4%)	4/50 (8%)
Adjusted rates	14.1%	5.0%	5.2%	13.2%
Terminal rates	2/28 (7%)	2/40 (5%)	0/28 (0%)	0/20 (0%)
First incidence (days)	653	729 (T)	687	581
Life table tests	P=0.494	P=0.138N	P=0.208N	P=0.596N
Logistic regression tests	P=0.516N	P=0.213N	P=0.216N	P=0.488N
Cochran-Armitage test	P=0.523N			
Fisher exact test		P=0.218N	P=0.218N	P=0.500N
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rates	3/50 (6%)	2/50 (4%)	0/50 (0%)	0/50 (0%)
Adjusted rates	9.1%	5.0%	0.0%	0.0%
Terminal rates	1/28 (4%)	2/40 (5%)	0/28 (0%)	0/20 (0%)
First incidence (days)	658	729 (T)	-	-
Life table tests	P=0.057N	P=0.374N	P=0.126N	P=0.167N
Logistic regression tests	P=0.042N	P=0.469N	P=0.120N	P=0.126N
Cochran-Armitage test	P=0.039N			
Fisher exact test		P=0.500N	P=0.121N	P=0.121N
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rates	6/50 (12%)	2/50 (4%)	2/50 (4%)	4/50 (8%)
Adjusted rates	17.0%	5.0%	5.2%	13.2%
Terminal rates	2/28 (7%)	2/40 (5%)	0/28 (0%)	0/20 (0%)
First incidence (days)	653	729 (T)	687	581
Life table tests	P=0.541N	P=0.075N	P=0.132N	P=0.482N
Logistic regression tests	P=0.391N	P=0.128N	P=0.134N	P=0.364N
Cochran-Armitage test	P=0.394N			
Fisher exact test		P=0.134N	P=0.134N	P=0.370N
Testes: Adenoma				
Overall rates	47/50 (94%)	47/49 (96%)	45/48 (94%)	49/50 (98%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	28/28 (100%)	39/39 (100%)	26/26 (100%)	20/20 (100%)
First incidence (days)	534	420	540	486
Life table tests	P=0.002	P=0.016N	P=0.518N	P=0.056
Logistic regression tests	P=0.176	P=0.519	P=0.582	P=0.239
Cochran-Armitage test	P=0.265			
Fisher exact test		P=0.510	P=0.641N	P=0.309

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3
(continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Thyroid Gland (C-cell): Adenoma				
Overall rates	4/50 (8%)	0/11 (0%)[f]	0/23 (0%)[f]	4/50 (8%)
Adjusted rates	11.5%			13.4%
Terminal rates	2/28 (7%)			1/20 (5%)
First incidence (days)	610			612
Life table tests				P=0.551
Logistic regression tests				P=0.631N
Fisher exact test				P=0.643N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	5/50 (10%)	1/11 (9%)[f]	0/23 (0%)[f]	5/50 (10%)
Adjusted rates	14.9%			16.5%
Terminal rates	3/28 (11%)			1/20 (5%)
First incidence (days)	610			612
Life table tests				P=0.520
Logistic regression tests				P=0.630N
Fisher exact test				P=0.630N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rates	2/50 (4%)	0/11 (0%)[f]	2/23 (9%)[f]	3/50 (6%)
Adjusted rates	6.5%			9.1%
Terminal rates	1/28 (4%)			0/20 (0%)
First incidence (days)	700			626
Life table tests				P=0.433
Logistic regression tests				P=0.502
Fisher exact test				P=0.500
Zymbal's Gland: Carcinoma				
Overall rates	0/50 (0%)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted rates	0.0%	0.0%	4.2%	9.6%
Terminal rates	0/28 (0%)	0/40 (0%)	0/28 (0%)	0/20 (0%)
First incidence (days)	-	-	575	624
Life table tests	P=0.021	-	P=0.237	P=0.103
Logistic regression tests	P=0.035	-	P=0.308	P=0.126
Cochran-Armitage test	P=0.027			
Fisher exact test		-	P=0.247	P=0.121
All Organs: Mononuclear Cell Leukemia				
Overall rates	22/50 (44%)	6/50 (12%)	2/50 (4%)	1/50 (2%)
Adjusted rates	55.1%	12.9%	5.8%	2.6%
Terminal rates	11/28 (39%)	2/40 (5%)	1/28 (4%)	0/20 (0%)
First incidence (days)	610	420	610	658
Life table tests	P≤0.001N	P≤0.001N	P≤0.001N	P≤0.001N
Logistic regression tests	P≤0.001N	P≤0.001N	P≤0.001N	P≤0.001N
Cochran-Armitage test	P≤0.001N			
Fisher exact test		P≤0.001N	P≤0.001N	P≤0.001N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3
(continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
All Organs: Malignant Mesothelioma				
Overall rates	3/50 (6%)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted rates	8.0%	2.5%	5.9%	11.5%
Terminal rates	1/28 (4%)	1/40 (3%)	1/28 (4%)	1/20 (5%)
First incidence (days)	553	729 (T)	682	690
Life table tests	P=0.356	P=0.239N	P=0.478N	P=0.590
Logistic regression tests	P=0.482	P=0.316N	P=0.489N	P=0.646N
Cochran-Armitage test	P=0.473			
Fisher exact test		P=0.309N	P=0.500N	P=0.661N
All Organs: Benign Tumors				
Overall rates	49/50 (98%)	50/50 (100%)	50/50 (100%)	49/50 (98%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	28/28 (100%)	40/40 (100%)	28/28 (100%)	20/20 (100%)
First incidence (days)	534	420	529	486
Life table tests	P=0.008	P=0.021N	P=0.543	P=0.101
Logistic regression tests	P=0.621N	P=0.507	P=0.498	P=0.717
Cochran-Armitage test	P=0.591N			
Fisher exact test		P=0.500	P=0.500	P=0.753N
All Organs: Malignant Tumors				
Overall rates	32/50 (64%)	22/50 (44%)	22/50 (44%)	16/50 (32%)
Adjusted rates	70.6%	45.5%	49.5%	42.7%
Terminal rates	15/28 (54%)	14/40 (35%)	8/28 (29%)	3/20 (15%)
First incidence (days)	553	420	529	567
Life table tests	P=0.081N	P=0.009N	P=0.078N	P=0.046N
Logistic regression tests	P≤0.001N	P=0.065N	P=0.033N	P≤0.001N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.035N	P=0.035N	P=0.001N
All Organs: Benign and Malignant Tumors				
Overall rates	49/50 (98%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	28/28 (100%)	40/40 (100%)	28/28 (100%)	20/20 (100%)
First incidence (days)	534	420	529	486
Life table tests	P=0.005	P=0.021N	P=0.543	P=0.080
Logistic regression tests	P=0.302	P=0.507	P=0.498	P=0.493
Cochran-Armitage test	P=0.309			
Fisher exact test		P=0.500	P=0.500	P=0.500

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no tumors in animal group
[f] Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus, no statistical analyses are provided.

TABLE A4a
Historical Incidence of Adrenal Medulla Pheochromocytomas in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Benign	Malignant	Benign or Malignant
Historical Incidence at Southern Research Institute			
C.I. Pigment Red 3	22/50	6/50	24/50
Nitrofurantoin	23/50	3/50	24/50
o-Nitroanisole	7/49	6/49	12/49
Polysorbate 80	21/50	1/50	21/50
Rhodamine 6G	18/50	10/50	23/50
Roxarsone	15/50	5/50	19/50
Total	106/299 (35.5%)	31/299 (10.4%)	123/299 (41.1%)
Standard deviation	12.0%	6.1%	9.2%
Range	14%-36%	2%-20%	24%-48%
Overall Historical Incidence			
Total	284/788 (36.0%)	39/788 (5.0%)	306/788[b] (38.8%)
Standard deviation	9.3%	5.8%	8.4%
Range	14%-47%	0%-20%	22%-48%

[a] Data as of 3 April 1991
[b] Includes one complex pheochromocytoma

TABLE A4b
Historical Incidence of Skin Tumors in Untreated Male F344/N Rats[a]

Study	Incidence in Controls			
	Keratoacanthoma	Squamous Cell Papilloma	Squamous Cell Carcinoma	Squamous Cell Papilloma or Carcinoma
Historical Incidence at Southern Research Institute				
C.I. Pigment Red 3	2/50	0/50	0/50	0/50
Nitrofurantoin	4/50	1/50	0/50	1/50
o-Nitroanisole	3/50	1/50	0/50	1/50
Polysorbate 80	2/50	2/50	0/50	2/50
Rhodamine 6G	1/50	2/50	0/50	2/50
Roxarsone	4/50	0/50	1/50	1/50
Total	16/300 (5.3%)	6/300 (2.0%)	1/300 (0.3%)	7/300 (2.3%)
Standard deviation	2.4%	1.8%	0.8%	1.5%
Range	2%-8%	0%-4%	0%-2%	0%-4%
Overall Historical Incidence				
Total	30/800 (3.8%)	16/800 (2.0%)	5/800 (0.6%)	20/800 (2.5%)
Standard deviation	2.5%	1.6%	1.2%	1.6%
Range	0%-8%	0%-4%	0%-4%	0%-4%

[a] Data as of 3 April 1991

TABLE A4c
Historical Incidence of Zymbal's Gland Carcinomas in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
C.I. Pigment Red 3	0/50
Nitrofurantoin	2/50
o-Nitroanisole	0/50
Polysorbate 80	0/50
Rhodamine 6G	0/50
Roxarsone	1/50
Total	3/300 (1.0%)
Standard deviation	1.7%
Range	0%-4%
Overall Historical Incidence	
Total	6/800 (0.8%)
Standard deviation	1.2%
Range	0%-4%

[a] Data as of 3 April 1991

TABLE A4d
Historical Incidence of Leukemia in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
C.I. Pigment Red 3	22/50
Nitrofurantoin	23/50
o-Nitroanisole	26/50
Polysorbate 80	23/50
Rhodamine 6G	27/50
Roxarsone	27/50
Total	148/300 (49.3%)
Standard deviation	4.5%
Range	44%-54%
Overall Historical Incidence	
Total	385/800 (48.1%)
Standard deviation	7.7%
Range	32%-62%

[a] Data as of 3 April 1991; includes lymphocytic, monocytic, mononuclear, or undifferentiated cell type

TABLE A4e
Historical Incidence of Hepatocellular Tumors in Untreated Male F344 Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
C.I. Pigment Red 3	0/50	0/50	0/50
Nitrofurantoin	1/50	0/50	1/50
o-Nitroanisole	0/50	0/50	0/50
Polysorbate 80	2/50	0/50	2/50
Rhodamine 6G	4/50	1/50	5/50
Roxarsone	0/50	2/50	2/50
Total	7/300 (2.3%)	3/300 (1.0%)	10/300 (3.3%)
Standard deviation	3.2%	1.7%	3.7%
Range	0%-8%	0%-4%	0%-10%
Overall Historical Incidence			
Total	19/799 (2.4%)	7/799 (0.9%)	24/799 (3.0%)
Standard deviation	2.9%	1.8%	3.4%
Range	0%-8%	0%-6%	0%-10%

[a] Data as of 3 April 1991

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3[a]

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-month interim evaluation[b]	10	10	10	10
Early deaths				
Natural death	5	3	6	5
Moribund	17	7	16	25
Survivors				
Terminal sacrifice	28	40	28	20
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(9)	(22)	(50)
Inflammation, subacute				1 (2%)
Intestine large, cecum	(49)	(10)	(19)	(50)
Parasite metazoan	2 (4%)		1 (5%)	3 (6%)
Artery, inflammation, subacute			1 (5%)	
Artery, necrosis, fibrinoid			1 (5%)	
Intestine large, colon	(50)	(10)	(22)	(50)
Parasite metazoan	2 (4%)		1 (5%)	6 (12%)
Lymphoid tissue, inflammation, subacute				1 (2%)
Lymphoid tissue, mineralization				1 (2%)
Wall, mineralization				1 (2%)
Intestine large, rectum	(50)	(10)	(22)	(49)
Parasite metazoan	9 (18%)			4 (8%)
Wall, mineralization				1 (2%)
Intestine small, ileum	(50)	(9)	(19)	(49)
Lymphoid tissue, inflammation, subacute				1 (2%)
Lymphoid tissue, mineralization				1 (2%)
Intestine small, jejunum	(50)	(10)	(20)	(49)
Inflammation, subacute, multifocal				1 (2%)
Necrosis, multifocal				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis, focal	5 (10%)	10 (20%)	4 (8%)	
Angiectasis, multifocal	3 (6%)	20 (40%)	21 (42%)	29 (58%)
Basophilic focus	18 (36%)	14 (28%)	12 (24%)	7 (14%)
Basophilic focus, multiple	3 (6%)	2 (4%)	1 (2%)	
Clear cell focus	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Congestion			1 (2%)	2 (4%)
Cyst			1 (2%)	1 (2%)
Degeneration, cystic, focal	7 (14%)	3 (6%)	5 (10%)	
Degeneration, cystic, multifocal	2 (4%)	33 (66%)	35 (70%)	36 (72%)
Eosinophilic focus	5 (10%)	16 (32%)	14 (28%)	4 (8%)
Eosinophilic focus, multiple	1 (2%)	21 (42%)	22 (44%)	37 (74%)
Fibrosis	1 (2%)		1 (2%)	
Granuloma			1 (2%)	
Granuloma, multiple	20 (40%)	31 (62%)	27 (54%)	27 (54%)
Hematopoietic cell proliferation	1 (2%)			
Hepatodiaphragmatic nodule	2 (4%)	5 (10%)	5 (10%)	5 (10%)
Hepatodiaphragmatic nodule, two, multiple			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Alimentary System (continued)				
Liver (continued)	(50)	(50)	(50)	(50)
Inflammation, subacute		1 (2%)	1 (2%)	
Mixed cell focus	2 (4%)	14 (28%)	15 (30%)	7 (14%)
Mixed cell focus, multiple		10 (20%)	6 (12%)	8 (16%)
Necrosis, focal		1 (2%)		1 (2%)
Necrosis, multifocal		1 (2%)	4 (8%)	
Pigmentation, hemosiderin	1 (2%)	1 (2%)	1 (2%)	
Pigmentation, cholesterol, multifocal	1 (2%)			1 (2%)
Regeneration	16 (32%)		1 (2%)	
Thrombus	1 (2%)			
Vacuolization cytoplasmic, diffuse		1 (2%)		1 (2%)
Biliary tract, cyst				2 (4%)
Biliary tract, proliferation	49 (98%)	45 (90%)	49 (98%)	50 (100%)
Centrilobular, necrosis		2 (4%)	2 (4%)	2 (4%)
Mesentery	(11)	(6)	(6)	(6)
Fat, inflammation, chronic, multifocal	1 (9%)			
Fat, necrosis, focal	5 (45%)	4 (67%)	3 (50%)	1 (17%)
Fat, necrosis, multifocal	2 (18%)			
Pancreas	(50)	(50)	(49)	(50)
Basophilic focus	1 (2%)	2 (4%)	6 (12%)	1 (2%)
Acinus, atrophy, focal			2 (4%)	
Acinus, atrophy, multifocal	24 (48%)	32 (64%)	37 (76%)	41 (82%)
Acinus, hyperplasia, focal	1 (2%)	1 (2%)	3 (6%)	4 (8%)
Acinus, hyperplasia, multifocal	1 (2%)	1 (2%)		
Artery, hypertrophy				1 (2%)
Artery, inflammation, subacute	1 (2%)	1 (2%)		3 (6%)
Duct, cyst	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Salivary glands	(50)	(10)	(22)	(50)
Acinus, atrophy, multifocal				1 (2%)
Acinus, hyperplasia, multifocal			1 (5%)	
Stomach, forestomach	(50)	(10)	(22)	(49)
Edema			3 (14%)	2 (4%)
Erosion			1 (5%)	
Hyperplasia		1 (10%)	2 (9%)	1 (2%)
Inflammation, subacute		1 (10%)	5 (23%)	3 (6%)
Mineralization				1 (2%)
Perforation			1 (5%)	
Ulcer		1 (10%)		1 (2%)
Ulcer, multiple	1 (2%)		2 (9%)	
Stomach, glandular	(50)	(10)	(22)	(49)
Edema			2 (9%)	
Inflammation, subacute			2 (9%)	
Mineralization	1 (2%)		5 (23%)	16 (33%)
Tongue	(1)			
Foreign body, multiple	1 (100%)			
Granuloma, multiple	1 (100%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Cardiovascular System				
Blood vessel	(1)		(5)	(7)
Abdominal, hypertrophy			2 (40%)	4 (57%)
Abdominal, inflammation, subacute			1 (20%)	1 (14%)
Abdominal, mineralization			1 (20%)	4 (57%)
Abdominal, thrombus				1 (14%)
Aorta, mineralization	1 (100%)		2 (40%)	4 (57%)
Heart	(50)	(11)	(27)	(50)
Cardiomyopathy	40 (80%)	6 (55%)	22 (81%)	45 (90%)
Fibrosis, focal	1 (2%)		1 (4%)	1 (2%)
Inflammation, subacute, multifocal	1 (2%)			
Mineralization, multifocal	1 (2%)		2 (7%)	5 (10%)
Atrium, thrombus	1 (2%)	3 (27%)	5 (19%)	4 (8%)
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Cyst				1 (2%)
Degeneration, fatty, focal	11 (22%)	12 (24%)	11 (22%)	15 (30%)
Degeneration, fatty, multifocal	2 (4%)	1 (2%)	4 (8%)	1 (2%)
Hyperplasia, focal	8 (16%)	10 (20%)	14 (28%)	16 (32%)
Hyperplasia, multifocal	2 (4%)		4 (8%)	
Inflammation, granulomatous, multifocal			2 (4%)	1 (2%)
Necrosis, multifocal	1 (2%)			
Pigmentation, cholesterol, multifocal			2 (4%)	1 (2%)
Capsule, accessory adrenal cortical nodule	2 (4%)	5 (10%)	5 (10%)	
Capsule, hemorrhage	1 (2%)			
Adrenal gland, medulla	(50)	(50)	(50)	(50)
Hyperplasia, focal	22 (44%)	4 (8%)	9 (18%)	21 (42%)
Hyperplasia, multifocal		4 (8%)	3 (6%)	5 (10%)
Thrombus				1 (2%)
Islets, pancreatic	(50)	(50)	(49)	(50)
Hyperplasia	1 (2%)			
Parathyroid gland	(48)	(12)	(21)	(49)
Hyperplasia	2 (4%)	2 (17%)	9 (43%)	34 (69%)
Pituitary gland	(50)	(16)	(25)	(50)
Pars distalis, angiectasis	18 (36%)	9 (56%)	6 (24%)	7 (14%)
Pars distalis, cyst	5 (10%)	3 (19%)	5 (20%)	8 (16%)
Pars distalis, hemorrhage	1 (2%)	1 (6%)	2 (8%)	1 (2%)
Pars distalis, hyperplasia, focal	5 (10%)	3 (19%)	2 (8%)	8 (16%)
Pars distalis, necrosis			2 (8%)	
Pars distalis, pigmentation, hemosiderin	2 (4%)	1 (6%)	2 (8%)	1 (2%)
Thyroid gland	(50)	(11)	(23)	(50)
Inflammation, suppurative, acute				1 (2%)
Ultimobranchial cyst			1 (4%)	1 (2%)
C-cell, hyperplasia, focal	4 (8%)	1 (9%)	1 (4%)	5 (10%)
Follicle, cyst	1 (2%)		1 (4%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
General Body System				
None				
Genital System				
Coagulating gland	(1)			
Dilatation	1 (100%)			
Inflammation	1 (100%)			
Epididymis	(50)	(10)	(23)	(50)
Granuloma sperm				1 (2%)
Inflammation, subacute	1 (2%)			
Preputial gland	(49)	(13)	(25)	(50)
Foreign body				1 (2%)
Hyperplasia	4 (8%)	2 (15%)		1 (2%)
Inflammation, subacute	5 (10%)	3 (23%)	3 (12%)	4 (8%)
Duct, cyst	5 (10%)	2 (15%)	2 (8%)	1 (2%)
Prostate	(50)	(10)	(22)	(50)
Inflammation, subacute	31 (62%)	7 (70%)	15 (68%)	22 (44%)
Seminal vesicle	(50)	(11)	(22)	(50)
Dilatation	2 (4%)	1 (9%)		
Hyperplasia, focal			1 (5%)	
Inflammation, subacute	1 (2%)	1 (9%)	1 (5%)	1 (2%)
Testes	(50)	(49)	(48)	(50)
Atrophy	10 (20%)	12 (24%)	8 (17%)	7 (14%)
Hemorrhage			1 (2%)	
Mineralization	1 (2%)		1 (2%)	
Interstitial cell, hyperplasia, focal		3 (6%)		
Interstitial cell, hyperplasia, multifocal	5 (10%)	7 (14%)	4 (8%)	10 (20%)
Hematopoietic System				
Blood	(1)		(1)	
Leukocytosis			1 (100%)	
Bone marrow	(50)	(10)	(22)	(49)
Hyperplasia	19 (38%)		3 (14%)	19 (39%)
Myelofibrosis	3 (6%)	1 (10%)		
Lymph node	(50)	(50)	(50)	(50)
Axillary, congestion			1 (2%)	
Axillary, ectasia			1 (2%)	
Inguinal, hyperplasia, lymphoid	1 (2%)			
Mediastinal, amyloid deposition			1 (2%)	
Mediastinal, congestion	2 (4%)	3 (6%)	6 (12%)	9 (18%)
Mediastinal, ectasia	4 (8%)	1 (2%)	5 (10%)	
Mediastinal, hyperplasia, macrophage, multifocal				1 (2%)
Mediastinal, pigmentation, hemosiderin	1 (2%)		1 (2%)	
Mesenteric, congestion	2 (4%)			2 (4%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Hematopoietic System (continued)				
Lymph node (continued)				
Mesenteric, ectasia	1 (2%)	6 (12%)	5 (10%)	3 (6%)
Mesenteric, fibrosis, focal				2 (4%)
Mesenteric, giant cell		1 (2%)		
Mesenteric, hyperplasia, macrophage, multifocal	50 (100%)	47 (94%)	48 (96%)	49 (98%)
Mesenteric, necrosis, focal			2 (4%)	2 (4%)
Mesenteric, necrosis, multifocal			1 (2%)	
Mesenteric, pigmentation, cholesterol, multifocal	50 (100%)	47 (94%)	48 (96%)	49 (98%)
Pancreatic, amyloid deposition		1 (2%)		
Pancreatic, ectasia	1 (2%)			1 (2%)
Pancreatic, hyperplasia, macrophage, multifocal	1 (2%)	3 (6%)	3 (6%)	5 (10%)
Pancreatic, pigmentation, cholesterol, multifocal	1 (2%)	4 (8%)	3 (6%)	5 (10%)
Renal, congestion			1 (2%)	
Renal, hyperplasia, macrophage, multifocal			1 (2%)	1 (2%)
Renal, pigmentation, cholesterol, multifocal			1 (2%)	1 (2%)
Lymph node, mandibular	(48)	(50)	(50)	(50)
Congestion	1 (2%)		1 (2%)	1 (2%)
Ectasia	16 (33%)	17 (34%)	16 (32%)	20 (40%)
Spleen	(50)	(50)	(50)	(49)
Fibrosis, focal	6 (12%)	4 (8%)	8 (16%)	9 (18%)
Fibrosis, multifocal	1 (2%)		1 (2%)	
Hematopoietic cell proliferation	1 (2%)		1 (2%)	
Infiltration cellular, lipocyte	1 (2%)			1 (2%)
Necrosis, focal	1 (2%)	1 (2%)		
Capsule, cyst		1 (2%)		
Thymus	(44)	(10)	(19)	(49)
Cyst	3 (7%)			2 (4%)
Integumentary System				
Mammary gland	(50)	(13)	(24)	(48)
Hyperplasia	5 (10%)	2 (15%)	2 (8%)	5 (10%)
Inflammation, chronic				1 (2%)
Duct, cyst	13 (26%)	5 (38%)	7 (29%)	11 (23%)
Duct, inflammation, subacute				1 (2%)
Skin	(50)	(31)	(47)	(50)
Hyperkeratosis, focal		2 (6%)		
Hyperkeratosis, multifocal			1 (2%)	
Hyperplasia, focal	1 (2%)	2 (6%)	4 (9%)	2 (4%)
Hyperplasia, multifocal			1 (2%)	
Inflammation, subacute, multifocal			1 (2%)	
Subcutaneous tissue, abscess, focal	1 (2%)			
Subcutaneous tissue, inflammation, subacute, focal			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Musculoskeletal System				
Bone	(50)	(10)	(22)	(50)
Fibrous osteodystrophy	1 (2%)		8 (36%)	36 (72%)
Cranium, hypertrophy, focal			1 (5%)	
Skeletal muscle		(1)		(1)
Fibrosis, focal		1 (100%)		
Nervous System				
Brain	(50)	(11)	(22)	(50)
Compression	3 (6%)		2 (9%)	2 (4%)
Hemorrhage, multifocal	1 (2%)	3 (27%)	4 (18%)	
Necrosis, focal			1 (5%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	1 (2%)		1 (2%)	
Inflammation, suppurative, acute		1 (2%)		
Necrosis		2 (4%)		
Pigmentation, hemosiderin, multifocal		1 (2%)		
Alveolar epithelium, hyperplasia, focal	1 (2%)		2 (4%)	2 (4%)
Alveolar epithelium, hyperplasia, multifocal	1 (2%)	1 (2%)		1 (2%)
Bronchus, fungus		1 (2%)		
Bronchus, inflammation, suppurative, acute		1 (2%)		
Pleura, congestion, multifocal				1 (2%)
Pleura, fibrosis, focal		1 (2%)		1 (2%)
Nose	(50)	(10)	(22)	(50)
Foreign body	9 (18%)	1 (10%)	7 (32%)	7 (14%)
Fungus	12 (24%)		9 (41%)	12 (24%)
Hyperkeratosis			1 (5%)	
Inflammation, suppurative, acute	13 (26%)	1 (10%)	10 (45%)	13 (26%)
Nasolacrimal duct, foreign body			1 (5%)	
Nasolacrimal duct, inflammation, subacute	13 (26%)	1 (10%)		22 (44%)
Nasolacrimal duct, inflammation, suppurative, acute			2 (9%)	
Special Senses System				
Eye	(15)	(16)	(15)	(12)
Cataract	13 (87%)	16 (100%)	14 (93%)	10 (83%)
Anterior chamber, hemorrhage		3 (19%)	2 (13%)	
Anterior chamber, inflammation, suppurative, acute			1 (7%)	
Conjunctiva, inflammation, suppurative, acute			1 (7%)	
Cornea, fibrosis		2 (13%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Special Senses System (continued)				
Eye (continued)				
Cornea, inflammation, subacute		1 (6%)	1 (7%)	
Cornea, inflammation, suppurative, acute			1 (7%)	
Lids, fibrosis, focal	2 (13%)			
Posterior chamber, hemorrhage	1 (7%)	4 (25%)	1 (7%)	
Retina, degeneration	13 (87%)	16 (100%)	14 (93%)	12 (100%)
Zymbal's gland			(2)	(3)
Inflammation, suppurative, acute				1 (33%)
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Hydronephrosis	1 (2%)			2 (4%)
Metaplasia, osseous	1 (2%)			
Nephropathy, chronic	50 (100%)	49 (98%)	50 (100%)	49 (100%)
Cortex, cyst	1 (2%)	2 (4%)	6 (12%)	2 (4%)
Cortex, cyst, multiple	2 (4%)	4 (8%)	7 (14%)	15 (31%)
Papilla, necrosis	1 (2%)			
Papilla, transitional epithelium, hyperplasia	7 (14%)	40 (80%)	43 (86%)	43 (88%)
Pelvis, transitional epithelium, hyperplasia			1 (2%)	
Renal tubule, hyperplasia	2 (4%)	3 (6%)	2 (4%)	7 (14%)
Renal tubule, mineralization, multifocal	1 (2%)		2 (4%)	4 (8%)
Urethra	(2)			
Bulbourethral gland, congestion	1 (50%)			
Bulbourethral gland, dilatation	2 (100%)			
Bulbourethral gland, inflammation, subacute	1 (50%)			
Urinary bladder	(50)	(11)	(22)	(50)
Inflammation, subacute	1 (2%)			

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Each dosed group contains one animal that died or was killed moribund prior to the interim evaluation.

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR FEED STUDY OF C.I. PIGMENT RED 3

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3[a]

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-month interim evaluation	10	10	10	10
Early deaths				
Natural death	3	2	3	3
Moribund	15	7	8	7
Survivors				
Terminal sacrifice	32	40	39	40
Died last week of study		1		
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(48)	(9)	(12)	(50)
Sarcoma, metastatic, uterus			1 (8%)	
Intestine large, rectum	(50)	(10)	(12)	(50)
Polyp adenomatous				1 (2%)
Intestine small, duodenum	(50)	(10)	(11)	(49)
Sarcoma, metastatic, uterus			1 (9%)	
Intestine small, jejunum	(48)	(9)	(9)	(49)
Sarcoma, metastatic, uterus			1 (11%)	
Liver	(50)	(50)	(50)	(50)
Hepatocellular adenoma			1 (2%)	9 (18%)
Hepatocellular adenoma, multiple				1 (2%)
Mesentery	(6)	(6)	(10)	(4)
Adenocarcinoma, metastatic, uterus	1 (17%)			
Sarcoma, metastatic, uterus			1 (10%)	
Pancreas	(50)	(50)	(50)	(49)
Sarcoma, metastatic, uterus			1 (2%)	
Pharynx		(2)	(1)	
Papilloma squamous		1 (50%)		
Squamous cell carcinoma			1 (100%)	
Stomach, forestomach	(50)	(9)	(12)	(50)
Sarcoma, metastatic, uterus			1 (8%)	
Stomach, glandular	(50)	(9)	(12)	(50)
Sarcoma, metastatic, uterus			1 (8%)	
Tongue			(2)	
Squamous cell carcinoma			2 (100%)	
Cardiovascular System				
Heart	(50)	(10)	(12)	(50)
Carcinoma, metastatic, thyroid gland		1 (10%)		

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Endocrine System				
Adrenal gland, cortex	(50)	(16)	(13)	(50)
Adenoma	2 (4%)	1 (6%)		
Hemangiosarcoma				1 (2%)
Capsule, sarcoma, metastatic, uterus			1 (8%)	
Adrenal gland, medulla	(49)	(16)	(13)	(50)
Pheochromocytoma malignant		1 (6%)		
Pheochromocytoma complex	1 (2%)		1 (8%)	
Pheochromocytoma benign	4 (8%)	3 (19%)		4 (8%)
Islets, pancreatic	(49)	(50)	(50)	(49)
Adenoma		1 (2%)		
Carcinoma		1 (2%)		
Pituitary gland	(50)	(22)	(20)	(50)
Pars distalis, adenoma	23 (46%)	13 (59%)	11 (55%)	21 (42%)
Pars distalis, adenoma, multiple			1 (5%)	
Pars distalis, adenoma, two, multiple	2 (4%)			1 (2%)
Pars distalis, carcinoma			1 (5%)	
Thyroid gland	(50)	(12)	(13)	(50)
C-cell, adenoma	6 (12%)	1 (8%)	1 (8%)	6 (12%)
C-cell, carcinoma	1 (2%)	2 (17%)	1 (8%)	
Follicular cell, adenoma	1 (2%)			2 (4%)
General Body System				
None				
Genital System				
Clitoral gland	(47)	(14)	(14)	(50)
Adenoma	9 (19%)	1 (7%)		1 (2%)
Ovary	(50)	(14)	(14)	(50)
Leiomyosarcoma		1 (7%)		
Uterus	(50)	(23)	(28)	(50)
Adenocarcinoma	1 (2%)			
Adenoma	1 (2%)			
Fibroma	1 (2%)			
Fibrous histiocytoma	1 (2%)			
Leiomyoma				1 (2%)
Leiomyosarcoma			1 (4%)	1 (2%)
Polyp stromal	9 (18%)	7 (30%)	5 (18%)	9 (18%)
Polyp stromal, two, multiple	1 (2%)		1 (4%)	1 (2%)
Sarcoma			1 (4%)	
Sarcoma stromal	1 (2%)			1 (2%)
Vagina	(7)		(5)	(1)
Sarcoma			1 (20%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Hematopoietic System				
Bone marrow	(50)	(10)	(12)	(50)
Histiocytic sarcoma				1 (2%)
Lymph node	(50)	(50)	(50)	(50)
Iliac, adenocarcinoma, metastatic, uterus	1 (2%)			
Mesenteric, sarcoma, metastatic, uterus			1 (2%)	
Renal, adenocarcinoma, metastatic, uterus	1 (2%)			
Lymph node, mandibular	(50)	(50)	(50)	(49)
Spleen	(50)	(50)	(50)	(50)
Sarcoma				1 (2%)
Thymus	(49)	(11)	(12)	(50)
Integumentary System				
Mammary gland	(50)	(50)	(49)	(50)
Adenocarcinoma	3 (6%)	1 (2%)		
Adenocarcinoma, multiple	1 (2%)			
Adenoma				1 (2%)
Fibroadenoma	15 (30%)	13 (26%)	16 (33%)	11 (22%)
Fibroadenoma, multiple	8 (16%)	3 (6%)	4 (8%)	1 (2%)
Myoepithelioma			1 (2%)	
Skin	(50)	(26)	(33)	(50)
Keratoacanthoma	2 (4%)			
Trichoepithelioma	1 (2%)			
Subcutaneous tissue, fibroma		1 (4%)	1 (3%)	
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (4%)	1 (3%)	
Subcutaneous tissue, lipoma	1 (2%)			
Musculoskeletal System				
Bone	(50)	(15)	(16)	(50)
Vertebra, coccygeal, chordoma		1 (7%)		
Nervous System				
Brain	(50)	(10)	(13)	(50)
Astrocytoma malignant			1 (8%)	
Carcinoma, metastatic, pituitary gland			1 (8%)	
Ependymoma malignant			2 (15%)	
Glioma malignant	1 (2%)			
Oligodendroglioma malignant		1 (10%)		

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Adenocarcinoma, metastatic, mammary gland	1 (2%)			
Adenocarcinoma, metastatic, uterus	1 (2%)			
Alveolar/bronchiolar adenoma	1 (2%)			2 (4%)
Alveolar/bronchiolar carcinoma			2 (4%)	
Special Senses System				
None				
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Lipoma	1 (2%)			
Urinary bladder	(50)	(10)	(12)	(50)
Adenocarcinoma, metastatic, uterus	1 (2%)			
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Leukemia mononuclear	10 (20%)	1 (2%)		2 (4%)
Tumor Summary				
Total animals with primary neoplasms[c]	46	35	38	41
Total primary neoplasms	109	55	57	79
Total animals with benign neoplasms	44	31	32	38
Total benign neoplasms	88	45	42	72
Total animals with malignant neoplasms	17	10	14	7
Total malignant neoplasms	21	10	15	7
Total animals with secondary neoplasms[d]	2	1	2	
Total secondary neoplasms	6	1	10	

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] Number of animals with any tissue examined microscopically
[c] Primary tumors: all tumors except metastatic tumors
[d] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm

Number of Days on Study	1 5 8	4 0 9	5 3 2	6 0 4	6 2 2	6 2 6	6 6 6	6 8 6	6 8 7	6 8 7	6 8 7	6 9 0	6 9 0	6 9 4	7 1 0	7 1 6	7 2 3	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	5 0 1	5 3 1	5 5 1	5 5 2	5 5 3	5 7 1	4 9 1	5 2 1	5 0 2	5 1 1	5 6 1	4 9 2	5 6 2	5 4 1	5 1 2	5 3 2	5 1 3	5 7 2	4 9 3	4 9 4	4 9 5	5 0 3	5 0 4	5 0 5	5 1 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+						+												+		+			
Adenocarcinoma, metastatic, uterus		X																							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma complex																									
Pheochromocytoma benign																	X	X							X
Islets, pancreatic	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X		X				X	X		X	X	X	X			X		X			
Pars distalis, adenoma, two, multiple																					X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma										X		X		X							X	X			
C-cell, carcinoma																									
Follicular cell, adenoma																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	5 1 5	5 2 2	5 2 3	5 2 4	5 2 5	5 3 3	5 3 4	5 3 5	5 4 2	5 4 3	5 4 4	5 4 5	5 5 4	5 5 5	5 6 3	5 6 4	5 6 5	5 7 3	5 7 4	5 7 5	5 8 1	5 8 2	5 8 3	5 8 4	5 8 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery										+										+						6
Adenocarcinoma, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X							X	2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma complex																					X					1
Pheochromocytoma benign			X																							4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma								X		X		X				X	X	X	X	X	X		X	X	X	23
Pars distalis, adenoma, two, multiple					X																					2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma														X												6
C-cell, carcinoma																	X									1
Follicular cell, adenoma						X																				1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	1 5 8	4 0 9	5 3 2	6 0 4	6 2 2	6 2 6	6 6 6	6 8 6	6 8 7	6 8 7	6 8 7	6 9 0	6 9 0	6 9 4	7 1 0	7 1 6	7 2 3	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	5 0 1	5 3 1	5 5 1	5 5 2	5 5 3	5 7 1	4 9 1	5 2 1	5 0 2	5 1 1	5 6 1	4 9 2	5 6 2	5 4 1	5 1 2	5 3 2	5 1 3	5 7 2	4 9 3	4 9 4	4 9 5	5 0 3	5 0 4	5 0 5	5 1 4
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X																		X				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma		X																							
Adenoma																									
Fibroma														X											
Fibrous histiocytoma		X																							
Polyp stromal		X			X	X	X																		
Polyp stromal, two, multiple																									
Sarcoma stromal																X									
Vagina				+	+	+		+																	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, adenocarcinoma, metastatic, uterus		X																							
Renal, adenocarcinoma, metastatic, uterus		X																							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma	X				X																				
Adenocarcinoma, multiple																									
Fibroadenoma						X			X		X	X	X					X			X				
Fibroadenoma, multiple				X										X										X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																								X	
Trichoepithelioma																									
Subcutaneous tissue, fibrosarcoma											X														
Subcutaneous tissue, lipoma																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	5 1 5	5 2 2	5 2 3	5 2 4	5 2 5	5 3 3	5 3 4	5 3 5	5 4 2	5 4 3	5 4 4	5 4 5	5 5 4	5 5 5	5 6 3	5 6 4	5 6 5	5 7 3	5 7 4	5 7 5	5 8 1	5 8 2	5 8 3	5 8 4	5 8 5	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	47
Adenoma	X		X				X		X	X				X			X									9
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Adenoma				X																						1
Fibroma																										1
Fibrous histiocytoma																										1
Polyp stromal				X	X			X						X						X						9
Polyp stromal, two, multiple							X																			1
Sarcoma stromal																										1
Vagina				+	+														+							7
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Iliac, adenocarcinoma, metastatic, uterus																										1
Renal, adenocarcinoma, metastatic, uterus																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																X										3
Adenocarcinoma, multiple																							X			1
Fibroadenoma												X	X		X		X		X	X	X				X	15
Fibroadenoma, multiple	X		X							X	X					X										8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma														X												2
Trichoepithelioma					X																					1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, lipoma						X																				1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	1 5 8	4 0 9	5 3 2	6 0 4	6 2 2	6 2 6	6 6 6	6 8 6	6 8 7	6 8 7	6 8 7	6 9 0	6 9 0	6 9 4	7 1 0	7 1 6	7 2 3	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	5 0 1	5 3 1	5 5 1	5 5 2	5 5 3	5 7 1	4 9 1	5 2 1	5 0 2	5 1 1	5 6 1	4 9 2	5 6 2	5 4 1	5 1 2	5 3 2	5 1 3	5 7 2	4 9 3	4 9 4	4 9 5	5 0 3	5 0 4	5 0 5	5 1 4
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant																	X								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, mammary gland					X																				
Adenocarcinoma, metastatic, uterus		X																							
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye							+	+							+		+							+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus		X																							
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X		X			X		X		X	X							

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	5 1 5	5 2 2	5 2 3	5 2 4	5 2 5	5 3 3	5 3 4	5 3 5	5 4 2	5 4 3	5 4 4	5 4 5	5 5 4	5 5 5	5 5 3	5 6 4	5 6 5	6 6 5	5 7 3	5 7 4	5 7 5	5 8 1	5 8 2	5 8 3	5 8 4	5 8 5	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant																											1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, mammary gland																											1
Adenocarcinoma, metastatic, uterus																											1
Alveolar/bronchiolar adenoma																X											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+													+	+	+	+	+			+		17
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																								X			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, uterus																											1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X	X									X				X							10

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 6,000 ppm

Number of Days on Study	3 9 0	4 5 7	5 0 8	5 1 8	5 8 7	6 1 2	6 3 9	6 6 5	6 9 4	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	9 3 1	9 4 1	9 4 2	8 9 1	8 7 1	8 5 1	8 6 1	9 1 1	9 1 2	8 5 2	8 5 3	8 5 4	8 5 5	8 6 2	8 6 3	8 6 4	8 6 5	8 7 2	8 7 3	8 7 4	8 7 5	8 8 1	8 8 2	8 8 3	8 8 4
Alimentary System																									
Esophagus	M	+	+	+	+	+	+	+	+																
Intestine large	+	+	+	+	+	+	+	+	+																
Intestine large, cecum	+	+	+	+	+	+	+	A	+																
Intestine large, colon	+	+	+	+	+	+	+	+	+																
Intestine large, rectum	+	+	+	+	+	+	+	+	+																
Intestine small	+	+	+	+	+	+	+	+	+																
Intestine small, duodenum	+	+	+	+	+	+	+	+	+																
Intestine small, ileum	+	+	+	+	+	+	+	+	+																
Intestine small, jejunum	+	+	+	+	+	+	+	A	+																
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery											+	+				+									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx								+															+		
Papilloma squamous																							X		
Salivary glands	+	+	+	+	+	+	+	+	+																
Stomach	+	+	+	+	+	+	+	+	+																
Stomach, forestomach	+	+	+	+	+	+	+	+	+																
Stomach, glandular	+	+	+	+	+	+	+	+	+																
Tooth			+																						
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+																
Carcinoma, metastatic, thyroid gland									X																
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+											+					
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+											+					
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+											+					
Pheochromocytoma malignant																									
Pheochromocytoma benign																				X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Carcinoma																									
Parathyroid gland	+	+	+	M	+	+	+	+	+																
Pituitary gland	+	+	+	+	+	+	+	+	+				+				+			+					
Pars distalis, adenoma							X	X	X				X				X			X					
Thyroid gland	+	+	+	+	+	+	+	+	+							+									
C-cell, adenoma																									
C-cell, carcinoma									X							X									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 6,000 ppm
(continued)

Number of Days on Study	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	8 8 5	8 9 2	8 9 3	8 9 4	8 9 5	9 0 1	9 0 2	9 0 3	9 0 4	9 0 5	9 1 3	9 1 4	9 1 5	9 2 1	9 2 2	9 2 3	9 2 4	9 2 5	9 3 2	9 3 3	9 3 4	9 3 5	9 4 3	9 4 4	9 4 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus																		+								9
Intestine large																		+								10
Intestine large, cecum																		+								9
Intestine large, colon																		+								10
Intestine large, rectum																		+								10
Intestine small																		+								10
Intestine small, duodenum																		+								10
Intestine small, ileum																		+								10
Intestine small, jejunum																		+								9
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery						+										+									+	6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pharynx																										2
Papilloma squamous																										1
Salivary glands																		+								10
Stomach																		+								10
Stomach, forestomach																										9
Stomach, glandular																										9
Tooth																										1
Cardiovascular System																										
Heart																		+								10
Carcinoma, metastatic, thyroid gland																										1
Endocrine System																										
Adrenal gland			+		+					+								+				+		+		16
Adrenal gland, cortex			+		+					+								+				+		+		16
Adenoma			X																							1
Adrenal gland, medulla			+		+					+								+				+		+		16
Pheochromocytoma malignant										X																1
Pheochromocytoma benign																								X	X	3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma														X												1
Parathyroid gland																		+								9
Pituitary gland		+				+		+		+				+			+	+					+		+	22
Pars distalis, adenoma		X				X		X						X			X	X					X			13
Thyroid gland			+															+								12
C-cell, adenoma			X																							1
C-cell, carcinoma																										2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 6,000 ppm
(continued)

Number of Days on Study	3	4	5	5	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	9	5	0	1	8	1	3	6	9	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	0	7	8	8	7	2	9	5	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Carcass ID Number	9	9	9	8	8	8	8	9	9	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
	3	4	4	9	7	5	6	1	1	5	5	5	5	6	6	6	6	7	7	7	7	8	8	8
	1	1	2	1	1	1	1	1	2	2	3	4	5	2	3	4	5	2	3	4	5	1	2	3	4
General Body System																									
Tissue NOS	+																								
Genital System																									
Clitoral gland	M	+	+	+	+	+	+	+	+						+									+	
Adenoma				X																					
Ovary	+	+	+	+	+	+	+	+	+																
Leiomyosarcoma																									
Uterus	+	+	+	+	+	+	+	+	+	+			+		+			+		+	+				
Polyp stromal					X					X								X		X					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+																
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+																
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma	X																								
Fibroadenoma				X	X				X				X	X							X				
Fibroadenoma, multiple								X														X			
Skin	+	+	+	+	+	+	+	+	+	+		+	+		+		+	+	+		+	+		+	
Subcutaneous tissue, fibroma																			X						
Subcutaneous tissue, fibrosarcoma						X																			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+									+							
Vertebra, coccygeal, chordoma																									
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+																
Oligodendroglioma malignant								X																	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 6,000 ppm
(continued)

Number of Days on Study	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	8 8 5	8 9 2	8 9 3	8 9 4	8 9 5	9 0 1	9 0 2	9 0 3	9 0 4	9 0 5	9 1 3	9 1 4	9 1 5	9 2 1	9 2 2	9 2 3	9 2 4	9 2 5	9 3 2	9 3 3	9 3 4	9 3 5	9 4 3	9 4 4	9 4 5	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS																										1
Genital System																										
Clitoral gland				+														+	+					+		14
Adenoma																										1
Ovary									+			+					+		+				+			14
Leiomyosarcoma									X																	1
Uterus				+				+			+	+					+		+			+		+		23
Polyp stromal				X				X			X															7
Hematopoietic System																										
Bone marrow																			+							10
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus																			+					+		11
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Fibroadenoma										X			X	X	X	X	X					X				13
Fibroadenoma, multiple		X																								3
Skin	+			+					+			+						+	+		+					26
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone			+		+														+		+		+			15
Vertebra, coccygeal, chordoma																							X			1
Skeletal muscle			+																							1
Nervous System																										
Brain																			+							10
Oligodendroglioma malignant																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 6,000 ppm
(continued)

Number of Days on Study	3	4	5	5	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	9	5	0	1	8	1	3	6	9	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	0	7	8	8	7	2	9	5	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Carcass ID Number	9	9	9	8	8	8	8	9	9	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
	3	4	4	9	7	5	6	1	1	5	5	5	5	6	6	6	6	7	7	7	7	8	8	8	8	8
	1	1	2	1	1	1	1	1	2	2	3	4	5	2	3	4	5	2	3	4	5	1	2	3	4	
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+																	
Trachea	+	+	+	+	+	+	+	+	+																	
Special Senses System																										
Eye																		+		+	+					
Harderian gland																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+																	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 6,000 ppm
(continued)

Number of Days on Study	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	8 8 5	8 9 2	8 9 3	8 9 4	8 9 5	9 0 1	9 0 2	9 0 3	9 0 4	9 0 5	9 1 3	9 1 4	9 1 5	9 2 1	9 2 2	9 2 3	9 2 4	9 2 5	9 3 2	9 3 3	9 3 4	9 3 5	9 4 3	9 4 4	9 4 5	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose																			+							10
Trachea																			+							10
Special Senses System																										
Eye											+			+					+	+	+	+	+	+	+	12
Harderian gland									+																	1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder																			+							10
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X																							1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm

Number of Days on Study	4 2 9	4 9 1	5 6 7	5 9 7	6 1 1	6 5 3	6 5 8	6 8 0	6 8 2	6 9 4	7 0 8	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	7 7 1	8 0 1	7 3 2	8 2 1	7 3 1	8 1 1	7 9 1	8 0 2	7 5 1	8 1 2	8 1 3	7 3 3	7 3 4	7 3 5	7 4 1	7 4 2	7 4 3	7 4 4	7 4 5	7 5 2	7 5 3	7 5 4	7 5 5	7 6 1	7 6 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+								+						
Intestine large	+	+	+	+	+	+	+	+	+	+	+								+						
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+								+						
Sarcoma, metastatic, uterus			X																						
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+								+						
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+								+						
Intestine small	+	+	+	+	+	+	+	+	+	+	+								+						
Intestine small, duodenum	+	+	+	+	+	+	M	+	+	+	+								+						
Sarcoma, metastatic, uterus			X																						
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	A								+						
Intestine small, jejunum	+	+	+	+	+	A	+	A	+	+	A								+						
Sarcoma, metastatic, uterus			X																						
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery			+															+						+
Sarcoma, metastatic, uterus			X																						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uterus			X																						
Pharynx											+														
Squamous cell carcinoma											X														
Salivary glands	+	+	+	+	+	+	+	+	+	+	+								+						
Stomach	+	+	+	+	+	+	+	+	+	+	+								+						
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+								+						
Sarcoma, metastatic, uterus			X																						
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+								+						
Sarcoma, metastatic, uterus			X																						
Tongue		+									+														
Squamous cell carcinoma		X									X														
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+								+						
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+							+						
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+							+						
Capsule, sarcoma, metastatic, uterus			X																						
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+							+						
Pheochromocytoma complex												X													
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+								+						

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	7 6 3	7 6 4	7 6 5	7 7 2	7 7 3	7 7 4	7 7 5	7 8 1	7 8 2	7 8 3	7 8 4	7 8 5	7 9 2	7 9 3	7 9 4	7 9 5	8 0 3	8 0 4	8 0 5	8 1 4	8 1 5	8 2 2	8 2 3	8 2 4	8 2 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus																										12
Intestine large																										12
Intestine large, cecum																										12
Sarcoma, metastatic, uterus																										1
Intestine large, colon																										12
Intestine large, rectum																										12
Intestine small																										12
Intestine small, duodenum																										11
Sarcoma, metastatic, uterus																										1
Intestine small, ileum																										11
Intestine small, jejunum																										9
Sarcoma, metastatic, uterus																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X																									1
Mesentery					+	+	+					+	+						+				+			10
Sarcoma, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, uterus																										1
Pharynx																										1
Squamous cell carcinoma																										1
Salivary glands																										12
Stomach																										12
Stomach, forestomach																										12
Sarcoma, metastatic, uterus																										1
Stomach, glandular																										12
Sarcoma, metastatic, uterus																										1
Tongue																										2
Squamous cell carcinoma																										2
Cardiovascular System																										
Heart																										12
Endocrine System																										
Adrenal gland																										13
Adrenal gland, cortex																										13
Capsule, sarcoma, metastatic, uterus																										1
Adrenal gland, medulla																										13
Pheochromocytoma complex																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland																										12

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	4 2 9	4 9 1	5 6 7	5 9 7	6 1 1	6 5 3	6 5 8	6 8 0	6 8 2	6 9 4	7 0 8	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	7 7 1	8 0 1	7 3 2	8 2 1	7 3 1	8 1 1	7 9 1	8 0 2	7 5 1	8 1 2	8 1 3	7 3 3	7 3 4	7 3 5	7 4 1	7 4 2	7 4 3	7 4 4	7 4 5	7 5 2	7 5 3	7 5 4	7 5 5	7 6 1	7 6 2
Endocrine System (continued)																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+				+		+		+						
Pars distalis, adenoma					X	X			X		X				X		X		X						
Pars distalis, adenoma, multiple																									
Pars distalis, carcinoma							X																		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+								+						
C-cell, adenoma									X																
C-cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+								+						
Ovary	+	+	+	+	+	+	+	+	+	+	+								+		+				
Uterus	+	+	+	+	+	+	+	+	+	+	+				+			+	+			+	+	+	+
Leiomyosarcoma																									
Polyp stromal					X										X								X		
Polyp stromal, two, multiple																		X							
Sarcoma			X																						
Vagina	+							+	+																+
Sarcoma								X																	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+								+						
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesenteric, sarcoma, metastatic, uterus			X																						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+								+						
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Fibroadenoma					X		X			X	X	X									X				
Fibroadenoma, multiple									X															X	
Myoepithelioma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+			+			+	+	+	+	+		+
Subcutaneous tissue, fibroma																X									
Subcutaneous tissue, fibrosarcoma																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	7 6 3	7 6 4	7 6 5	7 7 2	7 7 3	7 7 4	7 7 5	7 8 1	7 8 2	7 8 3	7 8 4	7 8 5	7 9 2	7 9 3	7 9 4	7 9 5	8 0 3	8 0 4	8 0 5	8 1 4	8 1 5	8 2 2	8 2 3	8 2 4	8 2 5	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Pituitary gland			+			+	+						+								+		+			20
Pars distalis, adenoma						X	X														X		X			11
Pars distalis, adenoma, multiple													X													1
Pars distalis, carcinoma																										1
Thyroid gland				+																						13
C-cell, adenoma																										1
C-cell, carcinoma				X																						1
General Body System																										
None																										
Genital System																										
Clitoral gland						+										+										14
Ovary																				+						14
Uterus				+				+			+		+		+	+	+		+	+					+	28
Leiomyosarcoma													X													1
Polyp stromal											X								X							5
Polyp stromal, two, multiple																										1
Sarcoma																										1
Vagina															+											5
Sarcoma																										1
Hematopoietic System																										
Bone marrow																										12
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesenteric, sarcoma, metastatic, uterus																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus																										12
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma	X		X	X			X		X			X				X			X	X				X		16
Fibroadenoma, multiple					X																	X				4
Myoepithelioma													X													1
Skin	+	+	+	+		+		+	+		+			+			+	+			+	+				33
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma						X																				1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	4	4	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	2	9	6	9	1	5	5	8	8	9	0	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	1	7	7	1	3	8	0	2	4	8	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Carcass ID Number	7	8	7	8	7	8	7	8	7	8	8	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	7	0	3	2	3	1	9	0	5	1	1	3	3	3	4	4	4	4	4	5	5	5	5	6	6
	1	1	2	1	1	1	1	2	1	2	3	3	4	5	1	2	3	4	5	2	3	4	5	1	2
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+								+		+				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+								+						
Astrocytoma malignant																									
Carcinoma, metastatic, pituitary gland							X																		
Ependymoma malignant	X			X																					
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																				X					
Nose	+	+	+	+	+	+	+	+	+	+	+								+						
Trachea	+	+	+	+	+	+	+	+	+	+	+								+						
Special Senses System																									
Eye									+	+										+	+	+	+		+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+								+						
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	7 6 3	7 6 4	7 6 5	7 7 2	7 7 3	7 7 4	7 7 5	7 8 1	7 8 2	7 8 3	7 8 4	7 8 5	7 9 2	7 9 3	7 9 4	7 9 5	8 0 3	8 0 4	8 0 5	8 1 4	8 1 5	8 2 2	8 2 3	8 2 4	8 2 5	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone			+										+			+										16
Nervous System																										
Brain			+																							13
Astrocytoma malignant			X																							1
Carcinoma, metastatic, pituitary gland																										1
Ependymoma malignant																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																							X			2
Nose																										12
Trachea																										12
Special Senses System																										
Eye		+	+															+		+	+	+				13
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder																										12
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm

Number of Days on Study	4 2 7	4 7 7	5 1 9	5 5 3	5 7 4	6 1 1	6 8 2	6 8 7	7 1 1	7 2 3	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	6 7 1	6 8 1	6 5 1	7 0 1	6 9 1	6 4 1	7 0 2	6 7 2	6 5 2	7 0 3	6 1 1	6 1 2	6 1 3	6 1 4	6 1 5	6 2 1	6 2 2	6 2 3	6 2 4	6 2 5	6 3 1	6 3 2	6 3 3	6 3 4	6 3 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma				X		X											X								
Hepatocellular adenoma, multiple										X															
Mesentery		+																						+	
Pancreas	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X																			
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign													X												
Islets, pancreatic	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X						X	X	X		X	X	X	X	X		X	X	X			X		X
Pars distalis, adenoma, two, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma											X				X						X				
Follicular cell, adenoma																									X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	6 4 2	6 4 3	6 4 4	6 4 5	6 5 3	6 5 4	6 5 5	6 6 1	6 6 2	6 6 3	6 6 4	6 6 5	6 7 3	7 7 4	7 7 5	6 8 2	6 8 3	6 8 4	6 8 5	6 9 2	6 9 3	6 9 4	6 9 5	7 0 4	7 0 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp adenomatous									X																	1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma								X		X		X	X											X	X	9
Hepatocellular adenoma, multiple																										1
Mesentery											+					+										4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign				X				X						X												4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X			X	X												X		X		X	X	21
Pars distalis, adenoma, two, multiple			X																							1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma											X				X										X	6
Follicular cell, adenoma							X																			2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	4 2 7	4 7 7	5 1 9	5 5 3	5 7 4	6 1 1	6 8 2	6 8 7	7 1 1	7 2 3	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	6 7 1	6 8 1	6 5 1	7 0 1	6 9 1	6 4 1	7 0 2	6 7 2	6 5 2	7 0 3	6 1 1	6 1 2	6 1 3	6 1 4	6 1 5	6 2 1	6 2 2	6 2 3	6 2 4	6 2 5	6 3 1	6 3 2	6 3 3	6 3 4	6 3 5
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma										X															
Leiomyosarcoma																									
Polyp stromal		X				X												X		X					
Polyp stromal, two, multiple																									
Sarcoma stromal			X																						
Vagina							+																		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									X
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								
Fibroadenoma				X					X	X					X						X			X	
Fibroadenoma, multiple														X											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	6 4 2	6 4 3	6 4 4	6 4 5	6 5 3	6 5 4	6 5 5	6 6 1	6 6 2	6 6 3	6 6 4	6 6 5	6 6 3	6 7 4	6 7 5	6 8 2	6 8 3	6 8 4	6 8 5	6 9 2	6 9 3	6 9 4	6 9 5	7 0 4	7 0 5	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Leiomyosarcoma																					X					1
Polyp stromal		X									X		X	X	X											9
Polyp stromal, two, multiple				X																						1
Sarcoma stromal																										1
Vagina																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																X										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Fibroadenoma		X	X				X									X									X	11
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	4 2 7	4 7 7	5 1 9	5 5 3	5 7 4	6 1 1	6 8 2	6 8 7	7 1 1	7 2 3	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	6 7 1	6 8 1	6 5 1	7 0 1	6 9 1	6 4 1	7 0 2	6 7 2	6 5 2	7 0 3	6 1 1	6 1 2	6 1 3	6 1 4	6 1 5	6 2 1	6 2 2	6 2 3	6 2 4	6 2 5	6 3 1	6 3 2	6 3 3	6 3 4	6 3 5
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye								+		+											+			+	+
Urinary System																									
Kidney	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear							X																		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	6 4 2	6 4 3	6 4 4	6 4 5	6 5 3	6 5 4	6 5 5	6 6 1	6 6 2	6 6 3	6 6 4	6 6 5	6 7 3	6 7 4	6 7 5	6 8 2	6 8 3	6 8 4	6 8 5	6 9 2	6 9 3	6 9 4	6 9 5	7 0 4	7 0 5	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X													2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye				+													+				+	+		+		10
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																X										1
Leukemia mononuclear							X																			2

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	4/49 (8%)	3/16 (19%)[e]	0/13 (0%)[e]	4/50 (8%)
Adjusted rates[b]	12.0%			10.0%
Terminal rates[c]	2/31 (6%)			4/40 (10%)
First incidence (days)	723			729 (T)
Life table tests[d]				P=0.508N
Logistic regression tests[d]				P=0.548N
Fisher exact test[d]				P=0.631N
Adrenal Medulla: Pheochromocytoma (Benign, Complex, or Malignant)				
Overall rates	5/49 (10%)	4/16 (25%)[e]	1/13 (8%)[e]	4/50 (8%)
Adjusted rates	15.0%			10.0%
Terminal rates	3/31 (10%)			4/40 (10%)
First incidence (days)	723			729 (T)
Life table tests				P=0.354N
Logistic regression tests				P=0.388N
Fisher exact test				P=0.487N
Clitoral Gland: Adenoma				
Overall rates	9/47 (19%)	1/14 (7%)[e]	0/14 (0%)[e]	1/50 (2%)
Adjusted rates	29.1%			2.5%
Terminal rates	8/29 (28%)			1/40 (3%)
First incidence (days)	532			729 (T)
Life table tests				P=0.002N
Logistic regression tests				P=0.007N
Fisher exact test				P=0.006N
Liver: Hepatocellular Adenoma				
Overall rates	0/50 (0%)	0/50 (0%)	1/50 (2%)	10/50 (20%)
Adjusted rates	0.0%	0.0%	2.6%	23.0%
Terminal rates	0/32 (0%)	0/41 (0%)	1/39 (3%)	7/40 (18%)
First incidence (days)	–[f]	–	729 (T)	553
Life table tests	P≤0.001	–	P=0.539	P=0.004
Logistic regression tests	P≤0.001	–	P=0.539	P=0.001
Cochran-Armitage test	P≤0.001			
Fisher exact test		–	P=0.500	P≤0.001
Mammary Gland: Adenocarcinoma				
Overall rates	4/50 (8%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
Adjusted rates	10.1%	2.0%	0.0%	0.0%
Terminal rates	2/32 (6%)	0/41 (0%)	0/39 (0%)	0/40 (0%)
First incidence (days)	158	390	–	–
Life table tests	P=0.018N	P=0.157N	P=0.054N	P=0.054N
Logistic regression tests	P=0.033N	P=0.209N	P=0.094N	P=0.087N
Cochran-Armitage test	P=0.020N			
Fisher exact test		P=0.181N	P=0.059N	P=0.059N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Mammary Gland: Fibroadenoma				
Overall rates	23/50 (46%)	16/50 (32%)	20/50 (40%)	12/50 (24%)
Adjusted rates	56.6%	35.4%	45.4%	27.8%
Terminal rates	15/32 (47%)	12/41 (29%)	15/39 (38%)	9/40 (23%)
First incidence (days)	604	518	611	553
Life table tests	P=0.013N	P=0.038N	P=0.173N	P=0.006N
Logistic regression tests	P=0.024N	P=0.103N	P=0.310N	P=0.015N
Cochran-Armitage test	P=0.028N			
Fisher exact test		P=0.109N	P=0.343N	P=0.018N
Mammary Gland: Adenoma or Fibroadenoma				
Overall rates	23/50 (46%)	16/50 (32%)	20/50 (40%)	13/50 (26%)
Adjusted rates	56.6%	35.4%	45.4%	30.1%
Terminal rates	15/32 (47%)	12/41 (29%)	15/39 (38%)	10/40 (25%)
First incidence (days)	604	518	611	553
Life table tests	P=0.022N	P=0.038N	P=0.173N	P=0.010N
Logistic regression tests	P=0.041N	P=0.103N	P=0.310N	P=0.025N
Cochran-Armitage test	P=0.047N			
Fisher exact test		P=0.109N	P=0.343N	P=0.030N
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma				
Overall rates	26/50 (52%)	17/50 (34%)	20/50 (40%)	13/50 (26%)
Adjusted rates	60.9%	36.7%	45.4%	30.1%
Terminal rates	16/32 (50%)	12/41 (29%)	15/39 (38%)	10/40 (25%)
First incidence (days)	158	390	611	553
Life table tests	P=0.006N	P=0.020N	P=0.073N	P=0.002N
Logistic regression tests	P=0.013N	P=0.056N	P=0.157N	P=0.007N
Cochran-Armitage test	P=0.012N			
Fisher exact test		P=0.053N	P=0.158N	P=0.007N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	25/50 (50%)	13/22 (59%)[e]	12/20 (60%)[e]	22/50 (44%)
Adjusted rates	60.3%			49.9%
Terminal rates	16/32 (50%)			18/40 (45%)
First incidence (days)	604			477
Life table tests				P=0.128N
Logistic regression tests				P=0.313N
Fisher exact test				P=0.344N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	25/50 (50%)	13/22 (59%)[e]	13/20 (65%)[e]	22/50 (44%)
Adjusted rates	60.3%			49.9%
Terminal rates	16/32 (50%)			18/40 (45%)
First incidence (days)	604			477
Life table tests				P=0.128N
Logistic regression tests				P=0.313N
Fisher exact test				P=0.344N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3 *(continued)*

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Skin: Keratoacanthoma or Trichoepithelioma				
Overall rates	3/50 (6%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rates	9.4%	0.0%	0.0%	0.0%
Terminal rates	3/32 (9%)	0/41 (0%)	0/39 (0%)	0/40 (0%)
First incidence (days)	729 (T)	–	–	–
Life table tests	P=0.038N	P=0.081N	P=0.088N	P=0.085N
Logistic regression tests	P=0.038N	P=0.081N	P=0.088N	P=0.085N
Cochran-Armitage test	P=0.049N			
Fisher exact test		P=0.121N	P=0.121N	P=0.121N
Thyroid Gland (C-cell): Adenoma				
Overall rates	6/50 (12%)	1/12 (8%)[e]	1/13 (8%)[e]	6/50 (12%)
Adjusted rates	16.1%			15.0%
Terminal rates	3/32 (9%)			6/40 (15%)
First incidence (days)	687			729 (T)
Life table tests				P=0.486N
Logistic regression tests				P=0.597N
Fisher exact test				P=0.620N
Thyroid Gland (C-cell): Carcinoma				
Overall rates	1/50 (2%)	2/12 (17%)[e]	1/13 (8%)[e]	0/50 (0%)
Adjusted rates	3.1%			0.0%
Terminal rates	1/32 (3%)			0/40 (0%)
First incidence (days)	729 (T)			–
Life table tests				P=0.455N
Logistic regression tests				P=0.455N
Fisher exact test				P=0.500N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	7/50 (14%)	3/12 (25%)[e]	2/13 (15%)[e]	6/50 (12%)
Adjusted rates	19.0%			15.0%
Terminal rates	4/32 (13%)			6/40 (15%)
First incidence (days)	687			729 (T)
Life table tests				P=0.360N
Logistic regression tests				P=0.471N
Fisher exact test				P=0.500N
Uterus: Stromal Polyp				
Overall rates	10/50 (20%)	7/50 (14%)	6/50 (12%)	10/50 (20%)
Adjusted rates	25.6%	16.5%	14.7%	23.4%
Terminal rates	6/32 (19%)	6/41 (15%)	5/39 (13%)	8/40 (20%)
First incidence (days)	409	587	611	477
Life table tests	P=0.511N	P=0.189N	P=0.141N	P=0.449N
Logistic regression tests	P=0.473	P=0.304N	P=0.221N	P=0.575
Cochran-Armitage test	P=0.485			
Fisher exact test		P=0.298N	P=0.207N	P=0.598N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rates	11/50 (22%)	7/50 (14%)	6/50 (12%)	11/50 (22%)
Adjusted rates	27.7%	16.5%	14.7%	25.0%
Terminal rates	6/32 (19%)	6/41 (15%)	5/39 (13%)	8/40 (20%)
First incidence (days)	409	587	611	477
Life table tests	P=0.532N	P=0.131N	P=0.095N	P=0.445N
Logistic regression tests	P=0.440	P=0.222N	P=0.154N	P=0.563
Cochran-Armitage test	P=0.459			
Fisher exact test		P=0.218N	P=0.143N	P=0.595N
All Organs: Mononuclear Cell Leukemia				
Overall rates	10/50 (20%)	1/50 (2%)	0/50 (0%)	2/50 (4%)
Adjusted rates	25.6%	2.4%	0.0%	4.7%
Terminal rates	4/32 (13%)	1/41 (2%)	0/39 (0%)	1/40 (3%)
First incidence (days)	686	729 (T)	-	682
Life table tests	P=0.006N	P=0.003N	P=0.001N	P=0.010N
Logistic regression tests	P=0.007N	P=0.005N	P=0.001N	P=0.014N
Cochran-Armitage test	P=0.007N			
Fisher exact test		P=0.004N	P≤0.001N	P=0.014N
All Organs: Benign Tumors				
Overall rates	44/50 (88%)	31/50 (62%)	32/50 (64%)	38/50 (76%)
Adjusted rates	91.6%	67.4%	71.1%	82.6%
Terminal rates	28/32 (88%)	26/41 (63%)	26/39 (67%)	32/40 (80%)
First incidence (days)	409	518	611	477
Life table tests	P=0.088N	P≤0.001N	P=0.002N	P=0.014N
Logistic regression tests	P=0.235N	P=0.002N	P=0.003N	P=0.071N
Cochran-Armitage test	P=0.277N			
Fisher exact test		P=0.002N	P=0.005N	P=0.096N
All Organs: Malignant Tumors				
Overall rates	17/50 (34%)	10/50 (20%)	14/50 (28%)	7/50 (14%)
Adjusted rates	39.4%	22.0%	29.7%	15.8%
Terminal rates	7/32 (22%)	6/41 (15%)	7/39 (18%)	4/40 (10%)
First incidence (days)	158	390	429	519
Life table tests	P=0.024N	P=0.054N	P=0.244N	P=0.012N
Logistic regression tests	P=0.034N	P=0.093N	P=0.380N	P=0.020N
Cochran-Armitage test	P=0.030N			
Fisher exact test		P=0.088N	P=0.333N	P=0.017N
All Organs: Benign and Malignant Tumors				
Overall rates	46/50 (92%)	35/50 (70%)	38/50 (76%)	41/50 (82%)
Adjusted rates	92.0%	72.9%	76.0%	85.4%
Terminal rates	28/32 (88%)	28/41 (68%)	27/39 (69%)	33/40 (83%)
First incidence (days)	158	390	429	477
Life table tests	P=0.125N	P=0.002N	P=0.023N	P=0.027N
Logistic regression tests	P=0.333N	P=0.006N	P=0.062N	P=0.115N
Cochran-Armitage test	P=0.325N			
Fisher exact test		P=0.005N	P=0.027N	P=0.117N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3 *(continued)*

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus, no statistical analyses are provided.
[f] Not applicable; no tumors in animal group

TABLE B4a
Historical Incidence of Hepatocellular Adenomas in Untreated Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
C.I. Pigment Red 3	0/50
Nitrofurantoin	0/50
o-Nitroanisole	0/50
Polysorbate 80	0/50
Rhodamine 6G	0/50
Roxarsone	0/50
Overall Historical Incidence	
Total	3/800 (0.4%)
Standard deviation	1.5%
Range	0%-6%

[a] Data as of 3 April 1991

TABLE B4b
Historical Incidence of Leukemia in Untreated Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
C.I. Pigment Red 3	10/50
Nitrofurantoin	13/50
o-Nitroanisole	14/50
Polysorbate 80	26/50
Rhodamine 6G	11/50
Roxarsone	14/50
Total	88/300 (29.3%)
Standard deviation	11.6%
Range	20%-52%
Overall Historical Incidence	
Total	213/800 (26.6%)
Standard deviation	8.8%
Range	14%-52%

[a] Data as of 3 April 1991; includes lymphocytic, monocytic, mononuclear, or undifferentiated cell type

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3[a]

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-month interim evaluation	10	10	10	10
Early deaths				
Natural death	3	2	3	3
Moribund	15	7	8	7
Survivors				
Terminal sacrifice	32	40	39	40
Died last week of study		1		
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large	(50)	(10)	(12)	(50)
Wall, inflammation, subacute				1 (2%)
Intestine large, cecum	(48)	(9)	(12)	(50)
Parasite metazoan	2 (4%)			2 (4%)
Intestine large, colon	(50)	(10)	(12)	(48)
Parasite metazoan	2 (4%)	2 (20%)		8 (17%)
Intestine large, rectum	(50)	(10)	(12)	(50)
Parasite metazoan	10 (20%)	1 (10%)	1 (8%)	6 (12%)
Liver	(50)	(50)	(50)	(50)
Angiectasis, focal	1 (2%)			
Angiectasis, multifocal			2 (4%)	
Basophilic focus	1 (2%)	11 (22%)	17 (34%)	11 (22%)
Basophilic focus, multiple	37 (74%)	29 (58%)	26 (52%)	30 (60%)
Clear cell focus				2 (4%)
Degeneration, cystic, focal		1 (2%)	2 (4%)	3 (6%)
Degeneration, cystic, multifocal			1 (2%)	2 (4%)
Eosinophilic focus	1 (2%)	7 (14%)	13 (26%)	14 (28%)
Eosinophilic focus, multiple			5 (10%)	2 (4%)
Granuloma, multiple	27 (54%)	21 (42%)	43 (86%)	44 (88%)
Hepatodiaphragmatic nodule	4 (8%)	6 (12%)	12 (24%)	3 (6%)
Mixed cell focus	4 (8%)	10 (20%)	13 (26%)	3 (6%)
Mixed cell focus, multiple		6 (12%)	17 (34%)	37 (74%)
Necrosis, focal	2 (4%)			
Necrosis, multifocal	1 (2%)			1 (2%)
Pigmentation, cholesterol, multifocal		3 (6%)	14 (28%)	41 (82%)
Regeneration	6 (12%)			
Vacuolization cytoplasmic, diffuse	4 (8%)	1 (2%)		1 (2%)
Vacuolization cytoplasmic, multifocal			1 (2%)	
Biliary tract, dilatation, focal			2 (4%)	4 (8%)
Biliary tract, proliferation	18 (36%)	12 (24%)	18 (36%)	29 (58%)
Centrilobular, necrosis	1 (2%)	1 (2%)		
Mesentery	(6)	(6)	(10)	(4)
Inflammation, chronic				1 (25%)
Inflammation, granulomatous		1 (17%)		
Fat, necrosis, focal	4 (67%)	6 (100%)	10 (100%)	3 (75%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Alimentary System (continued)				
Pancreas	(50)	(50)	(50)	(49)
Basophilic focus	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Acinus, atrophy, multifocal	22 (44%)	33 (66%)	40 (80%)	36 (73%)
Acinus, hyperplasia, focal	2 (4%)			
Acinus, hyperplasia, multifocal	1 (2%)			
Artery, hypertrophy			1 (2%)	
Artery, inflammation, subacute		1 (2%)		
Duct, hyperplasia				2 (4%)
Pharynx		(2)	(1)	
Hyperplasia		1 (50%)		
Salivary glands	(50)	(10)	(12)	(50)
Acinus, atrophy, focal	4 (8%)			2 (4%)
Acinus, atrophy, multifocal	1 (2%)		1 (8%)	6 (12%)
Stomach, forestomach	(50)	(9)	(12)	(50)
Hyperplasia			2 (17%)	1 (2%)
Inflammation, subacute			2 (17%)	1 (2%)
Mineralization	1 (2%)			
Perforation			1 (8%)	
Ulcer			1 (8%)	1 (2%)
Stomach, glandular	(50)	(9)	(12)	(50)
Erosion			1 (8%)	
Mineralization	1 (2%)			4 (8%)
Tooth		(1)		
Dysplasia		1 (100%)		
Cardiovascular System				
Heart	(50)	(10)	(12)	(50)
Cardiomyopathy	33 (66%)	6 (60%)	7 (58%)	34 (68%)
Inflammation, subacute, focal	1 (2%)			2 (4%)
Atrium, thrombus		1 (10%)		1 (2%)
Valve, inflammation, subacute				1 (2%)
Endocrine System				
Adrenal gland, cortex	(50)	(16)	(13)	(50)
Angiectasis	1 (2%)	1 (6%)	1 (8%)	1 (2%)
Congestion	1 (2%)			
Degeneration, fatty, focal	8 (16%)	1 (6%)	6 (46%)	15 (30%)
Degeneration, fatty, multifocal		3 (19%)	1 (8%)	
Hyperplasia, focal	18 (36%)	3 (19%)	2 (15%)	20 (40%)
Hyperplasia, multifocal				1 (2%)
Hypertrophy, focal	4 (8%)		1 (8%)	6 (12%)
Inflammation, granulomatous, multifocal	1 (2%)			
Pigmentation, cholesterol, multifocal				1 (2%)
Capsule, accessory adrenal cortical nodule	4 (8%)	2 (13%)		4 (8%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Endocrine System (continued)				
Adrenal gland, medulla	(49)	(16)	(13)	(50)
Hyperplasia, focal	10 (20%)	2 (13%)	2 (15%)	11 (22%)
Hyperplasia, multifocal	1 (2%)			
Islets, pancreatic	(49)	(50)	(50)	(49)
Hyperplasia	1 (2%)			
Parathyroid gland	(50)	(9)	(12)	(50)
Hyperplasia	1 (2%)			1 (2%)
Pituitary gland	(50)	(22)	(20)	(50)
Cyst		1 (5%)	1 (5%)	
Pars distalis, angiectasis	35 (70%)	15 (68%)	12 (60%)	26 (52%)
Pars distalis, cyst	26 (52%)	10 (45%)	6 (30%)	19 (38%)
Pars distalis, hemorrhage		2 (9%)		
Pars distalis, hyperplasia, focal	15 (30%)	5 (23%)	3 (15%)	14 (28%)
Pars distalis, pigmentation, hemosiderin	24 (48%)	4 (18%)	4 (20%)	9 (18%)
Thyroid gland	(50)	(12)	(13)	(50)
Pigmentation, cholesterol, focal				1 (2%)
Ultimobranchial cyst	1 (2%)		1 (8%)	1 (2%)
C-cell, hyperplasia, focal	8 (16%)		2 (15%)	10 (20%)
Follicle, cyst				3 (6%)
General Body System				
None				
Genital System				
Clitoral gland	(47)	(14)	(14)	(50)
Hyperplasia	7 (15%)	2 (14%)	1 (7%)	3 (6%)
Inflammation, subacute	9 (19%)	3 (21%)		2 (4%)
Duct, cyst	14 (30%)	1 (7%)	2 (14%)	4 (8%)
Ovary	(50)	(14)	(14)	(50)
Cyst	5 (10%)	3 (21%)	5 (36%)	8 (16%)
Inflammation, granulomatous, multifocal	1 (2%)			
Uterus	(50)	(23)	(28)	(50)
Dilatation	3 (6%)	2 (9%)	2 (7%)	9 (18%)
Hemorrhage		1 (4%)		
Cervix, abscess	5 (10%)	5 (22%)	12 (43%)	6 (12%)
Cervix, abscess, multiple		1 (4%)		
Cervix, cyst	5 (10%)	5 (22%)	13 (46%)	6 (12%)
Cervix, cyst, multiple		1 (4%)		
Endometrium, hyperplasia, cystic	1 (2%)			3 (6%)
Mucosa, cyst	3 (6%)		1 (4%)	6 (12%)
Wall, cervix, hypertrophy	1 (2%)			
Vagina	(7)		(5)	(1)
Wall, hypertrophy	1 (14%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Hematopoietic System				
Bone marrow	(50)	(10)	(12)	(50)
Hyperplasia	8 (16%)	1 (10%)	1 (8%)	9 (18%)
Infiltration cellular, histiocyte	2 (4%)			4 (8%)
Myelofibrosis	2 (4%)			2 (4%)
Pigmentation, cholesterol, multifocal	2 (4%)			4 (8%)
Lymph node	(50)	(50)	(50)	(50)
Inguinal, hyperplasia, lymphoid	1 (2%)			
Mediastinal, congestion	2 (4%)	2 (4%)	7 (14%)	4 (8%)
Mediastinal, ectasia		3 (6%)	4 (8%)	3 (6%)
Mesenteric, ectasia			2 (4%)	3 (6%)
Mesenteric, fibrosis, focal			1 (2%)	
Mesenteric, hyperplasia, macrophage, multifocal	49 (98%)	48 (96%)	48 (96%)	48 (96%)
Mesenteric, necrosis, focal			3 (6%)	1 (2%)
Mesenteric, necrosis, multifocal			1 (2%)	4 (8%)
Mesenteric, pigmentation, cholesterol, multifocal	49 (98%)	45 (90%)	47 (94%)	48 (96%)
Pancreatic, ectasia	2 (4%)			2 (4%)
Pancreatic, hyperplasia, macrophage, multifocal				2 (4%)
Pancreatic, pigmentation, cholesterol, multifocal				2 (4%)
Lymph node, mandibular	(50)	(50)	(50)	(49)
Congestion		1 (2%)	1 (2%)	1 (2%)
Ectasia	21 (42%)	17 (34%)	18 (36%)	21 (43%)
Spleen	(50)	(50)	(50)	(50)
Atrophy		1 (2%)	1 (2%)	1 (2%)
Fibrosis, focal	2 (4%)			3 (6%)
Hematopoietic cell proliferation	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, focal	1 (2%)			
Thymus	(49)	(11)	(12)	(50)
Atrophy				1 (2%)
Cyst	3 (6%)	1 (9%)		3 (6%)
Inflammation, subacute		1 (9%)		
Artery, mediastinum, inflammation, subacute				1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(49)	(50)
Duct, cyst	1 (2%)			
Skin	(50)	(26)	(33)	(50)
Inflammation, suppurative, acute, focal				1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Musculoskeletal System				
Bone	(50)	(15)	(16)	(50)
Fibrous osteodystrophy	1 (2%)			
Inflammation, chronic		1 (7%)		
Cranium, osteopetrosis	5 (10%)		3 (19%)	7 (14%)
Femur, osteopetrosis	4 (8%)	3 (20%)	3 (19%)	11 (22%)
Turbinate, osteopetrosis	2 (4%)	2 (13%)	1 (6%)	9 (18%)
Nervous System				
Brain	(50)	(10)	(13)	(50)
Compression	4 (8%)	1 (10%)	1 (8%)	3 (6%)
Hemorrhage, multifocal		1 (10%)		1 (2%)
Hydrocephalus	1 (2%)			1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	1 (2%)		1 (2%)	
Granuloma, multiple	1 (2%)			
Hemorrhage, multifocal			1 (2%)	
Infiltration cellular, histiocyte, diffuse	1 (2%)			1 (2%)
Pigmentation, hemosiderin, multifocal		1 (2%)		
Alveolar epithelium, hyperplasia, focal				3 (6%)
Mediastinum, inflammation, chronic				1 (2%)
Pleura, congestion, multifocal				3 (6%)
Pleura, fibrosis, focal	1 (2%)			
Nose	(50)	(10)	(12)	(50)
Foreign body	2 (4%)			5 (10%)
Fungus	2 (4%)			4 (8%)
Inflammation, suppurative, acute	2 (4%)			6 (12%)
Nasolacrimal duct, foreign body				1 (2%)
Nasolacrimal duct, inflammation, subacute	19 (38%)		1 (8%)	21 (42%)
Special Senses System				
Eye	(17)	(12)	(13)	(10)
Cataract	17 (100%)	12 (100%)	13 (100%)	10 (100%)
Anterior chamber, hemorrhage		2 (17%)		1 (10%)
Posterior chamber, hemorrhage		1 (8%)		
Retina, degeneration	17 (100%)	11 (92%)	13 (100%)	10 (100%)
Harderian gland		(1)		
Hyperplasia		1 (100%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(49)
Fibrosis, focal				1 (2%)
Hydronephrosis	1 (2%)			1 (2%)
Inflammation, subacute		1 (2%)	1 (2%)	
Metaplasia, osseous, focal				1 (2%)
Mineralization, multifocal				1 (2%)
Nephropathy, chronic	49 (98%)	49 (98%)	50 (100%)	48 (98%)
Artery, inflammation, subacute			1 (2%)	
Cortex, cyst	1 (2%)			
Papilla, necrosis				1 (2%)
Papilla, transitional epithelium, hyperplasia	1 (2%)	5 (10%)	4 (8%)	12 (24%)
Pelvis, transitional epithelium, hyperplasia			1 (2%)	2 (4%)
Renal tubule, pigmentation, hemosiderin, multifocal	2 (4%)			
Urinary bladder	(50)	(10)	(12)	(50)
Calculus micro observation only				1 (2%)
Hemorrhage, multifocal				1 (2%)
Mucosa, hyperplasia				2 (4%)

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR STUDY OF C.I. PIGMENT RED 3

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3[a]

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-month interim evaluation[b]	10	10	10	10
Early deaths				
Natural death	9	9	9	7
Moribund	8	13	10	10
Survivors				
Terminal sacrifice	33	28	31	33
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, duodenum	(46)	(18)	(16)	(45)
Polyp adenomatous			1 (6%)	
Intestine small, ileum	(45)	(18)	(16)	(44)
Intestine small, jejunum	(46)	(19)	(14)	(46)
Liver	(50)	(48)	(50)	(49)
Hemangiosarcoma		1 (2%)	1 (2%)	
Hepatocellular carcinoma	4 (8%)	7 (15%)	8 (16%)	4 (8%)
Hepatocellular carcinoma, multiple		3 (6%)		
Hepatocellular carcinoma, multiple, three	1 (2%)			
Hepatocellular adenoma	6 (12%)	11 (23%)	9 (18%)	13 (27%)
Hepatocellular adenoma, multiple			2 (4%)	2 (4%)
Hepatocellular adenoma, multiple, two	2 (4%)	1 (2%)		1 (2%)
Histiocytic sarcoma			1 (2%)	
Stomach, forestomach	(49)	(21)	(22)	(50)
Papilloma squamous		1 (5%)		
Cardiovascular System				
None				
Endocrine System				
Adrenal gland, cortex	(50)	(23)	(19)	(50)
Adrenal gland, medulla	(50)	(21)	(18)	(50)
Pheochromocytoma malignant		1 (5%)		
Pituitary gland	(46)	(20)	(18)	(49)
Thyroid gland	(50)	(49)	(50)	(50)
Follicular cell, adenoma			1 (2%)	5 (10%)
General Body System				
None				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3
(continued)

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Genital System				
Epididymis	(50)	(22)	(19)	(50)
Fibrosarcoma, metastatic, skin			1 (5%)	
Prostate	(50)	(22)	(19)	(50)
Testes	(50)	(22)	(19)	(50)
Interstitial cell, adenoma	1 (2%)			
Hematopoietic System				
Bone marrow	(50)	(22)	(19)	(49)
Lymph node	(49)	(27)	(26)	(50)
Axillary, fibrosarcoma, metastatic, skin			1 (4%)	
Mediastinal, hepatocellular carcinoma, metastatic, liver		1 (4%)		
Lymph node, mandibular	(46)	(18)	(17)	(48)
Fibrosarcoma, metastatic, skin	1 (2%)			
Spleen	(48)	(47)	(49)	(48)
Hemangiosarcoma			1 (2%)	
Thymus	(46)	(18)	(19)	(45)
Integumentary System				
Skin	(49)	(39)	(45)	(50)
Subcutaneous tissue, fibroma	4 (8%)	1 (3%)	3 (7%)	1 (2%)
Subcutaneous tissue, fibroma, multiple	1 (2%)			
Subcutaneous tissue, fibrosarcoma	11 (22%)	7 (18%)	8 (18%)	4 (8%)
Subcutaneous tissue, fibrosarcoma, multiple	1 (2%)			1 (2%)
Subcutaneous tissue, neurofibroma		1 (3%)		
Subcutaneous tissue, neurofibrosarcoma				1 (2%)
Subcutaneous tissue, rhabdomyosarcoma, metastatic, skeletal muscle			1 (2%)	
Subcutaneous tissue, schwannoma malignant		2 (5%)		
Musculoskeletal System				
Skeletal muscle			(1)	
Rhabdomyosarcoma			1 (100%)	
Nervous System				
Brain	(50)	(22)	(19)	(50)
Histiocytic sarcoma			1 (5%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3
(continued)

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Respiratory System				
Lung	(50)	(25)	(26)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	5 (20%)	7 (27%)	5 (10%)
Alveolar/bronchiolar carcinoma		2 (8%)		
Fibrosarcoma, metastatic, skin		1 (4%)		
Hepatocellular carcinoma, metastatic, multiple, greater than five, liver	1 (2%)	1 (4%)		
Nose	(50)	(21)	(20)	(50)
Sarcoma			1 (5%)	
Special Senses System				
Harderian gland	(2)	(3)	(1)	(1)
Adenoma	2 (100%)	2 (67%)	1 (100%)	1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cortex, adenoma				5 (10%)
Cortex, adenoma, multiple				1 (2%)
Urethra	(1)	(2)	(3)	(2)
Transitional epithelium, carcinoma			1 (33%)	
Systemic Lesions				
Multiple organs[c]	(50)	(50)	(50)	(50)
Histiocytic sarcoma			2 (4%)	
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant mixed	2 (4%)	2 (4%)	6 (12%)	6 (12%)
Tumor Summary				
Total animals with primary neoplasms[d]	25	27	33	35
Total primary neoplasms	37	47	53	51
Total animals with benign neoplasms	16	17	20	28
Total benign neoplasms	18	22	24	34
Total animals with malignant neoplasms	18	23	25	17
Total malignant neoplasms	19	25	29	17
Total animals with secondary neoplasms[e]	2	2	3	
Total secondary neoplasms	2	3	3	

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] One male receiving 25,000 ppm and two males receiving 50,000 ppm died prior to the interim evaluation.
[c] Number of animals with any tissue examined microscopically
[d] Primary tumors: all tumors except metastatic tumors
[e] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm

Number of Days on Study	1 5 1	2 4 0	2 9 1	3 2 4	4 1 6	4 5 0	4 8 9	5 8 3	5 9 9	6 3 0	6 5 3	6 8 0	6 8 1	6 8 1	6 9 7	7 0 0	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 4 2	0 4 3	0 8 1	0 5 1	0 8 3	0 2 1	0 7 1	0 7 3	0 1 4	0 3 3	0 3 5	0 3 2	0 1 5	0 9 3	0 6 3	1 0 1	0 8 5	1 1 1	1 1 2	1 1 3	2 2 2	2 2 3	2 2 4	2 2 5	3 3 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	A	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	A	+	A	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	A	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	A	A	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	A	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma													X	X	X										
Hepatocellular carcinoma, multiple, three											X														
Hepatocellular adenoma													X												
Hepatocellular adenoma, multiple, two																									
Mesentery																	+								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth															+		+	+	+			+		+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 3 4	0 4 1	0 4 4	0 4 5	0 5 2	0 5 3	0 5 4	0 5 5	0 6 1	0 6 2	0 6 4	0 6 5	0 7 2	0 7 4	0 8 2	0 8 4	0 9 2	0 7 5	0 9 1	0 9 4	0 9 5	1 0 2	1 0 3	1 0 4	1 0 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																				X						4
Hepatocellular carcinoma, multiple, three																										1
Hepatocellular adenoma		X					X				X						X		X							6
Hepatocellular adenoma, multiple, two					X									X												2
Mesentery																				+						2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth	+	+				+	+					+			+	+			+			+				16
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	1 5 1	2 4 0	2 9 1	3 2 4	4 1 6	4 5 0	4 8 9	5 8 3	5 9 9	6 3 0	6 5 3	6 8 0	6 8 1	6 8 1	6 9 7	7 0 0	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 4 2	0 4 3	0 8 1	0 5 1	0 8 3	0 2 1	0 7 1	0 7 3	0 1 4	0 3 3	0 3 5	0 3 2	0 1 5	0 9 3	0 6 3	1 0 1	0 8 5	1 1 1	1 1 2	1 2 3	2 2 2	2 2 3	2 2 4	2 2 5	3 3 1
General Body System																									
Tissue NOS				+																					
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland												+		+		+		+	+	+					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma														X											
Hematopoietic System																									
Blood						+																			
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Fibrosarcoma, metastatic, skin																X									
Spleen	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibroma, multiple																									
Subcutaneous tissue, fibrosarcoma								X		X				X		X	X	X							
Subcutaneous tissue, fibrosarcoma, multiple						X																			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 3 4	0 4 1	0 4 4	0 4 5	0 5 2	0 5 3	0 5 4	0 5 5	0 6 1	0 6 2	0 6 4	0 6 5	0 7 2	0 7 4	0 8 2	0 8 4	0 9 2	0 7 5	0 9 1	0 9 4	0 9 5	1 0 2	1 0 3	1 0 4	1 0 5		**Total Tissues/ Tumors**
General Body System																											
Tissue NOS																											1
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Preputial gland		+						+	+			+			+					+		+	+	+	+		16
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Interstitial cell, adenoma																											1
Hematopoietic System																											
Blood																											1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		46
Fibrosarcoma, metastatic, skin																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		46
Integumentary System																											
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Subcutaneous tissue, fibroma	X					X								X						X							4
Subcutaneous tissue, fibroma, multiple											X																1
Subcutaneous tissue, fibrosarcoma	X		X									X		X			X										11
Subcutaneous tissue, fibrosarcoma, multiple																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	1 5 1	2 4 0	2 9 1	3 2 4	4 1 6	4 5 0	4 8 9	5 8 3	5 9 9	6 3 0	6 5 3	6 8 0	6 8 1	6 8 1	6 9 7	7 0 0	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 4 2	0 4 3	0 8 1	0 5 1	0 8 3	0 2 1	0 7 1	0 7 3	0 1 4	0 3 3	0 3 5	0 3 2	0 1 5	0 9 3	0 6 3	1 0 1	0 8 5	1 1 1	1 1 2	1 2 3	2 2 2	2 2 3	2 2 4	2 2 5	3 3 1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X										
Hepatocellular carcinoma, metastatic, multiple, greater than five, liver											X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Harderian gland										+															
Adenoma										X															
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra		+																							
Urinary bladder	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																							X		

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 3 4	0 4 1	0 4 4	0 4 5	0 5 2	0 5 3	0 5 4	0 5 5	0 6 1	0 6 2	0 6 4	0 6 5	0 7 2	0 7 4	0 8 2	0 8 4	0 9 2	0 7 5	0 9 1	0 9 4	0 9 5	1 0 2	1 0 3	1 0 4	1 0 5	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X																	2
Hepatocellular carcinoma, metastatic, multiple, greater than five, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye							+																		+	2
Harderian gland																									+	2
Adenoma																									X	2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed											X															2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm

Number of Days on Study	0 5 6	1 8 0	2 2 8	2 8 3	2 9 5	3 1 6	3 2 2	3 3 6	3 8 8	4 0 2	4 8 4	5 1 2	5 7 6	5 8 8	6 4 8	6 5 0	6 5 3	6 5 3	6 7 9	7 0 3	7 0 4	7 1 0	7 2 9	7 2 9	7 3 2
Carcass ID Number	4 5 3	4 1 1	4 0 2	4 0 3	4 1 2	3 7 2	3 7 3	3 8 2	4 3 1	4 3 2	4 5 5	4 2 5	4 1 5	4 6 3	4 3 3	4 3 4	4 0 1	4 3 5	4 8 5	3 9 2	3 9 4	4 2 1	3 8 4	4 6 2	3 7 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Gallbladder	M	M	A	M	M	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine large	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine large, cecum	A	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine large, colon	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine large, rectum	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine small	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine small, duodenum	A	+	A	+		+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+			
Intestine small, ileum	A	+	A	+		+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+			
Intestine small, jejunum	A	+	A	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Liver	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																						X			
Hepatocellular carcinoma																X	X								
Hepatocellular carcinoma, multiple											X									X					
Hepatocellular adenoma																X	X			X				X	
Hepatocellular adenoma, multiple, two																									
Mesentery										+				+											
Pancreas	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Stomach	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	
Stomach, forestomach	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	
Papilloma squamous																								X	
Stomach, glandular	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Tooth														+			+		+						
Cardiovascular System																									
Blood vessel																			+						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Adrenal gland, medulla	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Pheochromocytoma malignant													X												
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Parathyroid gland	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Pituitary gland	M	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 7 4	3 7 5	3 8 1	3 8 3	3 9 1	3 9 3	3 9 5	4 0 4	4 0 5	4 1 3	4 1 4	4 2 2	4 2 3	4 2 4	4 4 1	4 4 2	4 4 3	4 4 4	4 4 5	4 5 1	4 5 2	4 5 4	4 6 1	4 6 4	4 6 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus																										22
Gallbladder																										15
Intestine large																										19
Intestine large, cecum																										18
Intestine large, colon																										19
Intestine large, rectum																										19
Intestine small													+													20
Intestine small, duodenum													+													18
Intestine small, ileum																										18
Intestine small, jejunum																										19
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Hepatocellular carcinoma					X				X	X						X		X								7
Hepatocellular carcinoma, multiple																									X	3
Hepatocellular adenoma	X		X	X					X						X			X							X	11
Hepatocellular adenoma, multiple, two																						X				1
Mesentery		+																								3
Pancreas																										20
Salivary glands																										22
Stomach								+																		21
Stomach, forestomach								+																		21
Papilloma squamous																										1
Stomach, glandular								+																		20
Tooth																										3
Cardiovascular System																										
Blood vessel																										1
Heart																										22
Endocrine System																										
Adrenal gland					+																					23
Adrenal gland, cortex					+																					23
Adrenal gland, medulla																										21
Pheochromocytoma malignant																										1
Islets, pancreatic																										22
Parathyroid gland																										19
Pituitary gland																										20
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	0 5 6	1 8 0	2 2 8	2 8 3	2 9 5	3 1 6	3 2 2	3 3 6	3 8 8	4 0 2	4 8 4	5 1 2	5 7 6	5 8 8	6 4 8	6 5 0	6 5 3	6 5 3	7 7 9	7 0 3	7 0 4	7 1 0	7 2 9	7 2 9	7 3 2
Carcass ID Number	4 5 3	4 1 1	4 0 2	4 0 3	4 1 2	3 7 2	3 7 3	3 8 2	4 3 1	4 3 2	4 5 5	4 2 5	4 1 5	4 6 3	4 3 3	4 3 4	4 0 1	4 3 5	4 3 5	3 9 2	3 9 4	4 2 1	3 8 4	4 2 1	3 6 2	3 7 1
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Penis					+	+											+								
Preputial gland								+	+								+						+		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Seminal vesicle	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Hematopoietic System																									
Blood														+											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mediastinal, hepatocellular carcinoma, metastatic, liver																				X					
Lymph node, mandibular	M	+	+	+	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+			
Spleen	A	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M			
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Subcutaneous tissue, fibroma																							X		
Subcutaneous tissue, fibrosarcoma															X			X			X		X	X	
Subcutaneous tissue, neurofibroma																									
Subcutaneous tissue, schwannoma malignant														X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 7 4	3 7 5	3 8 1	3 8 3	3 9 1	3 9 3	3 9 5	4 0 4	4 0 5	4 1 3	4 1 4	4 2 2	4 2 3	4 2 4	4 4 1	4 4 2	4 4 3	4 4 4	4 4 5	4 5 1	4 5 2	4 5 4	4 6 1	4 6 4	4 6 5	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Epididymis																										22
Penis																										3
Preputial gland	+	+	+		+	+			+				+			+			+			+				14
Prostate																										22
Seminal vesicle																										21
Testes																										22
Hematopoietic System																										
Blood																										1
Bone marrow																										22
Lymph node	+								+						+											27
Mediastinal, hepatocellular carcinoma, metastatic, liver																										1
Lymph node, mandibular																										18
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus																										18
Integumentary System																										
Mammary gland																										
Skin	+		+	+	+	+		+	+	+			+	+			+					+	+	+	+	39
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma				X										X												7
Subcutaneous tissue, neurofibroma																								X		1
Subcutaneous tissue, schwannoma malignant																								X		2
Musculoskeletal System																										
Bone																										22
Nervous System																										
Brain																										22

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	0 5 6	1 8 0	2 2 8	2 8 3	2 9 5	3 1 6	3 2 2	3 3 6	3 8 8	4 0 2	4 8 4	5 1 2	5 7 6	5 8 8	6 4 8	6 5 0	6 5 3	6 5 3	6 7 9	7 0 3	7 0 4	7 1 0	7 2 9	7 2 9	7 3 2
Carcass ID Number	4 5 3	4 1 1	4 0 2	4 0 3	4 1 2	3 7 2	3 7 3	3 8 2	4 3 1	4 3 2	4 5 5	4 2 5	4 1 5	4 6 3	4 3 3	4 3 4	4 0 1	4 3 5	4 3 5	3 9 2	3 9 4	4 2 1	3 8 4	4 6 2	3 7 1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+
Alveolar/bronchiolar adenoma																X	X					X			X
Alveolar/bronchiolar carcinoma																						X			
Fibrosarcoma, metastatic, skin																		X							
Hepatocellular carcinoma, metastatic, multiple, greater than five, liver																				X					
Nose	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Special Senses System																									
Ear				+																					
Harderian gland																				+					
Adenoma																				X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra				+					+																
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																							X		

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 7 4	3 7 5	3 7 1	3 8 3	3 8 1	3 9 3	3 9 5	4 0 4	4 0 5	4 1 3	4 1 4	4 2 2	4 2 3	4 2 4	4 4 1	4 4 2	4 4 3	4 4 4	4 4 5	4 5 1	4 5 2	4 5 4	4 6 1	4 6 4	4 6 5	**Total Tissues/ Tumors**
Respiratory System																										
Lung													+									+				25
Alveolar/bronchiolar adenoma																						X				5
Alveolar/bronchiolar carcinoma																						X				2
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, multiple, greater than five, liver																										1
Nose																										21
Trachea																										22
Special Senses System																										
Ear																										1
Harderian gland						+	+																			3
Adenoma						X																				2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra																										2
Urinary bladder							+																			22
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed	X																									2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm

Number of Days on Study	0 8 5	2 2 1	2 7 9	3 7 2	4 3 0	4 6 9	5 2 1	5 4 1	5 5 3	5 5 6	5 7 0	6 4 2	6 5 8	6 6 2	6 9 7	6 9 7	7 0 3	7 0 4	7 2 4	7 2 9	7 2 9	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	3 3 2	3 2 3	2 8 1	2 6 1	3 0 4	2 6 3	2 6 2	2 0 5	3 1 3	3 0 2	3 4 3	3 1 4	2 5 5	3 5 4	3 3 3	3 4 5	2 8 4	2 5 1	2 8 2	2 5 2	3 1 5	2 5 3	2 6 4	2 6 5	2 7 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Gallbladder	A	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+						
Intestine large	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Intestine large, cecum	A	+	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+						
Intestine large, colon	A	+	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+						
Intestine large, rectum	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+						
Intestine small	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Intestine small, duodenum	A	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+						
Polyp adenomatous																									
Intestine small, ileum	A	+	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+						
Intestine small, jejunum	A	+	A	+	A	A	+	A	+	+	+	A	+	+	+	+	+	+	+						
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma																			X				X	X	
Hepatocellular adenoma											X						X		X			X	X	X	
Hepatocellular adenoma, multiple							X																		
Histiocytic sarcoma											X														
Mesentery															+										
Pancreas	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Stomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+			
Stomach, forestomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+			
Stomach, glandular	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Tooth									+	+		+				+									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Adrenal gland, medulla	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Islets, pancreatic	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Parathyroid gland	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+						
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma													X												

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 7 2	2 7 3	2 7 4	2 7 5	2 8 3	2 8 5	2 9 2	2 9 1	2 9 3	2 9 4	2 9 5	3 0 1	3 0 3	3 1 1	3 1 2	3 2 1	3 2 2	3 2 4	3 2 5	3 3 1	3 3 4	3 3 5	3 4 1	3 4 2	3 4 4	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus																										19
Gallbladder																										15
Intestine large																										18
Intestine large, cecum																										15
Intestine large, colon																										15
Intestine large, rectum																										16
Intestine small			+													+							+			19
Intestine small, duodenum			+																							16
Polyp adenomatous			X																							1
Intestine small, ileum																+										16
Intestine small, jejunum																							+			14
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																								X		1
Hepatocellular carcinoma		X											X						X	X		X				8
Hepatocellular adenoma				X													X							X		9
Hepatocellular adenoma, multiple																									X	2
Histiocytic sarcoma																										1
Mesentery																						+				2
Pancreas																							+			18
Salivary glands																										19
Stomach													+						+				+			22
Stomach, forestomach													+						+				+			22
Stomach, glandular																										18
Tooth																										4
Cardiovascular System																										
Heart																										19
Endocrine System																										
Adrenal gland																										19
Adrenal gland, cortex																										19
Adrenal gland, medulla																										18
Islets, pancreatic																										17
Parathyroid gland																										16
Pituitary gland																										18
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	0 8 5	2 2 1	2 7 9	3 7 2	4 3 0	4 6 9	5 2 1	5 4 1	5 5 3	5 5 6	5 5 0	6 4 2	6 5 8	6 6 2	6 9 7	6 9 7	7 0 3	7 0 4	7 2 4	7 2 9	7 2 9	7 3 1	7 3 1	7 3 1
Carcass ID Number	3 3 2	3 2 3	2 8 1	2 6 1	3 0 4	2 6 3	2 6 2	3 0 5	3 1 3	3 0 2	3 4 3	3 1 4	3 5 5	2 5 4	3 3 3	3 4 5	3 8 4	2 5 1	2 8 2	2 5 2	3 1 5	2 5 3	2 6 4	2 6 5	2 7 1
General Body System																								
None																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Fibrosarcoma, metastatic, skin																		X						
Preputial gland		+																				+		+
Prostate	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Seminal vesicle	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Hematopoietic System																								
Blood										+														
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+			
Axillary, fibrosarcoma, metastatic, skin																	X							
Lymph node, mandibular	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+					
Spleen	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Integumentary System																								
Mammary gland	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																				X		X		
Subcutaneous tissue, fibrosarcoma								X					X			X	X	X	X					
Subcutaneous tissue, rhabdomyosarcoma, metastatic, skeletal muscle																				X				
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Skeletal muscle																				+				
Rhabdomyosarcoma																				X				
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Histiocytic sarcoma									X															

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 7 2	2 7 3	2 7 4	2 7 5	2 8 3	2 8 5	2 9 2	2 9 1	2 9 3	2 9 4	2 9 5	2 9 9	3 0 1	3 0 3	3 1 1	3 1 2	3 2 1	3 2 2	3 2 4	3 2 5	3 3 1	3 3 4	3 3 5	3 4 1	3 4 2	3 4 4	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Epididymis																										19
Fibrosarcoma, metastatic, skin																										1
Preputial gland			+			+		+											+							7
Prostate															+											19
Seminal vesicle																										18
Testes																										19
Hematopoietic System																										
Blood																										1
Bone marrow																										19
Lymph node	+				+								+	+		+							+			26
Axillary, fibrosarcoma, metastatic, skin																										1
Lymph node, mandibular																										17
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																								X		1
Thymus																										19
Integumentary System																										
Mammary gland																										1
Skin	+	+		+	+	+	+	+	+	+	+	+	+		+	+	+		+	+	+		+	+	+	45
Subcutaneous tissue, fibroma																				X						3
Subcutaneous tissue, fibrosarcoma		X																		X						8
Subcutaneous tissue, rhabdomyosarcoma, metastatic, skeletal muscle																										1
Musculoskeletal System																										
Bone																										19
Skeletal muscle																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain																										19
Histiocytic sarcoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	0	2	2	3	4	4	5	5	5	5	5	6	6	6	6	7	7	7	7	7	7	7	7	7	
	8	2	7	7	3	6	2	4	5	5	7	4	5	6	9	9	0	0	2	2	2	3	3	3	
	5	1	9	2	0	9	1	1	3	6	0	2	8	2	7	7	3	4	4	9	9	1	1	1	
Carcass ID Number	3	3	2	2	3	2	2	3	3	3	3	3	2	2	3	3	2	2	2	2	3	2	2	2	
	3	2	8	6	0	6	6	0	1	0	4	1	5	5	3	4	8	5	8	5	1	5	6	6	
	2	3	1	1	4	3	2	5	3	2	3	4	5	4	3	5	4	1	2	2	5	3	4	5	
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Alveolar/bronchiolar adenoma								X											X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Sarcoma							X																		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Special Senses System																									
Harderian gland																						+			
Adenoma																						X			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra								+				+	+												
Transitional epithelium, carcinoma													X												
Urinary bladder	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X		X														
Lymphoma malignant mixed										X											X				

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	2 7 2	2 7 3	2 7 4	2 7 5	2 8 3	2 8 5	2 9 2	2 9 1	2 9 3	2 9 4	2 9 5	3 0 1	3 0 3	3 1 1	3 1 2	3 2 1	3 2 2	3 2 4	3 2 5	3 3 1	3 3 4	3 3 5	3 4 1	4 4 2	4 4 4	**Total Tissues/ Tumors**
Respiratory System																										
Lung		+		+							+	+	+		+				+							26
Alveolar/bronchiolar adenoma				X								X	X		X				X							7
Nose														+												20
Sarcoma																										1
Trachea																										19
Special Senses System																										
Harderian gland																										1
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra																										3
Transitional epithelium, carcinoma																										1
Urinary bladder																										18
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant mixed	X													X		X						X				6

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 50,000 ppm

Number of Days on Study	2 1 0	2 1 8 0 0	2 1 8 0 9	2 2 9 4	3 0 1	3 2 3	3 2 5	3 2 6	4 5 4	5 5 5	5 5 7	5 5 7	5 5 7	5 5 7	5 5 6 7	5 6 7 8	6 3 5	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	1 7 1	1 8 3	1 3 1	2 2 2	1 4 1	1 7 2	2 1 2	1 4 2	1 9 5	1 9 2	1 3 4	1 7 5	2 0 2	2 2 5	1 4 3	1 3 2	2 1 3	1 3 3	1 3 5	1 4 4	1 4 5	1 5 1	1 5 2	1 5 3	1 5 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine small	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	+	+	A	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	A	A	+	A	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	A	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma														X											X
Hepatocellular adenoma											X				X					X	X			X	X
Hepatocellular adenoma, multiple																									
Hepatocellular adenoma, multiple, two																									
Mesentery																								+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																	+	+	+	+		+		+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma														X							X				
General Body System																									
None																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 50,000 ppm
(continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 5 5	1 6 1	1 6 2	1 6 3	1 6 4	1 6 5	1 7 3	1 7 4	1 8 1	1 8 2	1 8 4	1 8 5	1 9 1	1 9 3	1 9 4	2 0 1	2 0 3	2 0 4	2 0 5	2 1 1	2 1 4	2 1 5	2 2 1	2 2 3	2 2 4	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma										X						X										4
Hepatocellular adenoma				X	X		X						X				X	X			X					13
Hepatocellular adenoma, multiple											X								X							2
Hepatocellular adenoma, multiple, two	X																									1
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+	+	+	+		+	+		+	+		+	+			+	+	+		+		+	+		+	24
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma							X							X										X		5
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 50,000 ppm
(continued)

Number of Days on Study	2 1 0	2 8 0	2 8 9	2 9 4	3 0 1	3 2 3	3 2 5	3 2 6	4 5 4	5 5 5	5 5 7	5 5 7	5 5 7	5 5 7	5 6 7	5 7 8	6 6 5	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	1 7 1	1 8 3	1 3 1	2 2 2	1 4 1	1 7 2	2 1 2	1 4 2	1 9 5	1 9 2	1 3 4	1 7 5	1 0 2	2 2 5	1 4 3	1 3 2	2 1 3	1 3 3	1 3 5	1 4 4	1 4 5	1 5 1	1 5 2	1 5 3	1 5 4
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis											M														
Preputial gland								+																	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Blood				+									+			+									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Spleen	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma				X									X				X								
Subcutaneous tissue, fibrosarcoma, multiple																									
Subcutaneous tissue, neurofibrosarcoma												X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X						X			X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 50,000 ppm
(continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 5 5	1 6 1	1 6 2	1 6 3	1 6 4	1 6 5	1 7 3	1 7 4	1 8 1	1 8 2	1 8 4	1 8 5	1 9 1	1 9 3	1 9 4	2 0 1	2 0 3	2 0 4	2 0 5	2 1 1	2 1 4	2 1 5	2 2 1	2 2 3	2 2 4	**Total Tissues/ Tumors**
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										
Preputial gland	+	+																					+			4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Blood																										3
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	45
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																			X							1
Subcutaneous tissue, fibrosarcoma																						X				4
Subcutaneous tissue, fibrosarcoma, multiple								X																		1
Subcutaneous tissue, neurofibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X							X										5
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 50,000 ppm
(continued)

Number of Days on Study	2	2	2	2	3	3	3	3	4	5	5	5	5	5	5	5	6	7	7	7	7	7	7	7	7
	1	8	8	9	0	2	2	2	5	5	5	5	5	5	5	6	7	6	3	3	3	3	3	3	3
	0	0	9	4	1	3	5	6	4	5	7	7	7	7	7	8	5	0	0	0	0	0	0	0	0
Carcass ID Number	1	1	1	2	1	1	2	1	1	1	1	1	2	2	1	1	2	1	1	1	1	1	1	1	1
	7	8	3	2	4	7	1	4	9	9	3	7	0	2	4	3	1	3	3	4	4	5	5	5	5
	1	3	1	2	1	2	2	2	5	2	4	5	2	5	3	2	3	3	5	4	5	1	2	3	4
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortex, adenoma																									
Cortex, adenoma, multiple																					X				
Urethra							+																		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic										X															
Lymphoma malignant mixed																X	X			X		X		X	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 50,000 ppm
(continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 5 5	1 6 1	1 6 2	1 6 3	1 6 4	1 6 5	1 7 3	1 7 4	1 8 1	1 8 2	1 8 4	1 8 5	1 9 1	1 9 3	1 9 4	2 0 1	2 0 3	2 0 4	2 0 5	2 1 1	2 1 4	2 1 5	2 2 1	2 2 3	2 2 4	**Total Tissues/ Tumors**
Special Senses System																										
Harderian gland																						+				1
Adenoma																						X				1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortex, adenoma		X		X					X	X										X						5
Cortex, adenoma, multiple																										1
Urethra																			+							2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed				X																						6

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Kidney (Cortex): Adenoma				
Overall rates[a]	0/50 (0%)	0/50 (0%)	0/50 (0%)	6/50 (12%)
Adjusted rates[b]	0.0%	0.0%	0.0%	18.2%
Terminal rates[c]	0/33 (0%)	0/28 (0%)	0/31 (0%)	6/33 (18%)
First incidence (days)	–[e]	–	–	729 (T)
Life table tests[d]	P≤0.001	–	–	P=0.017
Logistic regression tests[d]	P≤0.001	–	–	P=0.017
Cochran-Armitage test[d]	P≤0.001			
Fisher exact test[d]		–	–	P=0.013
Liver: Hepatocellular Adenoma				
Overall rates	8/50 (16%)	12/48 (25%)	11/50 (22%)	16/49 (33%)
Adjusted rates	23.3%	38.1%	30.7%	45.4%
Terminal rates	7/33 (21%)	9/28 (32%)	7/31 (23%)	14/33 (42%)
First incidence (days)	681	650	521	557
Life table tests	P=0.059	P=0.124	P=0.266	P=0.043
Logistic regression tests	P=0.026	P=0.126	P=0.279	P=0.021
Cochran-Armitage test	P=0.046			
Fisher exact test		P=0.197	P=0.306	P=0.044
Liver: Hepatocellular Carcinoma				
Overall rates	5/50 (10%)	10/48 (21%)	8/50 (16%)	4/49 (8%)
Adjusted rates	12.9%	30.1%	25.0%	11.4%
Terminal rates	1/33 (3%)	6/28 (21%)	7/31 (23%)	3/33 (9%)
First incidence (days)	653	512	724	557
Life table tests	P=0.280N	P=0.084	P=0.249	P=0.541N
Logistic regression tests	P=0.319N	P=0.091	P=0.254	P=0.548N
Cochran-Armitage test	P=0.281N			
Fisher exact test		P=0.113	P=0.277	P=0.513N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	12/50 (24%)	16/48 (33%)	16/50 (32%)	19/49 (39%)
Adjusted rates	32.0%	49.2%	45.2%	52.4%
Terminal rates	8/33 (24%)	12/28 (43%)	12/31 (39%)	16/33 (48%)
First incidence (days)	653	512	521	557
Life table tests	P=0.116	P=0.129	P=0.212	P=0.087
Logistic regression tests	P=0.050	P=0.137	P=0.219	P=0.043
Cochran-Armitage test	P=0.090			
Fisher exact test		P=0.212	P=0.252	P=0.085
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	2/50 (4%)	5/25 (20%)[f]	7/26 (27%)[f]	5/50 (10%)
Adjusted rates	5.7%			14.3%
Terminal rates	1/33 (3%)			4/33 (12%)
First incidence (days)	697			557
Life table tests				P=0.211
Logistic regression tests				P=0.184
Fisher exact test				P=0.218

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3
(continued)

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	2/50 (4%)	5/25 (20%)[f]	7/26 (27%)[f]	5/50 (10%)
Adjusted rates	5.7%			14.3%
Terminal rates	1/33 (3%)			4/33 (12%)
First incidence (days)	697			557
Life table tests				P=0.211
Logistic regression tests				P=0.184
Fisher exact test				P=0.218
Skin (Subcutaneous Tissue): Fibroma				
Overall rates	5/50 (10%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rates	15.2%	3.6%	9.7%	3.0%
Terminal rates	5/33 (15%)	1/28 (4%)	3/31 (10%)	1/33 (3%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Life table tests	P=0.105N	P=0.142N	P=0.389N	P=0.101N
Logistic regression tests	P=0.105N	P=0.142N	P=0.389N	P=0.101N
Cochran-Armitage test	P=0.114N			
Fisher exact test		P=0.102N	P=0.357N	P=0.102N
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rates	12/50 (24%)	7/50 (14%)	8/50 (16%)	5/50 (10%)
Adjusted rates	30.0%	21.8%	21.7%	13.2%
Terminal rates	6/33 (18%)	4/28 (14%)	3/31 (10%)	3/33 (9%)
First incidence (days)	450	648	541	294
Life table tests	P=0.072N	P=0.272N	P=0.282N	P=0.080N
Logistic regression tests	P=0.066N	P=0.204N	P=0.233N	P=0.059N
Cochran-Armitage test	P=0.059N			
Fisher exact test		P=0.154N	P=0.227N	P=0.054N
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rates	15/50 (30%)	7/50 (14%)	10/50 (20%)	6/50 (12%)
Adjusted rates	37.8%	21.8%	27.3%	16.1%
Terminal rates	9/33 (27%)	4/28 (14%)	5/31 (16%)	4/33 (12%)
First incidence (days)	450	648	541	294
Life table tests	P=0.048N	P=0.115N	P=0.238N	P=0.039N
Logistic regression tests	P=0.045N	P=0.071N	P=0.186N	P=0.030N
Cochran-Armitage test	P=0.039N			
Fisher exact test		P=0.045N	P=0.178N	P=0.024N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rates	0/50 (0%)	0/49 (0%)	1/50 (2%)	5/50 (10%)
Adjusted rates	0.0%	0.0%	2.6%	14.3%
Terminal rates	0/33 (0%)	0/28 (0%)	0/31 (0%)	4/33 (12%)
First incidence (days)	-	-	658	557
Life table tests	P=0.002	-	P=0.495	P=0.033
Logistic regression tests	P=0.001	-	P=0.500	P=0.027
Cochran-Armitage test	P=0.002			
Fisher exact test		-	P=0.500	P=0.028

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
All Organs: Malignant Lymphoma (Histiocytic or Mixed)				
Overall rates	2/50 (4%)	2/50 (4%)	6/50 (12%)	7/50 (14%)
Adjusted rates	6.1%	7.1%	18.2%	19.2%
Terminal rates	2/33 (6%)	2/28 (7%)	5/31 (16%)	4/33 (12%)
First incidence (days)	729 (T)	729 (T)	556	555
Life table tests	P=0.032	P=0.635	P=0.115	P=0.075
Logistic regression tests	P=0.022	P=0.635	P=0.125	P=0.067
Cochran-Armitage test	P=0.027			
Fisher exact test		P=0.691N	P=0.134	P=0.080
All Organs: Benign Tumors				
Overall rates	16/50 (32%)	17/50 (34%)	20/50 (40%)	28/50 (56%)
Adjusted rates	42.8%	52.8%	53.3%	75.5%
Terminal rates	12/33 (36%)	13/28 (46%)	14/31 (45%)	24/33 (73%)
First incidence (days)	630	650	521	557
Life table tests	P=0.008	P=0.288	P=0.218	P=0.010
Logistic regression tests	P=0.001	P=0.302	P=0.230	P=0.002
Cochran-Armitage test	P=0.005			
Fisher exact test		P=0.500	P=0.266	P=0.013
All Organs: Malignant Tumors				
Overall rates	18/50 (36%)	23/50 (46%)	25/50 (50%)	17/50 (34%)
Adjusted rates	42.6%	60.3%	60.5%	42.0%
Terminal rates	9/33 (27%)	13/28 (46%)	15/31 (48%)	10/33 (30%)
First incidence (days)	450	512	521	294
Life table tests	P=0.396N	P=0.106	P=0.112	P=0.563N
Logistic regression tests	P=0.429N	P=0.111	P=0.101	P=0.550N
Cochran-Armitage test	P=0.376N			
Fisher exact test		P=0.208	P=0.113	P=0.500N
All Organs: Benign and Malignant Tumors				
Overall rates	25/50 (50%)	27/50 (54%)	33/50 (66%)	35/50 (70%)
Adjusted rates	59.4%	70.9%	78.3%	83.3%
Terminal rates	16/33 (48%)	17/28 (61%)	22/31 (71%)	26/33 (79%)
First incidence (days)	450	512	521	294
Life table tests	P=0.041	P=0.193	P=0.076	P=0.042
Logistic regression tests	P=0.004	P=0.216	P=0.057	P=0.009
Cochran-Armitage test	P=0.016			
Fisher exact test		P=0.421	P=0.078	P=0.033

(T)Terminal sacrifice
[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no tumors in animal group
[f] Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus, no statistical analyses are provided.

TABLE C4a
Historical Incidence of Renal Tubule Adenomas in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
C.I. Pigment Red 3	0/50
Ethylene Glycol	1/54
Nitrofurantoin	0/50
o-Nitroanisole	1/50
Polysorbate 80	0/49
Rhodamine 6G	0/50
Roxarsone	0/50
Total	2/353 (0.6%)
Standard deviation	1.0%
Range	0%-2%
Overall Historical Incidence	
Total	2/865 (0.2%)
Standard deviation	0.7%
Range	0%-2%

[a] Data as of 3 April 1991

TABLE C4b
Historical Incidence of Thyroid Gland Follicular Cell Tumors in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
C.I. Pigment Red 3	0/50	0/50	0/50
Ethylene Glycol	0/53	1/53	1/53
Nitrofurantoin	2/48	0/48	2/48
o-Nitroanisole	2/49	0/49	2/49
Polysorbate 80	1/49	0/49	1/49
Rhodamine 6G	0/50	0/50	0/50
Roxarsone	0/50	0/50	0/50
Total	5/349 (1.4%)	1/349 (0.3%)	6/349 (1.7%)
Standard deviation	1.9%	0.8%	1.8%
Range	0%-4%	0%-2%	0%-4%
Overall Historical Incidence			
Total	14/856 (1.6%)	4/856 (0.5%)	18/856 (2.1%)
Standard deviation	1.7%	0.9%	1.8%
Range	0%-4%	0%-2%	0%-6%

[a] Data as of 3 April 1991

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3[a]

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-month interim evaluation[b]	10	10	10	10
Early deaths				
Natural death	9	9	9	7
Moribund	8	13	10	10
Survivors				
Terminal sacrifice	33	28	31	33
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(47)	(15)	(15)	(48)
Mineralization, focal				1 (2%)
Epithelium, hyperplasia	1 (2%)			
Intestine small, duodenum	(46)	(18)	(16)	(45)
Lymphoid tissue, hyperplasia, lymphoid		1 (6%)		
Liver	(50)	(48)	(50)	(49)
Angiectasis	1 (2%)	1 (2%)		
Basophilic focus	3 (6%)	2 (4%)	3 (6%)	8 (16%)
Clear cell focus				1 (2%)
Cytologic alterations		21 (44%)	41 (82%)	43 (88%)
Eosinophilic focus		4 (8%)		3 (6%)
Hematopoietic cell proliferation	1 (2%)		2 (4%)	
Inflammation, granulomatous		1 (2%)	10 (20%)	38 (78%)
Inflammation, subacute, multifocal	2 (4%)		1 (2%)	
Mixed cell focus	2 (4%)	3 (6%)	1 (2%)	2 (4%)
Necrosis, focal	4 (8%)	3 (6%)	2 (4%)	
Necrosis, multifocal	1 (2%)			1 (2%)
Centrilobular, necrosis	1 (2%)	1 (2%)		
Kupffer cell, pigmentation		5 (10%)	30 (60%)	41 (84%)
Sinusoid, amyloid deposition	1 (2%)			
Sinusoid, infiltration cellular, polymorphonuclear	1 (2%)			1 (2%)
Mesentery	(2)	(3)	(2)	(1)
Cyst		1 (33%)		
Fat, mineralization, focal				1 (100%)
Fat, necrosis, focal	2 (100%)	2 (67%)	2 (100%)	1 (100%)
Pancreas	(50)	(20)	(18)	(50)
Inflammation, suppurative, acute	1 (2%)			
Acinus, atrophy, focal	1 (2%)			1 (2%)
Acinus, atrophy, multifocal		1 (5%)		
Acinus, hyperplasia, focal	1 (2%)			
Acinus, inflammation, subacute, focal				1 (2%)
Acinus, necrosis	1 (2%)			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Alimentary System (continued)				
Stomach, forestomach	(49)	(21)	(22)	(50)
Erosion			3 (14%)	
Hyperplasia		1 (5%)	5 (23%)	2 (4%)
Inflammation, subacute		2 (10%)		
Ulcer			1 (5%)	
Stomach, glandular	(49)	(20)	(18)	(50)
Erosion		1 (5%)		
Inflammation, subacute		1 (5%)		
Mineralization				1 (2%)
Tooth	(16)	(3)	(4)	(24)
Dysplasia	15 (94%)	3 (100%)	4 (100%)	24 (100%)
Cardiovascular System				
Blood vessel		(1)		
Abdominal, inflammation, subacute		1 (100%)		
Heart	(50)	(22)	(19)	(50)
Fibrosis, focal				1 (2%)
Inflammation, subacute		1 (5%)		
Atrium, thrombus	1 (2%)	1 (5%)		
Endocrine System				
Adrenal gland	(50)	(23)	(19)	(50)
Capsule, hyperplasia	1 (2%)			1 (2%)
Adrenal gland, cortex	(50)	(23)	(19)	(50)
Angiectasis	1 (2%)			
Cyst	1 (2%)	1 (4%)		
Fibrosis, focal	1 (2%)			
Hyperplasia, focal	1 (2%)			
Hypertrophy, focal	5 (10%)			8 (16%)
Hypertrophy, multifocal	1 (2%)			
Mineralization, focal	1 (2%)			
Necrosis	1 (2%)			
Pigmentation, hematoidin, focal	1 (2%)			
Capsule, accessory adrenal cortical nodule	2 (4%)	1 (4%)		1 (2%)
Spindle cell, hyperplasia	4 (8%)		1 (5%)	2 (4%)
Adrenal gland, medulla	(50)	(21)	(18)	(50)
Hyperplasia, focal				1 (2%)
Islets, pancreatic	(50)	(22)	(17)	(50)
Hyperplasia	1 (2%)	1 (5%)	2 (12%)	1 (2%)
Necrosis	1 (2%)			
Pituitary gland	(46)	(20)	(18)	(49)
Pars distalis, cyst	3 (7%)			1 (2%)
Thyroid gland	(50)	(49)	(50)	(50)
Follicle, cyst	3 (6%)	4 (8%)	19 (38%)	38 (76%)
Follicle, degeneration, cystic	1 (2%)			
Follicular cell, hyperplasia	2 (4%)	10 (20%)	24 (48%)	41 (82%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
General Body System				
Tissue NOS	(1)			
Hemorrhage	1 (100%)			
Genital System				
Epididymis	(50)	(22)	(19)	(50)
Granuloma sperm		1 (5%)		2 (4%)
Inflammation, subacute	3 (6%)		2 (11%)	4 (8%)
Penis		(3)		
Developmental malformation		1 (33%)		
Preputial gland	(16)	(14)	(7)	(4)
Inflammation, subacute	9 (56%)	10 (71%)	4 (57%)	2 (50%)
Duct, cyst	3 (19%)	6 (43%)	2 (29%)	2 (50%)
Prostate	(50)	(22)	(19)	(50)
Hemorrhage	1 (2%)	1 (5%)		
Inflammation, subacute	6 (12%)	7 (32%)	2 (11%)	8 (16%)
Seminal vesicle	(50)	(21)	(18)	(50)
Dilatation			1 (6%)	
Fibrosis	1 (2%)			
Inflammation, subacute	2 (4%)	1 (5%)	2 (11%)	2 (4%)
Testes	(50)	(22)	(19)	(50)
Interstitial cell, hyperplasia				1 (2%)
Seminiferous tubule, degeneration				2 (4%)
Hematopoietic System				
Blood	(1)	(1)	(1)	(3)
Leukocytosis	1 (100%)	1 (100%)	1 (100%)	1 (33%)
Bone marrow	(50)	(22)	(19)	(49)
Hyperplasia, histiocytic			1 (5%)	
Myeloid cell, hypercellularity	9 (18%)	2 (9%)	5 (26%)	6 (12%)
Lymph node	(49)	(27)	(26)	(50)
Axillary, hyperplasia, lymphoid			1 (4%)	1 (2%)
Iliac, hyperplasia, lymphoid			1 (4%)	
Inguinal, ectasia	1 (2%)			
Inguinal, hyperplasia, lymphoid	6 (12%)	4 (15%)	3 (12%)	8 (16%)
Mediastinal, hyperplasia, lymphoid		1 (4%)		
Mesenteric, angiectasis	14 (29%)	7 (26%)	4 (15%)	14 (28%)
Mesenteric, hyperplasia, lymphoid				4 (8%)
Renal, hyperplasia, lymphoid			1 (4%)	
Spleen	(48)	(47)	(49)	(48)
Atrophy		2 (4%)		
Congestion	1 (2%)			
Hematopoietic cell proliferation	12 (25%)	9 (19%)	11 (22%)	5 (10%)
Hemorrhage			1 (2%)	
Necrosis	1 (2%)			
Pigmentation		6 (13%)	23 (47%)	39 (81%)
Thymus	(46)	(18)	(19)	(45)
Atrophy	1 (2%)	1 (6%)		2 (4%)
Cyst	4 (9%)			
Necrosis		1 (6%)	1 (5%)	3 (7%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Integumentary System				
Skin	(49)	(39)	(45)	(50)
Inflammation, subacute, focal	6 (12%)	8 (21%)	5 (11%)	1 (2%)
Inflammation, subacute, multifocal	3 (6%)			
Ulcer	3 (6%)	6 (15%)	4 (9%)	
Epidermis, hyperplasia		1 (3%)		
Epidermis, hyperplasia, focal	5 (10%)	4 (10%)	3 (7%)	4 (8%)
Epidermis, hyperplasia, multifocal	3 (6%)			
Subcutaneous tissue, edema, focal	1 (2%)			
Subcutaneous tissue, fibrosis, focal	6 (12%)	6 (15%)	8 (18%)	7 (14%)
Subcutaneous tissue, fibrosis, multifocal	3 (6%)	1 (3%)	1 (2%)	
Subcutaneous tissue, hemorrhage				1 (2%)
Subcutaneous tissue, inflammation, subacute, focal	1 (2%)		1 (2%)	3 (6%)
Subcutaneous tissue, mineralization, focal	2 (4%)			2 (4%)
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(22)	(19)	(50)
Hemorrhage	1 (2%)		1 (5%)	
Mineralization, multifocal	31 (62%)	11 (50%)	15 (79%)	36 (72%)
Necrosis, multifocal		1 (5%)		
Respiratory System				
Lung	(50)	(25)	(26)	(50)
Congestion	1 (2%)	1 (4%)		1 (2%)
Hemorrhage, multifocal	1 (2%)			
Infiltration cellular, histiocyte, multifocal		2 (8%)		
Alveolar epithelium, hyperplasia			4 (15%)	
Nose	(50)	(21)	(20)	(50)
Foreign body	1 (2%)			
Inflammation, suppurative, acute				1 (2%)
Nasolacrimal duct, inflammation, suppurative	1 (2%)			
Special Senses System				
Eye	(2)			
Cataract	1 (50%)			
Conjunctiva, inflammation, subacute	1 (50%)			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Bacterium	1 (2%)			
Hydronephrosis	1 (2%)	1 (2%)	1 (2%)	
Inflammation, focal, chronic			1 (2%)	
Inflammation, suppurative	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Nephropathy, chronic	34 (68%)	39 (78%)	42 (84%)	45 (90%)
Artery, inflammation		1 (2%)		1 (2%)
Cortex, cyst		2 (4%)	4 (8%)	9 (18%)
Glomerulus, amyloid deposition	1 (2%)			
Left, fibrosis, focal				1 (2%)
Papilla, necrosis	1 (2%)		1 (2%)	
Renal tubule, dilatation, multifocal				1 (2%)
Renal tubule, hyperplasia		1 (2%)	7 (14%)	7 (14%)
Renal tubule, hyperplasia, cystic				4 (8%)
Renal tubule, mineralization, multifocal	1 (2%)	6 (12%)	5 (10%)	4 (8%)
Renal tubule, epithelium, cytomegaly		40 (80%)	47 (94%)	46 (92%)
Right, atrophy	1 (2%)			
Urethra	(1)	(2)	(3)	(2)
Dilatation		1 (50%)		1 (50%)
Inflammation, suppurative	1 (100%)	1 (50%)		1 (50%)
Bulbourethral gland, cyst				1 (50%)
Bulbourethral gland, hemorrhage			2 (67%)	
Bulbourethral gland, inflammation, subacute				1 (50%)
Urinary bladder	(49)	(22)	(18)	(50)
Hemorrhage		2 (9%)		
Hyperplasia				1 (2%)
Inflammation, subacute	2 (4%)	2 (9%)	1 (6%)	1 (2%)
Inflammation, suppurative	1 (2%)	1 (5%)		
Mineralization				1 (2%)
Wall, mineralization, focal	1 (2%)			

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] One male receiving 25,000 ppm and two males receiving 50,000 ppm died prior to the interim evaluation.

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR STUDY OF C.I. PIGMENT RED 3

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3[a]

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-month interim evaluation[b]	10	10	10	10
Early deaths				
Natural death	2	4	8	5
Moribund	7	9	11	20
Accidental death	2			
Survivors				
Terminal sacrifice	39	37	31	25
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(48)	(12)	(17)	(48)
Intestine large, rectum wall,	(48)	(12)	(18)	(49)
fibrosarcoma, metastatic, skin	1 (2%)			
Intestine small, ileum	(49)	(13)	(19)	(48)
Intestine small, jejunum	(49)	(13)	(17)	(48)
Liver	(50)	(50)	(49)	(50)
Fibrosarcoma, metastatic, multiple, three, skin	1 (2%)			
Fibrous histiocytoma, metastatic, mesentery				1 (2%)
Hemangioma	1 (2%)			
Hemangiosarcoma		1 (2%)		
Hepatocellular carcinoma	4 (8%)	6 (12%)	2 (4%)	1 (2%)
Hepatocellular carcinoma, multiple		1 (2%)		
Hepatocellular carcinoma, multiple, two		1 (2%)		
Hepatocellular adenoma	7 (14%)	8 (16%)	2 (4%)	7 (14%)
Hepatocellular adenoma, multiple, two				1 (2%)
Histiocytic sarcoma		2 (4%)	2 (4%)	2 (4%)
Mast cell tumor malignant				1 (2%)
Mesentery	(8)	(4)	(4)	(6)
Fibrosarcoma, metastatic, multiple, greater than five, skin	1 (13%)			
Fibrous histiocytoma, multiple, greater than five				1 (17%)
Pancreas	(50)	(12)	(19)	(50)
Fibrosarcoma, metastatic, skin	1 (2%)			
Fibrous histiocytoma, metastatic, mesentery				1 (2%)
Salivary glands	(50)	(13)	(18)	(50)
Stomach, forestomach	(50)	(16)	(24)	(49)
Hemangioma				1 (2%)
Papilloma squamous			1 (4%)	1 (2%)
Stomach, glandular	(50)	(12)	(18)	(49)
Cardiovascular System				
Heart	(50)	(13)	(19)	(50)
Histiocytic sarcoma			1 (5%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3
(continued)

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Endocrine System				
Adrenal gland, cortex	(50)	(15)	(18)	(50)
Adenoma		1 (7%)		
Osteosarcoma, metastatic, bone	1 (2%)			
Adrenal gland, medulla	(50)	(14)	(18)	(50)
Pheochromocytoma malignant		1 (7%)		
Pheochromocytoma benign	1 (2%)	1 (7%)		
Islets, pancreatic	(50)	(12)	(18)	(50)
Carcinoma	1 (2%)			
Pituitary gland	(49)	(14)	(17)	(50)
Pars distalis, adenoma	8 (16%)	2 (14%)		2 (4%)
Thyroid gland	(50)	(50)	(49)	(50)
Follicular cell, adenoma	2 (4%)	1 (2%)		3 (6%)
Follicular cell, adenoma, multiple	2 (4%)			
Follicular cell, carcinoma		1 (2%)		
General Body System				
None				
Genital System				
Ovary	(50)	(49)	(50)	(50)
Cystadenoma		1 (2%)		
Cystadenoma, papillary				1 (2%)
Histiocytic sarcoma				1 (2%)
Granulosa cell, adenoma			1 (2%)	2 (4%)
Uterus	(50)	(38)	(43)	(50)
Adenoma, cystic				1 (2%)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma		1 (3%)	1 (2%)	
Polyp stromal	2 (4%)	1 (3%)		
Sarcoma		1 (3%)	1 (2%)	1 (2%)
Cervix, histiocytic sarcoma		1 (3%)	1 (2%)	1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)		1 (2%)	
Mast cell tumor malignant				1 (2%)
Lymph node	(50)	(20)	(23)	(50)
Axillary, fibrosarcoma, metastatic, skin			1 (4%)	
Axillary, histiocytic sarcoma				1 (2%)
Deep cervical, histiocytic sarcoma				1 (2%)
Iliac, histiocytic sarcoma				2 (4%)
Inguinal, fibrosarcoma, metastatic, skin			1 (4%)	1 (2%)
Inguinal, histiocytic sarcoma				1 (2%)
Mediastinal, fibrosarcoma, metastatic, skin	1 (2%)			

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Hematopoietic System (continued)				
Lymph node (continued)				
Mediastinal, fibrous histiocytoma, metastatic, mesentery				1 (2%)
Mesenteric, histiocytic sarcoma				1 (2%)
Renal, histiocytic sarcoma				2 (4%)
Lymph node, mandibular	(50)	(15)	(18)	(49)
Spleen	(50)	(49)	(49)	(50)
Fibrous histiocytoma, metastatic, mesentery				1 (2%)
Hemangioma	1 (2%)			1 (2%)
Hemangiosarcoma	1 (2%)	2 (4%)	2 (4%)	
Histiocytic sarcoma				2 (4%)
Mast cell tumor malignant				1 (2%)
Thymus	(50)	(13)	(19)	(50)
Fibrous histiocytoma, metastatic, mesentery				1 (2%)
Integumentary System				
Skin	(50)	(29)	(33)	(50)
Histiocytic sarcoma				1 (2%)
Squamous cell carcinoma			1 (3%)	
Subcutaneous tissue, fibroma				1 (2%)
Subcutaneous tissue, fibrosarcoma	2 (4%)		1 (3%)	
Subcutaneous tissue, fibrosarcoma, multiple				1 (2%)
Subcutaneous tissue, hemangioma		1 (3%)		
Subcutaneous tissue, hemangiosarcoma		1 (3%)		
Subcutaneous tissue, osteosarcoma, metastatic, bone	1 (2%)			
Subcutaneous tissue, sarcoma	1 (2%)			
Subcutaneous tissue, sarcoma, multiple			1 (3%)	
Subcutaneous tissue, schwannoma benign			1 (3%)	
Musculoskeletal System				
Bone	(50)	(13)	(19)	(50)
Osteosarcoma	1 (2%)		1 (5%)	
Nervous System				
None				

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3
(continued)

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Respiratory System				
Lung	(50)	(13)	(21)	(50)
Alveolar/bronchiolar adenoma	3 (6%)			3 (6%)
Alveolar/bronchiolar carcinoma	1 (2%)		1 (5%)	
Fibrosarcoma, metastatic, skin				1 (2%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)			
Hepatocellular carcinoma, metastatic, multiple, greater than five, liver		1 (8%)		
Histiocytic sarcoma		1 (8%)		
Osteosarcoma, metastatic, multiple, greater than five, bone	1 (2%)		1 (5%)	
Special Senses System				
Harderian gland	(3)	(2)	(1)	(1)
Adenoma	3 (100%)	1 (50%)	1 (100%)	1 (100%)
Carcinoma		1 (50%)		
Urinary System				
Kidney	(50)	(49)	(49)	(50)
Histiocytic sarcoma		1 (2%)		1 (2%)
Mast cell tumor malignant				1 (2%)
Osteosarcoma, metastatic, multiple, two, bone	1 (2%)			
Urinary bladder	(50)	(12)	(18)	(50)
Systemic Lesions				
Multiple organs[c]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		2 (4%)	2 (4%)	3 (6%)
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant mixed	14 (28%)	9 (18%)	8 (16%)	6 (12%)
Lymphoma malignant undifferentiated cell	1 (2%)			
Tumor Summary				
Total animals with primary neoplasms[d]	36	29	23	33
Total primary neoplasms	58	44	27	43
Total animals with benign neoplasms	21	15	6	23
Total benign neoplasms	30	17	6	25
Total animals with malignant neoplasms	21	20	19	15
Total malignant neoplasms	28	27	21	18
Total animals with secondary neoplasms[e]	3	1	2	2
Total secondary neoplasms	10	1	3	7

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] One control female was sacrificed moribund prior to the interim evaluation.
[c] Number of animals with any tissue examined microscopically
[d] Primary tumors: all tumors except metastatic tumors
[e] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm

Number of Days on Study	0 0 4	0 0 4	5 0 8	5 2 8	6 3 0	6 5 3	6 8 0	6 9 1	7 0 3	7 1 9	7 2 4	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	5 4 1	5 4 2	5 5 1	5 5 4	5 0 5	5 7 3	5 3 5	5 4 5	5 6 4	5 7 4	5 1 2	4 9 1	4 9 2	4 9 3	4 9 4	4 9 5	5 0 1	5 0 2	5 0 3	5 0 4	5 1 1	5 1 3	5 1 4	5 1 5	5 2 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Wall, fibrosarcoma, metastatic, skin											X														
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, multiple, three, skin											X														
Hemangioma																									
Hepatocellular carcinoma																							X		
Hepatocellular adenoma						X																			
Mesentery					+		+				+														
Fibrosarcoma, metastatic, multiple, greater than five, skin											X														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin											X														
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone										X															
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																								X	

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	5 2 2	5 2 3	5 2 4	5 2 5	5 3 1	5 3 2	5 3 3	5 3 4	5 4 3	5 4 4	5 5 2	5 5 3	5 5 5	5 6 1	5 6 2	5 6 3	5 6 5	5 7 1	5 7 2	5 7 5	5 8 1	5 8 2	5 8 3	5 8 4	5 8 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Wall, fibrosarcoma, metastatic, skin																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, multiple, three, skin																										1
Hemangioma																									X	1
Hepatocellular carcinoma	X																		X	X						4
Hepatocellular adenoma		X							X							X		X		X		X				7
Mesentery						+		+					+		+										+	8
Fibrosarcoma, metastatic, multiple, greater than five, skin																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth			+																							1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	0 0 5 5 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7
	0 0 0 2 3 5 8 9 0 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2
	4 4 8 8 0 3 0 1 3 9 4 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9
Carcass ID Number	5 5 5 5 5 5 5 5 5 5 5 4 4 4 4 4 5 5 5 5 5 5 5 5 5
	4 4 5 5 0 7 3 4 6 7 1 9 9 9 9 9 0 0 0 0 1 1 1 1 2
	1 2 1 4 5 3 5 5 4 4 2 1 2 3 4 5 1 2 3 4 1 3 4 5 1
Endocrine System (continued)	
Islets, pancreatic	+ +
Carcinoma	X
Parathyroid gland	+ + + + + + + + + + + + + + + + M + + + + + + + +
Pituitary gland	+ M +
Pars distalis, adenoma	X X X X
Thyroid gland	+ +
Follicular cell, adenoma	
Follicular cell, adenoma, multiple	X X
General Body System	
None	
Genital System	
Ovary	+ +
Uterus	+ +
Hemangiosarcoma	
Polyp stromal	X X
Hematopoietic System	
Bone marrow	+ +
Hemangiosarcoma	X
Lymph node	+ +
Mediastinal, fibrosarcoma, metastatic, skin	X
Lymph node, mandibular	+ +
Spleen	+ +
Hemangioma	X
Hemangiosarcoma	X
Thymus	+ +
Integumentary System	
Mammary gland	+ +
Skin	+ +
Subcutaneous tissue, fibrosarcoma	X X
Subcutaneous tissue, osteosarcoma, metastatic, bone	X
Subcutaneous tissue, sarcoma	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	5 2 2	5 2 3	5 2 4	5 2 5	5 3 1	5 3 2	5 3 3	5 3 4	5 4 3	5 4 4	5 5 2	5 5 3	5 5 5	5 6 1	5 6 2	5 6 3	5 6 5	5 7 1	5 7 2	5 7 5	5 8 1	5 8 2	5 8 3	5 8 4	5 8 5	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma								X							X		X									8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma			X												X											2
Follicular cell, adenoma, multiple																										2
General Body System																										
None																										
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																									X	1
Polyp stromal																										2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, fibrosarcoma, metastatic, skin																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										2
Subcutaneous tissue, osteosarcoma, metastatic, bone																										1
Subcutaneous tissue, sarcoma				X																						1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	0 0 5 5 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 0 0 0 2 3 5 8 9 0 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 4 4 8 8 0 3 0 1 3 9 4 9 9 9 9 9 9 9 9 9 9 9 9 9 9
Carcass ID Number	5 5 5 5 5 5 5 5 5 5 5 4 4 4 4 4 5 5 5 5 5 5 5 5 5 4 4 5 5 0 7 3 4 6 7 1 9 9 9 9 9 0 0 0 0 1 1 1 1 2 1 2 1 4 5 3 5 5 4 4 2 1 2 3 4 5 1 2 3 4 1 3 4 5 1
Musculoskeletal System	
Bone	+ +
Osteosarcoma	X
Nervous System	
Brain	+ +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X X
Alveolar/bronchiolar carcinoma	
Hepatocellular carcinoma, metastatic, liver	
Osteosarcoma, metastatic, multiple, greater than five, bone	X
Nose	+ +
Trachea	+ +
Special Senses System	
Eye	
Harderian gland	+
Adenoma	X
Urinary System	
Kidney	+ +
Osteosarcoma, metastatic, multiple, two, bone	X
Urinary bladder	+ +
Systemic Lesions	
Multiple organs	+ +
Lymphoma malignant mixed	X X X X X X
Lymphoma malignant undifferentiated cell type	X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 0 ppm
(continued)

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	5 2 2	5 2 3	5 2 4	5 2 5	5 3 1	5 3 2	5 3 3	5 3 4	5 4 3	5 4 4	5 5 2	5 5 3	5 5 5	5 6 1	5 6 2	5 6 3	5 6 5	5 7 1	5 7 2	5 7 5	5 8 1	5 8 2	5 8 3	5 8 4	5 8 5	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X																								3
Alveolar/bronchiolar carcinoma						X																				1
Hepatocellular carcinoma, metastatic, liver	X																									1
Osteosarcoma, metastatic, multiple, greater than five, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																	+									1
Harderian gland									+								+									3
Adenoma									X								X									3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, multiple, two, bone																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed	X		X	X		X	X			X										X				X	X	14
Lymphoma malignant undifferentiated cell type																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm

Number of Days on Study	3	5	5	5	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	3	4	6	6	9	9	2	5	5	8	9	1	2	3	3	3	3	3	3	3	3	3	3	3	3
	7	0	1	8	9	9	7	3	3	0	6	9	4	2	2	2	2	2	2	2	2	2	2	2	2
Carcass ID Number	8	8	8	8	9	9	8	8	9	8	8	9	9	8	8	8	8	8	8	8	8	8	8	8	8
	8	5	9	8	1	1	7	8	0	5	9	0	3	5	5	5	6	6	6	6	6	7	7	7	7
	1	3	5	4	1	2	4	5	4	4	1	2	3	1	2	5	1	2	3	4	5	1	2	3	5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+		+										
Gallbladder	A	+	+	+	+	+	+	+	+	+	+	+	+												
Intestine large	A	+	+	+	+	+	+	+	+	+	+	+	+												
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+												
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+												
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+												
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+									+			
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+									+			
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+									+			
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+									+			
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma									X						X		X					X			
Hepatocellular carcinoma, multiple																									
Hepatocellular carcinoma, multiple, two							X																		
Hepatocellular adenoma						X	X	X							X								X		
Histiocytic sarcoma				X						X															
Mesentery											+						+								
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+												
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+											+	
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+											+	
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+												
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+												
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+												
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+												
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+												
Pheochromocytoma malignant																									
Pheochromocytoma benign		X																							
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+												
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+												
Pituitary gland	A	+	+	+	+	+	+	+	+	+	+	+	+						+			+			
Pars distalis, adenoma																			X			X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma														X											
Follicular cell, carcinoma																		X							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	8 8 2	8 8 3	8 9 2	8 9 3	8 9 4	9 0 1	9 0 3	9 0 5	9 1 3	9 1 4	9 1 5	9 2 1	9 2 2	9 2 3	9 2 4	9 2 5	9 3 1	9 3 2	9 3 4	9 3 5	9 4 1	9 4 2	9 4 3	9 4 4	9 4 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus																										14
Gallbladder																										12
Intestine large																										12
Intestine large, cecum																										12
Intestine large, colon																										12
Intestine large, rectum																										12
Intestine small																										13
Intestine small, duodenum																										13
Intestine small, ileum																										13
Intestine small, jejunum																										13
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma									X																	1
Hepatocellular carcinoma																					X				X	6
Hepatocellular carcinoma, multiple																			X							1
Hepatocellular carcinoma, multiple, two																										1
Hepatocellular adenoma						X		X			X															8
Histiocytic sarcoma																										2
Mesentery		+								+																4
Pancreas																										12
Salivary glands																										13
Stomach													+		+				+							16
Stomach, forestomach													+		+				+							16
Stomach, glandular																										12
Cardiovascular System																										
Heart																										13
Endocrine System																										
Adrenal gland						+							+													15
Adrenal gland, cortex						+							+													15
Adenoma						X																				1
Adrenal gland, medulla													+													14
Pheochromocytoma malignant													X													1
Pheochromocytoma benign																										1
Islets, pancreatic																										12
Parathyroid gland																										13
Pituitary gland																										14
Pars distalis, adenoma																										2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1
Follicular cell, carcinoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	3 3 7	5 4 0	5 6 1	5 6 8	5 9 9	5 9 9	6 2 7	6 5 3	6 5 3	6 8 0	6 9 6	7 1 9	7 2 4	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	8 8 1	8 5 3	8 9 5	8 8 4	9 1 1	9 1 2	8 7 4	8 8 5	9 0 4	8 5 4	8 9 1	9 0 2	9 3 3	8 5 1	8 5 2	8 5 5	8 6 1	8 6 2	8 6 3	8 6 4	8 6 5	8 7 1	8 7 2	8 7 3	8 7 5
General Body System																									
Tissue NOS	+																								
Genital System																									
Ovary	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Uterus	A	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+		+		+	+	+
Histiocytic sarcoma										X															
Polyp stromal																						X			
Sarcoma			X																						
Cervix, histiocytic sarcoma				X																					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+		+							+		+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+		+										
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma															X										
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+												
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+									+			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+		+			
Subcutaneous tissue, hemangioma														X											
Subcutaneous tissue, hemangiosarcoma												X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+												
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+									+			

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	8 8 2	8 8 3	8 9 2	8 9 3	8 9 4	9 0 1	9 0 3	9 0 5	9 1 3	9 1 4	9 1 5	9 2 1	9 2 2	9 2 3	9 2 4	9 2 5	9 3 1	9 3 2	9 3 4	9 3 5	9 4 1	9 4 2	9 4 3	9 4 4	9 4 5	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS																										1
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma																						X				1
Uterus	+	+	+	+	+	+	+	+			+	+		+			+	+			+	+	+	+		38
Histiocytic sarcoma																										1
Polyp stromal																										1
Sarcoma																										1
Cervix, histiocytic sarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node								+							+							+			+	20
Lymph node, mandibular																									+	15
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma									X																	2
Thymus																										13
Integumentary System																										
Mammary gland																										14
Skin	+					+			+	+					+						+	+			+	29
Subcutaneous tissue, hemangioma																										1
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																										
Bone																										13
Nervous System																										
Brain																										14

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	3	5	5	5	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	3	4	6	6	9	9	2	5	5	8	9	1	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	7	0	1	8	9	9	7	3	3	0	6	9	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Carcass ID Number	8	8	8	8	9	9	8	8	9	8	8	9	9	8	8	8	8	8	8	8	8	8	8	8	8	8	8
	8	5	9	8	1	1	7	8	0	5	9	0	3	5	5	5	6	6	6	6	6	7	7	7	7	7	7
	1	3	5	4	1	2	4	5	4	4	1	2	3	1	2	5	1	2	3	4	5	1	2	3	5		
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+														
Hepatocellular carcinoma, metastatic, multiple, greater than five, liver							X																				
Histiocytic sarcoma				X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+														
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+														
Special Senses System																											
Harderian gland										+																	
Adenoma										X																	
Carcinoma																											
Urinary System																											
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																							
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+														
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X						X																	
Lymphoma malignant mixed		X			X																		X				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 12,500 ppm
(continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	8 8 2	8 8 3	8 9 2	8 9 3	8 9 4	9 0 1	9 0 3	9 0 5	9 1 3	9 1 4	9 1 5	9 2 1	9 2 2	9 2 3	9 2 4	9 2 5	9 3 1	9 3 2	9 3 4	9 3 5	9 4 1	9 4 2	9 4 3	9 4 4	9 4 5	**Total Tissues/ Tumors**
Respiratory System																										
Lung																										13
Hepatocellular carcinoma, metastatic, multiple, greater than five, liver																										1
Histiocytic sarcoma																										1
Nose																										13
Trachea																										13
Special Senses System																										
Harderian gland																									+	2
Adenoma																										1
Carcinoma																									X	1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Urinary bladder																										12
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant mixed								X	X	X					X				X						X	9

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm

Number of Days on Study	4	4	5	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7		
	7	9	4	4	6	9	9	0	1	1	2	7	7	7	9	9	0	2	2	3	3	3	3	3	3
	4	7	2	7	8	5	7	6	3	6	7	0	6	9	6	6	9	4	4	1	1	1	1	1	1
Carcass ID Number	7	8	7	8	8	7	7	7	8	8	8	7	7	7	7	7	7	7	8	7	7	7	7	7	7
	5	1	7	2	0	5	3	7	2	0	0	3	8	3	3	9	5	7	0	3	4	4	4	4	4
	4	3	4	5	2	5	2	5	2	1	5	1	2	5	4	3	3	3	3	3	1	2	3	4	5
Alimentary System																									
Esophagus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Gallbladder	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+						
Intestine large	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Intestine large, cecum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Intestine large, colon	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+						
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Intestine small	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Intestine small, duodenum	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+						
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Intestine small, jejunum	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+						
Liver	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular adenoma																									
Histiocytic sarcoma					X						X														
Mesentery							+					+													
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Salivary glands	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Stomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Stomach, forestomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Papilloma squamous																									
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Histiocytic sarcoma					X																				
Endocrine System																									
Adrenal gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Adrenal gland, cortex	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Adrenal gland, medulla	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Parathyroid gland	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Pituitary gland	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Thyroid gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	
Carcass ID Number	7 5 1	7 5 2	7 6 1	7 6 2	7 6 3	7 6 4	7 6 5	7 7 1	7 7 2	7 8 1	7 8 3	7 8 4	7 8 5	7 9 1	7 9 2	7 9 4	7 9 5	8 0 4	8 1 1	8 1 2	8 1 4	8 2 1	8 2 3	8 2 4	8 2 5	**Total Tissues/ Tumors**	
Alimentary System																											
Esophagus																										18	
Gallbladder																										17	
Intestine large																										18	
Intestine large, cecum																										17	
Intestine large, colon																										16	
Intestine large, rectum																										18	
Intestine small															+											19	
Intestine small, duodenum															+											17	
Intestine small, ileum															+											19	
Intestine small, jejunum															+											17	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Hepatocellular carcinoma										X								X								2	
Hepatocellular adenoma																							X	X		2	
Histiocytic sarcoma																										2	
Mesentery										+															+	4	
Pancreas																									+	19	
Salivary glands																										18	
Stomach												+				+			+	+		+	+			24	
Stomach, forestomach												+				+			+	+		+	+			24	
Papilloma squamous																X										1	
Stomach, glandular																										18	
Cardiovascular System																											
Heart																										19	
Histiocytic sarcoma																										1	
Endocrine System																											
Adrenal gland																										18	
Adrenal gland, cortex																										18	
Adrenal gland, medulla																										18	
Islets, pancreatic																										18	
Parathyroid gland																										17	
Pituitary gland																										17	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
General Body System																											
None																											

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	4 7 4	4 9 7	5 4 2	5 4 7	5 6 8	5 9 5	5 9 7	6 0 6	6 1 3	6 1 6	6 2 7	6 7 0	6 7 6	6 7 9	6 9 6	6 9 6	7 0 9	7 2 4	7 2 4	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	7 5 4	8 1 3	7 7 4	8 2 5	8 0 2	7 5 5	7 3 2	7 7 5	8 2 2	8 0 1	8 0 5	7 3 1	7 8 2	7 3 5	7 3 4	7 9 3	7 5 3	7 7 3	8 0 3	7 3 3	7 4 1	7 4 2	7 4 3	7 4 4	7 4 5
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell, adenoma																						X			
Uterus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Histiocytic sarcoma					X																				
Sarcoma																									
Cervix, histiocytic sarcoma											X														
Hematopoietic System																									
Blood	+				+																				
Bone marrow	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		+		
Axillary, fibrosarcoma, metastatic, skin																			X						
Inguinal, fibrosarcoma, metastatic, skin																			X						
Lymph node, mandibular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Spleen	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+	+	+
Squamous cell carcinoma															X										
Subcutaneous tissue, fibrosarcoma																			X						
Subcutaneous tissue, sarcoma, multiple														X											
Subcutaneous tissue, schwannoma benign																								X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Osteosarcoma																		X							
Nervous System																									
Brain	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	
Carcass ID Number	7 5 1	7 5 2	7 6 1	7 6 2	7 6 3	7 6 4	7 6 5	7 7 1	7 7 2	7 8 1	7 8 3	7 8 4	7 8 5	7 9 1	7 9 2	7 9 4	7 9 5	8 0 4	8 1 1	8 1 2	8 1 4	8 2 1	8 2 3	8 2 4	8 2 5	8 1 5	**Total Tissues/ Tumors**
Genital System																											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell, adenoma																											1
Uterus	+	+	+	+	+	+	+		+	+	+	+		+		+	+	+	+	+	+		+	+			43
Histiocytic sarcoma																											1
Sarcoma									X																		1
Cervix, histiocytic sarcoma																											1
Hematopoietic System																											
Blood																											2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma														X													1
Lymph node					+										+											+	23
Axillary, fibrosarcoma, metastatic, skin																											1
Inguinal, fibrosarcoma, metastatic, skin																											1
Lymph node, mandibular																											18
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma														X										X			2
Thymus					+																						19
Integumentary System																											
Mammary gland																											19
Skin	+		+					+	+				+	+	+					+	+	+			+	33
Squamous cell carcinoma																											1
Subcutaneous tissue, fibrosarcoma																											1
Subcutaneous tissue, sarcoma, multiple																											1
Subcutaneous tissue, schwannoma benign																											1
Musculoskeletal System																											
Bone																											19
Osteosarcoma																											1
Nervous System																											
Brain																											18

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	4 7 4	4 9 7	5 4 2	5 4 7	5 6 8	5 9 5	5 9 7	6 0 6	6 1 3	6 1 6	6 2 7	6 7 0	6 7 6	6 7 9	6 9 6	6 9 6	7 0 9	7 2 4	7 2 4	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	7 5 4	8 1 3	7 7 4	8 2 5	8 0 2	7 5 5	7 3 2	7 7 5	8 2 2	8 0 1	8 0 5	7 3 1	7 8 2	7 3 5	7 3 4	7 9 3	7 5 3	7 7 3	8 0 3	7 3 3	7 4 1	7 4 2	7 4 3	7 4 4	7 4 5
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+			+	
Alveolar/bronchiolar carcinoma																								X	
Osteosarcoma, metastatic, multiple, greater than five, bone																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Trachea	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Special Senses System																									
Harderian gland																									
Adenoma																									
Urinary System																									
Kidney	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X						X														
Lymphoma malignant mixed	X					X								X			X				X				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 25,000 ppm
(continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	
Carcass ID Number	7 5 1	7 5 2	7 6 1	7 6 2	7 6 3	7 6 4	7 6 5	7 7 1	7 7 2	7 8 1	7 8 3	7 8 4	7 8 5	7 9 1	7 9 2	7 9 4	7 9 5	8 0 4	8 1 1	8 1 2	8 1 4	8 2 1	8 2 3	8 2 4	8 2 5	**Total Tissues/ Tumors**	
Respiratory System																											
Lung																										21	
Alveolar/bronchiolar carcinoma																										1	
Osteosarcoma, metastatic, multiple, greater than five, bone																										1	
Nose																										19	
Trachea																										18	
Special Senses System																											
Harderian gland																			+							1	
Adenoma																			X							1	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Urinary bladder																										18	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma																										2	
Lymphoma malignant mixed					X							X			X											8	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 50,000 ppm

Number of Days on Study	2 8 6	3 5 8	5 4 0	5 5 7	5 5 7	5 8 8	5 8 8	5 9 9	5 9 9	6 0 3	6 1 6	6 1 8	6 2 5	6 2 5	6 2 5	6 2 5	6 2 5	6 2 7	6 2 7	6 2 7	6 2 7	6 8 0	6 8 0	7 0 7	7 1 7
Carcass ID Number	6 4 1	6 1 1	6 1 2	6 2 5	6 3 2	6 3 4	6 4 3	6 2 3	6 5 2	6 7 2	6 6 2	6 8 5	6 1 5	6 5 3	6 8 1	6 8 4	6 9 4	6 2 1	6 2 4	6 4 2	6 6 5	6 1 3	6 8 2	6 9 1	6 7 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, mesentery																	X								
Hepatocellular carcinoma																									
Hepatocellular adenoma											X			X											
Hepatocellular adenoma, multiple, two																X									
Histiocytic sarcoma									X													X			
Mast cell tumor malignant																									X
Mesentery			+			+							+	+			+								
Fibrous histiocytoma, multiple, greater than five																	X								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, mesentery																	X								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Papilloma squamous										X															
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 50,000 ppm
(continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	6 1 4	6 2 2	6 3 1	6 3 3	6 3 5	6 4 4	6 4 5	6 5 1	6 5 4	6 5 5	6 6 1	6 6 3	6 6 4	6 7 1	6 7 3	6 7 5	6 8 3	6 9 2	6 9 3	6 9 5	7 0 1	7 0 2	7 0 3	7 0 4	7 0 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, mesentery																										1
Hepatocellular carcinoma																	X									1
Hepatocellular adenoma		X		X		X				X															X	7
Hepatocellular adenoma, multiple, two																										1
Histiocytic sarcoma																										2
Mast cell tumor malignant																										1
Mesentery																			+							6
Fibrous histiocytoma, multiple, greater than five																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, mesentery																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma												X														1
Papilloma squamous																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma											X		X													2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma						X	X		X																	3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 50,000 ppm
(continued)

Number of Days on Study	2	3	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7
	8	5	4	5	5	8	8	9	9	0	1	1	2	2	2	2	2	2	2	2	2	8	8	0	1
	6	8	0	7	7	8	8	9	9	3	6	8	5	5	5	5	5	7	7	7	7	0	0	7	7
Carcass ID Number	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	4	1	1	2	3	3	4	2	5	7	6	8	1	5	8	8	9	2	2	4	6	1	8	9	7
	1	1	2	5	2	4	3	3	2	2	2	5	5	3	1	4	4	1	4	2	5	3	2	1	4
General Body System																									
None																									
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, papillary																									
Histiocytic sarcoma																						X			
Granulosa cell, adenoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, cystic					X																				
Sarcoma													X												
Cervix, histiocytic sarcoma																						X			
Hematopoietic System																									
Blood							+																		
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant																									X
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, histiocytic sarcoma		X																							
Deep cervical, histiocytic sarcoma									X																
Iliac, histiocytic sarcoma		X																				X			
Inguinal, fibrosarcoma, metastatic, skin											X														
Inguinal, histiocytic sarcoma		X																							
Mediastinal, fibrous histiocytoma, metastatic, mesentery																	X								
Mesenteric, histiocytic sarcoma									X																
Renal, histiocytic sarcoma		X																				X			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, mesentery																	X								
Hemangioma																									
Histiocytic sarcoma		X							X																
Mast cell tumor malignant																									X
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, mesentery																	X								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 50,000 ppm
(continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	6 1 4	6 2 2	6 3 1	6 3 3	6 3 5	6 4 4	6 4 5	6 5 1	6 5 4	6 5 5	6 6 1	6 6 3	6 6 4	6 7 1	6 7 3	6 7 5	6 8 3	6 9 2	6 9 3	6 9 5	7 0 1	7 0 2	7 0 3	7 0 4	7 0 5	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma, papillary																			X							1
Histiocytic sarcoma																										1
Granulosa cell, adenoma			X															X								2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, cystic																										1
Sarcoma																										1
Cervix, histiocytic sarcoma																										1
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Axillary, histiocytic sarcoma																										1
Deep cervical, histiocytic sarcoma																										1
Iliac, histiocytic sarcoma																										2
Inguinal, fibrosarcoma, metastatic, skin																										1
Inguinal, histiocytic sarcoma																										1
Mediastinal, fibrous histiocytoma, metastatic, mesentery																										1
Mesenteric, histiocytic sarcoma																										1
Renal, histiocytic sarcoma																										2
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, mesentery																										1
Hemangioma					X																					1
Histiocytic sarcoma																										2
Mast cell tumor malignant																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, mesentery																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 50,000 ppm
(continued)

Number of Days on Study	2 8 6	3 5 8	5 4 0	5 5 7	5 5 7	5 8 8	5 8 8	5 9 9	5 9 9	6 0 3	6 1 6	6 1 8	6 2 5	6 2 5	6 2 5	6 2 5	6 2 5	6 2 7	6 2 7	6 2 7	6 2 7	6 2 7	6 2 7	6 2 7	6 2 7	6 2 7
Carcass ID Number	6 4 1	6 1 1	6 1 2	6 2 5	6 3 2	6 3 4	6 4 3	6 2 3	6 5 2	6 7 2	6 6 2	6 8 5	6 1 5	6 5 3	6 8 1	6 8 4	6 9 4	6 2 1	6 2 4	6 4 2	6 6 5	6 1 3	6 8 2	6 9 1	6 7 4
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Subcutaneous tissue, fibroma								X																	
Subcutaneous tissue, fibrosarcoma, multiple											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X					
Fibrosarcoma, metastatic, skin											X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+																								
Harderian gland															+										
Adenoma															X										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Mast cell tumor malignant																									X
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X							X													X			
Lymphoma malignant histiocytic																									
Lymphoma malignant mixed								X												X		X			

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3: 50,000 ppm
(continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	6 1 4	6 2 2	6 3 1	6 3 3	6 3 5	6 4 4	6 4 5	6 5 1	6 5 4	6 5 5	6 6 1	6 6 3	6 6 4	6 7 1	6 7 3	6 7 5	6 8 3	6 9 2	6 9 3	6 9 5	7 0 1	7 0 2	7 0 3	7 0 4	7 0 5	**Total Tissues/ Tumors**
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma, multiple																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																		X					X			3
Fibrosarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland																										1
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Mast cell tumor malignant																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										3
Lymphoma malignant histiocytic										X																1
Lymphoma malignant mixed		X			X											X										6

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Harderian Gland: Adenoma				
Overall rates[a]	3/50 (6%)	1/50 (2%)	1/50 (2%)	1/50 (2%)
Adjusted rates[b]	7.2%	2.4%	3.2%	2.6%
Terminal rates[c]	2/39 (5%)	0/37 (0%)	1/31 (3%)	0/25 (0%)
First incidence (days)	630	680	729 (T)	625
Life table tests[d]	P=0.364N	P=0.330N	P=0.385N	P=0.451N
Logistic regression tests[d]	P=0.243N	P=0.305N	P=0.309N	P=0.306N
Cochran-Armitage test[d]	P=0.242N			
Fisher exact test[d]		P=0.309N	P=0.309N	P=0.309N
Harderian Gland: Adenoma or Carcinoma				
Overall rates	3/50 (6%)	2/50 (4%)	1/50 (2%)	1/50 (2%)
Adjusted rates	7.2%	5.1%	3.2%	2.6%
Terminal rates	2/39 (5%)	1/37 (3%)	1/31 (3%)	0/25 (0%)
First incidence (days)	630	680	729 (T)	625
Life table tests	P=0.323N	P=0.527N	P=0.385N	P=0.451N
Logistic regression tests	P=0.204N	P=0.497N	P=0.309N	P=0.306N
Cochran-Armitage test	P=0.199N			
Fisher exact test		P=0.500N	P=0.309N	P=0.309N
Liver: Hepatocellular Adenoma				
Overall rates	7/50 (14%)	8/50 (16%)	2/49 (4%)	8/50 (16%)
Adjusted rates	17.3%	19.2%	6.5%	26.1%
Terminal rates	6/39 (15%)	5/37 (14%)	2/31 (6%)	5/25 (20%)
First incidence (days)	653	599	729 (T)	616
Life table tests	P=0.248	P=0.461	P=0.145N	P=0.209
Logistic regression tests	P=0.482	P=0.506	P=0.107N	P=0.406
Cochran-Armitage test	P=0.541			
Fisher exact test		P=0.500	P=0.085N	P=0.500
Liver: Hepatocellular Carcinoma				
Overall rates	4/50 (8%)	8/50 (16%)	2/49 (4%)	1/50 (2%)
Adjusted rates	10.3%	20.0%	6.5%	4.0%
Terminal rates	4/39 (10%)	6/37 (16%)	2/31 (6%)	1/25 (4%)
First incidence (days)	729 (T)	627	729 (T)	729 (T)
Life table tests	P=0.138N	P=0.157	P=0.447N	P=0.334N
Logistic regression tests	P=0.086N	P=0.176	P=0.447N	P=0.334N
Cochran-Armitage test	P=0.047N			
Fisher exact test		P=0.178	P=0.349N	P=0.181N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	10/50 (20%)	14/50 (28%)	4/49 (8%)	9/50 (18%)
Adjusted rates	24.8%	33.5%	12.9%	29.8%
Terminal rates	9/39 (23%)	10/37 (27%)	4/31 (13%)	6/25 (24%)
First incidence (days)	653	599	729 (T)	616
Life table tests	P=0.475	P=0.207	P=0.156N	P=0.325
Logistic regression tests	P=0.354N	P=0.246	P=0.119N	P=0.550
Cochran-Armitage test	P=0.242N			
Fisher exact test		P=0.241	P=0.080N	P=0.500N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	3/50 (6%)	0/13 (0%)[e]	0/21 (0%)[e]	3/50 (6%)
Adjusted rates	7.7%			10.8%
Terminal rates	3/39 (8%)			2/25 (8%)
First incidence (days)	729 (T)			627
Life table tests				P=0.456
Logistic regression tests				P=0.565
Fisher exact test				P=0.661N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	4/50 (8%)	0/13 (0%)[e]	1/21 (5%)[e]	3/50 (6%)
Adjusted rates	10.3%			10.8%
Terminal rates	4/39 (10%)			2/25 (8%)
First incidence (days)	729 (T)			627
Life table tests				P=0.583
Logistic regression tests				P=0.636N
Fisher exact test				P=0.500N
Lymph Node: Histiocytic Sarcoma				
Overall rates	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rates	0.0%	0.0%	0.0%	7.6%
Terminal rates	0/39 (0%)	0/37 (0%)	0/31 (0%)	0/25 (0%)
First incidence (days)	–[f]	–	–	358
Life table tests	P=0.009	–	–	P=0.097
Logistic regression tests	P=0.008	–	–	P=0.094
Cochran-Armitage test	P=0.012			
Fisher exact test		–	–	P=0.121
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	8/49 (16%)	2/14 (14%)[e]	0/17 (0%)[e]	2/50 (4%)
Adjusted rates	19.9%			8.0%
Terminal rates	7/39 (18%)			2/25 (8%)
First incidence (days)	703			729 (T)
Life table tests				P=0.166N
Logistic regression tests				P=0.154N
Fisher exact test				P=0.043N
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rates	3/50 (6%)	0/50 (0%)	2/50 (4%)	1/50 (2%)
Adjusted rates	7.0%	0.0%	5.7%	2.5%
Terminal rates	1/39 (3%)	0/37 (0%)	0/31 (0%)	0/25 (0%)
First incidence (days)	508	–	679	616
Life table tests	P=0.448N	P=0.129N	P=0.570N	P=0.404N
Logistic regression tests	P=0.330N	P=0.127N	P=0.505N	P=0.300N
Cochran-Armitage test	P=0.337N			
Fisher exact test		P=0.121N	P=0.500N	P=0.309N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rates	3/50 (6%)	0/50 (0%)	2/50 (4%)	2/50 (4%)
Adjusted rates	7.0%	0.0%	5.7%	4.8%
Terminal rates	1/39 (3%)	0/37 (0%)	0/31 (0%)	0/25 (0%)
First incidence (days)	508	-	679	599
Life table tests	P=0.517	P=0.129N	P=0.570N	P=0.599N
Logistic regression tests	P=0.567N	P=0.127N	P=0.505N	P=0.494N
Cochran-Armitage test	P=0.577N			
Fisher exact test		P=0.121N	P=0.500N	P=0.500N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rates	4/50 (8%)	1/50 (2%)	0/49 (0%)	3/50 (6%)
Adjusted rates	9.9%	2.7%	0.0%	12.0%
Terminal rates	3/39 (8%)	1/37 (3%)	0/31 (0%)	3/25 (12%)
First incidence (days)	703	729 (T)	-	729 (T)
Life table tests	P=0.507	P=0.199N	P=0.097N	P=0.575
Logistic regression tests	P=0.525	P=0.190N	P=0.079N	P=0.596
Cochran-Armitage test	P=0.501N			
Fisher exact test		P=0.181N	P=0.061N	P=0.500N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rates	4/50 (8%)	2/50 (4%)	0/49 (0%)	3/50 (6%)
Adjusted rates	9.9%	5.4%	0.0%	12.0%
Terminal rates	3/39 (8%)	2/37 (5%)	0/31 (0%)	3/25 (12%)
First incidence (days)	703	729 (T)	-	729 (T)
Life table tests	P=0.555	P=0.364N	P=0.097N	P=0.575
Logistic regression tests	P=0.573	P=0.357N	P=0.079N	P=0.596
Cochran-Armitage test	P=0.433N			
Fisher exact test		P=0.339N	P=0.061N	P=0.500N
All Organs: Hemangiosarcoma				
Overall rates	2/50 (4%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rates	4.7%	7.8%	6.5%	0.0%
Terminal rates	1/39 (3%)	2/37 (5%)	2/31 (6%)	0/25 (0%)
First incidence (days)	653	719	729 (T)	-
Life table tests	P=0.244N	P=0.477	P=0.617	P=0.341N
Logistic regression tests	P=0.186N	P=0.501	P=0.684	P=0.243N
Cochran-Armitage test	P=0.134N			
Fisher exact test		P=0.500	P=0.691N	P=0.247N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rates	3/50 (6%)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted rates	7.2%	10.5%	6.5%	8.0%
Terminal rates	2/39 (5%)	3/37 (8%)	2/31 (6%)	2/25 (8%)
First incidence (days)	653	719	729 (T)	729 (T)
Life table tests	P=0.538N	P=0.472	P=0.596N	P=0.664
Logistic regression tests	P=0.474N	P=0.495	P=0.527N	P=0.610N
Cochran-Armitage test	P=0.319N			
Fisher exact test		P=0.500	P=0.500N	P=0.500N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
All Organs: Malignant Lymphoma (Histiocytic, Mixed, or Undifferentiated Cell Type)				
Overall rates	15/50 (30%)	9/50 (18%)	8/50 (16%)	7/50 (14%)
Adjusted rates	36.3%	22.3%	21.2%	23.2%
Terminal rates	13/39 (33%)	7/37 (19%)	4/31 (13%)	4/25 (16%)
First incidence (days)	528	540	474	599
Life table tests	P=0.222N	P=0.151N	P=0.190N	P=0.259N
Logistic regression tests	P=0.051N	P=0.116N	P=0.078N	P=0.079N
Cochran-Armitage test	P=0.043N			
Fisher exact test		P=0.121N	P=0.077N	P=0.045N
All Organs: Benign Tumors				
Overall rates	21/50 (42%)	15/50 (30%)	6/50 (12%)	23/50 (46%)
Adjusted rates	49.7%	34.9%	19.4%	67.5%
Terminal rates	18/39 (46%)	10/37 (27%)	6/31 (19%)	15/25 (60%)
First incidence (days)	630	540	729 (T)	557
Life table tests	P=0.031	P=0.209N	P=0.006N	P=0.032
Logistic regression tests	P=0.213	P=0.140N	P=0.002N	P=0.244
Cochran-Armitage test	P=0.332			
Fisher exact test		P=0.149N	P≤0.001N	P=0.420
All Organs: Malignant Tumors				
Overall rates	21/50 (42%)	20/50 (40%)	19/50 (38%)	15/50 (30%)
Adjusted rates	46.4%	43.7%	46.6%	40.1%
Terminal rates	15/39 (38%)	12/37 (32%)	10/31 (32%)	5/25 (20%)
First incidence (days)	508	540	474	358
Life table tests	P=0.480	P=0.559N	P=0.449	P=0.545
Logistic regression tests	P=0.112N	P=0.497N	P=0.419N	P=0.158N
Cochran-Armitage test	P=0.113N			
Fisher exact test		P=0.500N	P=0.419N	P=0.149N
All Organs: Benign and Malignant Tumors				
Overall rates	36/50 (72%)	29/50 (58%)	23/50 (46%)	33/50 (66%)
Adjusted rates	76.6%	61.3%	56.8%	79.7%
Terminal rates	28/39 (72%)	19/37 (51%)	14/31 (45%)	17/25 (68%)
First incidence (days)	508	540	474	358
Life table tests	P=0.060	P=0.224N	P=0.144N	P=0.071
Logistic regression tests	P=0.415N	P=0.091N	P=0.007N	P=0.407N
Cochran-Armitage test	P=0.357N			
Fisher exact test		P=0.104N	P=0.007N	P=0.333N

(T)Terminal sacrifice

[a] Number of tumor-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, bone marrow, brain, clitoral gland, epididymis, gallbladder (mouse), heart, kidney, larynx, liver, lung, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, testes, thyroid gland, and urinary bladder; for other tissues, denominator is number of animals necropsied.

[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality

[c] Observed incidence at terminal kill

[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by N.

[e] Tissue was examined microscopically only when it was observed to be abnormal at necropsy; thus, no statistical analyses are provided.

[f] Not applicable; no tumors in animal group

TABLE D4a
Historical Incidence of Ovarian Tumors in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Granulosa Cell Tumor Benign	Granulosa Cell Tumor Malignant	Adenoma
Historical Incidence at Southern Research Institute			
C.I. Pigment Red 3	0/50	0/50	0/50
Ethylene Glycol	0/49	0/49	0/49
Nitrofurantoin	0/50	0/50	0/50
o-Nitroanisole	0/49	0/49	1/49
Polysorbate 80	0/48	0/48	1/48
Rhodamine 6G	0/48	0/48	0/48
Roxarsone	0/49	0/49	0/49
Total			2/343 (0.6%)
Standard deviation			1.0%
Range			0%-2%
Overall Historical Incidence			
Total	4/846 (0.5%)	0/846 (0.0%)	4/846 (0.5%)
Standard deviation	1.1%		1.7%
Range	0%-4%		0%-7%

[a] Data as of 3 April 1991

TABLE D4b
Historical Incidence of Thyroid Gland Follicular Cell Tumors in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
C.I. Pigment Red 3	4/50	0/50	4/50
Ethylene Glycol	1/49	0/49	1/49
Nitrofurantoin	3/48	1/48	4/48
o-Nitroanisole	1/50	0/50	1/50
Polysorbate 80	1/49	0/49	1/49
Rhodamine 6G	1/50	0/50	1/50
Roxarsone	0/49	0/49	0/49
Total	11/345 (3.2%)	1/345 (0.3%)	12/345 (3.5%)
Standard deviation	2.8%	0.8%	3.2%
Range	0%-8%	0%-2%	0%-8%
Overall Historical Incidence			
Total	21/850 (2.5%)	1/850 (0.1%)	22/850 (2.6%)
Standard deviation	3.2%	0.5%	3.3%
Range	0%-9%	0%-2%	0%-9%

[a] Data as of 3 April 1991

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3[a]

	0 ppm	12,500 ppm	25,000 ppm	25,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-month interim evaluation[b]	10	10	10	10
Early deaths				
Natural death	2	4	8	5
Moribund	7	9	11	20
Accidental death	2			
Survivors				
Terminal sacrifice	39	37	31	25
Animals examined microscopically	50	50	50	50
Alimentary System				
Liver	(50)	(50)	(49)	(50)
Angiectasis	1 (2%)	1 (2%)		
Basophilic focus	1 (2%)	1 (2%)		2 (4%)
Cytologic alterations	1 (2%)	1 (2%)		15 (30%)
Eosinophilic focus		3 (6%)	2 (4%)	2 (4%)
Hematopoietic cell proliferation	2 (4%)	2 (4%)	7 (14%)	15 (30%)
Inflammation, granulomatous	1 (2%)	2 (4%)	2 (4%)	11 (22%)
Mixed cell focus		1 (2%)		2 (4%)
Necrosis, focal	4 (8%)	3 (6%)	1 (2%)	6 (12%)
Necrosis, multifocal	2 (4%)			4 (8%)
Kupffer cell, pigmentation	2 (4%)	1 (2%)	1 (2%)	29 (58%)
Sinusoid, infiltration cellular, polymorphonuclear	4 (8%)	2 (4%)	10 (20%)	18 (36%)
Mesentery	(8)	(4)	(4)	(6)
Inflammation, chronic	1 (13%)			
Inflammation, suppurative, acute	2 (25%)	1 (25%)	2 (50%)	3 (50%)
Artery, inflammation				1 (17%)
Fat, necrosis, focal	4 (50%)	3 (75%)	2 (50%)	1 (17%)
Pancreas	(50)	(12)	(19)	(50)
Cyst, multiple	1 (2%)			
Hemorrhage, focal				1 (2%)
Inflammation, chronic	1 (2%)			
Inflammation, subacute	2 (4%)			3 (6%)
Inflammation, suppurative, acute	1 (2%)		1 (5%)	2 (4%)
Acinus, atrophy, multifocal	3 (6%)	1 (8%)	5 (26%)	3 (6%)
Acinus, hyperplasia, focal				1 (2%)
Acinus, necrosis, multifocal	1 (2%)			
Duct, dilatation			2 (11%)	1 (2%)
Stomach, forestomach	(50)	(16)	(24)	(49)
Erosion	6 (12%)	5 (31%)	4 (17%)	4 (8%)
Hyperplasia	11 (22%)	5 (31%)	5 (21%)	10 (20%)
Hypertrophy	1 (2%)			
Ulcer			1 (4%)	1 (2%)
Stomach, glandular	(50)	(12)	(18)	(49)
Erosion, multiple	1 (2%)			1 (2%)
Hemorrhage	1 (2%)			
Tooth	(1)			
Dysplasia	1 (100%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Cardiovascular System				
Heart	(50)	(13)	(19)	(50)
Inflammation, subacute, focal		1 (8%)	1 (5%)	1 (2%)
Inflammation, subacute, multifocal		1 (8%)	2 (11%)	2 (4%)
Artery, inflammation, subacute	1 (2%)			1 (2%)
Endocrine System				
Adrenal gland, cortex	(50)	(15)	(18)	(50)
Cyst	1 (2%)			
Hyperplasia, focal	1 (2%)			2 (4%)
Hyperplasia, multifocal	1 (2%)			
Hypertrophy, diffuse	1 (2%)			
Hypertrophy, focal	2 (4%)			
Capsule, accessory adrenal cortical nodule	1 (2%)		1 (6%)	
X-zone, degeneration, fatty	2 (4%)			
Adrenal gland, medulla	(50)	(14)	(18)	(50)
Hyperplasia, focal	1 (2%)			1 (2%)
Islets, pancreatic	(50)	(12)	(18)	(50)
Hyperplasia			1 (6%)	
Pituitary gland	(49)	(14)	(17)	(50)
Pars distalis, angiectasis	10 (20%)			2 (4%)
Pars distalis, cyst	1 (2%)			
Pars distalis, hyperplasia	16 (33%)	2 (14%)	3 (18%)	12 (24%)
Pars distalis, pigmentation, hemosiderin	1 (2%)			
Thyroid gland	(50)	(50)	(49)	(50)
Ultimobranchial cyst	1 (2%)			
Artery, inflammation				1 (2%)
Follicle, cyst	7 (14%)	12 (24%)	11 (22%)	21 (42%)
Follicle, hyperplasia, cystic			1 (2%)	1 (2%)
Follicular cell, hyperplasia	11 (22%)	11 (22%)	24 (49%)	38 (76%)
General Body System				
Tissue NOS		(1)		
Hemorrhage		1 (100%)		
Genital System				
Ovary	(50)	(49)	(50)	(50)
Abscess		2 (4%)	6 (12%)	9 (18%)
Abscess, multiple	2 (4%)		6 (12%)	10 (20%)
Angiectasis	1 (2%)			
Cyst	18 (36%)	14 (29%)	13 (26%)	16 (32%)
Cyst, multiple		2 (4%)	4 (8%)	4 (8%)
Hemorrhage	1 (2%)		2 (4%)	
Hyperplasia, cystic	2 (4%)	1 (2%)		
Inflammation, chronic	2 (4%)		2 (4%)	
Pigmentation, hemosiderin	1 (2%)			
Fat, necrosis, focal	1 (2%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Genital System (continued)				
Uterus	(50)	(38)	(43)	(50)
Angiectasis				1 (2%)
Hemorrhage	1 (2%)			
Hydrometra	5 (10%)	3 (8%)	4 (9%)	
Inflammation, suppurative, acute	3 (6%)		1 (2%)	1 (2%)
Endometrium, hyperplasia	1 (2%)			
Endometrium, hyperplasia, cystic	47 (94%)	33 (87%)	39 (91%)	48 (96%)
Serosa, inflammation, suppurative, acute				1 (2%)
Hematopoietic System				
Blood			(2)	(1)
Leukocytosis				1 (100%)
Bone marrow	(50)	(50)	(49)	(50)
Fibrosis	1 (2%)			
Infiltration cellular, lipocyte	1 (2%)			
Myeloid cell, hypercellularity	1 (2%)	2 (4%)	11 (22%)	15 (30%)
Lymph node	(50)	(20)	(23)	(50)
Deep cervical, hyperplasia, lymphoid	1 (2%)			
Iliac, hyperplasia, lymphoid	1 (2%)	1 (5%)	4 (17%)	9 (18%)
Inguinal, hyperplasia, lymphoid		1 (5%)	1 (4%)	1 (2%)
Inguinal, infiltration cellular, polymorphonuclear				1 (2%)
Mediastinal, abscess	1 (2%)		1 (4%)	1 (2%)
Mediastinal, hyperplasia, lymphoid	3 (6%)	2 (10%)	3 (13%)	11 (22%)
Mesenteric, angiectasis	5 (10%)	1 (5%)	2 (9%)	5 (10%)
Mesenteric, hyperplasia, lymphoid	4 (8%)	2 (10%)	1 (4%)	6 (12%)
Mesenteric, infiltration cellular, polymorphonuclear				3 (6%)
Pancreatic, hyperplasia, lymphoid	1 (2%)	1 (5%)	1 (4%)	2 (4%)
Renal, hyperplasia, lymphoid	1 (2%)	1 (5%)	6 (26%)	12 (24%)
Lymph node, mandibular	(50)	(15)	(18)	(49)
Hyperplasia, lymphoid		1 (7%)		
Spleen	(50)	(49)	(49)	(50)
Fibrosis, focal	2 (4%)	1 (2%)	1 (2%)	
Hematopoietic cell proliferation	16 (32%)	14 (29%)	18 (37%)	21 (42%)
Pigmentation			4 (8%)	10 (20%)
Thrombus	1 (2%)			
Thymus	(50)	(13)	(19)	(50)
Cyst	1 (2%)			
Integumentary System				
Mammary gland	(50)	(14)	(19)	(50)
Inflammation, subacute				1 (2%)
Duct, cyst	2 (4%)			3 (6%)
Skin	(50)	(29)	(33)	(50)
Cyst epithelial inclusion	1 (2%)			
Subcutaneous tissue, fibrosis, focal				2 (4%)
Subcutaneous tissue, inflammation, subacute, focal	1 (2%)			1 (2%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3 (continued)

	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(14)	(18)	(50)
Compression	3 (6%)	1 (7%)		
Hemorrhage	1 (2%)			1 (2%)
Mineralization, multifocal	39 (78%)	6 (43%)	12 (67%)	30 (60%)
Respiratory System				
Lung	(50)	(13)	(21)	(50)
Hemorrhage	2 (4%)		1 (5%)	
Infiltration cellular, histiocyte, multifocal				1 (2%)
Inflammation, suppurative, acute			1 (5%)	
Alveolar epithelium, hyperplasia, focal			1 (5%)	
Nose	(50)	(13)	(19)	(50)
Nasolacrimal duct, inflammation, subacute	1 (2%)			1 (2%)
Special Senses System				
Eye	(1)			(1)
Cornea, fibrosis	1 (100%)			
Urinary System				
Kidney	(50)	(49)	(49)	(50)
Hydronephrosis				1 (2%)
Nephropathy, chronic	33 (66%)	45 (92%)	46 (94%)	45 (90%)
Capsule, inflammation, subacute				1 (2%)
Cortex, cyst	1 (2%)			1 (2%)
Cortex, fibrosis, focal	2 (4%)			
Cortex, metaplasia, osseous, focal	1 (2%)			3 (6%)
Glomerulus, inflammation				2 (4%)
Papilla, necrosis			1 (2%)	
Pelvis, inflammation, suppurative, acute			1 (2%)	
Renal tubule, degeneration, multifocal				2 (4%)
Renal tubule, dilatation, multifocal	1 (2%)			
Renal tubule, necrosis, multifocal	1 (2%)			
Urinary bladder	(50)	(12)	(18)	(50)
Inflammation, subacute				1 (2%)
Serosa, inflammation, subacute				1 (2%)

[a] Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.
[b] One control female was killed moribund prior to the interim evaluation.

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA PROTOCOL

Testing was performed as reported by Mortelmans *et al.* (1986). C.I. Pigment Red 3 was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains (TA100, TA1535, TA1537, and TA98) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C prior to the addition of soft agar supplemented with *l*-histidine and *d*-biotin, and subsequent plating on minimal glucose agar plates. Incubation continued for an additional 48 hours.

Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of C.I. Pigment Red 3. High dose was limited by solubility and did not exceed 3,333 μg/plate. All trials were repeated.

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

CHINESE HAMSTER OVARY CELL CYTOGENETICS ASSAYS

Testing was performed as reported by Galloway *et al.* (1985, 1987) and is presented briefly below. C.I. Pigment Red 3 was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCE) and chromosomal aberrations (Abs) both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each trial consisted of concurrent solvent and positive controls and of at least three doses of C.I. Pigment Red 3; the high dose was limited by toxicity or solubility, but did not exceed 160 μg/mL.

In the SCE test without S9, CHO cells were incubated for 26 hours with the C.I. Pigment Red 3 in McCoy's 5A medium supplemented with 10% fetal bovine serum, *l*-glutamine (2mM), and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing C.I. Pigment Red 3 was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with C.I. Pigment Red 3, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no C.I. Pigment Red 3 and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 to 3 hours. Harvesting and staining was the same as for cells treated without S9.

In the chromosomal aberration test without S9, cells were incubated in McCoy's 5A medium with C.I. Pigment Red 3 for 10 hours; Colcemid was added and incubation continued for 2 to 3 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with C.I. Pigment Red 3 and S9 for 2 hours, after which the treatment medium was removed and the cells incubated for 11 hours in fresh medium, with Colcemid present for the final 2 to 3 hours. Cells were harvested in the same manner as for the treatment without S9.

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

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Chromosomal aberration data is presented as percentage of cells with aberrations. As with SCE, both the dose-response curve and individual dose points were statistically analyzed. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) was considered weak evidence for a positive response (+w); significant differences for two or more doses indicated the trial was positive (+) (Galloway *et al.*, 1987).

RESULTS

C.I. Pigment Red 3 (33 to 3,333 μg/plate) was tested for induction of gene mutations in *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 using a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table E1) (Mortelmans *et al.*, 1986). Positive responses were obtained with strains TA100 and TA98 in the presence of hamster S9 and an equivocal response was obtained with TA100 in the presence of rat S9; no mutagenic activity was detected in any of the four tester strains in the absence of S9.

In cytogenetic tests with Chinese hamster ovary cells, C.I. Pigment Red 3 was negative for induction of sister chromatid exchanges (Table E2) and chromosomal aberrations (Table E3) in the presence and the absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9. Doses tested were 10 to 50 μg/mL in the SCE test without S9 and up to 160 μg/mL in all other trials.

TABLE E1
Mutagenicity of C.I. Pigment Red 3 in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	137 ± 10.1	124 ± 22.8	136 ± 6.6	143 ± 9.5	128 ± 5.7	136 ± 6.3
	33	139 ± 14.9		149 ± 4.3		142 ± 6.1	
	100	130 ± 4.4	127 ± 10.3	164 ± 11.0	154 ± 2.0	140 ± 4.3	149 ± 6.9
	333	130 ± 8.4	123 ± 6.6	190 ± 7.7	194 ± 5.2	169 ± 4.4	160 ± 29.5
	1,000	130 ± 10.5[c]	126 ± 18.5[c]	260 ± 11.1[c]	247 ± 6.1[c]	164 ± 6.5[c]	143 ± 25.0[c]
	2,500		115 ± 23.8[c]		245 ± 25.1[c]		160 ± 2.2[c]
	3,333	141 ± 1.5[c]	130 ± 5.0[c]	295 ± 1.5[c]	255 ± 9.4[c]	154 ± 4.2[c]	175 ± 6.7[c]
Trial summary		Negative	Negative	Positive	Weakly Positive	Equivocal	Equivocal
Positive control[d]		836 ± 20.9	656 ± 208.6	1,366 ± 49.9	1,021 ± 178.0	892 ± 153.5	806 ± 105.6
TA1535	0	33 ± 3.5		11 ± 2.3		17 ± 2.3	
	33	29 ± 3.2		14 ± 3.0		17 ± 1.5	
	100	32 ± 3.5		15 ± 1.5		16 ± 2.1	
	333	25 ± 4.2		17 ± 2.6		14 ± 2.9	
	1,000	35 ± 0.6[c]		12 ± 1.5[c]		17 ± 2.7[c]	
	2,500						
	3,333	32 ± 4.2[c]		15 ± 1.5[c]		13 ± 2.4[c]	
Trial summary		Negative		Negative		Negative	
Positive control		714 ± 21.7		74 ± 0.7		73 ± 3.5	
TA1537	0	10 ± 0.9	5 ± 1.3	7 ± 1.2	14 ± 3.3	10 ± 0.7	19 ± 3.8
	33	6 ± 1.3		12 ± 0.6		8 ± 2.0	
	100	8 ± 2.0	4 ± 0.3	14 ± 1.7	12 ± 3.3	11 ± 3.0	12 ± 2.3
	333	6 ± 1.2	5 ± 0.7	13 ± 3.5	11 ± 1.2	9 ± 1.2	15 ± 2.6
	1,000	7 ± 0.7[c]	7 ± 1.7[c]	13 ± 2.7[c]	17 ± 2.6[c]	11 ± 1.5[c]	13 ± 2.1[c]
	2,500		8 ± 2.0[c]		14 ± 3.1[c]		15 ± 1.7[c]
	3,333	6 ± 1.5[c]	9 ± 0.9[c]	22 ± 0.3[c]	18 ± 3.4[c]	13 ± 5.5[c]	10 ± 3.2[c]
Trial summary		Negative	Negative	Equivocal	Negative	Negative	Negative
Positive control		344 ± 23.5	181 ± 13.7	147 ± 13.9	50 ± 1.8	66 ± 15.2	60 ± 8.5
TA98	0	12 ± 2.7	16 ± 3.4	32 ± 4.7	28 ± 3.3	28 ± 1.3	25 ± 3.7
	33	17 ± 0.6		36 ± 2.7		32 ± 4.5	
	100	21 ± 1.2	23 ± 2.7	33 ± 2.9	29 ± 3.3	29 ± 4.0	32 ± 0.3
	333	18 ± 0.6	19 ± 2.0	44 ± 4.7	42 ± 5.2	31 ± 4.3	30 ± 1.5
	1,000	23 ± 0.9[c]	20 ± 1.5[c]	47 ± 2.5[c]	45 ± 4.8[c]	27 ± 3.8[c]	36 ± 4.3[c]
	2,500		22 ± 1.5[c]		59 ± 6.1[c]		40 ± 1.2[c]
	3,333	26 ± 2.5[c]	25 ± 6.7[c]	62 ± 4.2[c]	60 ± 8.5[c]	38 ± 1.5[c]	40 ± 3.6[c]
Trial summary		Weakly Positive	Negative	Weakly Positive	Positive	Negative	Negative
Positive control		1,279 ± 21.5	1,430 ± 72.1	1,484 ± 47.9	1,241 ± 88.1	936 ± 29.2	831 ± 20.5

[a] Study performed at EG&G Mason Research Institute. The detailed protocol and these data are presented in Mortelmans *et al.* (1986). Cells and C.I. Pigment Red 3 or solvent (dimethylsulfoxide) were incubated in the absence of exogenous metabolic activation (-S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague-Dawley rat liver. High dose was limited by solubility, but did not exceed 10 mg/plate; 0 μg/plate dose is the solvent control.

[b] Revertants are presented as mean ± standard error from three plates.

[c] Precipitate on plate

[d] 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537.

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by C.I. Pigment Red 3[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome (%)[b]
-S9[c]								
Trial 1								
Summary: Negative								
Dimethylsulfoxide		50	1,050	401	0.38	8.0	26.0	
Mitomycin-C	0.0005	50	1,049	495	0.47	9.9	26.0	23.56
	0.0050	10	211	299	1.41	29.9	26.0	271.06
C.I. Pigment Red 3	10	50	1,049	416	0.39	8.3	26.0	3.84
	16	50	1,051	436	0.41	8.7	26.0	8.63
	30	50	1,048	420	0.40	8.4	26.0	4.94
	50	50	1,048	422	0.40	8.4	26.0	5.44
								P=0.240[d]
+S9[e]								
Trial 1								
Summary: Negative								
Dimethylsulfoxide		50	1,048	444	0.42	8.9	26.0	
Cyclophosphamide	0.1000	50	1,049	610	0.58	12.2	26.0	37.26
	0.6000	10	210	325	1.54	32.5	26.0	265.30
C.I. Pigment Red 3	30	50	1,049	461	0.43	9.2	26.0	3.73
	50	50	1,049	448	0.42	9.0	26.0	0.80
	100	50	1,052	471	0.44	9.4	26.0	5.68
	160	50	1,051	451	0.42	9.0	26.0	1.29
								P=0.369

[a] Study performed at Environmental Health Research and Testing, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway *et al.* (1985, 1987). Briefly, Chinese hamster ovary cells were incubated with C.I. Pigment Red 3 or solvent (dimethylsulfoxide) as described in [c] and [e] below, and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained.

[b] SCE's/chromosome of culture exposed to C.I. Pigment Red 3 relative to those of culture exposed to solvent.

[c] In the absence of S9, cells were incubated with or solvent for 2 hours at 37° C. Then BrdU was added and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and Colcemid was added, and incubation was continued for 2 hours.

[d] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose

[e] In the presence of S9, cells were incubated with C.I. Pigment Red 3 or solvent for 2 hours at 37° C. The cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with Colcemid present for the final 2 to 3 hours. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by C.I. Pigment Red 3[a]

-S9[b]					+S9[c]				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 1 – Harvest time: 12.5 hours Summary: Negative					**Trial 1** – Harvest time: 13.0 hours Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
	200	2	0.01	1.0		50	6	0.12	3.0
Mitomycin-C					Cyclophosphamide				
0.0625	200	52	0.26	22.0	2.5	200	25	0.13	12.0
0.2500	50	21	0.42	34.0	7.5	200	12	0.06	20.0
C.I. Pigment Red 3					C.I. Pigment Red 3				
50	200	4	0.02	2.0	50	50	6	0.12	3.0
100	200	6	0.03	2.5	100	50	1	0.02	0.5
160	200	1	0.01	0.5	160	50	4	0.08	2.0
				P=0.562[d]					P=0.744

[a] Study performed at Environmental Health Research and Testing, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway *et al.* (1985, 1987). Briefly, Chinese hamster ovary cells were incubated with C.I. Pigment Red 3 or solvent (dimethylsulfoxide) as indicated in [b] and [c]. Cells were arrested in first metaphase by addition of Colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.

[b] In the absence of S9, cells were incubated with C.I. Pigment Red 3 or solvent for 10 hours at 37° C. Cells were then washed and fresh medium containing Colcemid was added for an additional 2 to 3 hours followed by harvest.

[c] In the presence of S9, cells were incubated with C.I. Pigment Red 3 or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 11 hours. Colcemid was added for the last 2 to 3 hours of incubation before harvest. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

[d] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose

APPENDIX F
ORGAN WEIGHTS
AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 2-Week Feed Studies of C.I. Pigment Red 3[a]

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm	100,000 ppm
Male						
n	4	5	5	5	4	5
Necropsy body wt	203 ± 8	206 ± 8	200 ± 5	194 ± 7	185 ± 3	194 ± 8
Brain						
Absolute	1.79 ± 0.03	1.85 ± 0.02	1.80 ± 0.03	1.79 ± 0.02	1.94 ± 0.18	1.77 ± 0.03
Relative	8.81 ± 0.38	8.98 ± 0.26	9.01 ± 0.18	9.31 ± 0.31	10.44 ± 1.06	9.18 ± 0.28
Heart						
Absolute	0.67 ± 0.08	0.75 ± 0.04	0.74 ± 0.04	0.71 ± 0.03	0.73 ± 0.05	0.80 ± 0.02
Relative	3.28 ± 0.27	3.65 ± 0.10	3.70 ± 0.10	3.67 ± 0.12	3.91 ± 0.21*	4.13 ± 0.22**
R. Kidney						
Absolute	0.88 ± 0.03	0.85 ± 0.03	0.81 ± 0.02	0.83 ± 0.03	0.80 ± 0.03	0.88 ± 0.07
Relative	4.32 ± 0.10	4.11 ± 0.04	4.03 ± 0.08	4.28 ± 0.06	4.31 ± 0.07	4.50 ± 0.22
Liver						
Absolute	7.73 ± 1.97	11.13 ± 0.62*	10.37 ± 0.61	10.74 ± 0.46	9.92 ± 0.40	10.95 ± 0.40
Relative	37.1 ± 9.0	53.9 ± 1.6**	51.6 ± 2.0**	55.5 ± 1.5**	53.2 ± 1.3**	56.6 ± 1.7**
Lung						
Absolute	1.01 ± 0.06	1.10 ± 0.05	1.01 ± 0.06	0.97 ± 0.02	1.06 ± 0.07	1.05 ± 0.07
Relative	4.97 ± 0.14	5.34 ± 0.21	5.03 ± 0.21	5.01 ± 0.17	5.69 ± 0.41	5.45 ± 0.43
Thymus						
Absolute	0.49 ± 0.03	0.36 ± 0.03	0.43 ± 0.04	0.41 ± 0.03	0.43 ± 0.02	0.45 ± 0.04
Relative	2.41 ± 0.18	1.75 ± 0.10	2.13 ± 0.20	2.13 ± 0.18	2.33 ± 0.14	2.33 ± 0.18
Female						
n	5	5	5	5	5	5
Necropsy body wt	155 ± 4	154 ± 3	152 ± 4	146 ± 2	149 ± 5	144 ± 3
Brain						
Absolute	1.68 ± 0.06	1.76 ± 0.02	1.72 ± 0.03	1.68 ± 0.01[b]	1.73 ± 0.02	1.69 ± 0.03
Relative	10.9 ± 0.4	11.4 ± 0.2	11.4 ± 0.3	11.5 ± 0.2[b]	11.6 ± 0.4	11.7 ± 0.3
Heart						
Absolute	0.54 ± 0.02	0.57 ± 0.03	0.57 ± 0.02	0.56 ± 0.02	0.58 ± 0.05	0.55 ± 0.01
Relative	3.46 ± 0.10	3.73 ± 0.24	3.75 ± 0.09	3.83 ± 0.10	3.88 ± 0.24	3.86 ± 0.14
R. Kidney						
Absolute	0.63 ± 0.01	0.64 ± 0.01	0.63 ± 0.02	0.62 ± 0.02	0.56 ± 0.04	0.59 ± 0.01
Relative	4.06 ± 0.04	4.15 ± 0.14	4.15 ± 0.10	4.22 ± 0.16	3.77 ± 0.22	4.10 ± 0.11
Liver						
Absolute	6.34 ± 0.18	6.63 ± 0.56	7.18 ± 0.21	7.09 ± 0.08	7.69 ± 0.41	5.97 ± 1.18
Relative	40.9 ± 0.3	43.0 ± 3.3	47.3 ± 0.5	48.6 ± 0.6	51.6 ± 1.6	42.0 ± 8.4
Lung						
Absolute	0.85 ± 0.04	0.89 ± 0.05	0.85 ± 0.04	0.80 ± 0.05	1.06 ± 173	0.88 ± 0.03
Relative	5.48 ± 0.20	5.81 ± 0.42	5.59 ± 0.15	5.46 ± 0.29	7.04 ± 0.97	6.13 ± 0.19
Thymus						
Absolute	0.32 ± 0.03	0.32 ± 0.02	0.34 ± 0.02	0.33 ± 0.04	0.35 ± 0.03	0.31 ± 0.04
Relative	2.06 ± 0.13	2.07 ± 0.14	2.27 ± 0.11	2.28 ± 0.29	2.35 ± 0.18	2.15 ± 0.23

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=4

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Studies of C.I. Pigment Red 3[a]

	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male						
n	10	10	10	10	10	10
Necropsy body wt	374 ± 4	371 ± 8	376 ± 9	385 ± 11	378 ± 8	357 ± 6
Brain						
Absolute	2.00 ± 0.02	1.99 ± 0.03	1.96 ± 0.02	2.01 ± 0.03	1.98 ± 0.03	1.99 ± 0.02
Relative	5.36 ± 0.07	5.38 ± 0.10	5.24 ± 0.12	5.24 ± 0.10	5.25 ± 0.14	5.58 ± 0.08
Heart						
Absolute	0.99 ± 0.02	0.96 ± 0.03	0.97 ± 0.03	1.02 ± 0.03	1.01 ± 0.03	1.01 ± 0.03
Relative	2.65 ± 0.05	2.59 ± 0.06	2.58 ± 0.05	2.65 ± 0.04	2.68 ± 0.06	2.82 ± 0.10
R. Kidney						
Absolute	1.11 ± 0.02	1.16 ± 0.04	1.13 ± 0.03	1.23 ± 0.04*	1.22 ± 0.04*	1.17 ± 0.02
Relative	2.98 ± 0.04	3.11 ± 0.08*	3.01 ± 0.06	3.19 ± 0.04*	3.23 ± 0.06**	3.28 ± 0.06**
Liver						
Absolute	12.78 ± 0.20	14.70 ± 0.41**	15.32 ± 0.42**	16.77 ± 0.59**	16.87 ± 0.50**	16.73 ± 0.43**
Relative	34.2 ± 0.4	39.6 ± 0.6**	40.7 ± 0.6**	43.5 ± 0.5**	44.5 ± 0.6**	46.8 ± 0.6**
Lung						
Absolute	1.44 ± 0.04	1.46 ± 0.06	1.52 ± 0.04	1.54 ± 0.05	1.57 ± 0.04*	1.56 ± 0.07
Relative	3.86 ± 0.14	3.92 ± 0.15	4.06 ± 0.12	4.00 ± 0.09	4.17 ± 0.13*	4.38 ± 0.17*
R. Testis						
Absolute	1.53 ± 0.02	1.56 ± 0.05	1.58 ± 0.03	1.57 ± 0.03	1.52 ± 0.03	1.50 ± 0.02
Relative	4.08 ± 0.08	4.20 ± 0.06	4.22 ± 0.09	4.09 ± 0.07	4.03 ± 0.07	4.21 ± 0.09
Thymus						
Absolute	0.44 ± 0.04	0.39 ± 0.03	0.39 ± 0.04	0.43 ± 0.04	0.40 ± 0.03	0.40 ± 0.03
Relative	1.16 ± 0.10	1.05 ± 0.06	1.02 ± 0.10	1.10 ± 0.09	1.07 ± 0.07	1.11 ± 0.09
Female						
n	10	10	10	10	10	10
Necropsy body wt	210 ± 3	200 ± 2*	197 ± 3**	196 ± 3**	195 ± 5**	190 ± 2**
Brain						
Absolute	1.81 ± 0.01	1.80 ± 0.02	1.81 ± 0.04	1.85 ± 0.04	1.79 ± 0.02	1.75 ± 0.02
Relative	8.64 ± 0.12	9.02 ± 0.08*	9.16 ± 0.26*	9.43 ± 0.20**	9.20 ± 0.20**	9.22 ± 0.17*
Heart						
Absolute	0.63 ± 0.01	0.60 ± 0.02	0.63 ± 0.02	0.65 ± 0.04	0.61 ± 0.01	0.60 ± 0.02
Relative	3.02 ± 0.05	3.01 ± 0.07	3.19 ± 0.12	3.32 ± 0.17	3.13 ± 0.08	3.17 ± 0.11
R. Kidney						
Absolute	0.67 ± 0.02	0.64 ± 0.02	0.65 ± 0.01	0.67 ± 0.03	0.65 ± 0.03	0.66 ± 0.02
Relative	3.19 ± 0.11	3.22 ± 0.09	3.31 ± 0.08	3.40 ± 0.14	3.30 ± 0.08	3.46 ± 0.11
Liver						
Absolute	6.94 ± 0.10	7.05 ± 0.15	7.41 ± 0.11*	7.43 ± 0.19*	7.93 ± 0.27**	7.82 ± 0.14**
Relative	33.1 ± 0.6	35.3 ± 0.6*	37.6 ± 0.8**	37.8 ± 0.5**	40.6 ± 0.8**	41.2 ± 0.8**
Lung						
Absolute	0.94 ± 0.03	1.03 ± 0.06[b]	0.99 ± 0.03	1.00 ± 0.03	1.08 ± 0.05*	1.05 ± 0.04
Relative	4.47 ± 0.11	5.21 ± 0.27*[b]	5.03 ± 0.19*	5.08 ± 0.14**	5.52 ± 0.21**	5.52 ± 0.24**
Thymus						
Absolute	0.31 ± 0.02	0.30 ± 0.02	0.30 ± 0.02	0.31 ± 0.04	0.30 ± 0.01	0.29 ± 0.03
Relative	1.46 ± 0.09	1.52 ± 0.08	1.50 ± 0.13	1.58 ± 0.19	1.52 ± 0.08	1.56 ± 0.16

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Studies of C.I. Pigment Red 3[a]

Organ	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Male				
n	15	14	14	14
Necropsy body wt	450 ± 9	443 ± 8	443 ± 9	422 ± 5**
Brain				
Absolute	2.10 ± 0.02	2.13 ± 0.03	2.08 ± 0.02	2.07 ± 0.02
Relative	4.70 ± 0.11	4.83 ± 0.08	4.71 ± 0.10	4.93 ± 0.08*
R. Kidney				
Absolute	1.36 ± 0.03	1.39 ± 0.03	1.33 ± 0.02	1.38 ± 0.02
Relative	3.05 ± 0.09	3.13 ± 0.05	3.02 ± 0.05	3.26 ± 0.04**
Liver				
Absolute	11.84 ± 0.28	13.15 ± 0.38*	13.74 ± 0.43**	14.23 ± 0.20**
Relative	26.4 ± 0.6	29.7 ± 0.5**	31.1 ± 0.8**	33.8 ± 0.3**
Spleen				
Absolute	0.88 ± 0.02	0.98 ± 0.03*	1.03 ± 0.02**	1.08 ± 0.02**
Relative	1.95 ± 0.04	2.21 ± 0.05**	2.32 ± 0.04**	2.55 ± 0.05**
Female				
n	15	15	15	15
Necropsy body wt	291 ± 5	289 ± 8	270 ± 8*	252 ± 5**
Brain				
Absolute	1.91 ± 0.02	1.85 ± 0.02	1.88 ± 0.01	1.85 ± 0.02*
Relative	6.58 ± 0.12	6.47 ± 0.18	7.05 ± 0.21	7.36 ± 0.15**
R. Kidney				
Absolute	0.80 ± 0.02	0.85 ± 0.02	0.84 ± 0.03	0.82 ± 0.01
Relative	2.76 ± 0.06	2.94 ± 0.04*	3.12 ± 0.07**	3.26 ± 0.05**
Liver				
Absolute	6.67 ± 0.14	7.82 ± 0.22**	8.06 ± 0.23**	8.53 ± 0.20**
Relative	23.0 ± 0.4	27.1 ± 0.4**	29.9 ± 0.5**	33.8 ± 0.7**
Spleen				
Absolute	0.52 ± 0.01	0.65 ± 0.02**	0.68 ± 0.02**	0.77 ± 0.02**
Relative	1.80 ± 0.03	2.25 ± 0.05**	2.52 ± 0.06**	3.07 ± 0.09**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 2-Week Feed Studies of C.I. Pigment Red 3[a]

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm	100,000 ppm
Male						
n	5	5	5	5	5	5
Necropsy body wt	27.8 ± 0.9	28.0 ± 0.6	28.4 ± 0.4	26.2 ± 0.9	27.8 ± 0.6	25.8 ± 0.7
Brain						
Absolute	0.460 ± 0.006	0.459 ± 0.006	0.443 ± 0.010	0.442 ± 0.009	0.449 ± 0.010	0.436 ± 0.003*
Relative	16.6 ± 0.4	16.4 ± 0.2	15.6 ± 0.2	16.9 ± 0.3	16.2 ± 0.5	16.9 ± 0.4
Heart						
Absolute	0.140 ± 0.006	0.126 ± 0.003	0.143 ± 0.004	0.123 ± 0.011	0.130 ± 0.004	0.127 ± 0.007
Relative	5.05 ± 0.23	4.51 ± 0.17	5.03 ± 0.07	4.67 ± 0.26	4.68 ± 0.07	4.93 ± 0.27
R. Kidney						
Absolute	0.203 ± 0.023	0.209 ± 0.007	0.212 ± 0.004	0.194 ± 0.011	0.210 ± 0.009	0.197 ± 0.008
Relative	7.35 ± 0.87	7.46 ± 0.12	7.48 ± 0.24	7.44 ± 0.51	7.57 ± 0.36	7.64 ± 0.24
Liver						
Absolute	1.51 ± 0.11	1.43 ± 0.05	1.70 ± 0.03	1.38 ± 0.03	1.59 ± 0.06	1.42 ± 0.09
Relative	54.0 ± 2.7	51.0 ± 0.9	59.9 ± 1.2	52.7 ± 0.6	57.3 ± 1.2	55.0 ± 2.7
Lung						
Absolute	0.159 ± 0.006	0.176 ± 0.010	0.162 ± 0.003	0.142 ± 0.008	0.157 ± 0.006	0.146 ± 0.002
Relative	5.73 ± 0.16	6.33 ± 0.48	5.71 ± 0.14	5.41 ± 0.19	5.66 ± 0.27	5.67 ± 0.17
Thymus						
Absolute	0.055 ± 0.004	0.036 ± 0.004*	0.045 ± 0.004	0.047 ± 0.008	0.051 ± 0.001[b]	0.035 ± 0.004*
Relative	1.99 ± 0.18	1.29 ± 0.15*	1.58 ± 0.15	1.78 ± 0.27	1.83 ± 0.02[b]	1.37 ± 0.16
Female						
n	5	5	5	5	5	5
Necropsy body wt	20.6 ± 0.8	22.8 ± 0.5*	21.8 ± 0.5	21.4 ± 0.4	22.4 ± 0.5	21.6 ± 0.6
Brain						
Absolute	0.464 ± 0.013	0.486 ± 0.021	0.445 ± 0.004	0.441 ± 0.008	0.460 ± 0.012	0.451 ± 0.010
Relative	22.6 ± 0.4	21.3 ± 0.9	20.5 ± 0.5*	20.6 ± 0.4*	20.5 ± 0.4*	20.9 ± 0.5*
Heart						
Absolute	0.105 ± 0.005	0.103 ± 0.003	0.101 ± 0.002[b]	0.109 ± 0.004	0.110 ± 0.005	0.108 ± 0.005
Relative	5.10 ± 0.16	4.53 ± 0.15	4.66 ± 0.06[b]	5.09 ± 0.17	4.91 ± 0.18	5.00 ± 0.21
R. Kidney						
Absolute	0.155 ± 0.012	0.152 ± 0.005	0.147 ± 0.004	0.142 ± 0.006	0.166 ± 0.009	0.147 ± 0.007
Relative	7.50 ± 0.36	6.68 ± 0.25	6.75 ± 0.14	6.64 ± 0.28	7.41 ± 0.33	6.80 ± 0.21
Liver						
Absolute	1.02 ± 0.05	0.94 ± 0.03	1.15 ± 0.03	1.06 ± 0.03	1.23 ± 0.07*	1.18 ± 0.06*
Relative	49.5 ± 1.1	41.0 ± 1.1	52.9 ± 1.4	49.5 ± 1.2	54.6 ± 2.0*	54.6 ± 1.8*
Lung						
Absolute	0.147 ± 0.010	0.144 ± 0.003	0.140 ± 0.008	0.140 ± 0.007	0.142 ± 0.004	0.151 ± 0.008
Relative	7.13 ± 0.38	6.32 ± 0.15	6.42 ± 0.33	6.56 ± 0.40	6.34 ± 0.13	6.98 ± 0.30
Thymus						
Absolute	0.050 ± 0.002	0.055 ± 0.003	0.053 ± 0.003	0.045 ± 0.004	0.047 ± 0.005	0.046 ± 0.005
Relative	2.44 ± 0.14	2.41 ± 0.11	2.44 ± 0.17	2.10 ± 0.16	2.09 ± 0.18	2.16 ± 0.28

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=4

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Studies of C.I. Pigment Red 3[a]

	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male						
n	9	10	10	9	10	10
Necropsy body wt	32.4 ± 0.6	31.4 ± 0.6	29.0 ± 1.3	32.0 ± 0.7	30.2 ± 1.1	31.7 ± 0.6
Brain						
Absolute	0.456 ± 0.009	0.461 ± 0.008	0.440 ± 0.012	0.448 ± 0.011	0.449 ± 0.007	0.444 ± 0.006
Relative	14.1 ± 0.2	14.7 ± 0.4	15.4 ± 0.7	14.0 ± 0.4	15.1 ± 0.7	14.0 ± 0.3
Heart						
Absolute	0.151 ± 0.006	0.133 ± 0.006	0.137 ± 0.010	0.130 ± 0.008	0.138 ± 0.008	0.149 ± 0.005
Relative	4.65 ± 0.15	4.25 ± 0.21	4.75 ± 0.35	4.06 ± 0.24	4.54 ± 0.12	4.70 ± 0.12
R. Kidney						
Absolute	0.269 ± 0.009	0.246 ± 0.010	0.214 ± 0.014*	0.237 ± 0.012	0.245 ± 0.011	0.242 ± 0.008
Relative	8.28 ± 0.17	7.82 ± 0.22	7.40 ± 0.39	7.41 ± 0.39	8.13 ± 0.24	7.65 ± 0.25
Liver						
Absolute	1.59 ± 0.08	1.55 ± 0.04	1.54 ± 0.11	1.68 ± 0.07	1.75 ± 0.09	1.71 ± 0.05
Relative	49.1 ± 2.1	49.5 ± 1.1	52.5 ± 2.1	52.6 ± 1.6	57.9 ± 2.1**	53.9 ± 0.8*
Lungs						
Absolute	0.170 ± 0.008	0.184 ± 0.014	0.172 ± 0.013	0.174 ± 0.009	0.156 ± 0.006	0.163 ± 0.007
Relative	5.23 ± 0.20	5.88 ± 0.45	5.93 ± 0.34	5.46 ± 0.29	5.18 ± 0.15	5.16 ± 0.23
R. Testis						
Absolute	0.103 ± 0.005	0.108 ± 0.008	0.100 ± 0.008	0.104 ± 0.007	0.106 ± 0.006	0.106 ± 0.003
Relative	3.18 ± 0.14	3.46 ± 0.25	3.46 ± 0.25	3.27 ± 0.22	3.51 ± 0.15	3.36 ± 0.12
Thymus						
Absolute	0.056 ± 0.010	0.041 ± 0.003[b]	0.047 ± 0.008	0.043 ± 0.004	0.038 ± 0.006	0.050 ± 0.005
Relative	1.69 ± 0.28	1.32 ± 0.10[b]	1.58 ± 0.24	1.35 ± 0.12	1.29 ± 0.22	1.58 ± 0.17
Female						
n	10	10	10	10	10	10
Necropsy body wt	24.6 ± 0.3	25.4 ± 0.4	24.5 ± 0.8	26.4 ± 0.8	24.0 ± 0.5	25.2 ± 0.6
Brain						
Absolute	0.455 ± 0.010	0.473 ± 0.008	0.454 ± 0.007	0.481 ± 0.014	0.445 ± 0.013	0.484 ± 0.007
Relative	18.5 ± 0.4	18.6 ± 0.3	18.7 ± 0.5	18.3 ± 0.5	18.6 ± 0.7	19.3 ± 0.5
Heart						
Absolute	0.107 ± 0.003	0.105 ± 0.007	0.107 ± 0.008	0.111 ± 0.004	0.095 ± 0.005	0.118 ± 0.004
Relative	4.34 ± 0.11	4.12 ± 0.22	4.43 ± 0.40	4.22 ± 0.14	3.98 ± 0.23	4.71 ± 0.21
R. Kidney						
Absolute	0.168 ± 0.004	0.156 ± 0.005	0.148 ± 0.009	0.177 ± 0.008	0.143 ± 0.006*	0.171 ± 0.009
Relative	6.83 ± 0.13	6.17 ± 0.24	6.03 ± 0.29	6.69 ± 0.18	5.98 ± 0.30	6.80 ± 0.38
Liver						
Absolute	1.07 ± 0.03	1.12 ± 0.03	1.06 ± 0.04	1.24 ± 0.04*	1.06 ± 0.03	1.18 ± 0.05
Relative	43.5 ± 1.1	43.9 ± 1.1	43.5 ± 1.0	47.1 ± 1.0*	44.1 ± 0.9	46.7 ± 1.3
Lungs						
Absolute	0.160 ± 0.009	0.161 ± 0.014	0.173 ± 0.026	0.158 ± 0.008	0.140 ± 0.009	0.156 ± 0.009
Relative	6.48 ± 0.30	6.30 ± 0.43	7.35 ± 1.47	6.00 ± 0.27	5.83 ± 0.34	6.19 ± 0.33
Thymus						
Absolute	0.054 ± 0.005	0.054 ± 0.004	0.048 ± 0.007	0.045 ± 0.004	0.037 ± 0.005	0.055 ± 0.004
Relative	2.19 ± 0.18	2.15 ± 0.18	1.98 ± 0.28	1.71 ± 0.13	1.56 ± 0.21	2.20 ± 0.18

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Studies of C.I. Pigment Red 3[a]

Organ	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male				
n	14	15	10	13
Necropsy body wt	34.4 ± 0.9	35.3 ± 1.1	35.5 ± 1.5	29.6 ± 0.6**
Brain				
Absolute	0.458 ± 0.005	0.474 ± 0.006[b]	0.478 ± 0.011	0.479 ± 0.015
Relative	13.4 ± 0.4	13.6 ± 0.4[b]	13.6 ± 0.6	16.3 ± 0.6**
R. Kidney				
Absolute	0.313 ± 0.007	0.334 ± 0.010	0.340 ± 0.013	0.306 ± 0.014
Relative	9.14 ± 0.19	9.52 ± 0.28	9.65 ± 0.39	10.33 ± 0.40**
Liver				
Absolute	1.46 ± 0.09	1.55 ± 0.05**	1.69 ± 0.07**	1.74 ± 0.05**[c]
Relative	42.7 ± 2.7	43.9 ± 0.7*	47.8 ± 1.7**	58.0 ± 1.1**[c]
Spleen				
Absolute	0.069 ± 0.003	0.073 ± 0.003	0.061 ± 0.002[d]	0.085 ± 0.014
Relative	2.01 ± 0.10	2.08 ± 0.10	1.73 ± 0.03[d]	2.95 ± 0.52
Female				
n	12	15	15	15
Necropsy body wt	34.4 ± 1.2	34.8 ± 1.4	33.7 ± 1.2	29.3 ± 1.1**
Brain				
Absolute	0.475 ± 0.009	0.487 ± 0.006	0.486 ± 0.003	0.483 ± 0.004
Relative	14.0 ± 0.6	14.3 ± 0.5	14.6 ± 0.5	16.7 ± 0.5**
R. Kidney				
Absolute	0.236 ± 0.003	0.241 ± 0.006	0.240 ± 0.005	0.259 ± 0.007*
Relative	6.92 ± 0.17	7.02 ± 0.18	7.21 ± 0.25	8.91 ± 0.28**
Liver				
Absolute	1.33 ± 0.03	1.46 ± 0.03*	1.53 ± 0.05**	1.59 ± 0.04**
Relative	39.1 ± 1.2	42.4 ± 1.1	45.8 ± 1.8**	54.4 ± 0.8**
Spleen				
Absolute	0.101 ± 0.008	0.100 ± 0.011[b]	0.090 ± 0.005	0.090 ± 0.003
Relative	2.98 ± 0.29	2.88 ± 0.25[b]	2.72 ± 0.18	3.10 ± 0.12

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=14
[c] n=11
[d] n=9

APPENDIX G
HEMATOLOGY, CLINICAL CHEMISTRY, AND URINALYSIS RESULTS

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 2-Week Feed Studies of C.I. Pigment Red 3[a]

Analysis	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm	100,000 ppm
Male						
n	5	5	5	5	5	5
Hematology						
Hematocrit (%)	43.9 ± 0.6	41.8 ± 0.6*	40.8 ± 1.5	36.6 ± 1.0**	35.4 ± 1.2**	32.5 ± 2.8**
Hemoglobin (g/dL)	15.4 ± 0.6	14.3 ± 0.2	13.9 ± 0.5	13.3 ± 0.4**	12.8 ± 0.7*	11.9 ± 1.0**
Erythrocytes ($10^6/\mu L$)	7.83 ± 0.40	7.37 ± 0.08	6.65 ± 0.23**	6.67 ± 0.29*	6.28 ± 0.37**	5.39 ± 0.41**
Platelets ($10^3/\mu L$)	139.0 ± 45.1	321.4 ± 18.8*	267.8 ± 16.5	252.0 ± 10.9	219.6 ± 68.7	237.7 ± 107[b]
Reticulocytes ($10^6/\mu L$)	3.20 ± 0.34	2.78 ± 0.27	4.38 ± 0.79	6.42 ± 1.00*	8.20 ± 1.06**	11.84 ± 1.22**
Leukocytes ($10^3/\mu L$)	13.28 ± 1.20	7.92 ± 0.40	8.22 ± 0.30	16.30 ± 2.48	16.00 ± 4.03	26.70 ± 5.58
Segmented neutrophils ($10^3/\mu L$)	2.00 ± 0.30	1.20 ± 0.25	1.28 ± 0.10	2.35 ± 0.64	1.28 ± 0.42	2.60 ± 0.89
Lymphocytes ($10^3/\mu L$)	11.15 ± 1.01	6.66 ± 0.53	6.91 ± 0.28	13.90 ± 1.92	14.69 ± 3.64	23.54 ± 4.78
Monocytes ($10^3/\mu L$)	0.08 ± 0.05	0.02 ± 0.02	0.02 ± 0.02	0.06 ± 0.04	0.00 ± 0.00	0.41 ± 0.16
Eosinophils ($10^3/\mu L$)	0.05 ± 0.05	0.04 ± 0.03	0.02 ± 0.02	0.00 ± 0.00	0.03 ± 0.03	0.15 ± 0.08
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.20 ± 0.20	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Clinical chemistry						
Urea nitrogen (mg/dL)	20.4 ± 1.2	23.2 ± 1.4	23.2 ± 1.2	23.0 ± 0.8	21.4 ± 0.5	20.0 ± 0.8
Creatinine (mg/dL)	0.46 ± 0.06	0.62 ± 0.02	0.76 ± 0.04*	0.70 ± 0.00*	0.46 ± 0.02	0.40 ± 0.03
Sodium (meq/L)	135 ± 1	143 ± 1**	141 ± 1	148 ± 1**	137 ± 1	141 ± 0
Potassium (meq/L)	7.5 ± 1.0	6.0 ± 0.4	6.5 ± 0.8	6.4 ± 0.5	5.9 ± 0.3	6.6 ± 0.3
Chloride (meq/L)	97 ± 1	103 ± 0**	99 ± 1	100 ± 0	98 ± 0	101 ± 0
Calcium (mg/dL)	12.2 ± 0.4[c]	12.9 ± 0.2	11.5 ± 0.2	11.3 ± 0.1	11.6 ± 0.2	11.3 ± 0.1
Phosphorus (mg/dL)	10.1 ± 0.4	10.2 ± 0.4	8.7 ± 0.7	8.6 ± 0.3	9.5 ± 0.3	9.2 ± 0.4
Total protein (g/dL)	5.2 ± 0.2	5.6 ± 0.1	5.8 ± 0.1**	5.8 ± 0.1*	5.6 ± 0.1	5.6 ± 0.1
Albumin (g/dL)	3.5 ± 0.0	4.1 ± 0.1**	3.9 ± 0.1	3.9 ± 0.1*	3.8 ± 0.0	3.9 ± 0.0
A/G ratio	2.1 ± 0.2	2.7 ± 0.2*	2.0 ± 0.1	2.1 ± 0.1	2.1 ± 0.1	2.2 ± 0.0
Total bilirubin (mg/dL)	0.2 ± 0.1	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.1	0.4 ± 0.1	0.8 ± 0.1**
ALT (IU/L)	15 ± 0[c]	31 ± 9[c]	33 ± 9	24 ± 4	14 ± 0	71 ± 40*
AST (IU/L)	53 ± 4	82 ± 10*	61 ± 4	72 ± 3	54 ± 1	72 ± 12
LDH (IU/L)	122 ± 19	660 ± 115**	143 ± 14	374 ± 56*	112 ± 17	251 ± 34
SDH (IU/L)	17 ± 2	-[d]	33 ± 4	52 ± 5**[c]	18 ± 1	40 ± 4[c]
Cholinesterase (IU/mL)	763 ± 194	741 ± 30	775 ± 63	862 ± 24*	811 ± 49	955 ± 61*
pH	7.32 ± 0.02[b]	7.28 ± 0.00	7.28 ± 0.02	7.25 ± 0.01	7.46 ± 0.08[b]	7.43 ± 0.07[c]

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 2-Week Feed Studies of C.I. Pigment Red 3
(continued)

Analysis	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm	100,000 ppm
Female						
n	5	5	5	5	5	5
Hematology						
Hematocrit (%)	40.4 ± 1.5	37.8 ± 1.3	37.0 ± 1.1	35.0 ± 0.8*	35.3 ± 1.5*	32.8 ± 2.0**
Hemoglobin (g/dL)	15.6 ± 0.2	14.1 ± 0.3**	13.4 ± 0.2**	13.2 ± 0.6**	13.3 ± 0.9**	12.6 ± 1.1**
Erythrocytes ($10^6/\mu L$)	7.59 ± 0.21	6.68 ± 0.23*	6.53 ± 0.16*	6.09 ± 0.47**	6.24 ± 0.37**	5.54 ± 0.52**
Platelets ($10^3/\mu L$)	246.0 ± 59.8	258.4 ± 62.5	242.2 ± 53.0	207.0 ± 47.5	397.2 ± 54.9	265.3 ± 75.5[c]
Reticulocytes ($10^6/\mu L$)	2.50 ± 0.91	3.00 ± 0.49	3.54 ± 0.61	6.54 ± 1.20*	9.12 ± 0.98**	12.22 ± 0.72**
Leukocytes ($10^3/\mu L$)	14.42 ± 1.45	8.42 ± 0.40	11.26 ± 1.76	10.14 ± 1.97	23.30 ± 2.82	18.66 ± 2.25
Segmented neutrophils ($10^3/\mu L$)	2.16 ± 0.38	0.98 ± 0.18	1.49 ± 0.26	1.11 ± 0.19	2.98 ± 0.62	2.17 ± 0.49
Lymphocytes ($10^3/\mu L$)	12.09 ± 1.29	7.38 ± 0.54	9.69 ± 1.48	8.87 ± 1.77	19.80 ± 2.29	16.32 ± 1.72
Monocytes ($10^3/\mu L$)	0.08 ± 0.06	0.02 ± 0.02	0.00 ± 0.00	0.03 ± 0.03	0.31 ± 0.10	0.08 ± 0.05
Eosinophils ($10^3/\mu L$)	0.09 ± 0.04	0.05 ± 0.03	0.08 ± 0.05	0.13 ± 0.05	0.22 ± 0.11	0.09 ± 0.09
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.40 ± 0.40	0.00 ± 0.00	0.00 ± 0.00
Clinical chemistry						
Urea nitrogen (mg/dL)	22.8 ± 1.2	21.0 ± 0.9	23.6 ± 0.9	22.2 ± 0.8	21.8 ± 0.6	20.2 ± 0.7
Creatinine (mg/dL)	0.60 ± 0.00[c]	0.68 ± 0.02	0.66 ± 0.02	0.64 ± 0.04	0.50 ± 0.00	0.40 ± 0.07
Sodium (meq/L)	139 ± 2	142 ± 1[c]	141 ± 1	149 ± 1*	137 ± 0	140 ± 3
Potassium (meq/L)	6.5 ± 0.2	7.0 ± 0.6[c]	6.3 ± 0.5	6.4 ± 0.3	5.9 ± 0.2	7.6 ± 1.4
Chloride (meq/L)	98 ± 1	103 ± 0**	103 ± 1*	101 ± 0[c]	99 ± 1	102 ± 1
Calcium (mg/dL)	11.2 ± 0.1	12.3 ± 0.2	12.0 ± 0.3	11.0 ± 0.2	11.4 ± 0.2	9.3 ± 1.9
Phosphorus (mg/dL)	7.8 ± 0.4	8.7 ± 0.3	7.7 ± 0.3	7.4 ± 0.3	8.6 ± 0.4	7.7 ± 0.5
Total protein (g/dL)	5.6 ± 0.1	5.6 ± 0.1	5.5 ± 0.1	5.6 ± 0.1	5.4 ± 0.1	5.3 ± 0.1
Albumin (g/dL)	3.9 ± 0.1	4.0 ± 0.1	4.1 ± 0.1	3.9 ± 0.0	3.8 ± 0.1	3.8 ± 0.1
A/G ratio	2.4 ± 0.3	2.6 ± 0.1	2.9 ± 0.2	2.3 ± 0.1	2.4 ± 0.2	2.6 ± 0.1
Total bilirubin (mg/dL)	0.2 ± 0.0[c]	0.1 ± 0.1	0.3 ± 0.0	0.4 ± 0.1[c]	0.6 ± 0.1**	1.0 ± 0.3**
ALT (IU/L)	13 ± 1	21 ± 3*	20 ± 1*[c]	38 ± 8**	21 ± 5*	20 ± 2*[c]
AST (IU/L)	59 ± 8	74 ± 5	55 ± 1	80 ± 14	57 ± 2	72 ± 7
LDH (IU/L)	185 ± 58	672 ± 108*	189 ± 31	485 ± 136	102 ± 16	261 ± 57
SDH (IU/L)	20 ± 3[c]	40 [e]	27 ± 3[b]	41 ± 7*[c]	28 ± 2*	48 ± 10**[f]
Cholinesterase (IU/mL)	2,535 ± 135[c]	2,161 ± 96	2,537 ± 182	2,082 ± 29*[b]	1,976 ± 75**	1,941 ± 91**
pH	7.25 ± 0.04[c]	7.34 ± 0.02[c]	7.30 ± 0.02[c]	7.27 ± 0.01[c]	7.42 ± 0.06[b]	7.30 ± 0.03

* Significantly different ($P \le 0.05$) from the control group by Dunn's or Shirley's test
** $P \le 0.01$
[a] Mean ± standard error. A/G ratio = albumin/globulin ratio; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; SDH = sorbitol dehydrogenase.
[b] n=3
[c] n=4
[d] n=0
[e] n=1; no standard error calculated
[f] n=2

TABLE G2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Studies of C.I. Pigment Red 3[a]

Male	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Hematology						
n	10	10	10	10	10	10
Hematocrit (%)	46.1 ± 1.6	39.6 ± 0.3**	39.9 ± 0.6**	39.6 ± 0.5**	49.2 ± 0.4*	35.0 ± 0.5**
Hemoglobin (g/dL)	14.5 ± 0.4	14.8 ± 0.1	14.5 ± 0.2	14.0 ± 0.2	13.3 ± 0.1**	13.0 ± 0.1**
Erythrocytes ($10^6/\mu L$)	7.65 ± 0.12	7.64 ± 0.06	7.32 ± 0.10**	7.25 ± 0.09**	7.45 ± 0.04**	6.43 ± 0.10**
Platelets ($10^3/\mu L$)	168.5 ± 9.8[b]	170.2 ± 10.4	179.6 ± 15.7	185.5 ± 7.8	182.7 ± 12.4[c]	220.4 ± 3.6**[d]
Reticulocytes (%)	1.58 ± 0.10	2.61 ± 0.29*	3.87 ± 0.22**	3.38 ± 0.38**	4.23 ± 0.24**	6.29 ± 0.60**
Leukocytes ($10^3/\mu L$)	5.79 ± 0.26	7.47 ± 0.23**	7.60 ± 0.42**	8.24 ± 0.28**	6.99 ± 0.17	6.64 ± 0.30
Segmented neutrophils ($10^3/\mu L$)	0.87 ± 0.08	0.96 ± 0.07	1.30 ± 0.19	1.23 ± 0.11	0.72 ± 0.13	0.71 ± 0.11
Lymphocytes ($10^3/\mu L$)	4.78 ± 0.29	6.38 ± 0.22**	6.22 ± 0.36*	6.83 ± 0.32**	5.91 ± 0.15	5.83 ± 0.28
Monocytes ($10^3/\mu L$)	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00	0.05 ± 0.02	0.05 ± 0.02*	0.20 ± 0.01
Eosinophils ($10^3/\mu L$)	0.04 ± 0.02	0.07 ± 0.02	0.05 ± 0.02	0.01 ± 0.01	0.02 ± 0.01	0.03 ± 0.02
Clinical chemistry						
n	10	10	10	10	10	10
Urea nitrogen (mg/dL)	18.7 ± 0.9	20.9 ± 0.3	20.0 ± 0.7	21.1 ± 0.6	17.2 ± 0.4	19.8 ± 0.4
Creatinine (mg/dL)	0.59 ± 0.02	0.95 ± 0.03**	0.86 ± 0.10*	0.76 ± 0.05*	0.62 ± 0.02	0.72 ± 0.03
Sodium (meq/L)	141 ± 1	151 ± 1**	167 ± 4**	159 ± 6**	143 ± 0	142 ± 1
Potassium (meq/L)	4.6 ± 0.1	4.8 ± 0.1	4.9 ± 0.2	5.0 ± 0.2	4.8 ± 0.1	4.9 ± 0.2
Chloride (meq/L)	98 ± 1	100 ± 0	98 ± 1	100 ± 0	98 ± 1	99 ± 1
Partial carbon dioxide (mm Hg)	61.9 ± 3.8[d]	68.3 ± 0.9[d]	65.8 ± 1.1	66.0 ± 2.4	66.9 ± 0.7	68.0 ± 2.2[b]
Calcium (mg/dL)	9.9 ± 0.3	10.5 ± 0.0	10.4 ± 0.2	10.9 ± 0.1**	10.1 ± 0.1	10.4 ± 0.1
Phosphorus (mg/dL)	5.1 ± 0.2	4.8 ± 0.1	5.4 ± 0.2	5.9 ± 0.1*	5.5 ± 0.1	5.8 ± 0.1**
Total protein (g/dL)	6.1 ± 0.1	6.4 ± 0.1*	6.1 ± 0.2	6.9 ± 0.1**	6.5 ± 0.0**	6.5 ± 0.1**
Albumin (g/dL)	3.9 ± 0.1	4.2 ± 0.0**	4.2 ± 0.1**	4.5 ± 0.0**	4.2 ± 0.0**	4.2 ± 0.0**
A/G ratio	1.9 ± 0.1	1.9 ± 0.1	2.3 ± 0.2*	1.9 ± 0.1	1.8 ± 0.0	1.8 ± 0.1
Total bilirubin (mg/dL)	0.2 ± 0.1	0.6 ± 0.0**	0.5 ± 0.1**	0.7 ± 0.0**	0.6 ± 0.0**	0.5 ± 0.0**
ALT (IU/L)	38 ± 6	42 ± 6	22 ± 3*	51 ± 11	46 ± 5	18 ± 1**
AST (IU/L)	68 ± 5	59 ± 3	51 ± 3**	57 ± 2*	70 ± 3	46 ± 1**
LDH (IU/L)	350 ± 97	115 ± 8	95 ± 18*	152 ± 22	594 ± 30	106 ± 13
SDH (IU/L)	15 ± 2	33 ± 3**	21 ± 3	21 ± 2	16 ± 2	19 ± 2
Cholinesterase (IU/L)	411 ± 18[d]	553 ± 38**[d]	476 ± 15*[d]	520 ± 18**	594 ± 18**	547 ± 18**
pH	7.26 ± 0.02[d]	7.23 ± 0.01[d]	7.26 ± 0.01	7.23 ± 0.01	7.23 ± 0.01	7.26 ± 0.02[b]
Urinalysis						
n	7	9	5	7	7	3
Urine total bilirubin (mg/dL)	0.6 ± 0.2	8.0 ± 1.3**	8.3 ± 1.8**	29.5 ± 7.0**	29.6 ± 7.1**	33.4 ± 7.8**

TABLE G2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Studies of C.I. Pigment Red 3 (continued)

Female	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Hematology						
n	9	10	9	10	9	7
Hematocrit (%)	43.6 ± 2.1	38.9 ± 0.8	37.9 ± 0.6	39.1 ± 0.5	47.0 ± 0.7	34.2 ± 2.6**
Hemoglobin (g/dL)	13.6 ± 0.3	14.5 ± 0.2	13.5 ± 0.2	13.8 ± 0.2	12.8 ± 0.2*	13.2 ± 0.1[c]
Erythrocytes ($10^6/\mu L$)	6.83 ± 0.14	6.79 ± 0.14	6.39 ± 0.10**	6.44 ± 0.07**	6.61 ± 0.08*	5.62 ± 0.42**
Platelets ($10^3/\mu L$)	125.7 ± 22.9[c]	143.5 ± 21.3	152.1 ± 26.2	163.3 ± 20.4	199.4 ± 19.3[e]	168.1 ± 31.9
Reticulocytes (%)	1.90 ± 0.13	1.96 ± 0.21	3.48 ± 0.41**	3.99 ± 0.41**	5.50 ± 0.25**[f]	5.37 ± 0.42**[f]
Leukocytes ($10^3/\mu L$)	3.26 ± 0.18	5.02 ± 0.43**	5.72 ± 0.30**	4.43 ± 0.27	4.86 ± 0.19*	3.86 ± 0.49
Segmented neutrophils ($10^3/\mu L$)	0.38 ± 0.07	0.83 ± 0.11*	0.68 ± 0.13	0.67 ± 0.09	0.95 ± 0.15**	0.45 ± 0.07
Lymphocytes ($10^3/\mu L$)	2.78 ± 0.17	4.12 ± 0.39*	4.94 ± 0.29**	3.71 ± 0.24	3.82 ± 0.19	3.33 ± 0.42
Monocytes ($10^3/\mu L$)	0.01 ± 0.01	0.02 ± 0.02	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.02 ± 0.01	0.04 ± 0.01	0.04 ± 0.02	0.01 ± 0.01	0.03 ± 0.01	0.00 ± 0.00
Clinical chemistry						
n	10	10	9	10	10	10
Urea nitrogen (mg/dL)	17.3 ± 0.7	16.8 ± 0.4	17.6 ± 0.5	19.7 ± 0.5	13.4 ± 0.7**	15.4 ± 0.5*
Creatinine (mg/dL)	0.54 ± 0.02	0.89 ± 0.06**	0.72 ± 0.03**	0.64 ± 0.02	0.57 ± 0.02	0.75 ± 0.05**
Sodium (meq/L)	141 ± 1	166 ± 5**	157 ± 5	189 ± 11**	180 ± 7**[b]	140 ± 1
Potassium (meq/L)	3.9 ± 0.1	5.1 ± 0.2**	4.3 ± 0.2*	5.4 ± 0.3**	6.4 ± 0.5**[b]	4.4 ± 0.1**
Chloride (meq/L)	98 ± 1	100 ± 1	100 ± 0	101 ± 1	101 ± 1	99 ± 0
Partial carbon dioxide (mm Hg)	66.1 ± 3.2[d]	70.8 ± 1.9[c]	66.1 ± 1.7[c]	66.0 ± 1.8[d]	65.5 ± 3.1[c]	62.3 ± 2.6[b]
Calcium (mg/dL)	9.7 ± 0.1	10.7 ± 0.2**	10.3 ± 0.1*	10.4 ± 0.1**	9.8 ± 0.1	10.3 ± 0.1
Phosphorus (mg/dL)	3.2 ± 0.2	3.8 ± 0.2	3.8 ± 0.2	3.7 ± 0.2	4.0 ± 0.4	4.3 ± 0.1**
Total protein (g/dL)	6.2 ± 0.1	6.6 ± 0.1	6.5 ± 0.1	6.8 ± 0.1**	6.3 ± 0.1	6.6 ± 0.2
Albumin (g/dL)	4.2 ± 0.1	4.4 ± 0.1	4.4 ± 0.1*	4.8 ± 0.1**	4.3 ± 0.0*	4.5 ± 0.0**
A/G ratio	2.2 ± 0.1	2.1 ± 0.1	2.2 ± 0.1	2.4 ± 0.1	2.2 ± 0.1	2.2 ± 0.1
Total bilirubin (mg/dL)	0.2 ± 0.0	0.7 ± 0.1**[g]	0.7 ± 0.0**	0.8 ± 0.0**	1.0 ± 0.1**	1.1 ± 0.1**
ALT (IU/L)	22 ± 4	20 ± 2	19 ± 2	32 ± 7	25 ± 5	17 ± 2[d]
AST (IU/L)	56 ± 2	60 ± 3	53 ± 4	57 ± 2	56 ± 2	52 ± 2
LDH (IU/L)	190 ± 26	226 ± 53	112 ± 18	137 ± 19	107 ± 14*	121 ± 18*
SDH (IU/L)	9 ± 2[d]	20 ± 3**	17 ± 1**	19 ± 2**	17 ± 1**	19 ± 1**
Cholinesterase (IU/L)	3,273 ± 133[d]	3,720 ± 110	3,248 ± 140	3,357 ± 110	2,878 ± 126	3,135 ± 123
pH	7.22 ± 0.02[d]	7.21 ± 0.02[c]	7.24 ± 0.02[c]	7.26 ± 0.02[d]	7.19 ± 0.02[c]	7.20 ± 0.02[b]
Urinalysis						
n	2	1	2	1	2	2
Urine total bilirubin (mg/dL)	0.7 ± 0.3	13.2 [a]	7.1 ± 1.2	26.6 [a]	27.7 ± 10.7*	36.7 ± 8.1*

* Significantly different ($P \le 0.05$) from the control group by Dunn's or Shirley's test
** $P \le 0.01$
[a] Mean ± standard error. ALT=alanine aminotransferase; AST=aspartate aminotransferase; LDH=lactate dehydrogenase; SDH=sorbitol dehydrogenase; no standard error calculated when n=1.
[b] n=8
[c] n=6
[d] n=9
[e] n=7
[f] n=10
[g] n=4

TABLE G3
Hematology, Clinical Chemistry, and Urinalysis Data for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Studies of C.I. Pigment Red 3[a]

Analysis	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm
Male				
n	15	13	12	13
Hematology				
Hematocrit (%)	44.9 ± 0.4	43.9 ± 0.6*	41.9 ± 0.9**	40.8 ± 0.5**
Hemoglobin (g/dL)	16.2 ± 0.1	15.3 ± 0.2**	14.8 ± 0.3**	14.4 ± 0.2**
Erythrocytes ($10^6/\mu L$)	6.88 ± 0.06	6.81 ± 0.07	6.54 ± 0.10**	6.41 ± 0.05**
Mean cell volume (μ^3)	65.2 ± 0.4	64.4 ± 0.4	64.0 ± 0.7	63.6 ± 0.4**
Mean cell hemoglobin (pg)	23.5 ± 0.2	22.5 ± 0.2**	22.6 ± 0.3**	22.5 ± 0.3**
Mean cell hemoglobin concentration (g/dL)	36.0 ± 0.3	34.9 ± 0.2**	35.4 ± 0.4*	35.2 ± 0.4*
Platelets ($10^3/\mu L$)	5.7 ± 0.1	6.3 ± 0.1**	6.7 ± 0.2**	6.6 ± 0.1**
Leukocytes ($10^3/\mu L$)	5.43 ± 0.32	6.20 ± 0.50	6.58 ± 0.39	6.22 ± 0.46
Clinical chemistry				
Total bilirubin (mg/dL)	0.3 ± 0.0	0.4 ± 0.0**[b]	0.5 ± 0.0**[c]	0.5 ± 0.1**[b]
Methemoglobin (g/dL)	0.56 ± 0.07	0.58 ± 0.07	0.60 ± 0.05	0.68 ± 0.07
Urinalysis				
Urine total bilirubin (mg/dL)	1.3 ± 0.2	45.5 ± 5.0**[b]	57.1 ± 14.3**[b]	63.5 ± 9.6**[b]
Female				
n	15	15	15	15
Hematology				
Hematocrit (%)	43.9 ± 0.4	41.9 ± 0.4**	40.9 ± 0.5**	38.9 ± 0.4**
Hemoglobin (g/dL)	15.2 ± 0.1	14.7 ± 0.1**	14.3 ± 0.2**	13.5 ± 0.1**
Erythrocytes ($10^6/\mu L$)	6.15 ± 0.06	5.84 ± 0.05**	5.65 ± 0.08**	5.34 ± 0.05**
Mean cell volume (μ^3)	71.3 ± 0.1	71.7 ± 0.2*	72.4 ± 0.2**	72.8 ± 0.2**
Mean cell hemoglobin (pg)	24.7 ± 0.1	25.2 ± 0.2	25.3 ± 0.2*	25.3 ± 0.2*
Mean cell hemoglobin concentration (g/dL)	34.7 ± 0.2	35.1 ± 0.3	35.0 ± 0.3	34.7 ± 0.2
Platelets ($10^3/\mu L$)	4.7 ± 0.1	5.4 ± 0.1**	5.4 ± 0.1**	5.5 ± 0.1**
Leukocytes ($10^3/\mu L$)	3.67 ± 0.20	3.94 ± 0.21	4.55 ± 0.26	3.88 ± 0.21
Clinical chemistry				
Total bilirubin (mg/dL)	0.2 ± 0.0	0.5 ± 0.0**	0.6 ± 0.1**	0.8 ± 0.0**
Methemoglobin (g/dL)	0.48 ± 0.06	0.61 ± 0.05	0.71 ± 0.04**	0.73 ± 0.08**
Urinalysis				
Urine total bilirubin (mg/dL)	0.8 ± 0.2	37.1 ± 6.6**	45.3 ± 9.7**	86.1 ± 14.2**

* Significantly different ($P \le 0.05$) from the control group by Dunn's or Shirley's test
** $P \le 0.01$
[a] Mean ± standard error
[b] n=14
[c] n=13

TABLE G4
Hematology and Clinical Chemistry Data for Mice in the 2-Week Feed Studies of C.I. Pigment Red 3[a]

Analysis	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm	100,000 ppm
Male						
Hematology						
n	5	3	5	5	4	4
Hematocrit (%)	37.8 ± 1.4[b]	28.8 ± 2.6**[b]	34.4 ± 1.0	34.7 ± 0.8	35.7 ± 1.2[c]	33.3 ± 0.9
Hemoglobin (g/dL)	13.9 ± 0.3	11.3 ± 0.4*	12.7 ± 0.2*	13.0 ± 0.2*	12.9 ± 0.5*	11.6 ± 0.5**
Erythrocytes (10^6/μL)	8.24 ± 0.15	6.64 ± 0.43*	7.56 ± 0.20*	7.60 ± 0.15*	7.92 ± 0.04*	6.85 ± 0.18**
Platelets (10^3/μL)	243.0 ± 14.1[b]	234.0 ± 26.9	230.0 ± 18.0	250.8 ± 28.9	157.6 ± 47.2[c]	198.5 ± 20.3
Reticulocytes (10^6/μL)	2.40 ± 0.21	8.65 ± 4.11*[b]	4.48 ± 1.71	2.36 ± 0.29	4.22 ± 0.56[d]	5.30 ± 0.76**[c]
Leukocytes (10^3/μL)	3.92 ± 0.40	11.47 ± 3.82**	6.02 ± 1.43	5.72 ± 0.19	4.78 ± 0.50	11.90 ± 3.73*
Segmented neutrophils (10^3/μL)	0.82 ± 0.15	4.31 ± 1.48*	1.93 ± 0.67	1.20 ± 0.15	1.00 ± 0.24	6.45 ± 2.85*
Lymphocytes (10^3/μL)	3.08 ± 0.29	7.11 ± 2.37*	4.06 ± 0.90	4.50 ± 0.26	3.78 ± 0.57	5.45 ± 1.70
Monocytes (10^3/μL)	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
Eosinophils (10^3/μL)	0.01 ± 0.01	0.05 ± 0.05	0.03 ± 0.01	0.01 ± 0.01	0.00 ± 0.00	0.00 ± 0.00
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00[b]	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00[c]	0.00 ± 0.00
Clinical chemistry						
n	5	3	5	5	5	3
Urea nitrogen (mg/dL)	23.0 ± 0.7	32.5 ± 0.5[d]	33.0 ± 1.5	28.0 ± 2.3	18.8 ± 1.0	28.3 ± 2.5[b]
Chloride (meq/L)	107 ± 1	-[e]	-	106 ± 1	111 ± 0[b]	112 ± 1*
Total protein (g/dL)	4.4 ± 0.2[d]	3.9 [f]	4.5 ± 0.1	4.2 ± 0.1	4.7 ± 0.1[b]	3.7 ± 0.3
Albumin (g/dL)	2.7 ± 0.1[b]	2.3 [f]	2.9 ± 0.1	2.7 ± 0.1	3.0 ± 0.1*[b]	2.8 ± 0.1
A/G ratio	1.4 ± 0.1[d]	1.4 [f]	1.7 ± 0.1	1.9 ± 0.1	1.7 ± 0.0[b]	3.6 ± 1.0**
Total bilirubin (mg/dL)	0.6 ± 0.1	0.6 ± 0.1	1.0 ± 0.1	0.6 ± 0.1	1.0 ± 0.1	0.9 ± 0.2[b]
AST (IU/L)	162 ± 37	149 [f]	86 ± 7	101 ± 12	190 ± 35	89 ± 13[b]
LDH (IU/L)	481 ± 43	739 ± 200[d]	580 ± 27	336 ± 16	564 ± 77	647 ± 91[b]
pH	7.37 ± 0.02[b]	7.24 ± 0.08	7.20 ± 0.06	7.28 ± 0.04[g]	7.25 ± 0.03[g]	7.38 ± 0.03
Females						
Hematology						
n	5	4	4	4	5	3
Hematocrit (%)	38.5 ± 1.0	39.0 ± 2.4	33.8 ± 0.7*[c]	35.4 ± 0.4[c]	36.4 ± 1.2	37.8 ± 1.0[b]
Hemoglobin (g/dL)	14.2 ± 0.1	14.5 ± 0.5	12.9 ± 0.3*	12.5 ± 0.3**	13.3 ± 0.4*	13.5 ± 0.2
Erythrocytes (10^6/μL)	8.55 ± 0.18	8.73 ± 0.30	7.57 ± 0.15*	7.42 ± 0.14**	7.73 ± 0.21*	8.01 ± 0.25
Platelets (10^3/μL)	219.6 ± 27.3	202.8 ± 33.8	104.6 ± 29.0[c]	252.4 ± 19.6[c]	171.8 ± 22.9	174.0 ± 16.2[b]
Reticulocytes (10^6/μL)	2.20 ± 0.36	2.13 ± 0.44	2.72 ± 0.50[c]	2.78 ± 0.49[c]	4.28 ± 0.88	3.28 ± 0.53[b]
Leukocytes (10^3/μL)	3.20 ± 0.33	3.05 ± 0.40	2.43 ± 0.36	5.53 ± 0.54*	8.12 ± 1.45*	6.73 ± 0.92*
Segmented neutrophils (10^3/μL)	0.44 ± 0.07	0.55 ± 0.09	0.34 ± 0.15	1.06 ± 0.12*	0.69 ± 0.12	1.12 ± 0.25*
Lymphocytes (10^3/μL)	2.73 ± 0.29	2.49 ± 0.30	2.09 ± 0.24	4.36 ± 0.51	7.43 ± 1.39*	5.62 ± 0.70*
Monocytes (10^3/μL)	0.02 ± 0.02	0.00 ± 0.00	0.00 ± 0.00	0.06 ± 0.03	0.00 ± 0.00	0.00 ± 0.00
Eosinophils (10^3/μL)	0.01 ± 0.01	0.01 ± 0.01	0.00 ± 0.00	0.05 ± 0.02	0.00 ± 0.00	0.00 ± 0.00
Nucleated erythrocytes (10^3/μL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00[c]	0.00 ± 0.00[c]	0.00 ± 0.00	0.00 ± 0.00[b]

TABLE G4
Hematology and Clinical Chemistry Data for Mice in the 2-Week Feed Studies of C.I. Pigment Red 3 (continued)

Analysis	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm	100,000 ppm
Females (continued)						
Clinical chemistry						
n	5	4	2	3	5	4
Urea nitrogen (mg/dL)	20.0 ± 0.9	25.0 [f]	26.0 ± 1.0	23.3 ± 0.3	17.0 ± 0.9	21.0 ± 0.9
Chloride (meq/L)	112 ± 2[g]	-	-	109 ± 1	-	115 [f]
Total bilirubin (mg/dL)	0.8 ± 0.2	1.5 ± 0.4[c]	1.1 ± 0.1[b]	1.1 ± 0.3	1.2 ± 0.2	1.1 ± 0.2
AST (IU/L)	253 ± 109[b]	-	106 ± 38	254 ± 147	295 ± 76[g]	120 ± 21[g]
LDH (IU/L)	515 ± 37	589 [f]	517 ± 79	604 ± 229	660 ± 177[g]	816 ± 277
pH	7.30 ± 0.02	7.30 ± 0.03	7.35 ± 0.01[c]	7.33 ± 0.01[b]	7.27 ± 0.02[b]	7.34 ± 0.05[d]

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. A/G ratio = albumin/globulin ratio; AST = aspartate aminotransferase; LDH = lactate dehydrogenase.
[b] n=4
[c] n=5
[d] n=2
[e] n=0; no data calculated
[f] n=1; no standard error calculated
[g] n=3

TABLE G5
Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Feed Studies of C.I. Pigment Red 3[a]

Analysis	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male						
Hematology						
n	9	10	10	9	10	10
Hematocrit (%)	32.5 ± 2.6	34.4 ± 1.9	26.3 ± 3.7	37.6 ± 1.1	36.8 ± 1.0	34.9 ± 1.3
Hemoglobin (g/dL)	11.1 ± 0.9	12.4 ± 0.7	9.0 ± 1.4	12.7 ± 0.4	12.4 ± 0.4	11.7 ± 0.5
Erythrocytes ($10^6/\mu L$)	6.61 ± 0.55	7.29 ± 0.41	5.46 ± 0.77	7.80 ± 0.23	7.50 ± 0.22	6.93 ± 0.31
Platelets ($10^3/\mu L$)	183.0 ± 25.0	178.3 ± 26.2	104.2 ± 19.8	167.3 ± 30.3	174.8 ± 29.9	198.7 ± 25.7
Reticulocytes (%)	6.42 ± 1.43	3.37 ± 0.33	5.80 ± 1.51[b]	3.38 ± 0.41[c]	3.97 ± 0.52	5.08 ± 0.63
Leukocytes ($10^3/\mu L$)	6.43 ± 1.53	3.58 ± 0.55	4.24 ± 1.04[c]	4.72 ± 0.67	4.95 ± 1.14	4.00 ± 0.90
Segmented neutrophils ($10^3/\mu L$)	2.95 ± 0.88	1.07 ± 0.25	6.02 ± 3.63[b]	1.25 ± 0.27[d]	2.03 ± 0.70	1.15 ± 0.37
Lymphocytes ($10^3/\mu L$)	3.29 ± 0.67	2.45 ± 0.36	8.32 ± 4.27[b]	4.17 ± 0.53[e]	2.86 ± 0.61	2.75 ± 0.57
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00[f]	0.00 ± 0.00[c]	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.07 ± 0.03	0.01 ± 0.01	0.00 ± 0.00[f]	0.00 ± 0.00[c]	0.03 ± 0.02	0.02 ± 0.01
Clinical chemistry						
n	9	8	6	7	9	10
Urea nitrogen (mg/dL)	26.4 ± 0.9	23.4 ± 4.5[f]	45.3 ± 7.4[g]	42.2 ± 6.8[d]	22.2 ± 2.1	19.1 ± 1.2*[f]
Sodium (meq/L)	163 ± 10[d]	166 ± 2	196 ± 24[d]	175 ± 10	180 ± 6	146 ± 1[c]
Potassium (meq/L)	7.1 ± 0.8[d]	8.0 ± 0.6	9.4 ± 2.1[d]	9.4 ± 0.8	7.5 ± 0.3	8.1 ± 0.3[c]
Chloride (meq/L)	124 ± 1[d]	139 ± 9[d]	144 [h]	-[i]	-	124.0 ± 0.6[f]
Partial carbon dioxide (mm Hg)	74.2 ± 2.8[f]	69.4 ± 2.6[e]	83.2 ± 1.3[g]	83.9 ± 2.9[e]	69.6 ± 2.5	78.5 ± 1.9[c]
ALT (IU/L)	38 ± 7	71 ± 23	77 ± 30	47 ± 14	31 ± 4	52 ± 15
AST (IU/L)	152 ± 22[c]	314 ± 84	550 ± 245	192 ± 70	190 ± 46	234 ± 68
LDH (IU/L)	496 ± 100	818 ± 200	1,276 ± 441	627 ± 162	422 ± 76	649 ± 101
SDH (IU/L)	71 ± 11[d]	127 ± 41	135 ± 72[j]	74 ± 9[k]	-	78 ± 13[f]
pH	7.14 ± 0.02[f]	7.15 ± 0.06[e]	7.17 ± 0.02[g]	7.19 ± 0.01[e]	7.16 ± 0.01	7.15 ± 0.01[c]
Urinalysis						
n	9	10	10	8	10	10
Urine total bilirubin (mg/dL)	1.4 ± 0.3	41.9 ± 3.5**	53.5 ± 6.1**	59.4 ± 4.5**	89.9 ± 3.2**	96.7 ± 9.6**

TABLE G5
Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Feed Studies of C.I. Pigment Red 3 (continued)

Analysis	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Female						
Hematology						
n	9	9	10	10	10	10
Hematocrit (%)	39.5 ± 1.3[l]	37.8 ± 1.1	35.3 ± 2.4	38.8 ± 0.6	36.3 ± 1.8	40.6 ± 1.2
Hemoglobin (g/dL)	13.0 ± 0.5[l]	13.4 ± 0.4	11.9 ± 0.8	13.1 ± 0.2	12.3 ± 0.7	13.5 ± 0.4
Erythrocytes ($10^6/\mu L$)	7.50 ± 0.41[l]	7.84 ± 0.20	7.22 ± 0.47	7.80 ± 0.14	7.42 ± 0.37	8.16 ± 0.23
Platelets ($10^3/\mu L$)	138.8 ± 18.0[l]	119.3 ± 23.0	147.0 ± 18.5	146.3 ± 17.7	112.5 ± 27.0	169.2 ± 8.8
Reticulocytes (%)	2.73 ± 0.27	2.63 ± 0.22	2.73 ± 0.11	4.12 ± 0.53*	2.99 ± 0.34[c]	3.36 ± 0.46
Leukocytes ($10^3/\mu L$)	3.19 ± 0.28	2.52 ± 0.38	4.03 ± 0.33	4.27 ± 0.52	3.45 ± 0.70	2.62 ± 0.19
Segmented neutrophils ($10^3/\mu L$)	0.70 ± 0.09	0.33 ± 0.07*	0.73 ± 0.11	0.57 ± 0.09	0.72 ± 0.14[c]	0.37 ± 0.05
Lymphocytes ($10^3/\mu L$)	2.37 ± 0.20	2.15 ± 0.34	3.26 ± 0.33	3.60 ± 0.50	2.68 ± 0.74[c]	2.18 ± 0.17
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00[c]	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.07 ± 0.04	0.00 ± 0.00*	0.00 ± 0.00**	0.00 ± 0.00**	0.01 ± 0.01**[c]	0.00 ± 0.00**
Clinical chemistry						
n	3	6	8	10	7	8
Urea nitrogen (mg/dL)	24.2 ± 1.9[e]	19.0 ± 3.0[d]	23.9 ± 2.4[b]	31.1 ± 1.4[f]	17.4 ± 1.2	–
Sodium (meq/L)	171 ± 23	153 ± 7[d]	166 ± 9	180 ± 2[f]	176 ± 15	162 ± 2[k]
Potassium (meq/L)	5.7 ± 0.8	5.6 ± 0.6[d]	7.3 ± 0.8	7.6 ± 0.5[e]	7.8 ± 0.8	5.9 ± 0.2[k]
Chloride (meq/L)	128 ± 1	133 ± 11[d]	150 ± 2[k]	–	–	–
Partial carbon dioxide (mm Hg)	69.5 ± 2.1[c]	71.5 ± 3.2[f]	76.8 ± 1.8	83.2 ± 2.6*[c]	61.3 ± 2.2[c]	71.5 ± 2.6
ALT (IU/L)	46 ± 13[f]	28 ± 4	34 ± 9	41 ± 13	57 ± 12[c]	40 ± 8
AST (IU/L)	258 ± 70[f]	156 ± 24	230 ± 62[b]	274 ± 102	357 ± 53	184 ± 50[d]
LDH (IU/L)	549 ± 137[f]	275 ± 39	641 ± 173[b]	655 ± 182	837 ± 151[c]	438 ± 104[d]
SDH (IU/L)	82 ± 19	37 ± 4	79 ± 13[b]	79 ± 29[j]	–	–
pH	7.14 ± 0.01[c]	7.18 ± 0.01[f]	7.20 ± 0.02*	7.16 ± 0.01[b]	7.17 ± 0.02[b]	7.21 ± 0.03**
Urinalysis						
n	10	10	10	10	10	10
Urine total bilirubin (mg/dL)	1.2 ± 0.2	48.5 ± 3.2**	64.7 ± 2.8**	71.8 ± 3.0**	96.9 ± 8.1**	127.4 ± 3.0**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. ALT=alanine aminotransferase; AST=aspartate aminotransferase; LDH=lactate dehydrogenase; SDH=sorbitol dehydrogenase.
[b] n=9
[c] n=8
[d] n=5
[e] n=6
[f] n=7
[g] n=3
[h] n=1
[i] n=0; no data calculated
[j] n=4
[k] n=2
[l] n=10

TABLE G6
Hematology, Clinical Chemistry, and Urinalysis Data for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Studies of C.I. Pigment Red 3[a]

Analysis	0 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male				
n	14	14	10	12
Hematology				
Hematocrit (%)	41.0 ± 0.5	40.2 ± 0.4	39.9 ± 0.3	42.6 ± 1.9
Hemoglobin (g/dL)	14.2 ± 0.1	14.0 ± 0.2	13.9 ± 0.1	14.7 ± 0.6
Erythrocytes ($10^6/\mu L$)	9.47 ± 0.11	9.13 ± 0.11*	9.20 ± 0.06*	9.92 ± 0.58
Mean cell volume (μ^3)	43.4 ± 0.3	44.1 ± 0.4	43.4 ± 0.3	45.0 ± 1.6
Mean cell hemoglobin (pg)	15.0 ± 0.1	15.3 ± 0.1	15.1 ± 0.1	15.6 ± 0.5
Mean cell hemoglobin concentration (g/dL)	34.7 ± 0.3	34.8 ± 0.2	34.9 ± 0.1	34.6 ± 0.2
Platelets ($10^3/\mu L$)	9.6 ± 0.4	9.3 ± 0.4	9.3 ± 0.5[b]	10.8 ± 0.4
Leukocytes ($10^3/\mu L$)	2.39 ± 0.24	2.86 ± 0.27	1.86 ± 0.23	1.60 ± 0.19*
Clinical chemistry				
Total bilirubin (mg/dL)	0.6 ± 0.0	0.6 ± 0.1[c]	0.6 ± 0.1[b]	0.9 ± 0.1**[d]
Methemoglobin (g/dL)	0.49 ± 0.05	0.57 ± 0.06[c]	0.53 ± 0.07	0.61 ± 0.06[d]
Urinalysis				
Urine total bilirubin (mg/dL)	1.1 ± 0.2	23.7 ± 5.0**[c]	42.1 ± 9.2**	24.6 ± 6.6**[d]
Female				
n	11	15	14	15
Hematology				
Hematocrit (%)	41.2 ± 0.5	40.7 ± 0.6	39.8 ± 0.5	39.4 ± 0.6*
Hemoglobin (g/dL)	14.6 ± 0.2	14.2 ± 0.3	14.2 ± 0.2[d]	13.7 ± 0.2**
Erythrocytes ($10^6/\mu L$)	9.35 ± 0.13	9.27 ± 0.16	9.19 ± 0.11	9.03 ± 0.12
Mean cell volume (μ^3)	43.4 ± 0.2	44.2 ± 0.2*	43.3 ± 0.4	43.5 ± 0.2
Mean cell hemoglobin (pg)	15.3 ± 0.1	15.4 ± 0.1	15.3 ± 0.1[d]	15.2 ± 0.1
Mean cell hemoglobin concentration (g/dL)	35.4 ± 0.3	34.9 ± 0.2	35.4 ± 0.3[d]	34.8 ± 0.2
Platelets ($10^3/\mu L$)	5.8 ± 0.1	6.1 ± 0.2	6.5 ± 0.2*	6.5 ± 0.1**
Leukocytes ($10^3/\mu L$)	1.96 ± 0.12	1.92 ± 0.12	2.11 ± 0.26	1.90 ± 0.20
Clinical chemistry				
Total bilirubin (mg/dL)	0.4 ± 0.1[e]	0.6 ± 0.1	0.5 ± 0.0[c]	0.6 ± 0.0*
Methemoglobin (g/dL)	0.99 ± 0.36	0.77 ± 0.21	0.83 ± 0.30	0.60 ± 0.11
Urinalysis				
Urine total bilirubin (mg/dL)	0.7 ± 0.2[e]	22.6 ± 5.3**	26.9 ± 6.4**[f]	22.1 ± 3.3**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error
[b] n=9
[c] n=15
[d] n=13
[e] n=12
[f] n=14

APPENDIX H
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF C.I. PIGMENT RED 3

C.I. Pigment Red 3 was obtained from American Cyanamid Company (Wayne, NJ; lot G-1292), and Sun Chemical Company (New York, NY; lot S051783). Lot G-1292 was used throughout the 2-week and 13-week studies and during a portion of the 2-year studies, and lot S051783 was used throughout the remainder of the 2-year studies. Reports from the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO), on analyses performed in support of the C.I. Pigment Red 3 studies are on file at the National Institute of Environmental Health Sciences.

Both lots of the study chemical, a red powder, were identified as C.I. Pigment Red 3 by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra (Figures H1 and H2) were consistent with those expected for the structure and with the literature description for the spectra of C.I. Pigment Red 3 (*Sadtler Standard Spectra*).

Initially, lot G-1292 was divided into two subbatches. The relative purity of the subbatches was determined by high-performance liquid chromatography (HPLC) with a μBondapak CN column with a solvent system of hexane:methylene chloride (90:10) at a flow rate of 1 mL/minute. Nitrobenzene was added as an internal standard. Ultraviolet detection was at 254 nm. The major peak area of one subbatch was 99.0 ± 0.5% of that of the second subbatch. Three subbatches of lot S051783 were analyzed using the same HPLC system, but with a solvent system of hexane:methylene chloride (85:15) The three subbatches were found to be identical within the limits of experimental error.

The purity of both lots was found to be greater than 97% by elemental analyses, weight loss on drying, thin-layer chromatography (TLC), and HPLC. TLC was performed on silica gel plates with two solvent systems: 1) methylene chloride and 2) chloroform:xylene:methanol (75:25:1). After drying, plates were examined under shortwave (254 nm) and longwave (366 nm) ultraviolet light and visible light. HPLC was performed with the same system described above, but with solvent ratios of 95:5 for lot G-1292 and 92:8 for lot S051783.

For lot G-1292, elemental analyses for carbon, hydrogen, and nitrogen were in agreement with the theoretical values for C.I. Pigment Red 3. Weight loss on drying indicated less than 0.05% water. TLC indicated a major spot and a slight trace impurity by one solvent system and a single homogeneous spot by a second solvent system. HPLC indicated a major peak and three impurities with a combined area of approximately 2% relative to the major peak. The largest impurity had a peak area of 1.8% of the major peak. More polar mobile phases revealed three additional impurities with combined areas of less than 1% of that of the major peak.

For lot S051783, elemental analyses for carbon and hydrogen were in agreement with the theoretical values for C.I. Pigment Red 3; the analysis for nitrogen was low. Weight loss on drying indicated 0.12 ± 0.01% water. TLC by both solvent systems indicated only a major spot. HPLC indicated a major peak and four impurities with a total area of approximately 2% relative to the major peak. The largest impurity had a peak area of 1.1% of the major peak. HPLC major peak comparison of the two lots indicated similar purity.

Stability studies on lot G-1292 were performed by the analytical chemistry laboratory using HPLC with the system described above but with a solvent ratio of 90:10 and with nitrobenzene added as an internal standard. These studies indicated that C.I. Pigment Red 3 was stable as a bulk chemical for 2 weeks at temperatures up to 60° C when protected from light. The stability of the bulk chemical was monitored periodically at the study laboratory with ultraviolet spectroscopy and HPLC analysis methods similar to those described above. No change in purity was observed.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by mixing amounts of C.I. Pigment Red 3 and feed in a blender (Patterson-Kelly Twin Shell with intensifier bar) and mixing for 15 minutes (Table H1). Studies were conducted by the analytical chemistry laboratory to determine homogeneity and stability of the dosed feed preparations. For homogeneity analyses, the formulations were extracted and diluted with methylene chloride, and the absorbance of the samples was measured versus methylene chloride by spectroscopy at 510 nm. For the stability studies, feed samples were extracted with methylene chloride, centrifuged, and further diluted with methylene chloride. The samples were then injected into a HPLC system equipped with a μBondapak CN column. The mobile phase was a mixture of hexane:methylene chloride at a ratio of 40:60 and a flow rate of 2 mL/minute. Visible detection was at 436 nm. Homogeneity was confirmed; stability of the formulations was established for 2 weeks when stored in the dark at temperatures up to 45° C.

Periodic analyses of the dose formulations of C.I. Pigment Red 3 were conducted at the study laboratory and the analytical chemistry laboratory with visible spectroscopy at 510 nm. During the 2-week studies, the dose formulations were analyzed at the beginning of the studies (Table H2). During the 13-week studies, the dose formulations were analyzed at the initiation and the midpoint of the studies (Table H3). During the 2-year studies, the dose formulations were analyzed at least once every 8 weeks and 99% (181/183) were within 10% of the target concentrations (Table H4). Results of the periodic referee analysis performed by the analytical chemistry laboratory indicated good agreement with the results obtained by the study laboratory (Table H5).

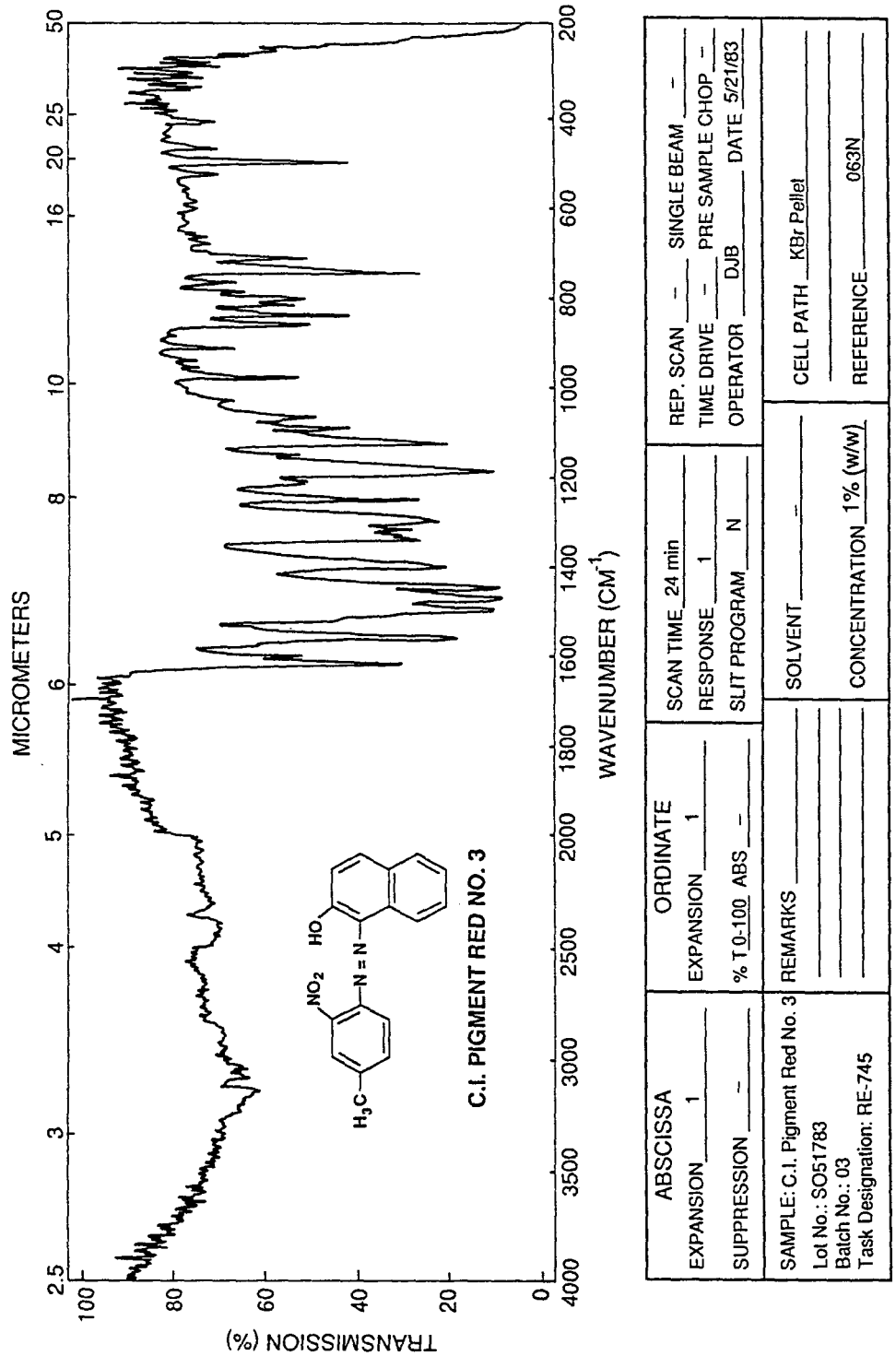

FIGURE H1
Infrared Absorption Spectrum of C.I. Pigment Red 3

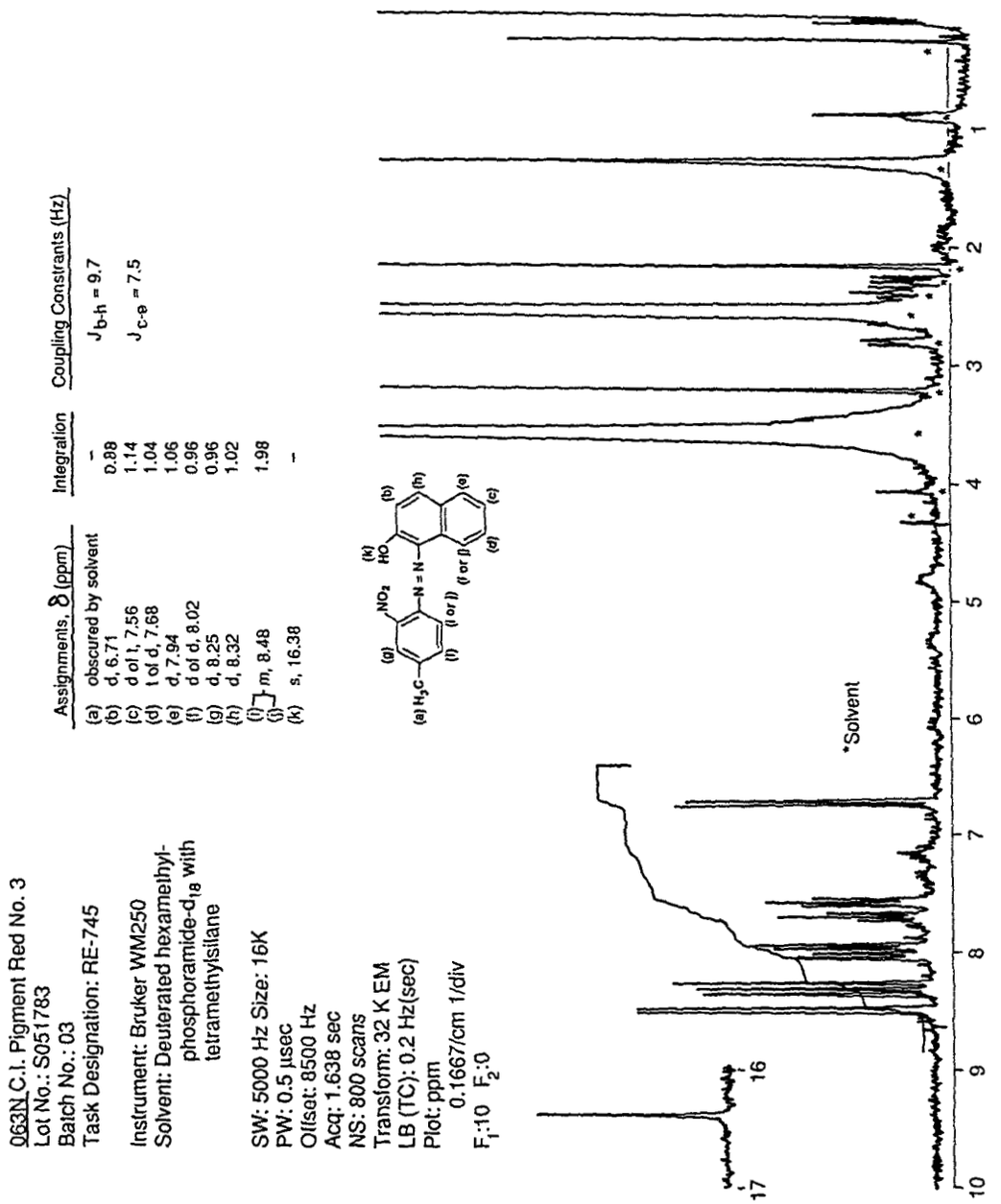

FIGURE H2
Nuclear Magnetic Resonance Spectrum of C.I. Pigment Red 3

TABLE H1
Preparation and Storage of Dose Formulations in the Feed Studies of C.I. Pigment Red 3

2-Week Studies	13-Week Studies	2-Year Studies
Preparation		
Dose formulations were prepared weekly. Premix was prepared by mixing C.I. Pigment Red 3 and feed (w:w); premix and remaining feed layered in a blender with intensifier bar and mixed for 15 minutes.	Same as 2-week studies	Same as 2-week studies
Lot Number		
G-1292	Same as 2-week studies	G-1292 and S051783
Maximum Storage Time		
13 days	Same as 2-week studies	Same as 2-week studies
Storage		
Room temperature, in double-thickness clear plastic bags in triple-thickness black plastic bags in rigid plastic containers	Same as 2-week studies	Same as 2-week studies
Study Laboratory		
Southern Research Institute, Birmingham, AL	Same as 2-week studies	Same as 2-week studies
Analytical Chemistry Laboratory		
Midwest Research Institute, Kansas City, MO	Same as 2-week studies	Same as 2-week studies

TABLE H2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Week Feed Studies of C.I. Pigment Red 3

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
28 May 1981	3 June 1981	6,000	6,100	+2
		12,500	12,800	+2
		25,000	25,400	+2
		50,000	50,200	0
		100,000	100,600	+1

TABLE H3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Feed Studies of C.I. Pigment Red 3

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
11 November 1981	13 November 1981	3,000	2,790	-7
		3,000	2,990	-1
		3,000	2,920	-3
		3,000	3,000[a]	0
		6,000	5,550	-7
		12,500	11,640	-7
		25,000	24,520	-2
		50,000	48,880	-2
		50,000	48,890	-2
		50,000	49,010	-2
6 January 1982	7 January 1982	3,000	3,000	0
		6,000	6,040	+1
		12,500	12,620	+1
		25,000	24,880	-1
		50,000	51,240	+2

[a] Dose formulation given to mice only.

TABLE H4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of C.I. Pigment Red 3[a]

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
2 March 1983[b]	3 March 1983	6,000	5,300	-12
		6,000	6,730	+12
		6,000	5,820	-3
		12,500	12,100	-3
		12,500	12,600	+1
		12,500	12,600	+1
		25,000	24,700	-1
		25,000	25,100	0
		25,000	25,100	0
4 March 1983[b]	7 March 1983	6,000	6,190	+3
		6,000	6,550	+9
27 April 1983	29 April 1983	6,000	5,990	0
		6,000	5,900	-2
		6,000	5,730	-4
		12,500	12,400	-1
		12,500	12,400	-1
		12,500	12,600	+1
		12,500	12,400	-1
		25,000	24,700	-1
		25,000	25,100	0
		25,000	24,300	-3
		25,000	25,100	0
		50,000	50,500	+1
		50,000	50,100	0
22 June 1983	23 June 1983	6,000	5,880	-2
		6,000	5,650	-6
		6,000	5,920	-1
		12,500	12,500	0
		12,500	12,500	0
		12,500	12,600	+1
		12,500	12,200	-2
		25,000	24,600	-1
		25,000	25,000	0
		25,000	24,900	0
		25,000	25,100	0
		50,000	50,000	0
		50,000	49,000	-2
17 August 1983	18 August 1983	6,000	5,900	-2
		6,000	5,960	-1
		6,000	5,840	-3
		12,500	12,000	-4
		12,500	12,200	-2
		12,500	12,400	-1
		12,500	12,000	-4
		25,000	23,800	-5
		25,000	24,200	-3
		25,000	24,400	-2
		25,000	23,900	-4
		50,000	48,200	-4
		50,000	49,700	-1

TABLE H4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of C.I. Pigment Red 3 (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
12 October 1983	13 October 1983	6,000	5,940	-1
		6,000	6,080	+1
		6,000	6,020	0
		12,500	12,700	+2
		12,500	12,600	+1
		12,500	12,600	+1
		12,500	12,500	0
		25,000	25,200	+1
		25,000	25,100	0
		25,000	25,200	+1
		25,000	25,600	+2
		50,000	49,300	-1
		50,000	49,800	0
7 December 1983	8 December 1983	6,000	5,870	-2
		6,000	5,960	-1
		6,000	6,090	+2
		12,500	12,200	-2
		12,500	12,400	-1
		12,500	12,100	-3
		12,500	12,200	-2
		25,000	24,400	-2
		25,000	24,600	-2
		25,000	24,600	-2
		25,000	25,000	0
		50,000	49,100	-2
		50,000	49,100	-2
1 February 1984	2 February 1984	6,000	5,900	-2
		6,000	6,300	+5
		6,000	6,140	+2
		12,500	12,600	+1
		12,500	12,300	-2
		12,500	12,600	+1
		12,500	12,500	0
		25,000	25,400	+2
		25,000	25,000	0
		25,000	25,000	0
		25,000	25,400	+2
		50,000	52,500	+5
		50,000	49,600	-1
28 March 1984	29 March 1984	6,000	6,120	+2
		6,000	6,040	+1
		6,000	5,930	-1
		12,500	12,200	-2
		12,500	12,100	-3
		12,500	12,600	+1
		12,500	12,000	-4
		25,000	24,800	-1
		25,000	24,800	-1
		25,000	24,900	0
		25,000	25,200	+1
		50,000	50,500	+1
		50,000	49,600	-1

TABLE H4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of C.I. Pigment Red 3 (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
18 April 1984[d]	21, 23 April 1984	12,500	12,600	+1
		12,500	12,600	+1
		12,500	12,400	-1
		25,000	25,200	+1
		25,000	25,200	+1
		25,000	25,100	0
16 May 1984	17 May 1984	6,000	5,900	-2
		6,000	6,140	+2
		6,000	6,080	+1
		12,500	12,200	-2
		12,500	12,400	-1
		12,500	12,400	-1
		12,500	12,600	+1
		12,500	12,600	+1
		25,000	24,900	0
		25,000	24,400	-2
		25,000	24,600	-2
		25,000[c]	24,800	-1
		25,000[c]	24,400	-2
		50,000	49,300	-1
		50,000	49,600	-1
27 June 1984	28 June 1984	6,000	5,830	-3
		6,000	5,860	-2
		6,000	5,940	-1
		12,500	13,000	+4
		12,500	12,400	-1
		12,500	12,600	+1
		12,500	12,100	-3
		25,000	25,200	+1
		25,000	25,400	+2
		25,000	24,600	-2
		25,000	24,800	-1
		50,000	50,600	+1
		50,000	49,200	-2
29 August 1984	30 August 1984	6,000	5,810	-3
		6,000	5,940	-1
		6,000	6,120	+2
		12,500	12,600	+1
		12,500	12,400	-1
		12,500	12,100	-3
		12,500	12,400	-1
		25,000	25,000	0
		25,000	24,600	-2
		25,000	24,400	-2
		25,000	24,800	-1
		50,000	49,500	-1
		50,000	49,000	-2

TABLE H4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of C.I. Pigment Red 3 (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
17 October 1984	22 October 1984	6,000	5,980	0
		6,000	5,870	-2
		6,000	5,690	-5
		12,500	12,300	-2
		12,500	12,700	+2
		12,500	12,600	+1
		12,500	12,500	0
		25,000	24,800	-1
		25,000	25,200	+1
		25,000	25,600	+2
		25,000	24,800	-1
		50,000	49,600	-1
		50,000	50,100	0
28 November 1984	29 November 1984	6,000	6,000	0
		6,000	5,880	-2
		12,500	12,500	0
		12,500	12,600	+1
		12,500	12,600	+1
		25,000	25,000	0
		25,000	25,200	+1
		25,000	24,600	-2
		50,000	50,200	0
30 January 1985	31 January 1985	6,000	5,980	0
		6,000	5,950	-1
		12,500	12,300	-2
		12,500	12,600	+1
		12,500	12,600	+1
		25,000	24,900	0
		25,000	25,000	0
		25,000	24,900	0
		50,000	50,000	0
13 March 1985[c]	14 March 1985	12,500	12,800	+2
		25,000	25,200	+1
		50,000	50,600	+1

[a] Dose formulations for rats: 0.600%, 1.25%, and 2.50% (w/w). Dose formulations of mice: 1.25%, 2.50%, and 5.00% (w/w).
[b] Dose formulations given to rats only.
[c] Dose formulations given to mice only.
[d] Special run requested to test the homogeneity of larger quantities of dosed-feed formulation. Samples taken from different points in the blender.

TABLE H5
Results of Referee Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week and 2-Year Feed Studies of C.I. Pigment Red 3

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
13-Week Studies				
11 November 1983	13 November 1983	3,000	3,000	0
2-Year Studies				
2 March 1983[a]	8 March 1983	6,000	5,500	−8
27 April 1983[a]	3 May 1983	6,000	6,190	+3
12 October 1983[b]	20 October 1983	50,000	49,800	0
1 February 1984	13 February 1984	25,000	25,000	0
29 August 1984	5 September 1984	12,500	12,500	0
30 January 1985[a]	12 February 1985	6,000	5,920	−1

[a] Dose formulations given to rats only.
[b] Dose formulation given to mice only.

APPENDIX I
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES

TABLE I1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of C.I. Pigment Red 3

Week	0 ppm		6,000 ppm			12,500 ppm			25,000 ppm		
	Feed (g/day)[a]	Body Wt. (g)	Feed (g/day)[a]	Body Wt. (g)	Dose/ Day[b]	Feed (g/day)[a]	Body Wt. (g)	Dose/ Day[b]	Feed (g/day)[a]	Body Wt. (g)	Dose/ Day[b]
1	16.3	112	16.5	114	870	16.3	115	1,780	16.2	112	3,622
2	16.7	162	16.4	164	600	16.6	165	1,265	16.8	162	2,593
5	19.7	256	20.5	256	481	20.5	258	996	20.7	252	2,051
6	19.6	274	20.0	274	438	20.0	276	907	20.4	270	1,887
9	18.4	318	18.4	314	351	18.8	317	742	20.1	312	1,609
10	20.4	327	18.3	324	338	20.0	326	768	20.9	319	1,643
13	16.9	356	18.0	346	313	18.0	351	641	20.3	337	1,503
17	18.4	380	18.3	372	295	18.2	375	608	18.3	363	1,258
21	16.9	405	17.4	396	263	17.1	402	530	18.4	390	1,183
25	16.8	419	16.5	409	242	16.2	413	490	17.1	397	1,077
30	20.8	435	19.2	422	274	19.3	421	572	19.8	407	1,216
34	21.5	449	20.7	433	287	20.3	432	586	19.3	418	1,152
38	22.2	459	21.5	442	292	20.4	431	590	21.4	427	1,254
42	17.8	462	19.5	448	262	19.4	444	545	19.0	433	1,098
46	20.3	471	20.6	446	276	21.0	450	583	20.5	440	1,162
50	22.5	480	21.7	465	281	22.3	463	603	21.8	448	1,218
54	20.2	487	18.4	463	239	18.8	465	506	19.9	454	1,096
58	20.1	495	19.4	468	249	18.0	468	482	18.8	456	1,029
62	18.1	492	19.2	468	246	18.6	466	498	18.4	456	1,007
66	12.1	482	13.2	458	173	12.8	458	349	12.9	445	728
70	13.1	476	13.4	454	178	15.3	454	422	14.2	438	810
74	15.4	476	16.8	452	222	16.9	451	469	16.1	439	916
78	14.2	472	14.6	449	195	14.4	446	404	14.8	427	866
82	14.5	468	15.9	447	213	15.3	436	439	14.5	416	871
86	14.6	457	14.6	431	204	14.8	429	433	14.9	408	912
90	14.7	449	15.1	429	211	15.3	422	455	16.1	403	1,001
94	14.6	444	15.7	426	222	14.9	417	448	15.4	396	971
98	14.2	436	14.9	415	215	15.7	403	487	14.5	383	944
102	16.3	426	15.3	407	226	15.4	391	494	15.3	374	1,023
Mean for weeks											
1-13	18.3	258	18.3	256	484	18.6	258	1,014	19.3	252	2,130
14-52	19.7	440	19.5	426	275	19.4	426	567	19.5	414	1,180
53-102	15.5	466	15.9	444	215	15.9	439	453	15.8	423	936

[a] Grams of feed consumed per animal per day
[b] Milligrams of C.I. Pigment Red 3 consumed per day per kilogram body weight

TABLE I2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of C.I. Pigment Red 3

Week	0 ppm		6,000 ppm			12,500 ppm			25,000 ppm		
	Feed (g/day)[a]	Body Wt. (g)	Feed (g/day)[a]	Body Wt. (g)	Dose/ Day[b]	Feed (g/day)[a]	Body Wt. (g)	Dose/ Day[b]	Feed (g/day)[a]	Body Wt. (g)	Dose/ Day[b]
1	14.0	95	13.5	98	829	13.5	97	1,737	13.7	96	3,565
2	13.6	127	14.0	130	646	13.8	128	1,349	13.6	127	2,668
5	14.2	162	14.8	162	546	14.5	161	1,127	14.5	161	2,243
6	9.8	154	16.1	172	563	14.8	169	1,090	10.8	151	1,791
9	13.9	189	13.3	189	421	12.7	188	842	13.2	188	1,752
10	16.1	193	13.7	193	425	13.9	190	912	14.1	190	1,854
13	13.2	202	12.7	198	387	12.7	195	812	12.4	196	1,587
17	11.9	211	11.7	210	334	12.0	204	731	12.3	201	1,528
21	10.1	218	10.5	212	298	10.9	210	647	10.5	209	1,254
25	12.0	228	12.4	218	342	12.4	216	720	12.0	214	1,400
30	16.7	234	13.4	224	358	12.9	221	729	12.7	216	1,467
34	15.3	240	12.2	227	322	13.3	226	736	13.8	222	1,554
38	14.9	247	12.5	236	318	12.8	233	686	13.1	227	1,440
42	13.9	256	14.6	242	361	15.2	239	794	13.5	228	1,479
46	15.2	266	14.9	248	361	13.8	245	704	14.2	238	1,499
50	17.0	278	17.7	260	409	18.0	255	884	16.7	240	1,744
54	15.6	287	13.6	269	303	14.7	263	700	15.1	251	1,506
58	14.9	303	16.1	284	340	14.9	276	672	14.8	261	1,413
62	14.2	314	13.1	290	272	13.9	282	618	13.7	268	1,276
66	10.3	320	10.0	295	204	10.1	285	444	9.7	271	899
70	11.6	330	10.6	299	212	10.5	290	454	11.0	276	995
74	12.4	338	12.2	308	238	12.6	301	524	12.0	282	1,061
78	12.2	348	11.3	313	216	11.2	307	457	11.0	286	960
82	13.3	351	12.0	313	231	12.4	309	500	12.1	290	1,049
86	11.7	352	11.6	316	221	11.3	308	460	11.0	288	954
90	20.4	354	12.3	315	235	12.3	308	501	12.3	290	1,056
94	13.1	360	11.9	319	223	12.1	311	485	12.7	295	1,077
98	11.0	356	11.8	315	226	11.4	304	471	11.0	289	954
102	12.6	355	13.3	322	248	13.0	308	528	12.8	290	1,102
Mean for weeks											
1-13	13.5	160	14.0	163	545	13.7	161	1,124	13.2	158	2,209
14-52	14.1	242	13.3	231	345	13.5	228	737	13.2	222	1,485
53-102	13.3	336	12.3	304	244	12.3	296	524	12.2	280	1,100

[a] Grams of feed consumed per animal per day
[b] Milligrams of C.I. Pigment Red 3 consumed per day per kilogram body weight

TABLE I3
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of C.I. Pigment Red 3

Week	0 ppm		12,500 ppm			25,000 ppm			50,000 ppm		
	Feed (g/day)[a]	Body Wt. (g)	Feed (g/day)[a]	Body Wt. (g)	Dose/ Day[b]	Feed (g/day)[a]	Body Wt. (g)	Dose/ Day[b]	Feed (g/day)[a]	Body Wt. (g)	Dose/ Day[b]
2	7.4	25.8	8.0	25.6	3,899	7.7	25.3	7,641	7.8	25.3	15,416
3	9.6	26.2	10.4	27.1	4,784	8.8	26.8	8,245	10.8	26.6	20,263
6	6.7	30.5	7.9	29.9	3,286	7.4	30.5	6,077	7.1	30.2	11,739
7	8.1	30.2	10.3	30.8	4,199	9.0	31.2	7,248	7.5	30.9	12,153
10	8.2	32.9	9.4	32.9	3,589	8.5	33.0	6,447	8.6	32.7	13,078
11	7.8	33.5	10.2	33.1	3,867	9.7	33.6	7,186	10.1	33.0	15,240
13	7.5	34.4	10.4	34.0	3,833	9.4	34.4	6,863	9.0	33.7	13,311
17	7.1	37.1	9.3	35.6	3,249	8.9	36.3	6,137	8.0	35.4	11,240
21	7.9	37.8	9.7	36.7	3,287	9.6	37.0	6,518	8.7	35.5	12,190
26	5.5	37.3	5.8	37.2	1,934	5.5	36.9	3,738	5.7	35.3	8,073
30	5.5	37.5	5.7	38.3	1,868	5.8	38.4	3,760	5.9	35.6	8,321
34	5.7	37.8	5.4	38.4	1,752	5.3	38.8	3,418	6.2	35.7	8,675
38	5.2	38.5	5.4	39.6	1,707	5.3	39.5	3,380	5.5	36.0	7,660
42	5.8	39.9	5.4	40.5	1,678	5.7	40.6	3,495	6.4	36.1	8,928
46	5.2	40.0	5.5	40.5	1,696	4.7	40.4	2,925	5.5	36.7	7,514
50	5.6	40.4	4.9	41.8	1,465	5.4	42.1	3,183	5.6	37.0	7,614
54	5.2	40.1	5.3	42.1	1,585	5.1	41.6	3,063	5.4	36.5	7,362
58	4.2	40.9	4.3	41.9	1,280	4.3	41.6	2,605	4.2	37.0	5,682
62	4.7	40.5	4.6	41.9	1,365	4.6	40.9	2,842	4.7	35.7	6,542
66	4.9	40.4	5.1	41.7	1,529	5.2	41.3	3,138	4.8	36.0	6,639
70	5.2	40.3	5.3	41.4	1,601	5.2	40.0	3,219	4.8	34.8	6,869
74	4.5	40.9	4.8	42.1	1,421	4.8	41.4	2,896	4.6	36.4	6,258
78	4.4	39.9	4.5	41.4	1,361	4.4	41.1	2,666	4.7	35.9	6,499
82	4.7	39.8	4.8	41.1	1,449	4.7	40.8	2,882	4.7	35.6	6,556
86	4.7	39.4	4.5	40.3	1,407	4.6	39.4	2,904	4.3	35.2	6,058
90	5.0	39.0	4.8	39.1	1,535	4.5	39.0	2,906	4.5	34.9	6,433
94	4.6	39.3	4.7	40.5	1,444	4.7	38.5	3,057	4.5	35.2	6,443
98	4.7	39.1	4.7	39.9	1,475	5.0	38.4	3,252	4.4	35.2	6,233
102	4.3	39.7	4.5	39.7	1,429	4.7	37.6	3,144	4.2	34.7	5,986
Mean for weeks											
1-13	7.9	30.5	9.5	30.5	3,922	8.7	30.7	7,101	8.7	30.3	14,457
14-52	6.0	38.5	6.3	38.7	2,071	6.3	38.9	4,062	6.4	35.9	8,913
53-102	4.7	39.9	4.8	41.0	1,452	4.8	40.1	2,967	4.6	35.6	6,428

[a] Grams of feed consumed per animal per day
[b] Milligrams of C.I. Pigment Red 3 consumed per day per kilogram body weight

TABLE I4
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of C.I. Pigment Red 3

Week	0 ppm		12,500 ppm			25,000 ppm			50,000 ppm		
	Feed (g/day)[a]	Body Wt. (g)	Feed (g/day)[a]	Body Wt. (g)	Dose/ Day[b]	Feed (g/day)[a]	Body Wt. (g)	Dose/ Day[b]	Feed (g/day)[a]	Body Wt. (g)	Dose/ Day[b]
2	7.0	18.4	6.8	18.6	4,599	7.5	18.4	10,039	6.7	18.5	18,100
3	9.0	19.3	9.6	20.0	5,975	7.6	19.8	9,632	9.3	19.7	23,568
6	6.4	22.1	6.7	22.3	3,783	6.6	22.1	7,522	6.6	22.0	15,003
7	7.8	22.6	7.1	23.3	3,817	7.3	22.9	7,923	7.9	22.9	17,148
10	6.6	24.3	7.4	24.5	3,767	7.2	24.4	7,343	7.6	24.2	15,751
11	7.7	24.6	9.5	25.1	4,733	8.5	24.7	8,637	9.7	24.1	20,046
13	6.4	25.7	7.0	25.8	3,375	5.9	25.5	5,806	6.7	25.3	13,333
17	6.6	27.6	6.7	27.4	3,058	6.4	25.9	6,219	6.8	25.9	13,065
21	6.9	28.7	6.3	28.3	2,795	6.6	26.9	6,104	7.3	27.0	13,440
26	3.7	29.6	4.3	29.7	1,791	3.7	28.7	3,201	4.9	28.0	8,791
30	6.3	30.8	6.3	31.6	2,505	5.8	30.3	4,786	6.2	28.2	10,935
34	7.4	32.1	6.7	33.0	2,520	6.9	31.7	5,474	7.7	28.9	13,279
38	6.3	34.0	6.0	35.2	2,131	6.7	33.1	5,075	7.1	30.1	11,744
42	6.7	35.9	6.4	37.0	2,170	7.1	35.4	5,003	8.9	31.2	14,228
46	7.0	37.8	6.1	38.4	1,985	6.7	36.9	4,558	7.4	32.4	11,390
50	6.1	40.5	5.7	42.0	1,709	6.0	39.0	3,843	6.4	33.9	9,383
54	5.8	41.1	5.1	42.5	1,493	5.9	39.2	3,734	5.4	33.5	8,114
58	3.9	40.8	3.9	42.3	1,138	3.6	38.7	2,308	3.7	33.9	5,525
62	4.1	39.8	4.1	41.6	1,229	4.0	38.1	2,634	4.4	32.5	6,747
70	5.7	40.9	6.0	41.9	1,785	6.8	38.6	4,409	5.7	33.0	8,673
74	7.1	42.3	5.9	44.0	1,678	6.3	39.3	4,023	6.5	34.1	9,586
78	5.3	42.8	5.5	42.2	1,634	5.2	38.9	3,334	5.2	33.6	7,668
82	6.0	41.5	5.3	41.7	1,580	4.7	38.3	3,084	5.6	33.9	8,255
86	6.2	41.5	6.3	42.3	1,873	5.5	37.9	3,606	6.2	33.3	9,350
90	5.6	41.5	5.7	41.3	1,711	5.2	36.7	3,516	5.5	32.5	8,527
94	6.1	41.6	5.6	42.5	1,656	6.3	38.2	4,127	5.7	32.9	8,712
98	5.2	42.1	4.6	42.5	1,362	4.5	37.8	3,007	5.1	33.4	7,574
102	5.0	41.0	4.9	40.9	1,511	4.9	38.4	3,188	4.9	32.8	7,434
Mean for weeks											
1-13	7.3	22.4	7.7	22.8	4,293	7.2	22.5	8,143	7.8	22.4	17,564
14-52	6.3	33.0	6.1	33.6	2,296	6.2	32.0	4,918	6.9	29.5	11,806
53-102	5.5	41.4	5.2	42.1	1,554	5.2	38.3	3,414	5.3	33.3	8,014

[a] Grams of feed consumed per animal per day
[b] Milligrams of C.I. Pigment Red 3 consumed per day per kilogram body weight

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

TABLE J1
Ingredients of NIH-07 Rat and Mouse Ration[a]

Ingredients[b]	Percent by Weight
Ground #2 yellow shelled corn	21.0
Ground whole wheat	35.5
Soybean meal (49% protein)	5.00
Fish meal (60% protein)	9.00
Wheat middlings	10.00
Alfalfa meal (dehydrated, 17% protein)	2.0
Corn gluten meal (60% protein)	2.0
Soy oil	1.5
Dried brewer's yeast	1.00
Dicalcium phosphate	1.5
Ground limestone	0.5
Salt	0.5
Premixes (vitamin and mineral)	0.5

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

TABLE J2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	20,000,000 IU	Stabilized vitamin A palmitate or acetate
D_3	3,800,000 IU	D-activated animal sterol
K_3	2.0 g	Menadione
d-α-Tocopherol acetate	15,000 IU	
Choline	700 g	Choline chloride
Folic acid	1.0 g	
Niacin	20.0 g	
d-Pantothenic acid	25.0 g	*d*-Calcium pantothenate
Riboflavin	5.0 g	
Thiamine	65.0 g	Thiamine mononitrate
B_{12}	14,000 μg	
Pyridoxine	2.0 g	Pyridoxine hydrochloride
Biotin	120.0 mg	*d*-Biotin
Minerals		
Iron	60.0 g	Iron sulfate
Manganese	100.0 g	Manganous oxide
Zinc	10.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.5 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate
Magnesium	400 g	

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

TABLE J3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.33 ± 0.83	21.0 - 24.3	25
Crude Fat (% by weight)	5.34 ± 0.67	4.2 - 6.4	25
Crude Fiber (% by weight)	3.59 ± 0.32	2.9 - 4.5	25
Ash (% by weight)	6.64 ± 0.28	5.9 - 7.3	25
Amino Acids (% of total diet)			
Arginine	1.308 ± 0.606	1.210 - 1.390	8
Cystine	0.306 ± 0.084	0.181 - 0.400	8
Glycine	1.150 ± 0.047	1.060 - 1.210	8
Histidine	0.576 ± 0.024	0.531 - 0.607	8
Isoleucine	0.917 ± 0.029	0.881 - 0.944	8
Leucine	1.946 ± 0.055	1.850 - 2.040	8
Lysine	1.270 ± 0.058	1.200 - 1.370	8
Methionine	0.448 ± 0.128	0.306 - 0.699	8
Phenylalanine	0.987 ± 0.140	0.665 - 1.110	8
Threonine	0.877 ± 0.042	0.824 - 0.940	8
Tryptophane	0.236 ± 0.176	0.107 - 0.671	8
Tyrosine	0.676 ± 0.105	0.564 - 0.794	8
Valine	1.103 ± 0.040	1.050 - 1.170	8
Essential Fatty Acids (% of total diet)			
Linoleic	2.393 ± 0.258	1.830 - 2.570	7
Linolenic	0.280 ± 0.040	0.210 - 0.320	7
Vitamins			
Vitamin A (IU/kg)	11,308 ± 4,691	4,200 - 22,000	25
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 - 6,300	4
α-Tocopherol (ppm)	37.95 ± 9.41	22.50 - 48.90	8
Thiamine (ppm)	20.08 ± 5.07	12.0 - 37.0	25
Riboflavin (ppm)	7.92 ± 0.87	6.10 - 9.00	8
Niacin (ppm)	103.38 ± 26.59	65.0 - 150.0	8
Pantothenic acid (ppm)	29.54 ± 3.60	23.0 - 34.0	8
Pyridoxine (ppm)	9.55 ± 3.48	5.60 - 14.0	8
Folic Acid (ppm)	2.25 ± 0.73	1.80 - 3.70	8
Biotin (ppm)	0.254 ± 0.042	0.19 - 0.32	8
Vitamin B_{12} (ppb)	38.45 ± 22.01	10.6 - 65.0	8
Choline (ppm)	3,089 ± 328.69	2,400 - 3,430	8
Minerals			
Calcium (%)[a]	1.20 ± 0.15	0.87 - 1.43	24
Phosphorus (%)	0.95 ± 0.06	0.84 - 1.10	25
Potassium (%)	0.883 ± 0.078	0.772 - 0.971	6
Chloride (%)	0.526 ± 0.092	0.380 - 0.635	8
Sodium (%)	0.313 ± 0.390	0.258 - 0.371	8
Magnesium (%)	0.168 ± 0.010	0.151 - 0.181	8
Sulfur (%)	0.280 ± 0.064	0.208 - 0.420	8
Iron (ppm)	360.54 ± 100	255.0 - 523.0	8
Manganese (ppm)	91.97 ± 6.01	81.70 - 99.40	8
Zinc (ppm)	54.72 ± 5.67	46.10 - 64.50	8
Copper (ppm)	11.06 ± 2.50	8.090 - 15.39	8
Iodine (ppm)	3.37 ± 0.92	1.52 - 4.13	6
Chromium (ppm)	1.79 ± 0.36	1.04 - 2.09	8
Cobalt (ppm)	0.681 ± 0.14	0.490 - 0.780	4

[a] The batch milled on 14 August 1985 was not analyzed for calcium.

TABLE J4
Contaminant Levels in NIH-07 Rat and Mouse Ration

Contaminants	Mean ± Standard Deviation[a]	Range	Number of Samples
Arsenic (ppm)	0.56 ± 0.18	0.18 - 0.80	25
Cadmium (ppm)[b]	0.11 ± 0.04	0.10 - 0.20	25
Lead (ppm)	0.55 ± 0.21	0.24 - 1.00	25
Mercury (ppm)	<0.05		25
Selenium (ppm)	0.33 ± 0.06	0.21 - 0.46	25
Aflatoxins (ppb)	<5.0		25
Nitrate nitrogen (ppm)	10.53 ± 5.18	2.50 - 22.0	25
Nitrite nitrogen (ppm)	0.79 ± 1.36	0.10 - 6.10	25
BHA (ppm)[c]	<2.00		25
BHT (ppm)[c]	2.48 ± 1.27	1.00 - 5.00	25
Aerobic plate count (CFU/g)[d]	151,468 ± 155,895	6,600 - 420,000	25
Coliform (MPN/g)[e]	290 ± 537	3.00 - 2400	25
E. coli (MPN/g)	8.96 ± 29.38	3.00 - 150	25
Total nitrosoamines (ppb)[f]	6.05 ± 5.93	0.80 - 30.30	25
N,N-Dimethylamine (ppb)[f]	5.39 ± 5.96	0.50 - 30.00	25
N-pyrrolidine (ppb)[f]	0.66 ± 0.71	0.30 - 2.70	25
Pesticides			
α-BHC[g]	<0.01		25
ß-BHC	<0.02		25
γ-BHC	<0.01		25
δ-BHC	<0.01		25
Heptachlor	<0.01		25
Aldrin	<0.01		25
Heptachlor epoxide	<0.01		25
DDE	<0.01		25
DDD	<0.01		25
DDT	<0.01		25
HCB	<0.01		25
Mirex	<0.01		25
Methoxychlor	<0.05		25
Dieldrin	<0.01		25
Endrin	<0.01		25
Telodrin	<0.01		25
Chlordane	<0.05		25
Toxaphene	<0.1		25
Estimated PCBs	<0.2		25
Ronnel	<0.01		25
Ethion	<0.02		25
Trithion	<0.05		25
Diazinon	<0.1		25
Methyl parathion	<0.02		25
Ethyl parathion	<0.02		25
Malathion[h]	0.17 ± 0.20	0.05 - 0.81	25
Endosulfan I	<0.01		25
Endosulfan II	<0.01		25
Endosulfan sulfate	<0.03		25

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] Four batches (02/22/84, 03/14/84, 05/09/84, and 06/13/84) contained 0.20 ppm; all others contained <0.10 ppm.
[c] Sources of contamination: soy oil and fish meal
[d] CFU = colony-forming unit
[e] MPN = most probable number
[f] All values were corrected for percent recovery.
[g] BHC is hexachlorocyclohexane or benzene hexachloride.
[h] Fourteen lots contained more than 0.05 ppm.

APPENDIX K
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. The sentinel animals come from the same production source and weanling groups as animals used for the studies of chemical compounds, and these animals and the study animals are subject to identical environmental conditions.

Rats

During the 13-week studies, five F344/N rats of each sex were maintained with the study animals to serve as sentinel animals. At termination of the 13-week studies, blood samples were taken from the sentinel rats. The blood was allowed to clot, and the serum was separated. The serum was cooled and sent to Microbiological Associates, Inc. (Bethesda, MD) for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
PVM (pneumonis virus of mice)	Study termination
Sendai	Study termination
KRV (Kilham rat virus)	Study termination
H-1 (Toolan's H-1 virus)	Study termination
Complement Fixation	
RCV (rat corona virus)	Study termination

During the 2-year studies, 15 F344/N rats of each sex were maintained with the study animals to serve as sentinel animals. Blood was drawn from five rats of each sex at 6, 12, and 18 months following study initiation. Five randomly selected control animals of each sex were bled at study termination (24 months). Blood collected from each animal was allowed to clot and the serum was separated. The serum was cooled on ice and shipped to Microbial Associates, Inc. (Bethesda, MD) for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
PVM	6 and 12 months
Sendai	6, 12, and 18 months
KRV	6, 12, 18, and 24 months
H-1	6, 12, 18, and 24 months
ELISA	
PVM	18 and 24 months
Sendai	18 and 24 months
RCV/SDA (rat corona virus/sialodacryoadenitis virus)	6, 12, 18, and 24 months
Mycoplasma pulmonis	6, 12, 18, and 24 months
Mycoplasma arthritidis	24 months

Mice

During the 13-week studies, five $B6C3F_1$ mice per sex were maintained with the study animals to serve as sentinel animals. At termination of the 13-week studies, blood samples were obtained from the sentinel mice. Blood collected from each animal was allowed to clot, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates, Inc. (Bethesda, MD) for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
PVM	Study termination
Reovirus 3	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
Polyoma virus	Study termination
Sendai	Study termination
MVM (minute virus of mice)	Study termination
Ectromelia virus (mouse pox)	Study termination
Complement Fixation	
Mouse adenoma virus	Study termination
LCM (lymphocytic choriomeningitis virus)	Study termination
ELISA	
MHV (mouse hepatitis virus)	Study termination

During the 2-year studies, 15 $B6C3F_1$ mice per sex were maintained with the study animals to serve as sentinel animals. Blood was drawn from five mice of each sex at 6, 12, and 18 months following study initiation. Five randomly selected control animals of each sex were bled at study termination (24 months). Blood collected from each animal was allowed to clot, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates, Inc. (Bethesda, MD) for determination of antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
PVM	6 and 12 months
Reovirus 3	6 and 12 months
GDVII	6 months
Polyoma virus	6, 12, 18, and 24 months
Sendai	6 and 12 months
MVM	6, 12, 18, and 24 months
Ectromelia virus	6 and 12 months
K (papovavirus)	24 months
Complement Fixation	
Mouse adenoma virus	6 and 12 months
LCM	6, 12, 18, and 24 months

Method of Analysis (continued)	Time of Analysis
ELISA	
PVM	18 and 24 months
Reovirus 3	18 and 24 months
GDVII	18 and 24 months
MHV	6, 12, 18, and 24 months
Mouse adenoma virus	18 and 24 months
Ectromelia virus	18 and 24 months
Sendai	18 and 24 months
Mycoplasma pulmonis	6, 12, 18, and 24 months
Mycoplasma arthritidis	18 and 24 months
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	18 and 24 months

TABLE K1
Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Feed Studies of C.I. Pigment Red 3

	Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-Week Studies			
Rats	13 weeks	10/10	Sendai
Mice	13 weeks	4/10	Sendai
2-Year Studies			
Rats	6 months	0/10	None positive
	12 months	0/10	None positive
	18 months	0/9	None positive
	24 months	0/10	None positive
Mice	6 months	0/9	None positive
	12 months	0/8	None positive
	18 months	0/10	None positive
	24 months	0/10	None positive

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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichloroethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	*L*-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	Telone II® (1,3-Dichloropropene)
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four Rat Strains)

TR No.	CHEMICAL
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3
336	Penicillin VK
337	Nitrofurazone

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TR No.	CHEMICAL
338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	*a*-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3'-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
386	Tetranitromethane
387	Amphetamine Sulfate
389	Sodium Azide
390	3,3'-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
393	Sodium Fluoride
395	Probenecid
396	Monochloroacetic Acid
399	Titanocene Dichloride
405	C.I. Acid Red 114
415	Polysorbate 80

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