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TOXICOLOGY AND CARCINOGENESIS STUDIES OF C.I. PIGMENT RED 23 (CAS NO. 6471-49-4) IN F344 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.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES

OF C.I. PIGMENT RED 23

(CAS NO. 6471-49-4)

IN F344 RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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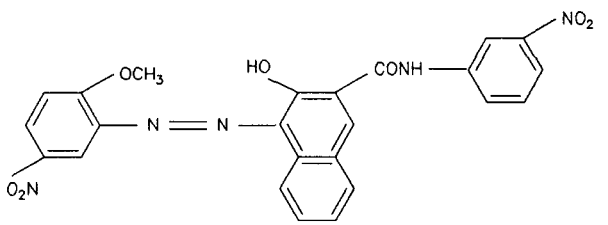
ABSTRACT



C.I. PIGMENT RED 23

CAS No. 6471-49-4

Chemical Formula: $C_{24}H_{17}N_5O_7$ Molecular Weight: 487.46

Synonyms: 2-Naphthalenecarboxamide; 3-hydroxy-4-((2-methoxy-5-nitrophenyl)azo)-N-(3-nitrophenyl); 3-hydroxy-4-((2-methoxy-5-nitrophenyl)azo)-3′-2-naphthanilide; Alkali Resistant Red Dark; Calcotone Red 3B; Carnation Red Toner B; CI 12355; Congo Red R-138; Fenalac Red FKB Extra; Malta Red X2284; Naphthol Red B; Naphthol Red T Toner 35-6001; Naphthol Red Deep 10459; Pigment Red BH; Rubescence Red MT-21; Sanyo Fast Red 10B; Sapona Red Lake RL-6280; Sengale Light Rubin RG; Textile Red WD-263

C.I. Pigment Red 23 is a bluish red commercial dye used as a coloring agent in paints, inks, rubber, plastics, lacquers, and paper. Toxicology and carcinogenicity studies were conducted by feeding groups of rats and mice diets containing C.I. Pigment Red 23 (greater than 96% pure) for 17 days, 13 weeks, and 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and in Chinese hamster ovary cells.

17-Day Studies

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 23 for 15 to 17 days. All rats and all female mice lived until the end of the studies. Two male mice in the 12,500 ppm dose group died accidentally. No other deaths occurred among male mice. Final mean body weights of rats and mice receiving C.I. Pigment Red 23 were within 10% of those of the controls. Feed consumption by exposed animals was similar to that of the controls. Hematocrit value, hemoglobin concentration, and erythrocyte count were decreased in the 50,000 and 100,000 ppm groups of rats. A corresponding decrease was not seen in mice. Absolute and relative organ weights of exposed animals were generally similar to those of the controls. No chemical-related gross lesions were seen in rats or mice.

13-Week Studies

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 23 for 13 weeks. All rats and mice lived until the end of the studies. Final mean body weights of rats and mice receiving C.I. Pigment Red 23 were within 10% of those of the controls. Feed consumption by exposed animals was similar to that of the controls.

In 50,000 ppm male rats, hematocrit and hemoglobin concentrations and erythrocyte counts were significantly less than those of the controls. In female rats receiving 3,000, 6,000 and 50,000 ppm C.I. Pigment Red 23, lymphocyte counts were significantly higher than the control values. Leukocyte counts in 3,000 ppm females were also significantly increased. Female mice in the 6,000 ppm dose group had significantly lower hematocrit and hemoglobin concentrations than did untreated females. Hematology parameters in exposed males were similar to those of untreated males.

There were no biologically significant differences in organ weights among dosed and control rats. Absolute and relative liver weights of male mice receiving 12,500 ppm C.I. Pigment Red 23 were significantly increased compared to those of the controls. Absolute and relative thymus weights for all but 12,500 ppm female mice were significantly lower than those of the controls. No chemical-related gross or histopathologic lesions occurred in rats or mice.

2-Year Studies

Survival, Body Weights, Feed Consumption, and Clinical Findings

Because levels of C.I. Pigment Red 23 as high as 50,000 or 100,000 ppm in the feed did not adversely affect survival and mean body weights in the 17-day and 13-week studies, nor cause any chemical-related lesions, doses of 0, 10,000, 25,000, or 50,000 ppm were selected for the 2-year studies. Doses higher than 50,000 ppm (5%) are not used in 2-year studies because they may lead to excessive dilution of nutrients in feed which in turn could produce nutritional deficiencies.

Survival rates of mid- and high-dose male and of high-dose female rats were significantly greater than those of the controls, due primarily to a chemical-related decreased incidence of mononuclear cell leukemia in these groups (survival in male rats: control, 22/50, low-dose, 29/50, mid-dose, 36/50, high-dose, 35/51; female rats: 29/50, 34/50, 33/50, 40/50). Survival of mice was not affected by the administration of C.I. Pigment Red 23, although survival of low-dose male mice was significantly lower than that of controls (male mice: 29/51, 17/53, 27/52, 30/51; female mice: 35/50, 34/49, 36/50, 35/49). The decreased survival in the low-dose males was associated with evidence of body trauma and secondary septicemia caused by fighting.

From approximately week 20 of the study, the group mean body weights of exposed female rats were consistently lower than those of controls; at week 101, mean body weights of mid-dose (25,000 ppm) and high-dose (50,000 ppm) females were 6% and 8% less, respectively. The final mean body weights of exposed male rats and male and female mice were similar to those of controls.

Feed consumption values for exposed male and female rats and mice were similar to those of the controls and there were no clinical signs associated with the administration of C.I. Pigment Red 23.

Pathology Findings

Renal tubule adenomas occurred in two high-dose male rats. Renal tubule carcinomas occurred in one high-dose male and one mid-dose male rat. No renal tubule neoplasms were seen in the controls. Renal tubule neoplasms are uncommon and have occurred in 8/499 (1.6%) untreated historical controls with a range of 0% to 6%. The residual halves of kidneys from control and high-dose males were step sectioned and examined; renal tubule adenomas were observed in a control male and in two additional high-dose males. Because of the low numbers of renal neoplasms, it is uncertain if they were related to chemical administration. The incidence of renal tubule hyperplasia (3/50, 6/48, 5/50, 8/50) and the mean severity of nephropathy were also slightly increased in high-dose male rats. The incidence of mononuclear cell leukemia occurred with a significant negative trend in exposed male and female rats.

No chemical-related increases in the incidence of neoplasms were observed in mice of either sex. There was a chemical-related increase in the incidence of hyperplasia (male mice: 0/49, 1/48, 1/50, 7/48; female

mice: 6/49, 14/49, 43/50, 47/49) and hyperkeratosis of the forestomach epithelium attributed to chemical administration.

Genetic Toxicology

C.I. Pigment Red 23 was mutagenic in *Salmonella typhimurium* strains TA100, TA1537, and TA98 with and without exogenous metabolic activation (S9), but it was not mutagenic in strain TA1535. C.I. Pigment Red 23 induced sister chromatid exchanges in Chinese hamster ovary cells in the absence of S9, but not with S9 activation. The pigment was negative for the induction of chromosomal aberrations in Chinese hamster ovary cells both in the presence and absence of S9.

Conclusions

Under the conditions of these 2-year feed studies, there was *equivocal evidence of carcinogenic activity** of C.I. Pigment Red 23 in male F344 rats as evidenced by a marginally increased incidence of renal tubule cell neoplasms. There was *no evidence of carcinogenic activity* of C.I. Pigment Red 23 in female F344 rats fed diets containing 10,000, 25,000, or 50,000 ppm. Mononuclear cell leukemia occurred with a decreased incidence in male and female rats receiving C.I. Pigment Red 23. There was *no evidence of carcinogenic activity* of C.I. Pigment Red 23 in male and female $B6C3F_1$ mice fed diets containing 10,000, 25,000 or 50,000 ppm.

The severity of kidney nephropathy was increased in exposed male rats. In mice, C.I. Pigment Red 23 caused an increase in hyperkeratosis and epithelial hyperplasia of the forestomach.

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* Explanation of Levels of Evidence of Carcinogenic Activity appears on page 9. A summary of peer review comments and public discussion on this Technical Report appear on page 11.

Summary of the 2-Year Carcinogenesis and the Genetic Toxicology Studies of C.I. Pigment Red 23

	Male F344 Rats	Female F344 Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 10,000, 25,000, or 50,000 ppm in feed	0, 10,000, 25,000, or 50,000 ppm in feed	0, 10,000, 25,000, or 50,000 ppm in feed	0, 10,000, 25,000, or 50,000 ppm in feed
Body weights	Dosed groups similar to controls	Dosed groups slightly lower than controls	Dosed groups similar to controls	Dosed groups similar to controls
2-Year survival rates	22/50, 29/50, 36/50, 35/51	29/50, 34/50, 33/50, 40/50	29/51, 17/53, 27/52, 30/51	35/50, 34/49, 36/50, 35/49
Nonneoplastic effects	Kidney: nephropathy (severity grades: 2.5, 2.8, 2.8, 2.9)	None	Forestomach: epithelial hyperplasia (0/49, 1/48, 1/50, 7/48); epithelial hyperkeratosis (0/49, 1/48, 3/50, 5/48)	Forestomach: epithelial hyperplasia (6/49, 14/49, 43/50, 47/49) epithelial hyperkeratosis (2/49, 1,49, 3/50, 18/49)
Neoplastic effects	None	None	None	None
Uncertain findings	Renal tubule cell adenoma or carcinoma: 0/50, 0/48, 1/50 3/50 Mononuclear cell leukemia: 28/50, 22/50, 10/50, 4/50	Mononuclear cell leukemia: 14/50, 7/50 3/50, 3/50	None	None
Level of evidence of carcinogenic activity	Equivocal evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutation	Positive with and without S9 in strains TA98, TA100, and TA1537 Negative with and without S9 strain TA1535			
Sister chromatid exchanges				
Chinese hamster ovary cells *in vitro*:	Positive without S9; negative with 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 cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the technical report 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 five categories 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 is demonstrated by 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 for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration 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 incidence 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.

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the NTP draft Technical Report on C.I. Pigment Red 23 on March 11, 1991, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, panel members have five major responsibilities 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 carcinogenicity activity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS

On March 11, 1991, the draft Technical Report on the toxicology and carcinogenesis studies of C.I. Pigment Red 23 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. K.M. Abdo, NIEHS, introduced the toxicology and carcinogenesis studies of C.I. Pigment Red 23 by discussing uses of the pigment, experimental design of the studies, survival and body weight effects on rodents in the study, and neoplasms in male rats and nonneoplastic lesions in male and female rats and mice. The proposed conclusions were *equivocal evidence of carcinogenic activity* of C.I. Pigment Red 23 for male F344 rats and *no evidence of carcinogenic activity* for female F344 rats or for male and female $B6C3F_1$ mice.

Because of the low numbers of renal neoplasms observed in this study in male rats, it was uncertain if the neoplasms were related to chemical exposure. For this reason, step sections of all kidneys from control and high-dose male rats were evaluated to further characterize the extent of these neoplasms. Step sections of kidneys from female rats were also evaluated.

Dr. Bailey, a principal reviewer, agreed with the proposed conclusions. He noted that one company supplied the lot of pigment used during the 17-day, 13-week, and initial part of the 2-year studies, while a second company supplied the lot used in the final part of the 2-year studies. Impurities were present in one lot, but not the other. Dr. Abdo said C.I. Pigment Red 23 was ordered from the second supplier when the first manufacturer discontinued production of the chemical.

Dr. Zeise, the second principal reviewer, agreed in principle with the proposed conclusions; however, she asked if the analysis of step sections from the kidney might affect the interpretation of the results.

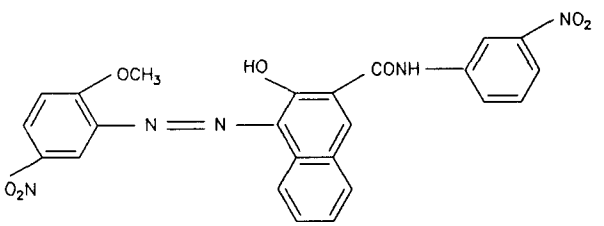
Dr. J.K. Haseman, NIEHS, said the P values obtained after step sectioning were less significant than one might have expected because there were almost twice as many high-dose male survivors compared to survivors in the control group. Dr. Zeise also noted that three high-dose female rats had astrocytomas; this neoplasm is uncommon and the incidence in the present studies falls outside the range of laboratory and overall historical control values. Dr. G. A. Boorman, NIEHS, said that although the number of astrocytomas reported in these studies appeared unusual, astrocytomas and other glial cell neoplasms are combined for analysis. The occurrence of other glial cell neoplasms in the control group negated the significance of the astrocytomas.

Dr. Klaassen, the third principal reviewer, agreed with the proposed conclusions, although he felt more emphasis could have been given to the possible anti-carcinogenic effects of C.I. Pigment Red 23 in rats. He noted the marked decreased incidence of mononuclear cell leukemia and increased survival values in exposed groups of each sex compared with the control group. Dr. R. A. Griesemer, NIEHS, said that the NTP alerts the National Cancer Institute when a chemical appears to have a direct effect in the inhibition of cancer formation.

The NTP generally limits the high dose in feed studies to a level of 5% in the diet. Dr. Zeise took exception to a statement in the present studies which said that doses greater than 5% could have led to dietary deficiencies as a result of excessive dilution of essential nutrients in the dosed feed; she commented that dietary restriction studies indicated otherwise.

Dr. Bailey moved that the Technical Report on C.I. Pigment Red 23 be accepted with the revisions discussed and the conclusions as written for male rats, *equivocal evidence of carcinogenic activity*, and for female rats and male and female mice, *no evidence of carcinogenic activity*. Dr. Zeise seconded the motion, which was accepted unanimously with nine votes. (Dr. McKnight was not present for the vote.)

INTRODUCTION



C.I. PIGMENT RED 23

CAS No. 6471-49-4

Chemical Formula: $C_{24}H_{17}N_5O_7$ Molecular Weight: 487.46

Synonyms: 2-Naphthalenecarboxamide; 3-hydroxy-4-((2-methoxy-5-nitrophenyl)azo)-N-(3-nitrophenyl); 3-hydroxy-4-((2-methoxy-5-nitrophenyl)azo)-3′-2-naphthanilide; Alkali Resistant Red Dark; Calcotone Red 3B; Carnation Red Toner B; CI 12355; Congo Red R-138; Fenalac Red FKB Extra; Malta Red X2284; Naphthol Red B; Naphthol Red T Toner 35-6001; Naphthol Red Deep 10459; Pigment Red BH; Rubescence Red MT-21; Sanyo Fast Red 10B; Sapona Red Lake RL-6280; Sengale Light Rubin RG; Textile Red WD-263

CHEMICAL AND PHYSICAL PROPERTIES

C.I. Pigment Red 23 is a bluish red commercial dye. It is insoluble in water, poorly soluble in ethanol or xylene, and highly soluble in 5% sodium carbonate solution or in oleic acid (*Colour Index*, 1971). This dye is produced by coupling 5-nitro-2-methoxyaniline with naphthol (*Kirk-Othmer*, 1978).

USE AND HUMAN EXPOSURE

In the United States, the production of C.I. Pigment Red 23 in 1984 was estimated at 47,700 kg (USITC, 1984). It is used in coloring paints, printing inks, linoleum, and as a coloring agent for textile printing, rubber, plastics, alkyl resin enamels, lacquers, emulsion paints, and paper. Although it has been reported that naphthol red pigments similar to C.I. Pigment Red 23 are used in inks in the packaging wrappers of foods, soaps, fertilizers, pharmaceuticals and chemicals, no specific mention of this pigment was made (*Colour Index*, 1971).

During the National Occupational Exposure Survey conducted from 1981 to 1983, the National Institute for Occupational Safety and Health found more than 15,000 workers in seven industries exposed to C.I. Pigment Red 23 (NIOSH, 1991). Workers in three industries (chemicals and allied products, paper and allied products, and rubber and plastic products) accounted for more than 80 percent of the workers exposed.

METABOLISM AND DISPOSITION

In male F344 rats (7 to 8 weeks old) given a single oral dose of 5.3 mg C.I. Pigment Red 23/kg body weight, nearly all of the pigment (93% ± 16%) was

recovered in the feces 48 hours after administration. No pigment was found in plasma, whole blood, liver, kidney, or lungs of treated animals at any time period even after administering 10 times this dose (El Dareer *et al.*, 1984). No other information on the metabolism and disposition of C.I. Pigment Red 23 was found in the literature.

TOXICITY

No data on the toxicity of C.I. Pigment Red 23 in humans or animals were found in the literature.

C.I. Pigment Red 23 is structurally similar to the carcinogenic phenylazonaphthols such as Citrus Red No. 2 and Oil Orange SS (IARC, 1975). Citrus Red No. 2 administered in feed to rats and mice produced increased incidences of hyperplasia and lesions of the urinary bladder in both species. Oil Orange SS produced increased incidences of intestinal lesions in rats and mice when given in feed and urinary bladder lesions in mice when implanted in the bladder. Reductive cleavage of the azo linkage of C.I. Pigment Red 3 would yield a single-ring aromatic compound related to the carcinogen 5-nitro-*o*-anisidine (NCI, 1978b). When administered in feed, this compound caused increased incidences of Zymbal's gland neoplasms, integumentary carcinomas, and clitoral gland neoplasms in rats. In mice, it caused increased incidences of hepatocellular carcinomas. Azo compounds may be reduced by digestive tract microflora or by liver enzymes to produce aromatic amine derivatives (Lynn *et al.*, 1980; Cerniglia *et al.*, 1982; Brown and Dietrich, 1983; Nony *et al.*, 1983; Bos *et al.*, 1986).

GENETIC TOXICITY

The genotoxicity data available for C.I. Pigment Red 23 are limited to results of the NTP tests presented in Appendix E of this report. These tests showed induction of gene mutations in three strains of *Salmonella typhimurium*, with and without S9 metabolic activation (Mortelmans *et al.*, 1986), and induction of sister chromatid exchanges in Chinese hamster ovary cells in the absence, but not in the presence, of induced S9. No metabolites for C.I. Pigment Red 23 were documented in the Hazardous Substances Data Base, but analysis of the chemical structure of the compound indicates that cleavage of the amide bond would generate 3-nitroaniline, and azo reduction of C.I. Pigment Red 23 would yield 2-methoxy-5-nitrobenzenamine. These putative metabolites showed varied mutagenicity in *S. typhimurium*. Some laboratories reported a requirement for S9 activation (Garner and Nutman, 1977; Melnikow *et al.*, 1981; Thompson *et al.*, 1983) or flavin mononucleotide activation (Dellarco and Prival, 1989), while others noted mutagenic activity independent of activation (Chiu *et al.*, 1978; Haworth *et al.*, 1983; Shahin, 1985; Shimizu and Yano, 1986). 2-Methoxy-5-nitrobenzenamine was also tested for induction of sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster*. Results varied when the chemical was administered by injection to adult males. In one trial, it was negative, but in a second trial, results were inconclusive (Valencia *et al.*, 1985). Adult feeding experiments were negative (Valencia *et al.*, 1985), and results of a larval feeding experiment were equivocal (Zimmering *et al.*, 1989).

Genotoxicity information on structural analogues of C.I. Pigment Red 23 is limited. C.I. Pigment Red 3 and C.I. Alizarin Yellow were mutagenic in *S. typhimurium* (Brown *et al.*, 1978; Mortelmans *et al.*, 1986), while C.I. Pigment Yellow 74 was not mutagenic in *S. typhimurium* (Cameron *et al.*, 1987; Zeiger *et al.*, 1988) or mouse L5178Y lymphoma cells (Cameron *et al.*, 1987).

In conclusion, the available data indicate that C.I. Pigment Red 23 is mutagenic. This is consistent with the presence of nitro groups and the generation of an arylamino group by reduction or hydrolysis, which are considered structural indicators of potential mutagenicity by Ashby *et al.*, 1989.

STUDY RATIONALE

C.I. Pigment Red 23 was nominated by the National Cancer Institute for testing because of the lack of information on the toxicity and carcinogenicity of this pigment and because of its structural resemblance to known phenylazonaphthol carcinogens such as Citrus Red No. 2 and Oil Orange SS. Additionally, the potential for human exposure to C.I. Pigment Red 23 is high because of the pigment's wide variety of uses. The dosed feed method of administration was selected to ensure systemic exposure.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF C.I. PIGMENT RED 23

The commercial dye, C.I. Pigment Red 23, was obtained in two lots, one from American Cyanamid Company (Wayne, NJ) (Lot G1723) and the second from Sun Chemical Company (New York, NY) (Lot UB2158). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix H). Lot G1723 was used in dose preparations for the 17-day and 13-week studies and during the initial part of the 2-year studies. Lot UB2158 was used to complete the 2-year studies.

The dye, a bluish red powder, was identified as C.I. Pigment Red 23 by infrared and nuclear magnetic resonance spectroscopy (Appendix H). Purity was evaluated by elemental analyses, water analysis, titration of phenol group, spark source mass spectroscopy, thin layer chromatography, and high performance liquid chromatography (HPLC). Purity was estimated at greater than 96% for both lots. Three impurities, all with the naphthol moiety, were identified by mass spectrometry. They were 3-hydroxy-4-[(2-methoxy-5-nitrosophenyl)-azo]-N-(3-aminophenyl)-2-naphthalene carboxamide; 3-hydroxy-N-(3-aminophenyl)-2-naphthalene carboxamide; and 3-hydroxy-4-[(2-methoxy-5-nitrophenyl)-azo]-N-phenyl-2-naphthalene carboxamide. The impurities in the sample were not quantitated because reference standards were not available.

The chemical dye was found to be stable in bulk form when stored protected from light for 2 weeks at temperatures up to 60° C. Based on the stability study results, the bulk dye was stored by the study laboratory at room temperature and protected from light. During the course of the studies, the study laboratory periodically monitored the stability of the bulk dye by HPLC and visible spectroscopy. No degradation of the dye was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

Dose formulations were prepared by forming a premix of NIH-07 Rat and Mouse Ration, as meal, with the appropriate amount of C.I. Pigment Red 23, and then blending with additional feed to obtain the desired dose level (Table H1). Composition of the NIH-07 Rat and Mouse Ration is presented in Appendix J. Homogeneity of the dose formulations was confirmed. Stability study results from the analytical chemistry laboratory indicated that dosed feed formulations of C.I. Pigment Red 23 were stable for at least 2 weeks at temperatures up to 45° C when stored in the dark. All dosed feed formulations were color coded, sealed in double-thickness plastic bags, and stored in the dark at 5° C prior to use. Once in use, the dosed feed formulations were stored at room temperature protected from light for not more than 14 days.

The dose formulations were analyzed periodically by visible spectroscopy at the study laboratory and at the analytical chemistry laboratory (Appendix H). Problems with the analytical method experienced during the 13-week studies were ultimately resolved after modifying the extraction solvent. Approximately 96% of the dose formulations sampled for analysis were within 10% of the target concentrations. Periodically, the dose formulations were sent for referee analyses by the analytical chemistry laboratory. The results from the study laboratory and from the referee analytical chemistry laboratory were generally in good agreement, with all value differences less than 13% (Table H3).

17-DAY STUDIES

Male and female F344 rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Center (Frederick, MD) and were observed for 19 days prior to the study. The average age of both species was 55 days when treatment was initiated. Before being

placed in a dose group, animals of each sex were weighed and assigned to a weight class, then randomly placed five animals per cage. After randomization, six rats were reassigned to obtain a more even weight distribution. Groups of five animals of each sex received 0, 6,000, 12,500, 25,000, 50,000, or 100,000 ppm C.I. Pigment Red 23 in feed for 15 to 17 consecutive days. Feed and water were supplied *ad libitum*. Animals were observed for clinical signs of toxicity twice daily through day 14, once on day 15, and at the end of the study. Animals were observed twice daily for mortality. Feed consumption for each species was measured daily by cage and calculated per animal. Details of the study design and animal maintenance are summarized in Table 1.

Body weights were measured at the initiation of treatment, on day 8 and on day 15. Hematology and clinical chemistry parameters were measured for all animals, except for mice in the 12,500 ppm group. Blood samples from the inferior vena cava of animals from the 12,500 ppm group were used for serological screening. Complete necropsies were performed on all animals at the end of the study. Organs weighed at necropsy included the brain, liver, heart, lung, right kidney, thymus, and right testis (males). All control and high-dose animals and two 12,500 ppm mice killed accidentally received complete histopathologic examinations. Table 1 lists those tissues and organs examined microscopically.

13-WEEK STUDIES

Based on findings in the 17-day studies, the 13-week studies were conducted to evaluate cumulative toxic effects of repeated dietary exposure to C.I. Pigment Red 23 and to determine dose levels for the 2-year studies. The strain and source of the animals were the same as the 17-day studies. Animals were randomly assigned by weight class to treatment groups and were caged as described for the 17-day studies. Rats were observed for 20 days prior to study initiation and were 56 days old at study start; mice were observed for 19 days before study initiation and were 62 days old when the study began.

Groups of 10 F344 rats and 10 B6C3F$_1$ mice of each sex received 0, 3,000, 6,000, 12,500, 25,000, or 50,000 ppm C.I. Pigment Red 23 in feed for 90 to 94 days. Feed and water were available *ad libitum*. Animals were observed twice daily for mortality and weekly and at sacrifice for clinical findings. Feed consumption was measured as in the 17-day studies; some animals received dosed feed until day 95, but measurement of group feed consumption ended on day 93. Details of the study design and animal maintenance are summarized in Table 1.

Body weights were measured weekly, and at the end of the studies. Complete necropsies were performed on all animals. The average age at necropsy was 150 days for rats and 156 days for mice. Organ weights were measured as in the 17-day study. Blood samples for measuring hematology and clinical chemistry parameters were drawn from the inferior vena cava (rats) or the heart (mice) prior to sacrifice. Complete histopathologic examinations were performed on all animals. Table 1 lists the tissues and organs examined microscopically.

2-YEAR STUDIES

Study Design

All animals were administered C.I. Pigment Red 23 in dosed feed for 103 weeks. Both species were separated by sex, weighed and grouped by weight class, randomly assigned to cages, and cages were randomly assigned to treatment groups, as previously described. Sixty animals of each species and sex received 0, 10,000, 25,000, or 50,000 ppm C.I. Pigment Red 23 in feed. Ten rats and mice of each sex were predesignated for interim evaluation at 15 months. Animals that died prior to the scheduled interim evaluation were examined and included with the 2-year core group evaluation.

Source and Specifications of Animals

Rats and mice were obtained from the same source as for the 17-day and 13-week studies. Rats were 5 weeks old and mice were 6 weeks old when received. Animals were observed for 20 days prior to treatment. During the quarantine period, 10 animals were randomly selected for examination for evidence of disease, for parasites, and for viral infections. Rats were 56 days old and mice were 63 days old when the study began. Fifteen male and female rats and mice not selected for treatment were monitored throughout the study according to the protocols of the NTP Sentinel Animal Program (Appendix K).

Animal Maintenance

Rats were housed five per cage throughout the study period. Cages were rotated vertically once every two weeks. Mice were housed five per cage from 13 December 1982 to 7 June 1984 (males) and 8 June 1984 (females), after which time they were housed individually because of excessive fighting. Feed and water were available *ad libitum*. Additional details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings for rats were noted and recorded during body weight measurements and at sacrifice; clinical findings for mice were recorded once every 4 weeks. Body weights for both species were recorded weekly for the first 13 weeks, and then every four weeks until the end of the study; body weights were also recorded at the end of the study. Feed consumption was recorded daily per cage for mice for 1 week every 4 weeks and calculated per animal.

At 15 months, 9 or 10 rats and 7 to 10 mice of each sex from each dose group were killed for interim evaluation. The parameters evaluated included body weights, organ weights, hematology, clinical chemistry, and gross and microscopic pathology. Blood samples for measuring hematology and clinical chemistry parameters were drawn from the inferior vena cava (rats) or the heart (mice). Analyses performed and tissues examined are listed in Table 1.

Complete necropsies were performed on all animals. During necropsy all organs and tissues were examined for grossly visible lesions. Tissues for microscopic examination were preserved in 10% neutral buffered formalin and routinely processed for microscopic examination (embedded in paraffin, sectioned at 4-5 μm, and stained with hematoxylin and eosin). Complete histopathologic evaluation was performed on animals from the control and high-dose group, on selected tissues, and on target organs and gross lesions from low- and mid-dose animals. Tissues examined microscopically are listed in Table 1.

Upon completion of the microscopic evaluation by the laboratory pathologist, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The microscope slides, individual animal necropsy records, and pathology tables were evaluated by an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slide and tissue counts were verified, and histotechnique was evaluated. A quality assessment pathologist reviewed all neoplastic diagnoses in all animals, and all diagnoses (neoplastic and nonneoplastic) in a random 10% of the animals from each control and high-dose group for accuracy and consistency of lesion diagnosis. In addition, the forestomachs of all male and female mice were reviewed for potential chemical-related lesions.

The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chair, who reviewed the slides of tissues with treatment-related lesions and of any other tissues for which there was disagreement in diagnosis between the laboratory and quality assessment pathologist. Representative histopathology slides of tissues with treatment-related lesions and examples of disagreements in diagnosis between the laboratory and quality assessment pathologist were shown to the PWG. The PWG included the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without knowledge of dose groups or previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the diagnosis was changed to reflect the opinion of the PWG. This procedure has been described, in part by Maronpot and Boorman (1982) and Boorman *et al.* (1985). The final pathology data represent a consensus of contractor pathologists and the NTP PWG. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type were 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 form of graphs. Animals were censored from the survival analyses at the time they were found dead from other than natural causes or were found to be missing; animals dying from natural causes were not censored. Statistical analysis for a possible dose-related effect on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analysis are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A5, B1, B5, C1, C4, D1, and D4 are given as the number of animals bearing such lesions at a specific anatomic site and number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and nonneoplastic lesions are given as the ratio of the number of affected animals to the number of animals with the site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Neoplasm Incidences

The majority of neoplasms in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was the logistic regression analysis, which assumed that the diagnosed neoplasms were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, neoplasm 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 exposed 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 neoplasms are incidental, this comparison of the time-specific neoplasm prevalences also provides a comparison of the time-specific neoplasm 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 neoplasms, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of neoplasm-bearing animals.

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of neoplasm 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).

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluation, the Fisher exact test was used, a procedure based on the overall proportion of affected animals.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology and clinical chemistry data, which typically have skewed distributions, were analyzed using nonparametric multiple comparison methods of Dunn

(1964) and Shirley (1977). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of 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).

For the 15-month interim evaluations in which each dose group was compared with the controls, Wilcoxon's rank sum test (Hollander and Wolfe, 1973) was used to evaluate organ weight, hematology, and clinical chemistry data. Average nephropathy severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

Historical Control Data

Although the concurrent control group is the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of neoplasm incidence. Neoplasm incidences from the NTP historical control database for 2-year studies (Haseman *et al.*, 1984, 1985) are included in the NTP report for neoplasms appearing to show compound-related effects.

Quality Assurance Methods

The 13-week and 2-year studies were conducted in compliance with FDA Good Laboratory Practice Regulations (21 CFR Part 58). In addition, as study records were submitted to the NTP Archives, they were audited retrospectively 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 NTP staff so that all findings had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of C.I. Pigment Red 23 was assessed by testing the ability of the chemical to induce mutations in *Salmonella typhimurium* (strains TA98, TA100, TA1535, and TA1537), and sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells. The protocols for these studies and tabular presentations of the results are given in Appendix E.

The genetic toxicity studies of C.I. Pigment Red 23 are part of a larger effort by the NTP to develop a database that would permit the evaluation of the evaluation of carcinogenicity in experimental animals from the structure of the chemical and its responses in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were developed to study mechanisms of chemically induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

Of the four *in vitro* tests evaluated by the NTP to date (mutagenicity in *Salmonella*, mutagenicity in mouse lymphoma cells, chromosomal aberrations in Chinese hamster ovary cells or sister chromatid exchanges in Chinese hamster ovary cells), there is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *S. typhimurium*, and carcinogenicity in rats and mice or at multiple tissue sites (Ashby and Tennant, 1991). The other *in vitro* tests do not correlate well with carcinogenicity in rodents (Tennant *et al.*, 1987; Zeiger *et al.*, 1990). Mutagenicity in *S. typhimurium* was the most predictive for rodent carcinogenicity (89% of the mutagens were carcinogens in rats and/or mice), while mutations in mouse lymphoma cells or chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary cells were less predictive of carcinogenicity; 63% of chemicals inducing mutations in mouse lymphoma cells, 73% of chemicals inducing chromosomal aberrations and 64% of chemicals inducing sister chromatid exchanges were carcinogenic in rodents. Moreover, no battery of tests that included the *S. typhimurium* test improved the predictability of the *S. typhimurium* test alone. The predictivity of a positive response in bone marrow chromosome aberration or micronucleus tests is not yet defined. The reader is referred to the articles cited above for details regarding the correlation of structural alerts (or absence thereof), mutagenicity, and carcinogenicity results of 301 chemicals in the NTP database.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of C.I. Pigment Red 23

17-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory		
Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)
Strain and Species		
F344 rats $B6C3F_1$ mice	F344 rats $B6C3F_1$ mice	F344 rats $B6C3F_1$ mice
Animal Source		
Frederick Cancer Research Center (Frederick, MD)	Frederick Cancer Research Center (Frederick, MD)	Frederick Cancer Research Center (Frederick, MD)
Time Held Before Study		
19 days	Rats: 20 days Mice: 19 days	20 days
Average Age When Placed on Study		
55 days	Rats: 56 days Mice: 62 days	Rats: 56 days Mice: 63 days
Date of First Dose		
Rats: 15 June 1981 Mice: 22 June 1981	Rats: 14 December 1981 Mice: 21 December 1981	Rats: 10 January 1983 Mice: 13 December 1982
Date of Last Dose		
Rats: 28-30 June 1981 Mice: 6-8 July 1981	Rats: 14-17 March 1982 Mice: 23-26 March 1982	Rats: 31 December 1984 Mice: 3 December 1984
Duration of Dosing		
15 to 17 consecutive days	Rats: 90 to 93 consecutive days Mice: 91 to 94 consecutive days	Rats: 720 consecutive days Mice: 720 consecutive days
Average Age at Necropsy		
70 days	Rats: 150 days Mice: 156 days	Rats: 789 days (terminal sacrifice) 514 days (15-month interim) Mice: 790 days (terminal sacrifice) 530 days (15-month interim)
Method of Sacrifice		
Thoracotomy	Thoracotomy	Thoracotomy
Necropsy Dates		
Rats: 29 June to 1 July 1981 Mice: 6 to 8 July 1981	Rats: 16 to 19 March 1982 Mice: 23 to 26 March 1982	Rats: 8 to 15 January 1985 (10 to 13 April 1984, 15-month interim) Mice: 5 to 12 December 1984 (20 to 27 March 1984, 15-month interim)
Size of Study Groups		
5 males and 5 females	10 males and 10 females	60 males and 60 females

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of C.I. Pigment Red 23 (continued)

17-Day Studies	13-Week Studies	2-Year Studies
Method of Animal Distribution Animals distributed to weight classes in 5 to 10 g intervals then randomized by cage to test and control groups and position in racks.	Same as 17-day studies	Same as 17-day studies
Animals per Cage 5	5	Rats were housed five per cage throughout the study; mice were housed five per cage from 13 December 1982 to 7 June 1984 (males) and 8 June 1984 (females), after which time they were housed individually because of excessive fighting.
Method of Animal Identification Ear mark	Ear mark	Ear mark and/or toe clip
Diet NIH-07 Rat and Mouse Ration, meal (Zeigler Bros., Inc., Gardners, PA), available *ad libitum*	Same as 17-day studies	Same as 17-day studies
Water Tap water (Birmingham Water Works) in glass water bottles with stainless steel sippers (Edstrom Automatic Watering Systems, Waterford, WI), available *ad libitum*	Same as 17-day studies	Same as 17-day studies
Cages Polycarbonate, solid bottom (Lab Products Inc., Garfield, NJ)	Same as 17-day studies	Same as 17-day studies
Bedding Heat-treated hardwood (BetaChips) (Northeastern Products Corp., Warrensburg, NY)	Same as 17-day studies	Same as 17-day studies
Cage Filters Reemay spun-boded polyester fiber filters (Snow Filtration, Cincinnati, OH)	Same as 17-day studies	Same as 17-day studies

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of C.I. Pigment Red 23 (continued)

17-Day Studies	13-Week Studies	2-Year Studies
Animal Room Environment		
Rats: Temperature: 22.2°-23.3° C; Relative humidity: 47%-55% Fluorescent light: 12 hours/day Room air changes: minimum 15 changes/hour Mice: Temperature: 21.7°-23.3° C Relative humidity: 47%-61% Fluorescent light: 12 hours/day Room air changes: minimum 15 changes/hour	Temperature: 20.0°-24.4° C Relative humidity: 38%-69% Fluorescent light: 12 hours/day Room air changes: minimum 15 changes/hour	Rats: Temperature: 17.8°-25.6° C Relative humidity: 15%-85% Fluorescent light: 12 hours/day Room air changes: minimum 15 changes/hour Mice: Temperature: 17.2°-26.7° C Relative humidity: 22%-84% Fluorescent light: 12 hours/day Room air changes: minimum 15 changes/hour
Doses		
0, 6,000, 12,500, 25,000, 50,000, or 100,000 ppm C.I. Pigment Red 23 in feed	0, 3,000, 6,000, 12,500, 25,000, or 50,000 ppm C.I. Pigment Red 23 in feed	0, 10,000, 25,000, or 50,000 ppm C.I. Pigment Red 23 in feed
Type and Frequency of Observation		
Observed twice/day; body weight initially, Day 8, Day 15, and at sacrifice; feed consumption daily/cage (calculated per animal); clinical observation twice daily through day 14, once on day 15, and at sacrifice. Blood was collected from the inferior vena cava (rats) and from cardiac puncture (mice).	Observed twice/day; body weight once/week, and at sacrifice; feed consumption daily/cage (calculated per animal); clinical observation once/week and at sacrifice. Blood was collected as in the 17-day studies.	Rats: Observed twice/day; body weight once/week for 13 weeks, once/month thereafter and at sacrifice; clinical observations at each weight check and at terminal sacrifice Mice: Observed twice/day; body weight once/week for 13 weeks, once/month thereafter and at sacrifice; clinical observations once/month; feed consumption measured daily/cage for one week out of 4 and calculated per animal
Necropsy		
Necropsy performed on all animals. Organ weights obtained at necropsy (brain, heart, liver, lung, right kidney, right testis, and thymus).	Necropsy performed on all animals. Organ weights measured were the same as in the 17-day studies.	Necropsy performed on all animals. 15-month interim sacrifice: organs weighed included brain, liver, and right kidney.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of C.I. Pigment Red 23 (continued)

17-Day Studies	13-Week Studies	2-Year Studies
Histopathology		
Complete histopathology on male and female control and high-dose (100,000 ppm) animals and on two mice in the 12,500 ppm dose group. The following organs were examined: adrenal gland, bone (femur including marrow), brain, clitoral gland (rats only), colon, epididymis, esophagus, gallbladder (mice only), gross lesions, heart, kidney, liver, lung (including mainstem bronchi), mammary gland, mandibular and mesenteric lymph nodes, nose (nasal cavity and turbinates), ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats only), prostate gland, salivary gland, seminal vesicles, skin, small intestine, spleen, stomach, testes, thigh muscle, thymus, thyroid gland, tissue masses, trachea, urinary bladder, and uterus. Selective examination was made on regional lymph nodes, spinal cord, eyes, and pharynx.	Complete histopathology on all male and female control and high-dose (50,000 ppm) animals included the same tissues and organs examined in the 17-day studies, with the exception of the epididymis.	Complete histopathology on all animals in control and 50,000 ppm dose groups. Tissues examined were the same as in the 17-day and 13-week studies, with the addition of target organs examined from animals in lower dose groups. Target organs examined included: ***15-month interim evaluation*** Rats: liver and gross lesions excluding red skin and hair; adrenal gland (females); and pituitary gland (females); Mice: lymphoid tissue of ileum (Peyer's patch); mandibular, mesenteric, and inguinal lymph nodes (other lymph tissue from other sites was substituted in some animals); and gross lesions excluding red hair. ***At study termination*** Rats (males and females): liver; spleen; thyroid gland; mammary gland; (females) clitoral gland, pancreas, pituitary gland, and uterus; Mice: stomach, small intestine, large intestine, lung, mesenteric lymph node, liver, and bone marrow (females only).
Clinical Pathology		
Clinical pathology studies conducted at the end of the study on both species and sexes for all dose levels, except 25,000 ppm mice. Rats: ***Hematology:*** hematocrit, hemoglobin, erythrocyte count, leukocyte count, differential leukocyte count, platelet count, reticulocyte count ***Clinical chemistry:*** albumin, albumin/globulin ratio, creatinine, blood urea nitrogen, total bilirubin, total protein, pH, sodium, potassium, calcium, chloride, inorganic phosphorus, alanine aminotransferase, aspartate aminotransferase, cholinesterase, lactate dehydrogenase Mice: ***Hematology:*** hematocrit, hemoglobin, erythrocyte count, leukocyte count, differential leukocyte count, platelet count, reticulocyte count ***Clinical chemistry:*** alanine aminotransferase, partial carbon dioxide, potassium, lactate dehydrogenase, pH, total bilirubin, sorbitol dehydrogenase.	Clinical pathology studies conducted at terminal sacrifice on both species and sexes at all dose levels. ***Hematology:*** hematocrit, hemoglobin, erythrocyte count, leukocyte count, differential leukocyte count, reticulocyte count, platelet count ***Clinical chemistry:*** Alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase (rats), sorbitol dehydrogenase (rats), total bilirubin (rats).	Clinical pathology studies conducted at 15-month interim evaluation on all species and sexes at all dose levels. ***Hematology:*** hematocrit, hemoglobin, erythrocyte count, leukocyte count, platelet count ***Clinical chemistry:*** total bilirubin.

RESULTS

RATS

17-Day Studies

All animals survived to the end of the studies. Differences in final mean body weight and in weight gain among treated and control animals were not statistically significant (Table 2). Final mean body weights of all dose groups were within 5% of those of the controls. Average feed consumption by dosed groups was similar to consumption by the control groups. The only change in hematology and clinical chemistry parameters attributed to chemical administration was a decreased erythrocyte count observed in all male dose groups and the two highest female dose groups, indicating a mild anemia. An associated increase in sodium concentration provides some evidence of hemoconcentration (dehydration) in high-dose animals; thus, the degree of anemia could have been more severe than indicated by the decreased erythrocyte counts (Table G1). No gross observations recorded at necropsy were indicative of chemical toxicity, nor did administration of the pigment in feed have a significant biological effect on organ weights at necropsy (Table F1).

TABLE 2
Survival and Mean Body Weights of Rats in the 17-Day Feed Studies of C.I. Pigment Red 23

Dose (ppm)	Survival[a]	Mean Body Weight (g)[b]			Final Weight Relative to Controls (%)	Feed Consumption[c]
		Initial	Final	Change		
Male						
0	5/5	167 ± 4	231 ± 6	64 ± 3		144
6,000	5/5	166 ± 7	234 ± 5	68 ± 5	101	130
12,500	5/5	166 ± 1	236 ± 3	70 ± 4	102	131
25,000	5/5	164 ± 6	234 ± 4	71 ± 6	101	136
50,000	5/5	166 ± 3	220 ± 3	54 ± 5	95	123
100,000	5/5	163 ± 6	223 ± 8	60 ± 2	97	122
Female						
0	5/5	130 ± 4	156 ± 2	26 ± 1		89
6,000	5/5	130 ± 3	157 ± 2	27 ± 2	101	89
12,500	5/5	129 ± 2	155 ± 3	25 ± 3	99	89
25,000	5/5	127 ± 2	155 ± 3	27 ± 2	99	90
50,000	5/5	130 ± 3	156 ± 2	25 ± 1	100	89
100,000	5/5	128 ± 1	153 ± 3	26 ± 3	98	89

[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the control group are not significant by Williams' or Dunnett's test.
[c] Grams per animal per week, based on average weekly consumption data per group per day for days 1 through 13.

13-Week Studies

All animals survived to the end of the studies. Differences in final mean body weight and in weight gain of exposed animals compared to those of the controls were not significant (Table 3). Average feed consumption by dosed groups was similar to consumption by the control groups (Table 4). There were no biologically significant differences in organ weights among exposed and control rats (Table F2).

In exposed male rats, hematocrit, hemoglobin concentration, and erythrocyte counts at the 50,000 ppm dose level were significantly less than those of the controls, indicating minimal anemia (Table G2). In female rats, the lymphocyte count at 3,000, 6,000, and 50,000 ppm and the leukocyte count at 3,000 ppm were significantly higher than those of the controls (Table G2). This mild increase in lymphocytes could be from antigenic stimulation secondary to a treatment-related inflammatory process or from physiologic leukocytosis (endogenous epinephrine release).

Feces, fur, and bedding of all treated animals were stained red from ingestion of C.I. Pigment Red 23. There were no chemical-related clinical signs of toxicity, no gross observations recorded at necropsy, and no significant histopathological observations.

Dose Selection Rationale: No mortality occurred in the 13-week studies and body weights were within 5% of those of the controls. Thus, for the 2-year studies, the dose levels administered to both rats and mice of each sex were 0, 10,000, 25,000, and 50,000 ppm. Doses higher than 50,000 ppm were not selected for the 2-year studies because higher levels would lead to excessive dilution of nutrients which could lead to nutritional deficiencies. The slight chemical-related changes in hematology and clinical chemistry parameters were not considered serious enough to warrant selection of lower doses.

TABLE 3
Survival and Mean Body Weights of Rats in the 13-Week Feed Studies of C.I. Pigment Red 23

Dose (ppm)	Survival[a]	Mean Body Weight (g)[b]			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	162 ± 7	353 ± 8	191 ± 5	
3,000	10/10	163 ± 6	360 ± 9	197 ± 5	102
6,000	10/10	157 ± 7	352 ± 11	196 ± 6	100
12,500	10/10	162 ± 8	348 ± 9	185 ± 4	99
25,000	10/10	164 ± 7	359 ± 10	196 ± 5	102
50,000	10/10	164 ± 6	360 ± 9	196 ± 6	102
Female					
0	10/10	130 ± 2	210 ± 3	81 ± 4	
3,000	10/10	129 ± 2	212 ± 4	83 ± 2	101
6,000	10/10	127 ± 2	210 ± 3	83 ± 3	100
12,500	10/10	129 ± 2	210 ± 3	81 ± 2	100
25,000	10/10	129 ± 2	214 ± 3	85 ± 2	102
50,000	10/10	128 ± 2	209 ± 5	81 ± 5	100

[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the control group are not significant by Williams' or Dunnett's test.

TABLE 4
Mean Feed Consumption by Rats in the 13-Week Feed Studies of C.I. Pigment Red 23[a]

Week on Study	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male						
1	80.1	85.4	88.2	84.6	78.8	84.3
2	83.5	80.6	77.0	79.4	75.5	83.3
3	67.2	71.7	66.4	66.2	65.0	65.0
4	64.3	61.9	61.5	60.7	59.4	63.9
5	57.6	59.8	51.0	31.9	59.8	59.3
6	58.1	56.6	57.4	58.7	57.5	58.7
7	26.0	53.7	50.8	54.1	54.8	52.8
8	53.7	52.1	52.7	54.8	47.5	51.4
9	44.1	47.6	43.6	48.2	44.3	44.9
10	49.4	50.1	49.7	49.5	47.7	49.0
11	45.7	45.5	43.2	44.1	44.5	45.8
12	49.4	47.0	45.2	45.3	43.6	46.0
13	37.1	40.9	42.3	45.5	44.8	17.2
Female						
1	86.3	86.9	82.0	80.9	93.1	79.6
2	79.9	77.2	72.5	75.7	75.2	77.0
3	66.0	63.6	61.8	31.8	67.1	65.0
4	63.3	63.7	61.5	63.3	64.1	64.5
5	63.8	60.8	55.2	61.4	67.5	67.0
6	64.2	61.1	58.1	61.2	63.5	41.1
7	52.9	55.2	47.1	62.2	59.3	59.3
8	53.1	58.4	55.8	62.8	58.6	56.9
9	56.7	55.8	61.2	53.2	57.6	50.2
10	58.9	52.0	57.5	57.1	58.7	56.4
11	48.9	55.5	52.5	50.4	51.6	46.5
12	53.4	64.9	57.9	58.9	54.5	54.7
13	50.4	48.6	48.5	51.9	51.0	54.4

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

2-Year Studies

Survival

Estimates of the probabilities of survival for male and female rats administered C.I. Pigment Red 23 and the untreated controls are presented in Table 5 and the Kaplan-Meier survival curves in Figure 1.

Survival rates of males in the mid- and high-dose group and females in the high-dose group were significantly greater than those of the controls. The greater survival of the exposed groups was due principally to the chemically related decreased incidence of mononuclear cell leukemia.

TABLE 5
Survival of Rats in the 2-Year Feed Studies of C.I. Pigment Red 23

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male				
Animals initially in study	60	60	60	60
Natural deaths	4	6	3	5
Moribund	24	15	11	11
15-month interim evaluation[a]	10	10	10	9
Animals surviving to study termination	22	29	36	35
Percent probability of survival at end of study[b]	44	58	72	69
Mean survival days[c]	630	644	661	655
Survival analysis[d]	P=0.011N	P=0.175N	P=0.005N	P=0.015N
Female				
Animals initially in study	60	60	60	60
Natural deaths	3	5	3	2
Moribund	18	11	14	8
15-month interim evaluation	10	10	10	10
Animals surviving to study termination	29	34	33	40
Percent probability of survival at end of study	59	69	67	80
Mean survival days	633	654	643	663
Survival analysis	P=0.043N	P=0.306N	P=0.547N	P=0.029N

[a] Censored from survival analyses
[b] Kaplan-Meier determinations. Survival rates adjusted for interim evaluations.
[c] Mean of all deaths (uncensored, censored, terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns. A negative trend or lower mortality in a dose group is indicated by N.

Body Weights, Feed Consumption, and Clinical Findings

At the end of the 15-month interim evaluation, the body weights of the mid- and high-dose female rats were significantly less than that of the controls (Table F3). Mean body weights of male rats were similar to that of the controls throughout the 2-year study; however, from week 20 to the end of the study, the mean body weights of mid- and high-dose females were consistently lower than that of the controls (Tables 6 and 7 and Figure 2). At week 102, the mean body weights of females in the mid- and high-dose groups were 6% and 8% lower, respectively. Feed consumption by exposed male and female rats was similar to that of to the controls (Tables I1 and I2). The average daily ingestion of C.I. Pigment Red 23 was approximately 425, 1,100, or 2,100 mg/kg body weight per day for male rats and 500, 1,300, or 2,600 mg/kg for females. There were no clinical findings in rats considered to be chemically related.

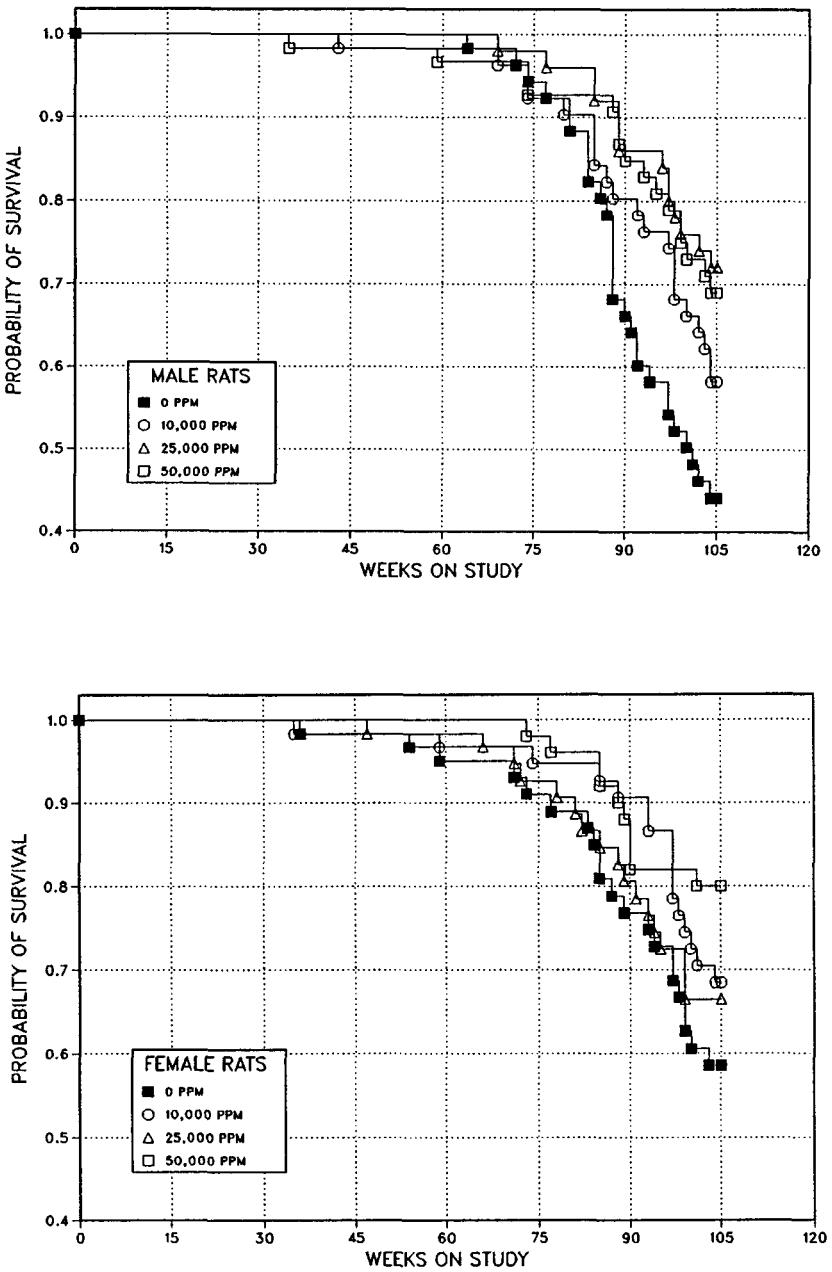


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Administered C.I. Pigment Red 23 in Feed for 2 Years

TABLE 6
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23

Weeks on Study	0 ppm		10,000 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	160	60	163	102	60	163	102	60	161	100	60
2	208	60	209	100	60	211	101	60	207	99	60
3	233	60	233	100	60	235	101	60	232	99	60
4	253	60	251	99	60	255	101	60	252	100	60
5	269	60	263	98	60	268	100	60	266	99	60
6	284	60	284	100	60	286	101	60	282	99	60
7	299	60	299	100	60	300	101	60	296	99	60
8	310	60	311	100	60	311	100	60	305	99	60
9	326	60	321	99	60	323	99	60	319	98	60
10	334	60	333	100	60	333	100	60	330	99	60
11	342	60	339	99	60	342	100	60	337	99	60
12	354	60	351	99	60	353	100	60	348	98	60
13	364	60	360	99	60	359	99	60	356	98	60
17	388	60	390	101	60	390	101	60	382	98	60
21	401	60	391	98	60	390	97	60	388	97	60
25	421	60	411	98	60	408	97	60	407	97	60
29	434	60	431	99	60	430	99	60	423	98	60
33	442	60	440	100	60	436	99	60	431	97	60
37	447	60	450	101	60	443	99	60	433	97	59
41	455	60	455	100	60	453	99	60	444	98	59
45	459	60	462	101	59	456	99	60	452	98	59
49	463	60	465	101	59	461	100	60	454	98	59
53	475	60	473	100	59	469	99	60	458	97	59
57	452	60	456	101	59	453	100	60	448	99	59
61	482	60	482	100	59	478	99	60	468	97	58
65	483	59	480	99	59	478	99	60	472	98	58
69[a]	478	49	485	101	48	479	100	49	469	98	49
73	479	48	481	100	48	480	100	49	473	99	49
77	467	47	467	100	46	463	99	49	458	98	47
81	456	46	459	101	45	454	100	48	443	97	47
85	463	41	456	99	45	447	97	48	439	95	47
89	456	34	447	98	40	444	97	44	435	96	44
93	445	30	437	98	39	435	98	43	429	96	43
97	425	29	422	99	37	423	100	40	418	98	41
101	431	25	415	97	33	416	97	38	408	95	37
Terminal sacrifice		22			29			36			35
Mean for weeks											
1-13	287		286	100		288	100		284	99	
14-52	434		433	100		430	99		424	98	
53-101	461		458	99		455	99		448	97	

[a] Interim evaluation occurred.

TABLE 7
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23

Weeks on Study	0 ppm		10,000 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	128	60	128	101	60	127	100	60	127	100	60
2	147	60	145	99	60	145	99	60	144	98	60
3	158	60	155	98	60	155	98	60	154	98	60
4	166	60	164	99	60	164	99	60	162	98	60
5	171	60	168	98	60	169	99	60	167	98	60
6	178	60	177	100	60	176	99	60	174	98	60
7	183	60	183	100	60	181	99	60	179	98	60
8	185	60	185	101	60	183	99	60	181	98	60
9	194	60	192	99	60	189	98	60	189	98	60
10	196	60	197	101	60	196	100	60	193	98	60
11	199	60	199	100	60	198	99	60	195	98	60
12	204	60	201	99	60	200	98	60	198	97	60
13	208	60	205	99	60	203	97	60	202	97	60
17	219	60	217	99	60	214	98	60	211	96	60
21	221	60	220	99	60	215	97	60	211	95	60
25	231	60	224	97	60	221	96	60	220	95	60
29	241	60	233	97	60	228	95	60	226	94	60
33	246	60	236	96	60	232	94	60	229	93	60
37	255	59	247	97	59	239	94	60	235	92	60
41	260	59	253	97	59	245	94	60	239	92	60
45	268	59	260	97	59	251	94	60	245	92	60
49	277	59	265	96	59	255	92	59	250	90	60
53	291	59	284	98	59	271	93	59	265	91	60
57	306	58	296	97	59	283	93	59	277	91	60
61	319	57	312	98	58	295	93	59	288	90	60
65	327	57	319	98	58	303	93	59	295	90	60
69[a]	339	47	326	96	48	316	93	48	308	91	50
73	341	46	332	97	48	323	95	46	315	93	49
77	348	44	335	96	47	325	94	46	316	91	48
81	349	44	335	96	47	329	94	45	319	91	48
85	357	42	343	96	47	333	93	43	324	91	48
89	358	38	344	96	45	334	93	40	328	92	44
93	357	38	343	96	44	332	93	39	325	91	41
97	354	35	344	97	39	330	93	36	325	92	41
101	355	30	343	97	35	333	94	33	328	92	41
Terminal sacrifice		29			34			33			40
Mean for weeks											
1-13	178		177	99		176	99		174	98	
14-52	246		239	97		233	95		230	93	
53-101	339		327	96		316	93		309	91	

[a] Interim evaluation occurred.

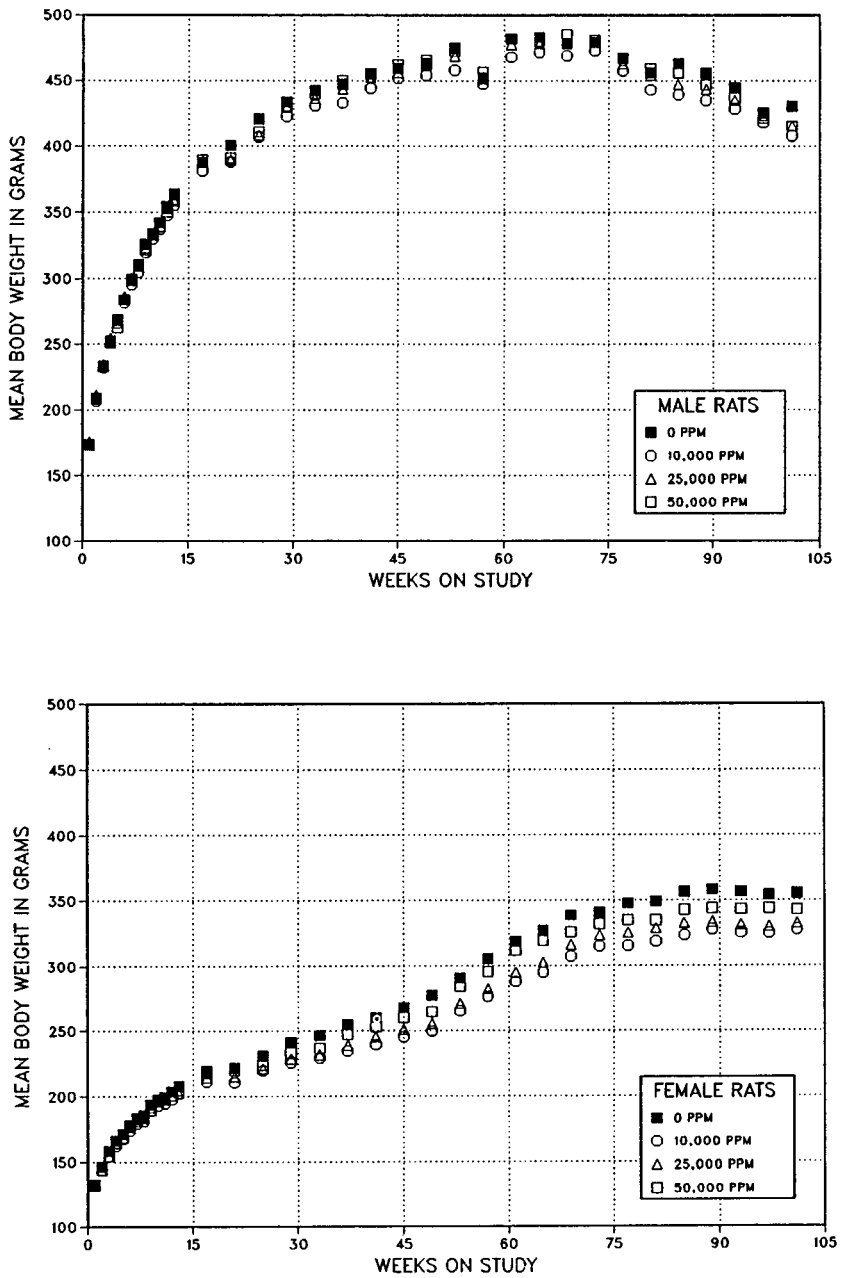


FIGURE 2
Growth Curves for Male and Female Rats Administered C.I. Pigment Red 23 in Feed for 2 Years

Hematology and Clinical Chemistry

Hematocrit values, hemoglobin concentration, and erythrocyte counts in 50,000 ppm female rats at the 15-month interim evaluation were significantly less than those of the controls, indicating mild anemia (Table G3). Serum total bilirubin was significantly increased in the 50,000 ppm females. This finding coupled with the mild anemia suggests a mild hemolytic process. In male rats, there were no biologically significant differences in hematology or clinical chemistry parameters related to chemical exposure.

Pathology and Statistical Evaluation

This section describes statistically significant or biologically noteworthy changes in the incidences of neoplasms or nonneoplastic lesions of kidney, multiple organs, and lymphoid tissue of rats.

Kidney: At the 15-month interim evaluation, relative kidney weights of mid- and high-dose females were significantly increased, due primarily to lower body weights in these groups.

Initially, in the 2-year studies, single sections of the left and right kidneys from each rat were examined microscopically. Four renal tubule cell adenomas or carcinomas were observed in males in the two highest dose groups and one renal tubule adenoma was observed in a high-dose female (Table 8). Although the trend for these renal neoplasms is significant, the incidences are low and do not exceed the historical control range of 0% to 6% in male rats (Table A4a). Because of the low number of neoplasms in the high-dose males, the residual halves of the formalin-fixed kidneys from all control and high-dose males were step sectioned to provide approximately eight additional sections for microscopic examination. During this re-evaluation, renal tubule focal hyperplasia was observed in four high-dose males and renal tubule adenomas were observed in four high-dose males (one of which had been identified in the initial evaluation and another in an animal with a carcinoma). Focal tubule hyperplasia was observed in three control males and a renal tubule adenoma was observed in one control male. The increased incidences of renal tubule hyperplasia and renal tubule neoplasms in high-dose males are supportive of equivocal evidence of carcinogenicity. No additional proliferative lesions were observed during the evaluation of the kidney step sections from female rats in the 2-year study; one renal tubule adenoma was observed in one interim evaluation high-dose female.

Renal tubule cell hyperplasia consisted of expanded tubules lined by two or more cell layers or completely filled by normal appearing renal epithelium (Plate 1). These lesions, some extremely small, were located in tubules of the cortex or in the medulla near the corticomedullary junction. The hyperplastic epithelium was characterized by hyperchromatic nuclei and more basophilic cytoplasm. These cells differed from the regenerative tubule epithelial cells commonly seen in the chronic nephropathy syndrome of older rats; therefore, renal tubule hyperplasia, as defined in this study, was considered a preneoplastic lesion. The renal tubule adenomas were larger than foci of renal tubule hyperplasia and consisted of focal proliferation of renal tubule epithelium that distinctly compressed but did not invade adjacent tissue (Plate 2). The carcinomas were large, grossly visible lesions composed of tubule epithelial cells with more abundant cytoplasm, a slightly increased incidence of mitosis, and invasion of adjacent renal tissue by tumor cells (Plate 3).

Males in the high-dose group showed a significant ($P \leq 0.05$) increase in the severity of nephropathy (Table 9). A marginally decreased severity of nephropathy in high-dose females was not statistically significant.

TABLE 8
Incidences of Kidney Lesions in F344 Rats in the 2-Year Feed Studies of C.I. Pigment Red 23

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male				
Initial Evaluation (Single Sections)				
Renal tubule: Hyperplasia				
Overall rates[a]	3/50 (6%)	6/48 (13%)	5/50 (10%)	8/50 (16%)
Logistic regression test[b]	P=0.187	P=0.288	P=0.570	P=0.198
Renal tubule: Adenoma	0/50	0/48	0/50	2/50
Renal tubule: Carcinoma	0/50	0/48	1/50	1/50
Renal Tubule: Adenoma or Carcinoma[c]				
Overall rates	0/50 (0%)	0/48 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rates[d]	0.0%	0.0%	2.8%	8.6%
Terminal rates[e]	0/22 (0%)	0/28 (0%)	1/36 (3%)	3/35 (9%)
First incidence (days)	–[f]	–	729 (T)	729 (T)
Logistic regression test	P=0.037	–	P=0.598	P=0.213
Evaluation of Step Sections				
Renal tubule: Hyperplasia	3/50	–[g]	–	4/50
Renal tubule: Adenoma	1/50	–	–	4/50[h]
Renal tubule: Carcinoma	0/50	–	–	0/50
Renal tubule: Adenoma or Carcinoma	1/50	–	–	4/50
Single and Step Sections Combined				
Renal tubule: Hyperplasia				
Overall rates	6/50 (12%)	–	–	12/50 (24%)
Logistic regression test	–	–	–	P=0.193
Renal tubule: Adenoma	1/50	–	–	5/50
Renal tubule: Carcinoma	0/50	–	–	1/50
Renal tubule: Adenoma or Carcinoma				
Overall rates	1/50 (2%)	–	–	5/50 (10%)
Adjusted rates	3.4%	–	–	14.3%
Terminal rates	0/22 (0%)	–	–	5/35 (14%)
First incidence (days)	676	–	–	729 (T)
Logistic regression test	–	–	–	P=0.190

(continued)

TABLE 8
Incidences of Kidney Lesions in F344 Rats in the 2-Year Feed Studies of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Female				
Initial Evaluation (Single Sections)				
Renal tubule: Hyperplasia				
Overall rates	2/50 (4%)	2/45 (4%)	0/44 (0%)	2/50 (4%)
Logistic regression test	P=0.564N	P=0.659	P=0.278N	P=0.657
Renal tubule: Adenoma	0/50	0/45	0/44	1/50
Renal tubule: Carcinoma	0/50	0/45	0/44	0/50
Renal Tubule: Adenoma or Carcinoma[i]				
Overall rates	0/50 (0%)	0/45 (0%)	0/44 (0%)	1/50 (2%)
Adjusted rates	0.0%	0.0%	0.0%	2.5%
Terminal rates	0/29 (0%)	0/32 (0%)	0/32 (0%)	1/40 (3%)
First incidence (days)	–	–	–	729 (T)
Logistic regression test	P=0.234	–	–	P=0.564
Evaluation of Step Sections				
Renal tubule: Hyperplasia	1/50	–	–	0/50
Renal tubule: Adenoma	0/50	–	–	0/50[j]
Renal tubule: Carcinoma	0/50	–	–	0/50
Renal tubule: Adenoma or Carcinoma	0/50	–	–	0/50
Single and Step Sections Combined				
Renal tubule: Hyperplasia				
Overall rates	2/50 (4%)	–	–	2/50 (4%)
Logistic regression test	–	–	–	P=0.657
Renal tubule: Adenoma	0/50	–	–	1/50
Renal tubule: Carcinoma	0/50	–	–	0/50
Renal tubule: Adenoma or Carcinoma				
Overall rates	0/50 (0%)	–	–	1/50 (2%)
Adjusted rates	0/0%	–	–	2.5%
Terminal rates	0/29 (0%)	–	–	1/40 (3%)
First incidence (days)	–	–	–	729 (T)
Logistic regression test	–	–	–	–

(T) Terminal sacrifice
[a] Number of lesion-bearing animals/number of animals with tissues examined microscopically.
[b] 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.
[c] Historical incidence for 2-year feed studies with untreated control groups (mean ± standard deviation): 8/499 (1.6% ± 2.3%); range 0%-6%.
[d] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Not applicable; no tumors in animal group
[g] Step sections were not evaluated in the 10,000 and 25,000 ppm dose groups.
[h] Includes one animal already diagnosed with adenoma and one diagnosed with carcinoma
[i] Historical incidence: 1/499 (0.2% ± 0.6%); range 0%-2%.
[j] Upon step sectioning, one renal tubule adenoma was observed in one interim evaluation high-dose female.

TABLE 9
Incidences and Severity of Nephropathy in F344 Rats in the 2-Year Feed Studies of C.I. Pigment Red 23[a]

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male				
Number of animals	50	48	50	50
Absent (Grade 0)	1	0	1	1
Minimal (Grade 1)	3	1	0	3
Mild (Grade 2)	19	13	15	6
Moderate (Grade 3)	23	29	28	31
Marked (Grade 4)	4	5	6	9
Group average severity grade	2.5 ± 0.1	2.8 ± 0.1	2.8 ± 0.1	2.9 ± 0.1.*
Female				
Number of animals	50	45	44	50
Absent (Grade 0)	2	1	1	4
Minimal (Grade 1)	15	11	8	17
Mild (Grade 2)	13	21	20	18
Moderate (Grade 3)	15	10	15	11
Marked (Grade 4)	5	2	0	0
Group average severity grade	2.2 ± 0.2	2.0 ± 0.1	2.2 ± 0.1	1.7 ± 0.1

* Significantly different ($P \leq 0.05$) from the control group by Mann-Whitney U test
[a] Number of animals with severity grade/number of animals with nephropathy. Severity grade was based on the percent of parenchyma involved: Minimal - usually less than 25% to 50% of cortex; moderate - 50% to 75% of the cortex; marked -greater than 75% of cortex. Average severity grade given as the mean ± standard error.

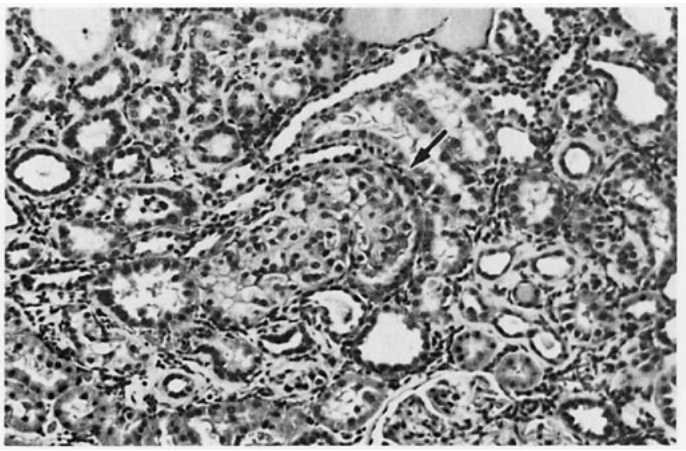


Plate 1
Mild renal tubular hyperplasia in the kidney of a male F344/N rat administered 25,000 ppm C.I. Pigment Red 23 in feed for 2 years. One tubule (arrow) is enlarged and lined by enlarged and stratified epithelial cells which obliterate the lumen of the tubule. Magnification 50×

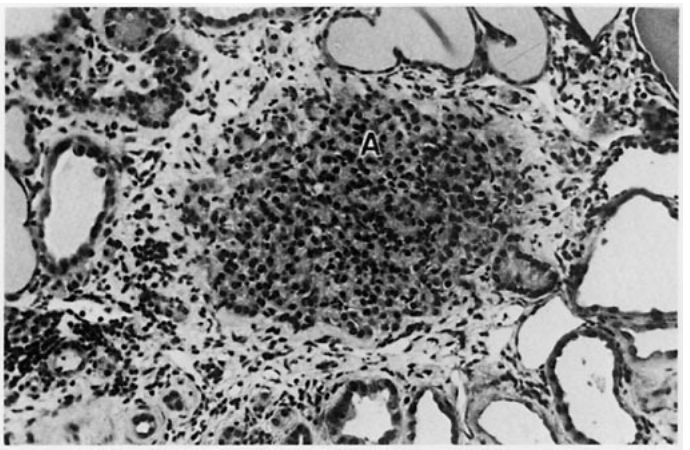


Plate 2
Renal tubular adenoma (A) in the kidney of a male F344/N rat administered 50,000 ppm C.I. Pigment Red 23 in feed for 2 years. Magnification 50×

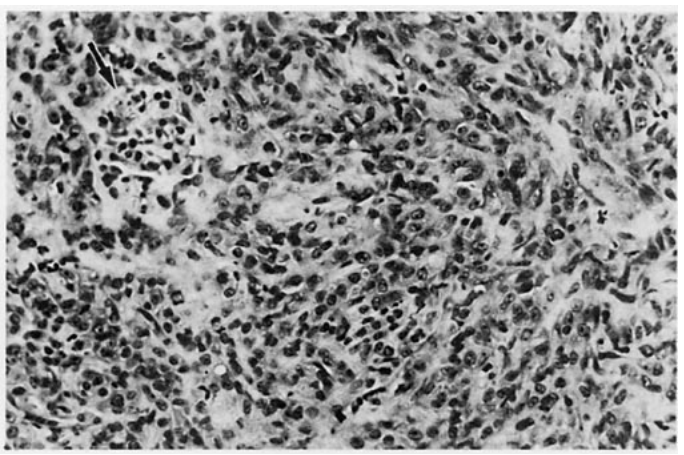


Plate 3
Renal tubular carcinoma in the kidney of a male F344/N rat administered 50,000 ppm C.I. Pigment Red 23 in feed for 2 years. Note the anaplastic carcinoma cells surrounding a remnant of a glomerulus (arrow). Magnification 66×

Brain: At the 15-month interim evaluation, relative brain weights of mid- and high-dose females were significantly increased, due primarily to lower body weights in these groups. In the 2-year study, astrocytomas occurred in three high-dose female rats; this neoplasm is uncommon and the incidence exceeds the laboratory and program historical control range (3/499, mean 0.6%, range 0%-4%; Table B4d). However, gliomas occurred in two control female rats; because astrocytomas are combined with other glial cell neoplasms for analysis, the significance of the three astrocytomas was negated.

Multiple Organs: A significant dose-related decrease in the incidence of mononuclear cell leukemia was observed for both males and females. The incidence of this neoplasm in the mid- and high-dose groups was significantly lower than that of controls (Table 10).

Pituitary Gland (Pars Distalis): Adenoma or carcinoma (combined) of the pars distalis occurred with a significant negative trend in female rats. The incidence in the high-dose group was significantly lower than in the control (Table 11); however, the incidence in each group was similar to the range of historical controls for pituitary gland (pars distalis, pars intermedia) all neoplasms (262/496, mean 53%, range 38%-64%). The incidences of hyperplasia at this site were similar among all groups (Table B5).

Lymphoid Tissue: Red pigment, presumably compound-related, was observed in the lymphoid tissue of the small intestine in females (Peyer's patches) and in the mesenteric lymph nodes in males (Tables A5 and B5). There was a dose-related increase in the amount of pigment present. The pigment consisted of distinct red granules or small elongated crystals within the cytoplasm of the macrophages.

TABLE 10
Incidence of Mononuclear Cell Leukemia in Rats in the 2-Year Feed Studies of C.I. Pigment Red 23

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male[a]				
Overall rates[b]	28/50 (56%)	22/50 (44%)	10/50 (20%)	4/50 (8%)
Adjusted rates[c]	63.7%	53.5%	25.3%	10.4%
Terminal rates[d]	8/22 (36%)	11/29 (38%)	7/36 (19%)	3/35 (9%)
First incidence (days)	502	301	617	412
Life table tests[e]	P<0.001N	P=0.072N	P<0.001N	P<0.001N
Logistic regression tests[e]	P<0.001N	P=0.232N	P=0.001N	P<0.001N
Female[f]				
Overall rates	14/50 (28%)	7/50 (14%)	3/50 (6%)	3/50 (6%)
Adjusted rates	41.2%	18.3%	7.8%	6.9%
Terminal rates	10/29 (34%)	4/34 (12%)	1/33 (3%)	1/40 (3%)
First incidence (days)	507	242	572	610
Life table tests	P<0.001N	P=0.038N	P=0.003N	P<0.001N
Logistic regression tests	P=0.002N	P=0.065N	P=0.003N	P=0.002N

[a] 2-year historical incidence for untreated control groups in NTP feed studies (mean ± standard deviation): 256/500 (51.2% ± 6.6%); range 40%-62%.
[b] Number of lesion-bearing animals/number of animals necropsied or 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 dosed group is indicated by N.
[f] 2-year historical incidence for untreated control groups in NTP feed studies (mean ± standard deviation): 124/500 (24.8% ± 6.1%); range 14%-36%

TABLE 11
Lesions of the Pituitary Gland in Female Rats in the 2-Year Feed Studies of C.I. Pigment Red 23

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Pars Distalis: Adenoma or Carcinoma				
Overall rates[a]	29/50 (58%)	25/50 (50%)	28/50 (56%)	18/50 (36%)
Adjusted rates[b]	74.2%	59.9%	66.3%	41.6%
Terminal rates[c]	19/29 (66%)	18/34 (53%)	19/33 (58%)	15/40 (38%)
First incidence (days)	582	592	501	592
Life table tests[d]	P=0.002N	P=0.102N	P=0.306N	P=0.001N
Logistic regression tests[d]	P=0.009N	P=0.138N	P=0.426N	P=0.005N

[a] Number of lesion-bearing animals/number of animals necropsied or examined microscopically
[b] Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal sacrifice
[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 these lesions as nonfatal. For all tests, a negative trend or a lower incidence in a dosed group is indicated by N.

MICE

17-Day Studies

Two male mice accidentally died after day 14. However, all other mice survived to the end of the studies. Weight gain for exposed male mice was less than that of the controls and was significantly less in the 50,000 ppm and 100,000 ppm groups (Table 12). In females, final mean body weights were similar for all dose groups except for the 12,500 ppm group. Weight gain for exposed females receiving 6,000, 12,500, and 25,000 ppm C.I. Pigment Red 23 was significantly less than that of controls. Feed consumption by exposed males was slightly lower than that of the controls; feed consumption by exposed females was similar to that of the controls. Relative liver weight was significantly increased in the 50,000 ppm females and in each sex receiving 100,000 ppm (Table F4).

Exposed male mice receiving C.I. Pigment Red 23 had significantly greater erythrocyte counts compared to the controls; the hemoglobin concentration of 50,000 ppm male mice was also significantly increased compared to control values (Table G4). The increase in erythrocyte count without corresponding increases in hematocrit and hemoglobin in all treatment groups suggested that the animals were dehydrated, producing a mild hemoconcentration. Lymphocyte and leukocyte counts in 50,000 ppm females were significantly greater than the control values; 100,000 ppm females also had significantly increased lymphocyte counts. The mild increase in lymphocytes in females in the two highest dose groups could be from antigenic stimulation secondary to a chemical-related inflammatory process or from physiologic leukocytosis due to endogenous epinephrine release. Significant increases in hemoglobin concentration and increased erythrocyte counts were observed for females in the 25,000, 50,000, and 100,000 ppm groups. These findings are compatible with dehydration.

Red-stained fur and feces were observed in all exposed groups. No gross observations recorded at necropsy were indicative of chemical toxicity, nor did administration of the pigment in feed significantly affect organ weights at necropsy.

TABLE 12
Survival and Mean Body Weights of Mice in the 17-Day Feed Studies of C.I. Pigment Red 23

Dose (ppm)	Survival[a]	Mean Body Weight (g)[b] Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c]
Male						
0	5/5	22.4 ± 0.6	25.4 ± 0.7	3.0 ± 0.5		60
6,000	5/5	23.2 ± 0.9	24.0 ± 1.1	0.8 ± 0.6	94	47
12,500	5/5[d]	23.2 ± 0.4	25.0 ± 0.5	1.8 ± 0.4	98	41
25,000	5/5	21.2 ± 0.7	23.6 ± 0.7	2.4 ± 0.2	93	53
50,000	5/5	23.2 ± 0.4	24.6 ± 0.4	1.4 ± 0.5*	97	46
100,000	5/5	22.4 ± 0.9	23.2 ± 0.9	0.8 ± 0.6**	91	45
Female						
0	5/5	18.0 ± 0.3	20.6 ± 0.4	2.6 ± 0.2		56
6,000	5/5	18.2 ± 0.2	19.4 ± 0.2	1.2 ± 0.2**	94	46
12,500	5/5	17.8 ± 0.4	18.6 ± 0.7*	0.8 ± 0.5**	90	49
25,000	5/5	17.8 ± 0.4	18.8 ± 0.4	1.0 ± 0.0**	91	41
50,000	5/5	18.0 ± 0.3	19.8 ± 0.5	1.8 ± 0.2	96	52
100,000	5/5	18.0 ± 0.5	19.6 ± 0.6	1.6 ± 0.2	95	45

* 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 initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Grams per animal per week, based on average weekly consumption data per group per day for days 1 through 13.
[d] Two males accidentally died on day 15 during urine collection.

13-Week Studies

All animals survived to the end of the studies. Final mean body weights and weight gains (Table 13) and feed consumption (Table 14) were similar for all exposed groups after 13 weeks. In males receiving 12,500 ppm of C.I. Pigment Red 23, absolute and relative liver weights were significantly increased compared to those of the controls (Table F5). Relative liver weight in the 3,000 ppm group was also increased compared to that of the controls. Both absolute and relative thymus weights were significantly lower than those of the controls for all female dose groups except those receiving 12,500 ppm C.I. Pigment Red 23. Hematology parameters in dosed males were similar to those of untreated males; however, females in the 6,000 ppm group had significantly lower hematocrit and hemoglobin concentrations than did untreated females (Table G5). Red-stained bedding, fur, feces, and extremities were noted in exposed animals but were not considered indicative of chemical toxicity. At necropsy, there were no gross nor histopathologic observations that were considered to be treatment related.

TABLE 13
Survival and Mean Body Weights of Mice in the 13-Week Feed Studies of C.I. Pigment Red 23

Dose (ppm)	Survival[a]	Mean Body Weight (g)[b]			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	21.1 ± 0.5	32.7 ± 0.8	11.6 ± 0.8	
3,000	10/10	20.2 ± 0.6	30.4 ± 0.7	10.2 ± 0.8	93
6,000	10/10	20.5 ± 0.6	30.1 ± 1.1	9.6 ± 0.8	92
12,500	10/10	20.9 ± 0.6	32.6 ± 1.1	11.7 ± 0.7	100
25,000	10/10	20.7 ± 0.6	31.1 ± 0.9	10.4 ± 0.5	95
50,000	10/10	21.1 ± 0.7	30.7 ± 0.5	9.6 ± 0.5	94
Female					
0	10/10	16.0 ± 0.4	23.9 ± 0.7	7.9 ± 0.5	
3,000	10/10	15.6 ± 0.5	22.3 ± 0.6	6.7 ± 0.3	93
6,000	10/10	15.7 ± 0.5	22.2 ± 0.4	6.5 ± 0.3	93
12,500	10/10	16.0 ± 0.5	22.4 ± 0.6	6.4 ± 0.5*	94
25,000	10/10	15.8 ± 0.5	22.8 ± 0.5	7.0 ± 0.3	95
50,000	10/10	16.5 ± 0.5	23.8 ± 0.8	7.3 ± 0.5	100

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

TABLE 14
Mean Feed Consumption by Mice in the 13-Week Feed Studies of C.I. Pigment Red 23[a]

Week on Study	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male						
1	208.5	183.9	236.8	224.1	199.1	147.8
2	154.2	234.4	235.0	229.5	270.7	105.0
3	171.8	194.7	200.0	200.0	196.9	210.9
4	157.3	186.1	190.7	234.2	203.1	192.5
5	191.2	213.0	214.6	176.5	222.2	217.7
6	273.0	208.3	154.4	169.6	177.1	185.5
7	155.7	177.4	141.3	213.8	185.7	202.8
8	137.5	250.0	158.3	199.3	261.5	209.2
9	191.3	242.2	146.4	183.3	191.6	296.2
10	221.1	227.3	190.1	196.8	200.7	185.8
11	232.8	229.6	206.4	273.0	294.7	189.4
12	203.1	259.0	18..9	204.3	238.6	194.2
13	165.1	167.3	289.0	184.0	237.9	101.0
Female						
1	304.6	170.7	351.2	250.0	270.6	306.4
2	219.3	222.9	195.5	228.3	312.5	216.2
3	241.4	262.9	248.7	186.9	212.4	221.7
4	242.6	191.9	203.0	281.4	183.7	231.5
5	243.9	194.0	232.3	248.8	263.4	253.7
6	145.5	245.1	243.9	311.3	289.1	296.8
7	218.6	236.7	238.3	203.7	254.6	202.7
8	185.7	245.3	177.6	231.5	310.5	236.6
9	287.7	295.5	254.6	324.1	230.8	302.2
10	346.7	360.7	283.1	280.5	274.0	313.0
11	388.6	224.2	267.0	300.0	309.7	285.1
12	284.5	400.0	391.3	294.1	361.7	320.8
13	330.5	363.2	364.9	325.9	320.2	218.5

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

2-Year Studies

Survival

Estimates of the probabilities of survival for male and female mice administered C.I. Pigment Red 23 and the untreated controls are presented in Table 15 and in the Kaplan-Meier survival curves in Figure 3. Survival of all female dose groups and mid- and high-dose males was similar to that of the controls. Survival in low-dose (10,000 ppm) males was 10% less than that of the controls by week 20 and continued to be lower than control values throughout the study. This decrease in survival was associated with evidence of trauma and secondary septicemia caused by fighting.

TABLE 15
Survival of Mice in the 2-Year Feed Studies of C.I. Pigment Red 23

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male				
Animals initially in study	60	60	60	60
Natural deaths	10	22	8	6
Moribund	12	14	17	15
15-month interim evaluation[a]	9	7	8	9
Animals surviving to study termination	29	17	27	30
Percent probability of survival at end of study[b]	58	34	53	59
Mean survival days[c]	616	525	602	639
Survival analysis[d]	P=0.177N	P=0.010	P=0.678	P=0.819N
Female				
Animals initially in study	60	60	60	60
Natural deaths	4	8	3	4
Moribund	11	7	11	10
Accidental deaths[a]		1		
Missing[a]				1
15-month interim evaluation	10	10	10	10
Animals surviving to study termination	35	34	36	35
Percent probability of survival at end of study	70	71	72	72
Mean survival days	657	628	655	637
Survival analysis	P=0.966N	P=0.972	P=0.972N	P=0.857

[a] Censored from survival analyses
[b] Kaplan-Meier determinations. Survival rates adjusted for accidental deaths, missing animals, and interim evaluations.
[c] Mean of all deaths (uncensored, censored, terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns. A negative trend or lower mortality in a dose group is indicated by N.

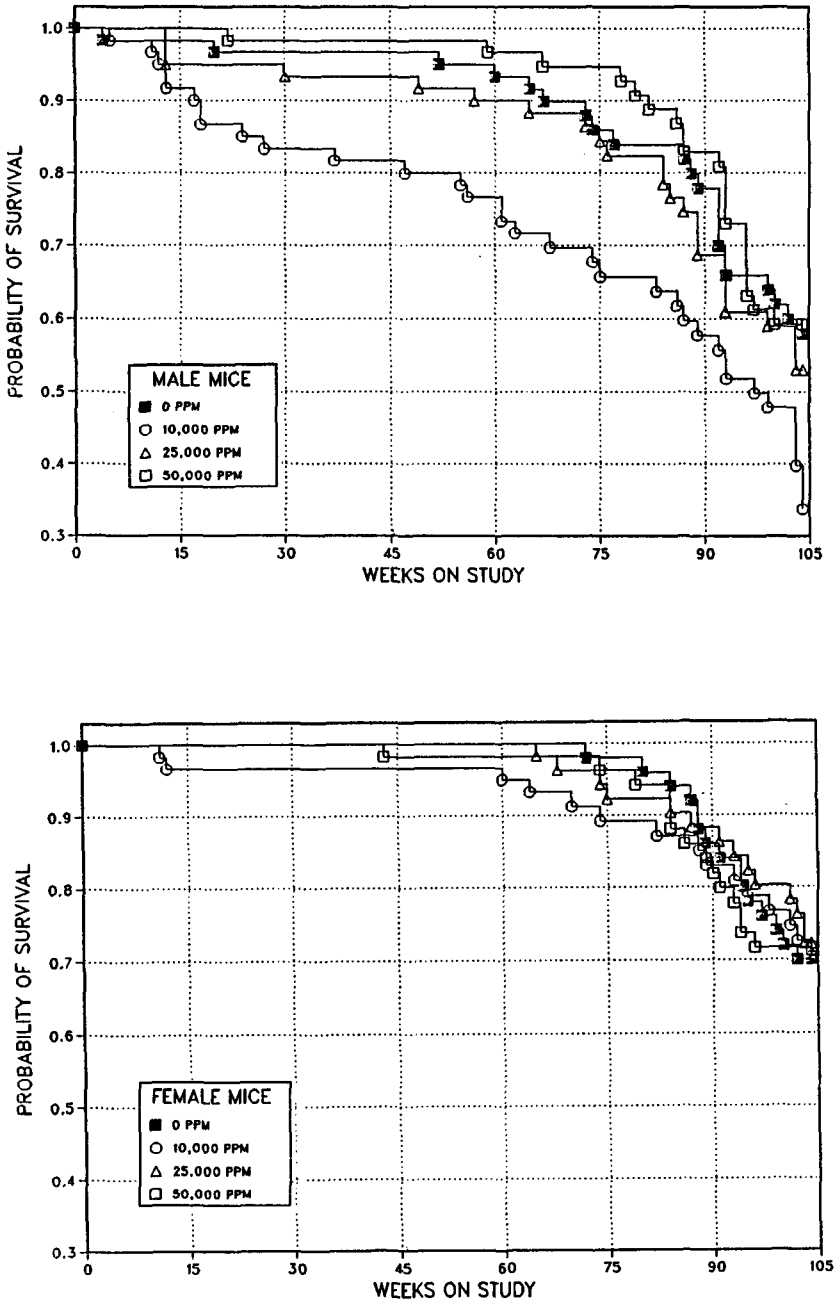


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Administered C.I. Pigment Red 23 in Feed for 2 Years

Body Weights, Feed Consumption, and Clinical Findings

Body weights from all dose groups of each sex were within 10% of the untreated controls throughout both the 15-month interim evaluation and the 2-year study (Figure 4 and Tables F6, 16, and 17). Feed consumption by both male and female mice was similar to that of the controls (Tables I3 and I4). The average daily ingestion of C.I. Pigment Red 23 was approximately 1,900, 4,500, or 9,500 mg/kg body weight per day for males and 2,100, 5,240, or 10,800 mg/kg for females. Clinical findings included red stained fur, extremities, and feces.

Clinical Chemistry and Hematology

At the 15-month interim evaluation, hematology and clinical chemistry parameters of all exposed groups were generally similar to those of the controls (Table G6).

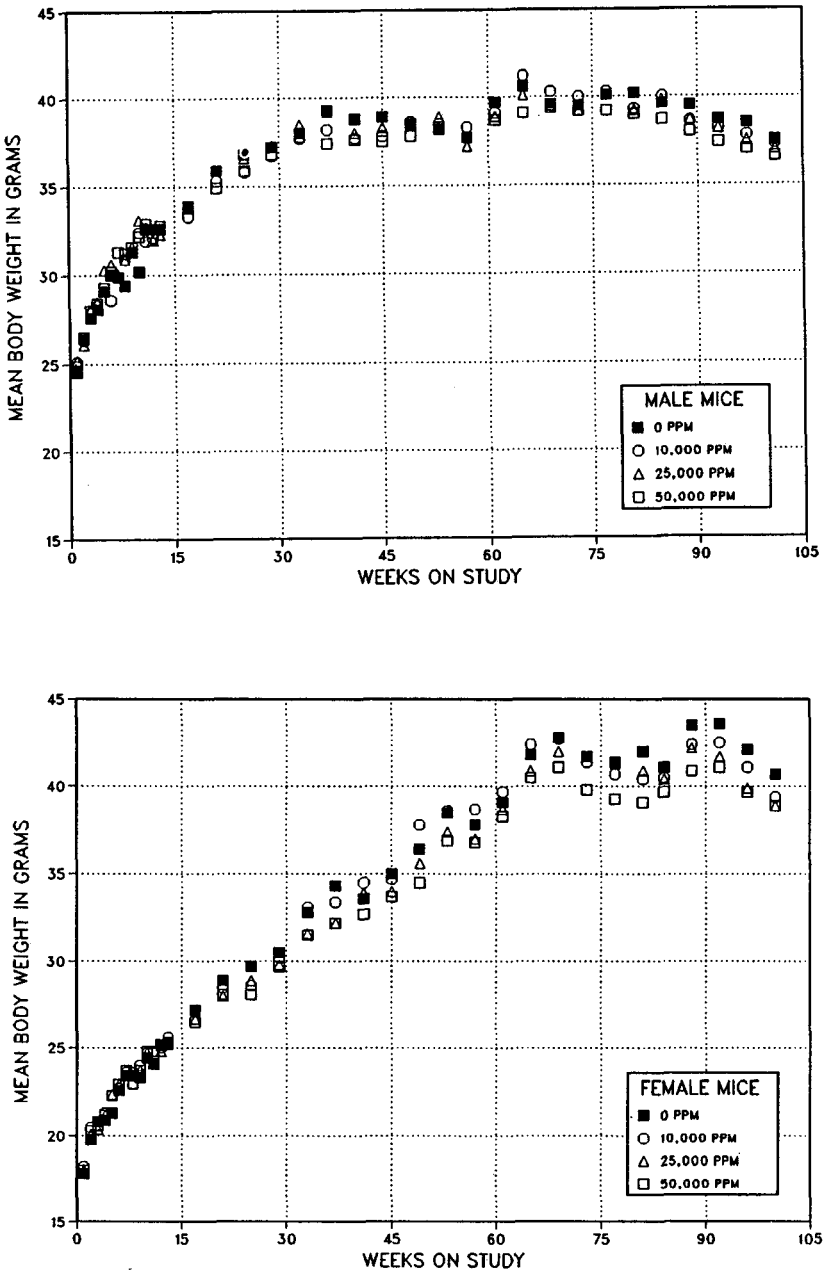


FIGURE 4
Growth Curves for Male and Female Mice Administered C.I. Pigment Red 23 in Feed for 2 Years

TABLE 16
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	10,000 ppm Av. Wt. (g)	10,000 ppm Wt. (% of controls)	10,000 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	25.5	60	25.7	101	60	25.7	101	60	25.7	101	60
2	27.6	60	27.9	101	60	28.1	102	60	28.0	101	60
3	28.1	60	28.3	101	60	28.5	101	60	28.4	101	60
4	29.1	59	29.3	101	60	30.3	104	60	29.3	101	60
5	30.0	59	28.6	95	60	30.6	102	60	30.3	101	60
6	29.9	59	29.9	100	59	30.1	101	60	31.2	104	60
7	29.4	59	30.9	105	59	30.9	105	60	31.2	106	60
8	31.3	59	31.3	100	59	31.6	101	60	31.6	101	60
9	30.2	59	32.4	107	59	33.1	110	60	32.2	107	60
10	32.6	59	32.0	98	59	32.7	100	60	33.0	101	60
11	32.6	59	32.1	99	59	32.0	98	60	32.4	99	60
12	32.6	59	32.6	100	57	32.3	99	60	32.8	101	60
16	33.9	59	33.3	98	55	33.9	100	57	33.8	100	60
20	35.9	58	35.3	98	52	35.9	100	57	34.9	97	60
25	36.8	58	35.8	97	51	36.6	100	57	35.9	98	59
28	37.2	58	36.7	99	50	37.3	100	57	36.8	99	59
32	38.1	58	37.7	99	50	38.5	101	56	37.8	99	59
36	39.3	58	38.2	97	50	39.2	100	56	37.4	95	59
40	38.8	58	37.7	97	49	38.0	98	56	37.6	97	59
44	38.9	58	37.8	97	49	38.3	99	56	37.5	96	59
48	38.5	58	38.6	100	48	38.4	100	56	37.8	98	59
52	38.2	56	38.5	101	48	38.9	102	55	38.2	100	59
56	37.7	56	38.3	102	46	37.2	99	55	37.7	100	59
60	39.7	55	39.1	99	46	38.9	98	54	38.7	98	58
64	40.6	55	41.2	102	43	40.1	99	54	39.1	96	58
68[a]	39.6	45	40.3	102	35	39.5	100	45	39.4	100	48
72	39.5	45	40.0	101	35	39.2	99	45	39.2	99	48
77	40.1	43	40.3	101	33	40.1	100	42	39.2	98	48
80	40.2	42	39.3	98	33	39.2	98	42	39.0	97	46
84	39.6	42	40.0	101	32	39.8	101	40	38.7	98	45
88	39.5	40	38.6	98	30	38.7	98	38	38.0	96	42
92	38.8	38	38.2	99	29	38.2	99	35	37.4	96	41
96	38.5	33	37.8	98	26	37.5	97	31	37.0	96	37
100	37.5	31	37.3	100	24	37.0	99	30	36.6	98	31
Terminal sacrifice		29			17			27			30
Mean for weeks											
1-15	29.9		30.1	101		30.5	102		30.5	102	
16-52	37.6		37.0	98		37.5	100		36.8	98	
53-100	39.3		39.2	100		38.8	99		38.3	97	

[a] Interim evaluation occurred.

TABLE 17
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23

Weeks on Study	0 ppm		10,000 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	18.8	60	19.3	103	60	19.0	101	60	19.1	102	60
2	20.8	60	20.6	99	60	20.4	98	60	20.6	99	59
3	20.9	60	21.3	102	60	21.2	101	60	21.2	101	59
4	21.3	60	22.3	105	60	22.4	105	60	22.3	105	59
5	22.6	60	22.7	100	60	22.9	101	60	22.9	101	59
6	23.4	60	23.6	101	60	23.4	100	60	23.7	101	59
7	23.4	60	23.6	101	60	23.4	100	60	23.0	98	59
8	23.3	60	24.0	103	60	23.7	102	60	23.7	102	59
9	24.4	60	24.7	101	60	24.7	101	60	24.8	102	59
10	24.1	60	24.8	103	60	24.1	100	60	24.7	103	59
11	25.2	60	25.0	99	60	24.8	98	60	25.1	100	59
12	25.3	60	25.6	101	58	25.3	100	60	25.2	100	59
16	27.2	60	27.1	100	58	26.7	98	60	26.5	97	59
20	28.9	60	28.5	99	58	28.0	97	60	28.1	97	59
25	29.7	60	28.6	96	58	28.9	97	60	28.1	95	59
28	30.5	60	30.2	99	58	29.8	98	60	29.7	97	59
32	32.8	60	33.1	101	58	31.7	97	60	31.5	96	59
36	34.3	60	33.4	97	58	32.2	94	60	32.2	94	59
40	33.6	60	34.5	103	58	33.9	101	60	32.7	97	59
44	35.0	60	34.7	99	58	34.0	97	60	33.7	96	58
48	36.4	60	37.8	104	58	35.6	98	60	34.5	95	58
52	38.5	60	38.6	100	58	37.4	97	60	36.9	96	58
56	37.8	60	38.7	102	58	37.0	98	60	36.8	97	58
60	39.1	60	39.7	102	58	38.7	99	60	38.3	98	58
64	41.8	60	42.4	101	56	40.9	98	60	40.5	97	58
68[a]	42.8	50	42.7	100	45	42.0	98	48	41.1	96	48
72	41.7	49	41.4	99	44	41.7	100	48	39.8	95	48
77	41.4	49	40.7	98	43	41.3	100	46	39.3	95	47
80	42.0	48	40.4	96	43	40.9	97	46	39.1	93	46
84	41.1	48	40.5	99	42	40.4	98	46	39.7	97	45
88	43.5	45	42.4	98	42	42.2	97	44	40.9	94	42
92	43.6	42	42.5	98	40	41.7	96	43	41.1	94	39
96	42.1	39	41.1	98	38	39.9	95	40	39.7	94	35
100	40.7	36	39.4	97	37	38.9	96	40	38.9	96	35
Terminal sacrifice		35			34			36			35
Mean for weeks											
1-15	22.8		23.1	101		22.9	100		23.0	101	
16-52	32.7		32.7	100		31.8	97		31.4	96	
53-100	41.5		41.0	99		40.5	98		39.6	95	

[a] Interim evaluation occurred.

Pathology and Statistical Evaluation

No chemical-related increases in neoplasm incidence were observed in mice of either sex at any dose level. This section describes significant or noteworthy changes in the incidences of mice with nonneoplastic lesions of the forestomach and other findings in lymphoid tissue of the small and large intestine.

Forestomach: In the 2-year study, the incidence and severity of forestomach epithelial hyperplasia increased with dose in males (control, 0/49; low-dose, 1/48; mid-dose, 1/50; high-dose, 7/48); and in females (6/49; 14/49; 43/50; and 47/49) (Tables C4 and D4). Hyperplasia of the forestomach epithelium also was seen in two mid-dose and two high-dose female mice at the 15-month interim evaluation. Histopathologically, the forestomach lesions were less severe but similar to those described at the end of the 2-year studies. Hyperplasia ranged in severity from minimal with focal areas of thickening of the prickle-cell layer and minimal surface thickening of the keratinized surface layer (hyperkeratosis) to moderate with short, finger-like projections from a broad base and numerous neutrophils in the lamina propria, as well as small mucosal erosions/ulcers. Occasionally, in severe lesions, foreign body granulomas were associated with hair. Hairs were also present in the inflammatory exudate on the surface and mucosa in some animals. Hyperplastic lesions observed in females at the end of the 2-year studies included more cases with acute inflammation in hyperplastic areas (neutrophils in the epithelium and lamina propria of the hyperplastic areas which were termed abscesses, and erosions /ulcers which were included under the term ulcer). Fewer forestomach lesions were observed in males and consisted primarily of thickening of the keratinized surface layer of epithelium (hyperkeratosis) with little thickening of the prickle-cell layer.

Squamous cell papillomas of the forestomach were observed in one high-dose male, one high-dose female, and one low-dose female (Tables C1 and D1). These neoplasms differed from forestomach hyperplasias and consisted of branching mucosal tissue originating from a central solitary core of the lamina propria. Because of the low incidence of these neoplasms, papillomas were not considered to be related to chemical exposure.

Lymphoid Tissue: The presence of red pigment, presumed to be C.I. Pigment Red 23 or a metabolite, was observed within intestinal lymphoid tissue (Peyer's patches), and to a lesser extent within mandibular and inguinal lymph nodes in mice at the 15-month interim evaluation and at the end of the 2-year study. The pigment was bright red and was observed in small intracellular granules and in large extracellular clumps.

GENETIC TOXICITY

C.I. Pigment Red 23 (10 to 3,333 μg/plate) was positive for induction of gene mutations in *Salmonella typhimurium* strains TA100, TA1537, and TA98 when tested in a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9; it was not mutagenic in strain TA1535 with or without S9 (Table E1; Mortelmans *et al.*, 1986).

In cytogenetic tests with Chinese hamster ovary cells, C.I. Pigment Red 23 induced sister chromatid exchanges over a concentration range of 5 to 30 μg/mL in the absence of S9 in an initial trial; the second trial performed without S9 also demonstrated an increase in sister chromatid exchanges, but only at a higher dose than was evaluated in the first trial (Table E2). At this dose (50 μg/mL) a delayed harvest protocol was employed to offset the toxic effect of the pigment on cell cycle progression. No induction of sister chromatid exchanges was observed in Chinese hamster ovary cells in the presence of liver S9 from Aroclor 1254-induced male Sprague-Dawley rats. C.I. Pigment Red 23 (30 to 100 μg/mL) was negative for induction of chromosomal aberrations in Chinese hamster ovary cells, with and without S9 (Table E3).

DISCUSSION AND CONCLUSIONS

C.I. Pigment Red 23 is used as a coloring agent in paints, inks, rubber, alkyl resin enamels, lacquers, emulsion paints, and paper. This pigment was nominated by the National Cancer Institute for testing because of lack of information on its toxicity and carcinogenicity, its structural resemblance to known phenylazonaphthol carcinogens such as Citrus Red No. 2 and Oil Orange SS, and its high potential for human exposure through its wide variety of uses. Toxicology and carcinogenicity studies were conducted by feeding F344 rats and B6C3F$_1$ mice diets containing C.I. Pigment Red 23 for 17 days, 13 weeks, and 2 years. The dosed feed method of administration was selected because human exposure to the compound is most likely to occur by ingestion.

C.I. Pigment Red 23, at doses as high as 100,000 ppm in the 17-day studies and 50,000 ppm in the 13-week studies, did not adversely affect survival, body weight, or feed consumption of rats and mice of either sex. No chemical-related lesions (gross or microscopic) were observed in rats or mice. The slight decreases in hematocrit values, hemoglobin concentrations, and erythrocyte counts in high-dose male rats (13-week studies) and high-dose female rats (15-month interim), and the elevation of serum total bilirubin in the high-dose female rats (15-month interim) are indicative of hemolytic anemia caused by C.I. Pigment Red 23. The increase in total bilirubin level possibly resulted from excess liberation of hemoglobin from erythrocytes into the plasma during hemolysis (Emerson and Wilkerson, 1966).

The detection of these hematologic changes suggested that C.I. Pigment Red 23 or its metabolites were absorbed from the gastrointestinal tract of rats and mice. Because C.I. Pigment Red 23 is water insoluble and its absorption from the gastrointestinal tract is negligible (El Dareer *et al.*, 1984), it is likely that the active agent may be a more soluble and easily absorbed microbial metabolite of the pigment. Azo reduction as well as peptide bond cleavage of C.I. Pigment Red 23 would yield 5-nitro-*o*-anisidine, 3-carboxyl-2-hydroxy-α-naphthol amine, and 3-nitroaniline. The observed hematologic changes in these studies could be caused by any one of these three aromatic amine metabolites, since structurally related amines produce similar effects (Beard and Noe, 1981). The amino group of these metabolites may undergo N-hydroxylation to yield N-hydroxy derivatives which are considered to be responsible for the hematologic effects of aromatic amines (Weisburger, 1983). Aromatic amines (e.g., anilines) are known to cause elevation in methemoglobin levels (Smith, 1983). However, methemoglobin levels were not determined in the present studies.

Although there was evidence for the occurrence of a slight compound-related hemolytic anemia in rats, no hematologic effects (decreased hemoglobin levels, hematocrit values, or erythrocyte counts) were seen in mice. The presence of the anemia in rats and its absence in mice may be related to the difference in the life span of erythrocytes, which is 50 to 65 days for rats versus 20 to 30 days for mice (Prankard, 1961). The short life-span of mouse erythrocytes enables mice to replace damaged cells faster than rats, thus keeping these hematologic parameters within normal values.

Because C.I. Pigment Red 23 at doses up to 100,000 ppm in the diet did not adversely affect the body weight or survival of rats of either sex, doses of 0, 10,000, 25,000, and 50,000 ppm were selected for the 2-year carcinogenicity studies. The 50,000 ppm level was selected because it is the highest recommended level for testing in the 2-year studies for compounds or substances other than a major nutrient (NCI, 1976). Using higher levels of this nonnutritional pigment in the diet could have led to dietary deficiencies as a result of excessive dilution of essential nutrients.

The doses selected for the 2-year studies of C.I. Pigment Red 23 were considered adequate because they did not adversely affect the survival of exposed rats and mice of either sex. The reduced survival observed in low-dose male mice was due to an

increased number of animals that died from natural causes or were killed moribund, but the reduction was not due to chemical administration. The greater survival rate for mid- and high-dose male and high-dose female rats was attributed to the increased number of control rats that died naturally or were killed in a moribund state because of mononuclear cell leukemia. Even though the survival of controls was less than that of exposed rats, more than 60% of control animals survived to week 90 of the study. The final mean body weights of exposed female and mid- and high-dose male rats were slightly lower than, but within 10% of, control values. Taking all these factors into consideration, the rat studies were considered adequate to determine the carcinogenic potential of C.I. Pigment Red 23.

In male rats receiving C.I. Pigment Red 23 for up to 2 years, there was a slight but statistically significant increase in the severity of nephropathy. Nephropathy is a common spontaneous disease of aging rats consisting of changes in glomerular permeability resulting in proteinuria, progressive glomerular sclerosis, tubule damage, inflammation, and interstitial fibrosis. It is unknown if the tubule damage is entirely secondary to the changes in the glomeruli or the direct effect of factors still not identified. Exacerbation of this disease process, particularly in male rats, was frequently observed with the administration of nephrotoxic chemicals such as nitrofurantoin (NTP, 1989a), furosemide (1989c), and hydroquinone (NTP, 1989e). Although nephropathy is typically more severe in male rats than in female rats, the apparent increased nephropathy in exposed male rats is likely due to the cumulative effects of C.I. Pigment Red 23.

In the initial evaluation of single sections from each left and right kidney, two renal tubule cell adenomas and one renal tubule carcinoma were seen in the high-dose male rats with a concomitant dose-related increase in renal tubule hyperplasia. Even though renal tubule neoplasms are relatively uncommon in NTP untreated historical control male rats (8/499, mean 1.6%, range 0%-6%; Table A4a), the low incidence of renal neoplasms in the high-dose group (6%) was difficult to interpret.

The NTP and Kurokawa *et al.* (1983) have found that multiple sectioning of the kidney may enable a more precise evaluation of the potential chemical-related induction of renal tubule neoplasms compared with observations from single-section sampling. The majority of renal neoplasms in these studies are microscopic (i.e., not observed by macroscopic examination at necropsy), thus, multiple sections might be expected to increase the number of neoplasms observed and allow for a more rigorous statistical evaluation. For example, when step sections of the kidneys were used to evaluate the carcinogenic response in male rats treated with nitrofurantoin for 2 years, the observed incidence of renal tubule cell neoplasms increased from 0/50 to 3/50 in control males and from 3/50 to 20/50 in high-dose males. Since the number of lesions in the high-dose male rats was small in the study of C.I. Pigment Red 23, the residual halves of the formalin-fixed kidneys from control and high-dose male rats were step sectioned to provide approximately eight additional sections for microscopic examination. The kidney step section of male rats consuming C.I. Pigment Red 23 provided a modest increase in the observed incidence of kidney neoplasms (Table 8). Renal tubule focal hyperplasia was observed in four high-dose males and renal tubule adenomas were observed in four high-dose males (two of these animals had neoplasms in the initial evaluation). Focal renal tubule hyperplasia was seen in three additional control males and a renal tubule adenoma was observed in one control male. The increased incidence of renal tubule hyperplasia (0 ppm, 6/50; 50,000 ppm, 12/50) and renal tubule adenomas in high-dose male rats (0 ppm, 1/50; 50,000 ppm, 5/50) is supportive of equivocal evidence of carcinogenic activity.

The dose-related increase of renal tubule cell hyperplasia is important in the interpretation of the potential association of renal tubule neoplasms with the administration of C.I. Pigment Red 23. Renal tubule hyperplasia, as diagnosed in this study, was distinguished from the background regenerative hyperplasia that commonly accompanies the degenerative tubule changes of age-related or chemically induced nephropathy, on the basis of cellular atypia and prominent stratification of the epithelium. These cytological features, atypia and stratification, suggest there is a loss of growth regulation and a failure of differentiation. This lesion is similar to those induced by potent renal carcinogens and appears to

represent early stages in the development of renal tubule adenomas and carcinomas (Hard, 1986; Tsuda *et al.*, 1986). Because renal tubule hyperplasia and neoplasia were marginally increased in high-dose male rats, these proliferative lesions may have been related to chemical administration.

Perhaps the most remarkable effect in these 2-year studies was the dose-related decrease in the incidence of mononuclear cell leukemia in male and female rats. Mononuclear cell leukemia of rats is generally thought to originate in the spleen, since splenomegaly (enlargement associated with the diffuse accumulation of neoplastic cells in the red pulp) is found in virtually all rats dying with leukemia, and the incidence of leukemia was reduced from 24% to 2% by splenectomizing rats at one to two months of age (Moloney and King, 1973). The neoplastic mononuclear cells have Fc receptors, natural killer cell activity, and the surface antigens thy 1.1, M1/70, OX-8, and Asialo GM_1. These cells seem to be morphologically, biochemically, and functionally similar to the large granular lymphocytes found in humans.

Low incidences of mononuclear cell leukemia have been associated with low body weights and/or feed restriction. In the present studies, the slight reduction in the body weights of exposed rats is not considered sufficient to account for the differences in incidence of leukemia between exposed and control groups. Previously, chemically related reductions in the incidence of leukemia have been observed in rats given structurally related chemicals such as aniline hydrochloride (NCI, 1978a), D&C Red No. 9 (NTP, 1982a), C.I. Solvent Yellow 14 (NTP, 1982b), *p*-chloroaniline hydrochloride (NTP, 1989b), and N,N-dimethylaniline (NTP, 1989d). C.I. Pigment Red 23, however, did not produce the spectrum of splenic toxicity and sarcomas seen with these aniline compounds.

The lower incidence of pituitary neoplasms observed in the high-dose female rats may be related to lower body weights; the final mean body weight of high-dose females was 8% less than that of controls. Rao and Haseman (1990) showed a significant positive association between the incidence of pituitary gland neoplasms and decreased body weight.

The presence of red pigment in the lymphoid tissue of the small intestine and mesenteric lymph nodes of rats and mice of each sex and the cecum of female mice was indicative of local absorption of C.I. Pigment Red 23.

The equivocal evidence of carcinogenic activity in rats and the lack of carcinogenic activity in mice for C.I. Pigment Red 23 contrasts with the finding that pigments with a similar structure (Citrus Red No. 2 and Oil Orange SS), as well as 5-nitroanisidine (a possible microbial metabolite of C.I. Pigment Red 23), were carcinogenic in rats and mice at lower doses (<16,000 ppm). The difference in response could be related either to differences in solubility of these compounds or to differences in metabolism. C.I. Pigment Red 23 is insoluble while the other compounds are slightly soluble. Although it is apparent from the hematologic changes and reduction in incidences of leukemia that C.I. Pigment Red 23 or a metabolite was absorbed from the intestine, the amount absorbed may not have been high enough to invoke a strong carcinogenic response.

Conclusions

Under the conditions of these 2-year feed studies, there was *equivocal evidence of carcinogenic activity** of C.I. Pigment Red 23 in male F344 rats as evidenced by a marginally increased incidence of renal tubule cell neoplasms. There was *no evidence of carcinogenic activity* of C.I. Pigment Red 23 in female F344 rats fed diets containing 10,000, 25,000, or 50,000 ppm. Mononuclear cell leukemia occurred with a decreased incidence in male and female rats receiving C.I. Pigment Red 23. There was *no evidence of carcinogenic activity* of C.I. Pigment Red 23 in male and female $B6C3F_1$ mice fed diets containing 10,000, 25,000 or 50,000 ppm.

The severity of kidney nephropathy was increased in exposed male rats. In mice, C.I. Pigment Red 23 caused an increase in hyperkeratosis and epithelial hyperplasia of the forestomach.

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* Explanation of Levels of Evidence of Carcinogenic Activity appears on page 9. A summary of peer review comments and public discussion on this Technical Report appear on page 11.

REFERENCES

Armitage, P. (1971). *Statistical Methods in Medical Research*, pp. 362-365. Wiley and Sons, New York.

Ashby, J., Tennant, R.W., Zeiger, E., and Stasiewicz, S. (1989). Classification according to chemical structure, mutagenicity to *Salmonella* and level of carcinogenicity of a further 42 chemicals tested for carcinogenicity by U.S. National Toxicology Program. *Mutat. Res.* **223**, 73-103.

Ashby, J., and Tennant, R.W. (1991). Definitive relationships among chemical structure, carcinogenicity, and mutagenicity for 301 chemicals tested by the U.S. NTP. *Mutat. Res.* **257**, 229-306.

Beard, R.R. and Noe, J.T. (1981). Aromatic nitro and amino compounds. In *Patty's Industrial Hygiene and Toxicology* (G.D. Clayton and F.E. Clayton, Eds.), pp. 2A: 2413-2489. Wiley and Sons, Inc., New York, NY.

Boorman, G.A., Montgomery, C.A., Jr., Eustis, S.L., Wolfe, M.J., McConnell, E.E., and Hardisty, J.F. (1985). Quality assurance in pathology for rodent carcinogenicity studies. In *Handbook of Carcinogen Testing* (H.A. Milman and E.K. Weisburger, Eds.), pp. 345-357. Noyes Publications, Park Ridge, NJ.

Bonser, G.M., Clayson, D.B., and Jull, J.W. (1954). Induction of tumors with 1-(2-tolylazo)-2-naphthol (Oil Orange, TX). *Nature (London)* **174**, 879-880.

Bos, R.P., van der Krieken, W., Smeijsters, L., Koopman, J.P., De Jonge, H.R., Theuws, J.L.G., and Henderson, P.T. (1986). Internal exposure of rats to benzidine derived from orally administered benzidine-based dyes after intestinal azo reduction. *Toxicology* **40**, 207-213.

Brown, J.P., Roehm, G.W., and Brown, R.J. (1978). Mutagenicity testing of certified food colors and related azo, xanthene, triphenylmethane dyes with the *Salmonella*/microsome system. *Mutat. Res.* **56**, 249-271.

Brown, J.P., and Dietrich, P.S. (1983). Mutagenicity of selected azo dyes in the *Salmonella*/microsome assay: Use of aerobic and anaerobic activation procedures. *Mutat. Res.* **116**, 305-345.

Cameron, T.P., Hughes, T.J., Kirby, P.E., Fung, V.A., and Dunkel, V.C. (1987). Mutagenic activity of 27 dyes and related chemicals in the *Salmonella*/ microsome and mouse lymphoma $TK^{+/-}$ assays. *Mutat. Res.* **189**, 223-261.

Cerniglia, C.E., Freeman, J.P., Franklin, W., and Pack, L.D. (1982). Metabolism of azo dyes derived from benzidine, 3,3'-dimethylbenzidine, and 3,3'-dimethoxybenzidine to potentially carcinogenic amines by intestinal bacteria. *Carcinogenesis* **3**, 1255-1260.

Chiu, C.W., Lee, L.H., Wang, C.Y., and Bryan, G.T. (1978). Mutagenicity of some commercially available nitro compounds for *Salmonella typhimurium*. *Mutat. Res.* **58**, 11-22.

Code of Federal Regulations (CFR), **21**, part 58.

Colour Index (1971), 3rd ed., Vol. 3, p. 3302-3303. The Society of Dyers and Colourists. Lund Humphries Printers, London.

Cox, D.R. (1972). Regression models and life tables. *J. R. Stat. Soc.* **B34**, 187-220.

Crawford, B.D. (1985). Perspectives on the somatic mutation model of carcinogenesis. In *Advances in Modern Environmental Toxicology* (W.G. Flamm and R.J. Lorentzen, Eds.), pp. 13-15, Princeton Scientific, Princeton, NJ.

Dellarco, V.L., and Prival, M.J. (1989). Mutagenicity of nitro compounds in *Salmonella typhimurium* in the presence of flavin mononucleotide in preincubation assay. *Environ. Mol. Mutagen.* **13**, 116-127.

Dinse, G.E., and Haseman, J.K. (1986). Logistic regression analysis of incidental-tumor data from animal carcinogenicity experiments. *Fundam. Appl. Toxicol.* **6**, 44-52.

Dinse, G.E., and Lagakos, S.W. (1983). Regression analysis of tumour prevalence data. *Appl. Statist.* **C32**, 236-248.

Dunn, O.J. (1964). Multiple comparisons using rank sums. *Technometrics* **6**, 241-252.

Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Am. Stat. Assoc.* **50**, 1095-1121.

El Dareer, S.M., Tillary, K.F., and Hill, D.L. (1984). Investigation on the disposition of oral doses of some water soluble pigments. *Bull. Environ. Contam. Toxicol.* **32**, 171-174.

Emerson, P.M., and Wilkerson, J.H. (1966). Lactate dehydrogenase in the diagnosis and assessment of the response to treatment of megaloblastic anemia. *Br. J. Hematol.* **12**, 678.

Galloway, S.M., Bloom, A.D., Resnick, M., Marolin, B.H., Nakamura, F., Archer, P., and Zeiger, E. (1985). Development of a standard protocol for *in vitro* cytogenetic testing with Chinese hamster ovary cells: comparison of results for 22 compounds in two laboratories. *Environ. Mol. Mutagen.* **7**, 1-51.

Galloway, S.M., Armstrong, M.J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A.D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B.H., Resnick, M.A., Anderson, B., and Zeiger, E. (1987). Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. *Environ. Mol. Mutagen.* **10** (Suppl. 10), 1-175.

Garner, R.C., and Nutman, C.A. (1977). Testing of some azo dyes and their reduction products for mutagenicity using *Salmonella typhimurium* TA1538. *Mutat. Res.* **44**, 9-19.

Gart, J.J., Chu, K.C., and Tarone, R.E. (1979). Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. *JNCI* **62**, 957-974.

Hard, G.C. (1986). Experimental models for the sequential analysis of chemically-induced renal carcinogenesis. *Toxicol. Pathol.* **14**, 112-122.

Haseman, J.K. (1984). Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. *Environ. Health Perspect.* **58**, 385-392.

Haseman, J.K., Huff, J., and Boorman, G.A. (1984). Use of historical control data in carcinogenicity studies in rodents. *Toxicol. Pathol.* **12**, 126-135.

Haseman, J.K., Huff, J., Rao, G.N., Arnold, J., Boorman, G.A., and McConnell, E.E. (1985). Neoplasms observed in untreated and corn oil gavage control groups of F344/N rats and (C57BL/6N × C3H/HeN)F_1 (B6C3F_1) mice. *JNCI* **75**, 975-984.

Haworth, S., Lawlor, T., Mortelmans, K., Speck, W., and Zeiger, E. (1983). *Salmonella* mutagenicity test results for 250 chemicals. *Environ. Mutagen.* **5** (Suppl. 1), 3-142.

Hollander, M., and Wolfe, D.A. (1973) *Nonparametric Statistical Methods.* pp. 120-123. Wiley and Sons, New York.

International Agency for Research on Cancer (IARC). (1975). *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 8, p. 155-165. World Health Organization, Lyon, France.

Jonckheere, A.R. (1954). A distribution-free *k*-sample test against ordered alternatives. *Biometrika* **41**, 133-145.

Kaplan, E.L., and Meier, P. (1958). Nonparametric estimation from incomplete observations. *J. Am. Stat. Assoc.* **53**, 457-481.

Kirk-Othmer (1978). *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 3. John Wiley and Sons, Inc., New York.

Kurokawa, Y., Hayashi, Y., Maekawa, A., Takahashi, M., Kokubo, T., and Odashima, S. (1983). Carcinogenicity of potassium bromate administered orally to F344 rats. *JNCI* **71**, 965-971.

Lynn, R.K., Donielson, D.W., Ilias, A.M., Kennish, J.M., Wong, K., and Matthews, H.B. (1980). Metabolism of bisazobiphenyl dyes derived from benzidine, 3,3′-dimethylbenzidine, or 3,3′-dimethoxybenzidine to carcinogenic aromatic amines in the dog and rat. *Toxicol. Appl. Pharmacol.* **56**, 248-258.

Maronpot, R.R., and Boorman, G.A. (1982). Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. *Toxicol. Pathol.* **10**, 71-80.

McConnell, E.E., Solleveld, H.A., Swenberg, J.A., and Boorman, G.A. (1986). Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *JNCI* **76**, 283-289.

McKnight, B., and Crowley, J. (1984). Tests for differences in tumor incidence based on animal carcinogenesis experiments. *J. Am. Stat. Assoc.* **79**, 639-648.

Melnikow, J., Keeffe, J.R., and Bernstein, R.L. (1981). Carcinogens and mutagens in the undergraduate laboratory. *J. Chem. Ed.* **58**, A11-A14.

The Merck Index. (1983). 10th ed. (M. Windholz, Ed.), Merck & Company, Rahway, NJ.

Miller, J.A., and Miller, E.C. (1977). Ultimate chemical carcinogens as reactive mutagenic electrophiles. In *Origins of Human Cancer.* (H.H. Hiatt, J.D. Watson, and J.A. Winsten, Eds.) pp. 605-628. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Moloney, W.C., and King, V.P. (1973). Reduction of leukemia incidence following splenectomy in the rat. *Cancer Res.* **33**, 573-574.

Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B., and Zeiger, E. (1986). *Salmonella* mutagenicity tests. II. Results from the testing of 270 chemicals. *Environ. Mutagen.* **8** (Suppl. 7), 1-119.

National Cancer Institute (NCI) (1976). Guidelines for Carcinogen Bioassay in Small Rodents. Technical Report Series No. 1. NIH Publication No. 76-801. U.S. Department of Health, Education, and Welfare; Public Health Service; National Institutes of Health; Bethesda, MD.

National Cancer Institute (NCI) (1978a). Bioassay of Aniline Hydrochloride for Possible Carcinogenicity (CAS No. 142-04-1). Technical Report Series No. 130. NIH Publication No. 78-1385. U.S. Department of Health, Education, and Welfare; Public Health Service; National Institutes of Health; Bethesda, MD.

National Cancer Institute (NCI) (1978b). Bioassay of 5-Nitro-*o*-anisidine for Possible Carcinogenicity (CAS No. 99-59-2) Technical Report Series No. 127. NIH Publication No. 78-1382. U.S. Department of Health, Education, and Welfare; Public Health Service; National Institutes of Health; Bethesda, MD.

National Cancer Institute (NCI) (1979). Bioassay of *p*-Chloroaniline for Possible Carcinogenicity (CAS No. 106-47-8) Technical Report Series No. 189. NIH Publication No. 79-1745. U.S. Department of Health, Education, and Welfare; Public Health Service; National Institutes of Health; Bethesda, MD.

National Institute of Occupational Safety and Health (NIOSH), National Occupational Exposure Survey (NOES) (1981-1983), unpublished provisional data as of July 1, 1989.

National Institutes of Health (NIH) (1978). Open Formula Rat and Mouse Ration (NIH-07). NIH Publication No. 11-1335. National Institutes of Health, Bethesda, MD.

National Toxicology Program (NTP) (1982a). Carcinogenesis Bioassay of D & C Red No. 9 (CAS No. 5160-02-01) in F344 Rats and B6C3F$_1$ Mice (Feed Study). Technical Report Series No. 225. NIH Publication No. 82-1781. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC, and Bethesda, MD.

National Toxicology Program (NTP) (1982b). Carcinogenesis Bioassay of C.I. Solvent Yellow 14 (CAS No. 842-07-9) in F344/N Rats and B6C3F$_1$ Mice (Feed Study). Technical Report Series No. 226. NIH Publication No. 82-1782. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC, and Bethesda, MD.

National Toxicology Program (NTP) (1989a). Toxicology and Carcinogenesis Studies of Nitrofurantoin (CAS No. 67-20-9) in F344/N Rats and B6C3F$_1$ Mice (Feed Studies). Technical Report Series No. 341. NIH Publication No. 89-2597. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1989b). Toxicology and Carcinogenesis Studies of *p*-Chloroaniline Hydrochloride (CAS No. 20265-96-7) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). Technical Report Series No. 351. NIH Publication No. 89-2806. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1989c). Toxicology and Carcinogenesis Studies of Furosemide (CAS No. 54-31-9) in F344/N Rats and B6C3F$_1$ Mice (Feed Studies). Technical Report Series No. 356. NIH Publication No. 89-2811. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1989d). Toxicology and Carcinogenesis Studies of *N,N*-Dimethylaniline (CAS No. 121-69-7) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). Technical Report Series No. 360. NIH Publication No. 89-2815. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

National Toxicology Program (NTP) (1989e). Toxicology and Carcinogenesis Studies of Hydroquinone (CAS No. 123-31-9) in F344/N Rats and B6C3F$_1$ Mice (Gavage Studies). Technical Report Series No. 366. NIH Publication No. 90-2821. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

Nony, C.R., Althaus, J.R., and Bowman, M.C. (1983). Chromatographic assays for traces of potentially carcinogenic metabolites of two azo dyes, Direct Red 2 and Direct Blue 15, in rat, hamster, and human urine. *J. Analyt. Toxicol.* **7**, 40-48.

Prankard, T.A.J. (1961). *The Red Cell. An Account of Its Chemical Physiology and Pathology.* Blackwell Scientific, Oxford, UK.

Rao, G.N., and Haseman, J.K. (1990). Growth body weight and survival trend, in F344 rats over a twelve-year period. *Proc. 1990 Summer Toxicol. Forum.* Washington. In press.

Sadtler Standard Spectra. Sadtler Research Laboratories, Philadelphia.

Shahin, M.M. (1985). Mutagenicity evaluation of nitroanilines and nitroaminophenols in *Salmonella typhimurium*. *Int. J. Cosmetic Res.* **7**, 277-289.

Shimizu, M., and Yano, E. (1986). Mutagenicity of mono-nitrobenzene derivatives in the Ames test and rec assay. *Mutat. Res.* **170**, 11-22.

Shirley, E. (1977). A non-parametric equivalent of Williams' test for contrasting increasing dose levels of a treatment. *Biometrics* **33**, 386-389.

Smith, R.P. (1983). Toxic responses of the blood. In *Cassaret and Doull's Toxicology: The Basic Science of Poisons.* 3rd ed. (C.D. Klaassen, M.O. Amdur, and J. Doull, Eds.). Macmillan, New York.

Tarone, R.E. (1975). Tests for trend in life table analysis. *Biometrika* **62**, 679-682.

Straus, D.S. (1981). Somatic mutation, cellular differentiation, and cancer causation. *JNCI* **67**, 233-241.

Tennant, R.W., Margolin, B.H., Shelby, M.D., Zeiger, E., Haseman, J.K., Spalding, J., Caspary, W., Resnick, M., Stasiewicz, S., Anderson, B., and Minor, R. (1987). Prediction of chemical carcinogenicity in rodents from *in vitro* genetic toxicity assay. *Science* **236**, 933-941.

Thompson, C.Z., Hill. L.E., Epp, J.K., and Probst, G.S. (1983). The induction of bacterial mutation and hepatocyte unscheduled DNA synthesis by monosubstituted anilines. *Environ. Mutagen.*, **5**, 803-811.

Tsuda, H., Hacker, H.J., Katayama, H., Masui, T., Ito, N., and Bannasch, P. (1986). Correlative histochemical studies on preneoplastic and neoplastic lesions in the kidney of rats treated with nitrosamines. *Virchows Arch. [Cell Pathol.]* **51**, 385-404.

U.S. International Trade Commission (USITC) (1984). *Synthetic Organic Chemicals, United States Production and Sales, 1983.* p. 42. Publication No. 1548. U.S. Government Printing Office, Washington, DC.

Valencia, R., Mason, J.M., Woodruff, R.C., and Zimmering, S. (1985). Chemical mutagenesis testing in *Drosophila.* III. Results of 48 coded compounds tested for the National Toxicology Program. *Environ. Mutagen.* **7**, 325-348.

Weisburger, E.K. (1983). Species differences in response to aromatic amines. In *Organ and Species Specificity in Chemical Carcinogenesis*, pp. 23-47. (R. Langenbach, S. Nesnow, and J.M. Rice, Eds.). Plenum, New York.

Williams, D.A. (1971). A test for differences between treatment means when several dose levels are compared with a zero dose control. *Biometrics* **27**, 103-117.

Williams, D.A. (1972). The comparison of several dose levels with a zero dose control. *Biometrics* **28**, 519-531.

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., and Mortelmans, K. (1988). *Salmonella* mutagenicity tests: IV. Results from the testing of 300 chemicals. *Environ. Mol. Mutagen.* **11** (Suppl. 12), 1-157.

Zeiger, E., Haseman, J.K., Shelby, M.D., Margolin, B.H., and Tennant, R.W. (1990). Evaluation of four *in vitro* genetic toxicity tests for predicting rodent carcinogenicity: confirmation of earlier results with 41 additional chemicals. *Environ. Mol. Mutagen.* **16**, (Suppl. 18), 1-14.

Zimmering, S., Mason, J.M., and Valencia, R. (1989). Chemical mutagenesis testing in *Drosophila.* VII. Results of 22 coded compounds tested in larval feeding experiments. *Environ. Mol. Mutagen.* **14**, 245-251.

APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR FEED STUDY OF C.I. PIGMENT RED 23

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	9
Early deaths				
Moribund	24	15	11	11
Dead	4	6	3	5
Survivors				
Terminal sacrifice	22	29	36	35
Animals examined microscopically	50	50	50	50[a]
Alimentary System				
Esophagus	(50)	(1)		(50)
Mixed tumor malignant, metastatic, salivary glands				1 (2%)
Intestine large, rectum	(50)	(1)		(50)
Intestine small, ileum	(50)	(7)	(17)	(50)
Intestine small, jejunum	(50)	(1)	(5)	(50)
Adenocarcinoma	1 (2%)			
Carcinoma			1 (20%)	
Leiomyoma	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Fibrous histiocytoma	1 (2%)			1 (2%)
Hepatocellular carcinoma	1 (2%)			1 (2%)
Hepatocellular adenoma	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Mesentery	(11)	(5)	(7)	(11)
Fibrosarcoma		1 (20%)		
Fibrous histiocytoma	1 (9%)			
Osteosarcoma, metastatic			1 (14%)	
Sarcoma			1 (14%)	
Pancreas	(50)		(2)	(49)
Carcinoma, metastatic, stomach				1 (2%)
Fibrous histiocytoma	1 (2%)			
Acinar cell, adenoma	2 (4%)		1 (50%)	1 (2%)
Salivary glands	(49)	(1)		(50)
Mixed tumor malignant				1 (2%)
Stomach, forestomach	(50)	(1)		(50)
Carcinoma, metastatic, stomach				1 (2%)
Stomach, glandular	(50)	(1)		(50)
Carcinoma				1 (2%)
Fibrous histiocytoma	1 (2%)			
Cardiovascular System				
Heart	(50)	(3)	(5)	(50)
Fibrosarcoma, metastatic, skin		1 (33%)		
Mixed tumor malignant, metastatic, salivary glands				1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Endocrine System				
Adrenal gland, cortex	(48)	(2)		(50)
Adenoma	1 (2%)			
Carcinoma		1 (50%)		
Adrenal gland, medulla	(48)	(6)	(5)	(50)
Ganglioneuroma		1 (17%)		
Pheochromocytoma malignant	1 (2%)		1 (20%)	1 (2%)
Pheochromocytoma complex			1 (20%)	1 (2%)
Pheochromocytoma benign	18 (38%)	2 (33%)	1 (20%)	15 (30%)
Bilateral, pheochromocytoma benign	12 (25%)	2 (33%)	2 (40%)	11 (22%)
Islets, pancreatic	(50)		(2)	(49)
Adenoma	1 (2%)			3 (6%)
Carcinoma	1 (2%)		2 (100%)	1 (2%)
Parathyroid gland	(49)	(1)	(1)	(49)
Adenoma	2 (4%)			2 (4%)
Mixed tumor malignant, metastatic, salivary glands				1 (2%)
Pituitary gland	(50)	(16)	(9)	(49)
Pars distalis, adenoma	12 (24%)	12 (75%)	8 (89%)	8 (16%)
Pars intermedia, adenoma	1 (2%)			
Pars nervosa, adenoma				1 (2%)
Thyroid gland	(50)	(50)	(49)	(50)
Mixed tumor malignant, metastatic, salivary glands				1 (2%)
C-cell, adenoma	3 (6%)	6 (12%)	5 (10%)	7 (14%)
C-cell, carcinoma	1 (2%)	3 (6%)	1 (2%)	3 (6%)
Follicular cell, adenoma	2 (4%)	2 (4%)		1 (2%)
Follicular cell, carcinoma	1 (2%)	2 (4%)	1 (2%)	3 (6%)
General Body System				
Tissue NOS	(4)	(1)		
Fibroma	2 (50%)			
Liposarcoma	1 (25%)			
Sarcoma		1 (100%)		
Genital System				
Epididymis	(50)	(2)		(48)
Fibrous histiocytoma	1 (2%)			
Preputial gland	(49)	(9)	(8)	(49)
Adenoma	3 (6%)	5 (56%)	8 (100%)	7 (14%)
Carcinoma	2 (4%)			1 (2%)
Prostate	(50)	(3)	(2)	(49)
Carcinoma, metastatic, stomach				1 (2%)
Fibrous histiocytoma	1 (2%)			
Seminal vesicle	(50)	(2)		(49)
Carcinoma, metastatic, stomach				1 (2%)
Fibrous histiocytoma	1 (2%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Genital System (continued)				
Testes	(50)	(44)	(44)	(49)
Bilateral, interstitial cell, adenoma	42 (84%)	43 (98%)	41 (93%)	44 (90%)
Interstitial cell, adenoma	6 (12%)	1 (2%)	3 (7%)	2 (4%)
Hematopoietic System				
Blood	(5)			
Bone marrow	(50)	(2)		(50)
Fibrous histiocytoma				1 (2%)
Sarcoma		1 (50%)		
Lymph node	(49)	(7)	(9)	(48)
Bronchial, carcinoma, metastatic, stomach				1 (2%)
Iliac, fibrous histiocytoma	1 (2%)			
Mesenteric, carcinoma, metastatic, stomach				1 (2%)
Mesenteric, fibrous histiocytoma	1 (2%)			
Pancreatic, carcinoma, metastatic, islets, pancreatic	1 (2%)			
Renal, fibrous histiocytoma	1 (2%)			
Lymph node, mandibular	(49)	(2)	(3)	(48)
Spleen	(50)	(50)	(48)	(50)
Fibrous histiocytoma	1 (2%)			1 (2%)
Hemangioma			1 (2%)	
Osteosarcoma, metastatic, bone marrow		1 (2%)		
Thymus	(49)	(1)		(46)
Carcinoma, metastatic, stomach				1 (2%)
Fibrosarcoma, metastatic, skin		1 (100%)		
Fibrous histiocytoma	1 (2%)			
Thymoma benign				1 (2%)
Integumentary System				
Mammary gland	(49)	(46)	(44)	(43)
Fibroadenoma	2 (4%)	2 (4%)	2 (5%)	3 (7%)
Fibroma				2 (5%)
Skin	(50)	(14)	(13)	(50)
Adenoma		1 (7%)		
Basal cell adenoma	1 (2%)		1 (8%)	
Basal cell carcinoma				2 (4%)
Fibroma			1 (8%)	
Keratoacanthoma	1 (2%)		3 (23%)	2 (4%)
Papilloma squamous	1 (2%)	2 (14%)		1 (2%)
Squamous cell carcinoma	1 (2%)		1 (8%)	
Face, keratoacanthoma				1 (2%)
Face, neurofibroma				1 (2%)
Sebaceous gland, adenoma				1 (2%)
Subcutaneous tissue, fibroma		3 (21%)	4 (31%)	2 (4%)
Subcutaneous tissue, fibrosarcoma		2 (14%)		
Subcutaneous tissue, fibrous histiocytoma				1 (2%)
Subcutaneous tissue, lipoma				1 (2%)
Subcutaneous tissue, myxoma		1 (7%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Musculoskeletal System				
Skeletal muscle				(1)
Nervous System				
Brain	(50)	(3)	(4)	(50)
Astrocytoma NOS		1 (33%)		2 (4%)
Oligodendroglioma NOS			1 (25%)	
Meninges, granular cell tumor malignant			1 (25%)	
Meninges, granular cell tumor benign	1 (2%)		1 (25%)	
Meninges, mixed tumor malignant, metastatic, salivary glands				1 (2%)
Respiratory System				
Lung	(50)	(6)	(3)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	1 (17%)		1 (2%)
Alveolar/bronchiolar carcinoma				1 (2%)
Carcinoma, metastatic, thyroid gland			1 (33%)	
Fibrosarcoma, metastatic, skin		1 (17%)		
Fibrous histiocytoma				1 (2%)
Osteosarcoma, metastatic		1 (17%)		
Osteosarcoma, metastatic, bone marrow		1 (17%)		
Squamous cell carcinoma, metastatic, skin			1 (33%)	
Nose	(50)	(1)	(1)	(49)
Basosquamous tumor benign		1 (100%)		
Special Senses System				
Ear		(1)		(1)
Pinna, neurofibroma				1 (100%)
Pinna, papilloma squamous		1 (100%)		
Zymbal's gland	(1)			
Carcinoma	1 (100%)			
Urinary System				
Kidney	(50)	(48)	(50)	(50)
Renal tubule, adenoma				2 (4%)
Renal tubule, carcinoma			1 (2%)	1 (2%)
Urinary bladder	(50)	(1)		(49)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	28 (56%)	22 (44%)	10 (20%)	4 (8%)
Lymphoma malignant histiocytic				1 (2%)
Mesothelioma malignant	2 (4%)		3 (6%)	3 (6%)
Mesothelioma NOS	2 (4%)			2 (4%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]	50	50	48	50
Total primary neoplasms	172	121	108	157
Total animals with benign neoplasms	50	48	48	49
Total benign neoplasms	117	87	83	123
Total animals with malignant neoplasms	33	30	21	22
Total malignant neoplasms	53	33	24	30
Total animals with metastatic neoplasms	2	3	3	2
Total metastatic neoplasms	2	6	3	12
Total animals with neoplasms uncertain-benign or malignant	2	1	1	4
Total uncertain neoplasms	6	1	1	13

[a] Does not include one early death that occurred prior to interim evaluation.
[b] Number of animals examined microscopically at site and the number of animals with lesions
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm

Number of Days on Study	4 4 8	5 0 2	5 1 3	5 3 5	5 3 3	5 6 4	5 6 2	5 8 2	5 8 2	5 8 5	5 9 7	6 0 5	6 1 2	6 1 2	6 1 2	6 1 2	6 1 2	6 3 0	6 3 1	6 4 0	6 4 0	6 5 5	6 7 6	6 7 6	6 8 1	7 0 0
Carcass ID Number	0 9 1	0 5 1	1 0 2	0 6 1	0 8 1	1 0 3	0 3 1	0 6 2	0 2 1	0 3 2	0 3 3	0 1 1	0 2 2	0 2 3	0 2 3	0 5 2	0 7 1	1 1 2	1 8 2	2 2 2	2 7 3	2 8 3	3 7 3	3 2 4	3 3 4	4 4 1	4 2 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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma															X											
Leiomyoma																					X					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma	X																									
Hepatocellular carcinoma													X													
Hepatocellular adenoma																									X	
Mesentery	+					+			+								+			+		+				
Fibrous histiocytoma	X																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma	X																									
Acinar cell, adenoma																										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma	X																									
Cardiovascular System																										
Blood vessel																								+		
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic																						X				
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+
Adenoma																										
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+
Pheochromocytoma malignant																										X
Pheochromocytoma benign		X			X				X	X			X												X	X
Bilateral, pheochromocytoma benign			X			X										X					X	X		X		

+: 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 23: 0 ppm (continued)

Number of Days on Study	7 0 7	7 0 9	7 2 8	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 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 4 2	0 5 3	1 0 4	0 1 3	0 1 4	0 1 5	0 3 5	0 4 3	0 4 4	0 4 5	0 5 4	0 5 5	0 6 3	0 6 4	0 6 5	0 7 4	0 7 5	0 8 4	0 8 5	1 0 1	0 9 2	0 9 3	0 9 4	0 9 5	1 0 5	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																									1
Leiomyoma																									1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																									1
Hepatocellular carcinoma																									1
Hepatocellular adenoma																	X								2
Mesentery			+				+											+	+	+					11
Fibrous histiocytoma																									1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																									1
Acinar cell, adenoma												X												X	2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																									1
Cardiovascular System																									
Blood vessel																									1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic																									1
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma	X																								1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma malignant																									1
Pheochromocytoma benign	X	X	X	X			X							X			X				X	X		X	X	18
Bilateral, pheochromocytoma benign						X						X	X		X					X			X			12

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm (continued)

Number of Days on Study	448	502	513	535	563	566	584	622	625	627	659	701	712	722	722	722	720	731	740	740	745	756	766	766	781	800
Carcass ID Number	09111	50112	02123	06121	08113	04133	03121	36122	22121	33123	33123	12111	22112	22123	52132	72111	12122	82222	72232	82333	72343	23344	42411	02515
Endocrine System (continued)																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X		
Carcinoma																										
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X		X		X										X			X							
Pars intermedia, adenoma																										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma						X									X											
C-cell, carcinoma																										
Follicular cell, adenoma																	X									
Follicular cell, carcinoma																										
General Body System																										
Tissue NOS																	+					+			+	
Fibroma																									X	
Liposarcoma																	X									
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma	X																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenoma												X							X								
Carcinoma																										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma	X																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma	X																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X			X	X		X	X	X	X	X		X	X	X			X	X	X	X	X		X
Interstitial cell, adenoma	X				X			X						X					X						X	
Hematopoietic System																										
Blood					+		+					+					+				+					
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, fibrous histiocytoma	X																									
Mesenteric, fibrous histiocytoma	X																									
Pancreatic, carcinoma, metastatic, islets, pancreatic																										
Renal, fibrous histiocytoma	X																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm (continued)

Number of Days on Study	7 0 7	7 0 9	7 2 8	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 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 4 2	0 5 3	1 0 4	0 1 3	0 1 4	0 1 5	0 3 5	0 4 3	0 4 4	0 4 5	0 5 4	0 5 5	0 6 3	0 6 4	0 6 5	0 7 4	0 7 5	0 8 4	0 8 5	1 0 1	0 9 2	0 9 3	0 9 4	0 9 5	1 0 5	**Total Tissues/ Tumors**
Endocrine System (continued)																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																									1
Carcinoma																X									1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																	X					X			2
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X									X	X				X		X		X		X			12
Pars intermedia, adenoma							X																		1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																					X				3
C-cell, carcinoma			X																						1
Follicular cell, adenoma																						X			2
Follicular cell, carcinoma															X										1
General Body System																									
Tissue NOS					+																				4
Fibroma					X																				2
Liposarcoma																									1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																									1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma													X												3
Carcinoma															X					X					2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																									1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																									1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	42
Interstitial cell, adenoma																									6
Hematopoietic System																									
Blood																									5
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Iliac, fibrous histiocytoma																									1
Mesenteric, fibrous histiocytoma																									1
Pancreatic, carcinoma, metastatic, islets, pancreatic																X									1
Renal, fibrous histiocytoma																									1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm (continued)

Number of Days on Study	4	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7
	4	0	1	3	6	6	8	8	8	9	0	1	1	1	1	1	3	3	4	4	5	7	7	8	0
	8	2	3	5	3	4	2	2	5	7	5	2	2	2	2	2	0	1	0	0	5	6	6	1	0
Carcass ID Number	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	9	5	0	6	8	0	3	6	2	3	3	1	2	2	5	7	1	8	7	8	7	2	3	4	2
	1	1	2	1	1	3	1	2	1	2	3	1	2	3	2	1	2	2	2	3	3	4	4	1	5
Hematopoietic System (continued)																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma	X																								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma	X																								
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																X									
Keratoacanthoma																									
Papilloma squamous																									
Squamous cell carcinoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meninges, granular cell tumor benign																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																					+				
Zymbal's gland																								+	
Carcinoma																								X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm (continued)

Number of Days on Study	7 0 7	7 0 9	7 2 8	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 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 4 2	0 5 3	1 0 4	0 1 3	0 1 4	0 1 5	0 3 5	0 4 3	0 4 4	0 4 5	0 5 4	0 5 5	0 6 3	0 6 4	0 6 5	0 7 4	0 7 5	0 8 4	0 8 5	1 0 1	0 9 2	0 9 3	0 9 4	0 9 5	1 0 5	**Total Tissues/ Tumors**
Hematopoietic System (continued)																										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Fibrous histiocytoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma																	X				X					2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Keratoacanthoma						X																				1
Papilloma squamous								X																		1
Squamous cell carcinoma							X																			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meninges, granular cell tumor benign																									X	1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Zymbal's gland																										1
Carcinoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm (continued)

Number of Days on Study	4	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7
	4	0	1	3	6	6	8	8	8	9	0	1	1	1	1	1	3	3	4	4	5	7	7	8	0
	8	2	3	5	3	4	2	2	5	7	5	2	2	2	2	2	0	1	0	0	5	6	6	1	0
Carcass ID Number	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	9	5	0	6	8	0	3	6	2	3	3	1	2	2	5	7	1	8	7	8	7	2	3	4	2
	1	1	2	1	1	3	1	2	1	2	3	1	2	3	2	1	2	2	2	3	3	4	4	1	5
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X		X	X	X	X	X	X	X	X	X	X	X		X	X		X		X		X	X
Mesothelioma malignant																					X				
Mesothelioma NOS									X							X									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm (continued)

Number of Days on Study	7 0 7	7 0 9	7 2 8	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 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	0 4 2	0 5 3	1 0 4	0 1 3	0 1 4	0 1 5	0 3 5	0 4 3	0 4 4	0 4 5	0 5 4	0 5 5	0 6 3	0 6 4	0 6 5	0 7 4	0 7 5	0 8 4	0 8 5	1 0 1	0 9 2	0 9 3	0 9 4	0 9 5	1 0 5	**Total Tissues/ Tumors**
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X					X					X			X	X		X			X				X	X	28
Mesothelioma malignant							X																			2
Mesothelioma NOS																										2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm

Number of Days on Study	3 0 1	4 7 7	5 1 3	5 1 3	5 5 7	5 9 2	5 9 2	5 9 2	6 0 4	6 1 0	6 4 4	6 4 7	6 7 5	6 8 1	6 8 6	6 8 6	6 8 9	6 9 1	7 1 0	7 2 3	7 2 8	7 2 9	7 2 9	7 2 9	7 3 5
Carcass ID Number	4 5 1	4 6 1	3 7 1	4 2 1	4 5 2	3 7 2	4 0 1	4 1 1	3 8 1	4 2 2	4 4 1	4 0 2	4 6 2	3 7 3	3 8 2	3 9 1	4 1 5	3 9 2	4 2 3	4 0 3	3 9 3	4 1 2	4 3 1	4 5 3	3 7 4
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																		+							
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma					X																				
Mesentery					+	+								+											
Fibrosarcoma					X																				
Pancreas																		A							
Salivary glands																		+							
Stomach																		+							
Stomach, forestomach																		+							
Stomach, glandular																		+							
Cardiovascular System																									
Heart																		+			+				
Fibrosarcoma, metastatic, skin																		X							
Endocrine System																									
Adrenal gland						+				+								+							
Adrenal gland, cortex										+								+							
Carcinoma										X															
Adrenal gland, medulla						+												+							
Ganglioneuroma																									
Pheochromocytoma benign																									
Bilateral, pheochromocytoma benign						X																			
Islets, pancreatic																		A							
Parathyroid gland																		+							
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													X		X										
Follicular cell, carcinoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm
(continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm
(continued)

Number of Days on Study	3	4	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7
	0	7	1	1	5	9	9	9	0	1	4	4	7	8	8	8	9	1	2	2	2	2	2	2	3
	1	7	3	3	7	2	2	2	4	0	4	7	5	1	6	6	9	1	0	3	8	9	9	9	5
Carcass ID Number	4	4	3	4	4	3	4	4	3	4	4	4	4	3	3	3	4	3	4	4	3	4	4	4	3
	5	6	7	2	5	7	0	1	8	2	4	0	6	7	8	9	1	9	2	0	9	1	3	5	7
	1	1	1	1	2	2	1	1	1	2	1	2	2	3	2	1	5	2	3	3	3	2	1	3	4
General Body System																									
Tissue NOS											+														
Sarcoma											X														
Genital System																									
Epididymis									+									+							
Preputial gland													+					+		+	+				
Adenoma													X												
Prostate		+														+		+							
Seminal vesicle		+																							
Testes			+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow																		+							
Sarcoma																									
Lymph node		+		+	+			+										+		+					
Lymph node, mandibular																		+							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone marrow																									
Thymus																		+							
Fibrosarcoma, metastatic, skin																		X							
Integumentary System																									
Mammary gland	I	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin			+					+	+									+				+	+		+
Adenoma																									
Papilloma squamous																									
Subcutaneous tissue, fibroma								X	X																
Subcutaneous tissue, fibrosarcoma																		X					X		
Subcutaneous tissue, myxoma			X																						

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm
(continued)

Number of Days on Study	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 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 7 5	3 8 3	3 8 4	3 8 5	3 9 4	3 9 5	4 0 4	4 0 5	4 1 3	4 1 4	4 2 4	4 2 5	4 3 2	4 3 3	4 3 4	4 3 5	4 4 2	4 4 3	4 4 4	4 4 5	4 5 4	4 5 5	4 6 3	4 6 4	4 6 5	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS																										1
Sarcoma																										1
Genital System																										
Epididymis																										2
Preputial gland		+										+								+		+			+	9
Adenoma		X										X								X		X				5
Prostate																										3
Seminal vesicle																				+						2
Testes	+		+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	44
Bilateral, interstitial cell, adenoma	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		43
Interstitial cell, adenoma																									X	1
Hematopoietic System																										
Bone marrow																				+						2
Sarcoma																				X						1
Lymph node																		+								7
Lymph node, mandibular																		+								2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone marrow																				X						1
Thymus																										1
Fibrosarcoma, metastatic, skin																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	46
Fibroadenoma											X												X			2
Skin			+		+	+				+						+	+							+	14
Adenoma					X																					1
Papilloma squamous					X					X																2
Subcutaneous tissue, fibroma																									X	3
Subcutaneous tissue, fibrosarcoma																										2
Subcutaneous tissue, myxoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm
(continued)

Number of Days on Study	3	4	5	5	5	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7		
	0	7	1	1	5	9	9	9	0	1	4	4	7	8	8	8	9	1	2	2	2	2	2	2	3
	1	7	3	3	7	2	2	2	4	0	4	7	5	1	6	6	9	1	0	3	8	9	9	9	5
Carcass ID Number	4	4	3	4	4	3	4	4	3	4	4	4	4	3	3	3	4	3	4	4	3	4	4	4	3
	5	6	7	2	5	7	0	1	8	2	4	0	6	7	8	9	1	9	2	0	9	1	3	5	7
	1	1	1	1	2	2	1	1	1	2	1	2	2	3	2	1	5	2	3	3	3	2	1	3	4
Musculoskeletal System																									
Bone																		+							
Nervous System																									
Brain	+															+		+							
Astrocytoma NOS																X									
Respiratory System																									
Lung	+			+			+				+							+							
Alveolar/bronchiolar adenoma							X																		
Fibrosarcoma, metastatic, skin																		X							
Osteosarcoma, metastatic											X														
Osteosarcoma, metastatic, bone marrow																									
Nose																		+							
Basosquamous tumor benign																		X							
Trachea																		+							
Special Senses System																									
Ear																									
Pinna, papilloma squamous																									
Eye																							+		
Urinary System																									
Kidney		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder																		+							
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X		X		X	X					X		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 23: 10,000 ppm
(continued)

Number of Days on Study	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 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 7 5	3 8 3	3 8 4	3 8 5	3 9 4	3 9 5	4 0 4	4 0 5	4 1 3	4 1 4	4 2 4	4 2 5	4 3 2	4 3 3	4 3 4	4 3 5	4 4 2	4 4 3	4 4 4	4 4 5	4 5 4	4 5 5	4 6 3	4 6 4	4 6 5	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone																										1
Nervous System																										
Brain																										3
Astrocytoma NOS																										1
Respiratory System																										
Lung																					+					6
Alveolar/bronchiolar adenoma																										1
Fibrosarcoma, metastatic, skin																										1
Osteosarcoma, metastatic																										1
Osteosarcoma, metastatic, bone marrow																					X					1
Nose																										1
Basosquamous tumor benign																										1
Trachea																										1
Special Senses System																										
Ear																	+									1
Pinna, papilloma squamous																	X									1
Eye																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X					X		X						X	X	X	X	X		X	X		22

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 ppm

Number of Days on Study	4 7 9	5 3 5	5 9 1	5 9 1	6 1 7	6 1 8	6 2 0	6 6 6	6 7 3	6 7 4	6 8 1	6 9 3	7 1 1	7 2 7	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
Carcass ID Number	2 5 1	2 8 2	2 5 3	3 1 1	3 0 1	2 5 2	2 8 3	3 0 2	3 4 1	3 2 1	2 6 1	3 3 1	2 9 1	3 0 3	3 6 2	2 5 4	2 5 5	2 6 3	2 6 4	2 6 5	2 7 1	2 7 2	2 7 3	2 7 4	2 7 5
Alimentary System																								
Intestine small	+		+		+				+	+	+		+		+		+				+	+		
Intestine small, ileum	+		+		+						+		+		+		+					+		
Intestine small, jejunum									+	+											+			
Carcinoma										X														
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma							X																	
Mesentery			+				+										+							+
Osteosarcoma, metastatic																	X							
Sarcoma			X																					
Pancreas								+																
Acinar cell, adenoma																								
Cardiovascular System																								
Heart													+						+					
Endocrine System																								
Adrenal gland					+										+									
Adrenal gland, medulla					+										+									
Pheochromocytoma malignant															X									
Pheochromocytoma complex																								
Pheochromocytoma benign																								
Bilateral, pheochromocytoma benign					X																			
Islets, pancreatic	+							+																
Carcinoma	X							X																
Parathyroid gland									+															
Pituitary gland				+					+						+		+							
Pars distalis, adenoma				X					X						X		X							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+
C-cell, adenoma							X		X															
C-cell, carcinoma																								
Follicular cell, carcinoma																								
General Body System																								
None																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 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 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	2 8 1	2 8 4	2 8 5	2 9 2	2 9 3	2 9 4	2 9 5	3 0 4	3 0 5	3 1 2	3 1 3	3 1 4	3 1 5	3 2 2	3 2 3	3 2 4	3 2 5	3 3 2	3 3 3	3 3 4	3 3 5	3 4 2	3 4 3	3 4 4	3 4 5	**Total Tissues/ Tumors**
Alimentary System																										
Intestine small			+		+				+	+	+	+	+	+	+						+			+		22
Intestine small, ileum			+						+	+	+	+	+	+							+			+		17
Intestine small, jejunum					+										+											5
Carcinoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery					+	+							+													7
Osteosarcoma, metastatic																										1
Sarcoma																										1
Pancreas						+																				2
Acinar cell, adenoma						X																				1
Cardiovascular System																										
Heart						+		+						+												5
Endocrine System																										
Adrenal gland					+		+												+							5
Adrenal gland, medulla					+		+												+							5
Pheochromocytoma malignant																										1
Pheochromocytoma complex					X																					1
Pheochromocytoma benign																			X							1
Bilateral, pheochromocytoma benign							X																			2
Islets, pancreatic																										2
Carcinoma																										2
Parathyroid gland																										1
Pituitary gland	+							+						+							+		+			9
Pars distalis, adenoma								X						X							X		X			8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma							X			X				X												5
C-cell, carcinoma					X																					1
Follicular cell, carcinoma						X																				1
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 ppm
(continued)

Number of Days on Study	4 7 9	5 3 5	5 9 1	5 9 1	6 1 7	6 1 8	6 2 0	6 6 6	6 7 3	6 7 4	6 8 1	6 9 3	7 1 1	7 2 7	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
Carcass ID Number	2 5 1	2 8 2	2 5 3	3 1 1	3 0 1	2 5 2	2 8 3	3 0 2	3 4 1	3 2 1	2 6 1	3 3 1	2 9 1	3 0 3	2 6 2	2 5 4	2 5 5	2 6 3	2 6 4	2 6 5	2 7 1	2 7 2	2 7 3	2 7 4	2 7 5
Genital System																								
Preputial gland						+						+				+	+		+					
Adenoma						X						X				X	X		X					
Prostate									+				+											
Testes	+		+		+	+	+	+		+	+	+	+	+		+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma	X		X		X	X	X	X		X	X	X	X	X		X	X	X		X	X	X	X	X
Interstitial cell, adenoma																			X					
Hematopoietic System																								
Lymph node					+				+			+	+	+										
Lymph node, mandibular					+									+										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+
Hemangioma																								
Integumentary System																								
Mammary gland	+	I	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																		X						
Skin		+									+						+				+			
Basal cell adenoma																								
Fibroma																								
Keratoacanthoma																					X			
Squamous cell carcinoma											X													
Subcutaneous tissue, fibroma		X															X							
Musculoskeletal System																								
None																								
Nervous System																								
Brain	+						+								+									
Oligodendroglioma NOS	X																							
Meninges, granular cell tumor malignant							X																	
Meninges, granular cell tumor benign																								
Respiratory System																								
Lung	+										+													
Carcinoma, metastatic, thyroid gland																								
Squamous cell carcinoma, metastatic, skin											X													
Nose					+																			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 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 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	2 8 1	2 8 4	2 8 5	2 9 2	2 9 3	2 9 4	2 9 5	3 0 4	3 0 5	3 1 2	3 1 3	3 1 4	3 1 5	3 2 2	3 2 3	3 2 4	3 2 5	3 3 2	3 3 3	3 3 4	3 3 5	3 4 2	3 4 3	3 4 4	3 4 5	**Total Tissues/ Tumors**
Genital System																										
Preputial gland	+										+						+									8
Adenoma	X										X						X									8
Prostate																										2
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	41
Interstitial cell, adenoma							X		X																	3
Hematopoietic System																										
Lymph node	+							+						+			+									9
Lymph node, mandibular														+												3
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	48
Hemangioma									X																	1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	I	+	+	+	+	+	I	+	I	+	+	+	+	I	+	+	+	44
Fibroadenoma											X															2
Skin			+				+			+	+				+			+		+	+				+	13
Basal cell adenoma																									X	1
Fibroma																			X							1
Keratoacanthoma											X									X						3
Squamous cell carcinoma																										1
Subcutaneous tissue, fibroma							X			X																4
Musculoskeletal System																										
None																										
Nervous System																										
Brain																								+		4
Oligodendroglioma NOS																										1
Meninges, granular cell tumor malignant																										1
Meninges, granular cell tumor benign																								X		1
Respiratory System																										
Lung					+																					3
Carcinoma, metastatic, thyroid gland					X																					1
Squamous cell carcinoma, metastatic, skin																										1
Nose																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 ppm
(continued)

Number of Days on Study	4	5	5	5	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	7	3	9	9	1	1	2	6	7	7	8	9	1	2	2	3	3	3	3	3	3	3	3	3	3	3
	9	5	1	1	7	8	0	6	3	4	1	3	1	7	9	2	2	2	2	2	2	2	2	2	2	2
Carcass ID Number	2	2	2	3	3	2	2	3	3	3	2	3	2	3	2	2	2	2	2	2	2	2	2	2	2	2
	5	8	5	1	0	5	8	0	4	2	6	3	9	0	6	5	5	6	6	6	7	7	7	7	7	7
	1	2	3	1	1	2	3	2	1	1	1	1	1	3	2	4	5	3	4	5	1	2	3	4	5	
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma																										
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					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 23: 25,000 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 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	2 8 1	2 8 4	2 8 5	2 9 2	2 9 3	2 9 4	2 9 5	3 0 4	3 0 5	3 1 2	3 1 3	3 1 4	3 1 5	3 2 2	3 2 3	3 2 4	3 2 5	3 3 2	3 3 3	3 3 4	3 3 5	3 4 2	3 4 3	3 4 4	3 4 5	**Total Tissues/ Tumors**	
Special Senses System																											
None																											
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Renal tubule, carcinoma																				X						1	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Leukemia mononuclear		X						X											X			X			X	10	
Mesothelioma malignant			X																							3	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 ppm

Number of Days on Study	4 1 2	5 1 3	5 1 4	6 1 2	6 1 8	6 1 8	6 2 9	6 4 8	6 4 4	6 6 6	6 7 7	6 8 8	6 8 8	6 9 6	7 1 8	7 2 7	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 5 1	1 5 2	1 8 1	2 1 1	2 0 1	2 0 2	2 2 1	2 1 2	1 7 1	1 9 1	1 8 2	1 8 3	1 8 3	2 1 3	1 3 1	1 9 2	1 3 2	1 3 3	1 3 4	1 3 5	1 4 1	1 4 2	1 4 3	1 4 4	1 4 5	1 5 3
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mixed tumor malignant, metastatic, salivary glands				X																						
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma														X												
Hepatocellular carcinoma																										
Hepatocellular adenoma																										
Mesentery		+										+		+		+	+	+								
Pancreas	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, stomach							X																			
Acinar cell, adenoma																						X				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mixed tumor malignant				X																						
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, stomach							X																			
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma							X																			
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mixed tumor malignant, metastatic, salivary glands				X																						
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																			X							
Pheochromocytoma complex																							X			
Pheochromocytoma benign		X			X	X	X					X		X		X			X	X	X		X	X		
Bilateral, pheochromocytoma benign								X	X																	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 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 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 4	1 5 5	1 6 1	1 6 2	1 6 3	1 6 4	1 6 5	1 7 2	1 7 3	1 7 4	1 7 5	1 8 4	1 8 5	1 9 3	1 9 4	1 9 5	2 0 3	2 0 4	2 0 5	2 1 4	2 1 5	2 2 2	2 2 3	2 2 4	2 2 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mixed tumor malignant, metastatic, salivary glands																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Hepatocellular carcinoma										X																1
Hepatocellular adenoma								X																	X	2
Mesentery										+	+			+	+								+			11
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, stomach																										1
Acinar cell, adenoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mixed tumor malignant																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, stomach																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mixed tumor malignant, metastatic, salivary glands																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma complex																										1
Pheochromocytoma benign												X												X	X	15
Bilateral, pheochromocytoma benign		X	X			X		X		X			X	X				X					X			11

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 ppm
(continued)

Number of Days on Study	4	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7
	1	1	1	1	1	1	2	4	6	7	8	8	9	1	2	3	3	3	3	3	3	3	3	3	3
	2	3	4	2	8	8	9	8	4	6	7	8	6	8	7	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	1	1	1	2	2	2	2	2	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1
	5	5	8	1	0	0	2	1	7	9	8	8	1	3	9	3	3	3	3	4	4	4	4	4	5
	1	2	1	1	1	2	1	2	1	1	2	3	3	1	2	2	3	4	5	1	2	3	4	5	3
Endocrine System (continued)																									
Islets, pancreatic	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X						X											
Carcinoma																							X		
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Mixed tumor malignant, metastatic, salivary glands				X																					
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X																X				
Pars nervosa, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mixed tumor malignant, metastatic, salivary glands				X																					
C-cell, adenoma								X																	X
C-cell, carcinoma								X																	
Follicular cell, adenoma																						X			
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X							X		X				X					X				
Carcinoma																						X			
Prostate	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, stomach							X																		
Seminal vesicle	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, stomach							X																		
Testes	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X	X	X		X	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma														X											
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma													X												

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 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 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 4	1 5 5	1 5 6 1	1 6 6 2	1 6 6 3	1 6 6 4	1 6 6 5	1 6 7 2	1 6 7 3	1 6 7 4	1 6 7 5	1 6 7 8	1 6 8 5	1 6 9 3	1 6 9 4	1 6 9 5	1 7 0 3	2 0 0 4	2 0 0 5	2 0 1 4	2 1 1 5	2 1 2 2	2 2 2 3	2 2 2 4	2 2 2 5	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma							X																			3
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma										X																2
Mixed tumor malignant, metastatic, salivary glands																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma							X			X	X	X		X										X		8
Pars nervosa, adenoma																					X					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mixed tumor malignant, metastatic, salivary glands																										1
C-cell, adenoma		X	X									X				X								X		7
C-cell, carcinoma											X											X				3
Follicular cell, adenoma																										1
Follicular cell, carcinoma		X																	X	X						3
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma												X					X									7
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, stomach																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, stomach																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	44
Interstitial cell, adenoma							X																			2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 ppm
(continued)

Number of Days on Study	4 1 2	5 1 3	5 1 4	6 1 2	6 1 8	6 1 8	6 2 9	6 4 8	6 6 4	6 7 6	6 8 7	6 8 8	6 9 6	7 1 8	7 2 7	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 5 1	1 5 2	1 8 1	2 1 1	2 0 1	2 0 2	2 2 1	2 1 2	1 7 1	1 9 1	1 8 2	1 8 3	2 1 3	1 3 1	1 9 2	1 3 2	1 3 3	1 3 4	1 3 5	1 4 1	1 4 2	1 4 3	1 4 4	1 4 5	1 5 3
Hematopoietic System (continued)																									
Lymph node	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, carcinoma, metastatic, stomach							X																		
Mesenteric, carcinoma, metastatic, stomach							X																		
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma													X												
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	I	+	+	I	I	+	+	+	+
Carcinoma, metastatic, stomach							X																		
Thymoma benign																			X						
Integumentary System																									
Mammary gland	+	M	+	+	I	+	I	+	+	+	+	+	+	+	+	M	+	+	+	+	+	I	+	I	+
Fibroadenoma											X														
Fibroma						X																			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																					X				
Keratoacanthoma																						X			
Papilloma squamous											X														
Face, keratoacanthoma																		X							
Face, neurofibroma																									
Sebaceous gland, adenoma																					X				
Subcutaneous tissue, fibroma															X										
Subcutaneous tissue, fibrous histiocytoma													X												
Subcutaneous tissue, lipoma																						X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma NOS														X											
Meninges, mixed tumor malignant, metastatic, salivary glands				X																					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 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 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 4	1 5 5	1 6 1	1 6 2	1 6 3	1 6 4	1 6 5	1 7 2	1 7 3	1 7 4	1 7 5	1 8 4	1 8 5	1 9 3	1 9 4	1 9 5	2 0 3	2 0 4	2 0 5	2 1 4	2 1 5	2 2 2	2 2 3	2 2 4	2 2 5	**Total Tissues/ Tumors**
Hematopoietic System (continued)																										
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bronchial, carcinoma, metastatic, stomach																										1
Mesenteric, carcinoma, metastatic, stomach																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma, metastatic, stomach																										1
Thymoma benign																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Fibroadenoma					X														X							3
Fibroma																							X			2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma										X																2
Keratoacanthoma								X																		2
Papilloma squamous																										1
Face, keratoacanthoma																										1
Face, neurofibroma						X																				1
Sebaceous gland, adenoma																										1
Subcutaneous tissue, fibroma				X																						2
Subcutaneous tissue, fibrous histiocytoma																										1
Subcutaneous tissue, lipoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma NOS													X													2
Meninges, mixed tumor malignant, metastatic, salivary glands																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 ppm
(continued)

Number of Days on Study	4 1 2	5 1 3	5 1 4	6 1 2	6 1 8	6 1 8	6 2 9	6 2 8	6 4 4	6 6 6	6 7 7	6 8 8	6 8 8	6 9 6	7 1 8	7 2 7	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 5 1	1 5 2	1 8 1	2 1 1	2 0 1	2 0 2	2 2 1	2 1 2	1 7 1	1 9 1	1 8 2	1 8 3	2 1 3	1 3 1	1 9 2	1 3 2	1 3 3	1 3 4	1 4 5	1 4 1	1 4 2	1 4 3	1 4 4	1 4 5	1 4 5	1 5 3
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Alveolar/bronchiolar carcinoma																								X		
Fibrous histiocytoma													X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear																										
Pinna, neurofibroma																										
Eye																								+		
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																										X
Renal tubule, carcinoma																					X					
Urinary bladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X																									
Lymphoma malignant histiocytic														X												
Mesothelioma malignant		X														X										
Mesothelioma NOS		X														X										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 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 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 4	1 5 5	1 6 1	1 6 2	1 6 3	1 6 4	1 6 5	1 7 2	1 7 3	1 7 4	1 7 5	1 8 4	1 8 5	1 9 3	1 9 4	1 9 5	2 0 3	2 0 4	2 0 5	2 1 4	2 1 5	2 2 2	2 2 3	2 2 4	2 2 5	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																			X							1
Alveolar/bronchiolar carcinoma																										1
Fibrous histiocytoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																+										1
Pinna, neurofibroma																X										1
Eye												+														2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																								X		2
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X	X	X																					4
Lymphoma malignant histiocytic																										1
Mesothelioma malignant																							X			3
Mesothelioma NOS																										2

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	30/48 (63%)	4/6 (67%)[e]	3/5 (60%)	26/50 (52%)
Adjusted rates[b]	77.8%			59.8%
Terminal rates[c]	14/22 (64%)			18/35 (51%)
First incidence (days)	502			513
Life table tests[d]				P=0.014N
Logistic regression tests[d]				P=0.156N
Fisher exact test[d]				P=0.199N
Adrenal Medulla: Pheochromocytoma (Benign, Complex, or Malignant)				
Overall rates	30/48 (63%)	4/6 (67%)	5/5 (100%)	26/50 (52%)
Adjusted rates	77.8%			59.8%
Terminal rates	14/22 (64%)			18/35 (51%)
First incidence (days)	502			513
Life table tests				P=0.014N
Logistic regression tests				P=0.156N
Fisher exact test				P=0.199N
Kidney (Renal Tubule): Adenoma or Carcinoma				
Overall rates	0/50 (0%)	0/48 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rates	0.0%	0.0%	2.8%	8.6%
Terminal rates	0/22 (0%)	0/28 (0%)	1/36 (3%)	3/35 (9%)
First incidence (days)	–[f]	–	729 (T)	729 (T)
Life table tests	P=0.037	–	P=0.598	P=0.213
Logistic regression tests	P=0.037	–	P=0.598	P=0.213
Cochran-Armitage test[d]	P=0.020			
Fisher exact test		–	P=0.500	P=0.121
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	3/50 (6%)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rates	10.4%	2.2%	2.3%	8.6%
Terminal rates	1/22 (5%)	0/29 (0%)	0/36 (0%)	3/35 (9%)
First incidence (days)	612	557	620	729 (T)
Life table tests	P=0.581N	P=0.256N	P=0.202N	P=0.466N
Logistic regression tests	P=0.447	P=0.319N	P=0.363N	P=0.596N
Cochran-Armitage test	P=0.481			
Fisher exact test		P=0.309N	P=0.309N	P=0.661N
Mammary Gland: Fibroadenoma				
Overall rates	2/50 (4%)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted rates	9.1%	6.9%	5.6%	8.1%
Terminal rates	2/22 (9%)	2/29 (7%)	2/36 (6%)	2/35 (6%)
First incidence (days)	729 (T)	729 (T)	729 (T)	687
Life table tests	P=0.567	P=0.593N	P=0.507N	P=0.659N
Logistic regression tests	P=0.525	P=0.593N	P=0.507N	P=0.654
Cochran-Armitage test	P=0.384			
Fisher exact test		P=0.691N	P=0.691N	P=0.500

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Mammary Gland: Fibroma or Fibroadenoma				
Overall rates	2/50 (4%)	2/50 (4%)	2/50 (4%)	5/50 (10%)
Adjusted rates	9.1%	6.9%	5.6%	12.8%
Terminal rates	2/22 (9%)	2/29 (7%)	2/36 (6%)	3/35 (9%)
First incidence (days)	729 (T)	729 (T)	729 (T)	618
Life table tests	P=0.234	P=0.593N	P=0.507N	P=0.422
Logistic regression tests	P=0.169	P=0.593N	P=0.507N	P=0.297
Cochran-Armitage test	P=0.112			
Fisher exact test		P=0.691N	P=0.691N	P=0.218
Pancreatic Islets: Adenoma				
Overall rates	1/50 (2%)	0/0	0/2 (0%)	3/49 (6%)
Adjusted rates	3.7%			7.7%
Terminal rates	0/22 (0%)			1/35 (3%)
First incidence (days)	681			648
Life table tests				P=0.466
Logistic regression tests				P=0.302
Fisher exact test				P=0.301
Pancreatic Islets: Adenoma or Carcinoma				
Overall rates	2/50 (4%)	0/0	2/2 (100%)	4/49 (8%)
Adjusted rates	8.1%			10.4%
Terminal rates	1/22 (5%)			2/35 (6%)
First incidence (days)	681			648
Life table tests				P=0.549
Logistic regression tests				P=0.411
Fisher exact test				P=0.329
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	12/50 (24%)	12/16 (75%)	8/9 (89%)	8/49 (16%)
Adjusted rates	38.3%			22.3%
Terminal rates	6/22 (27%)			7/34 (21%)
First incidence (days)	502			618
Life table tests				P=0.058N
Logistic regression tests				P=0.231N
Fisher exact test				P=0.242N
Preputial Gland: Adenoma				
Overall rates	3/49 (6%)	5/9 (56%)	8/8 (100%)	7/49 (14%)
Adjusted rates	9.9%			17.6%
Terminal rates	1/22 (5%)			4/35 (11%)
First incidence (days)	612			514
Life table tests				P=0.342
Logistic regression tests				P=0.138
Fisher exact test				P=0.159

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Preputial Gland: Adenoma or Carcinoma				
Overall rates	5/49 (10%)	5/9 (56%)	8/8 (100%)	8/49 (16%)
Adjusted rates	18.5%			20.2%
Terminal rates	3/22 (14%)			5/35 (14%)
First incidence (days)	612			514
Life table tests				P=0.552
Logistic regression tests				P=0.297
Fisher exact test				P=0.276
Skin: Keratoacanthoma				
Overall rates	1/50 (2%)	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted rates	4.5%	0.0%	8.3%	8.6%
Terminal rates	1/22 (5%)	0/29 (0%)	3/36 (8%)	3/35 (9%)
First incidence (days)	729 (T)	–	729 (T)	729 (T)
Life table tests	P=0.180	P=0.445N	P=0.493	P=0.482
Logistic regression tests	P=0.180	P=0.445N	P=0.493	P=0.482
Cochran-Armitage test	P=0.096			
Fisher exact test		P=0.500N	P=0.309	P=0.309
Skin (Subcutaneous Tissue): Fibroma				
Overall rates	0/50 (0%)	3/50 (6%)	4/50 (8%)	2/50 (4%)
Adjusted rates	0.0%	7.8%	10.2%	5.6%
Terminal rates	0/22 (0%)	1/29 (3%)	3/36 (8%)	1/35 (3%)
First incidence (days)	–	592	535	727
Life table tests	P=0.448	P=0.150	P=0.121	P=0.344
Logistic regression tests	P=0.294	P=0.113	P=0.053	P=0.336
Cochran-Armitage test	P=0.317			
Fisher exact test		P=0.121	P=0.059	P=0.247
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rates	0/50 (0%)	5/50 (10%)	4/50 (8%)	2/50 (4%)
Adjusted rates	0.0%	13.8%	10.2%	5.6%
Terminal rates	0/22 (0%)	2/29 (7%)	3/36 (8%)	1/35 (3%)
First incidence (days)	–	592	535	727
Life table tests	P=0.527N	P=0.058	P=0.121	P=0.344
Logistic regression tests	P=0.471	P=0.032	P=0.053	P=0.336
Cochran-Armitage test	P=0.475			
Fisher exact test		P=0.028	P=0.059	P=0.247
Testes: Adenoma				
Overall rates	48/50 (96%)	44/44 (100%)	44/44 (100%)	46/49 (94%)
Adjusted rates	100.0%	100.0%	100.0%	97.9%
Terminal rates	22/22 (100%)	26/26 (100%)	33/33 (100%)	34/35 (97%)
First incidence (days)	448	513	479	513
Life table tests	P<0.001N	P=0.059N	P<0.001N	P=0.001N
Logistic regression tests	P=0.147N	P=0.459	P=0.520	P=0.291N
Cochran-Armitage test	P=0.234N			
Fisher exact test		P=0.280	P=0.280	P=0.490N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Thyroid Gland (C-cell): Adenoma				
Overall rates	3/50 (6%)	6/50 (12%)	5/49 (10%)	7/50 (14%)
Adjusted rates	9.1%	18.7%	12.5%	19.1%
Terminal rates	1/22 (5%)	4/29 (14%)	3/36 (8%)	6/35 (17%)
First incidence (days)	564	675	620	648
Life table tests	P=0.383	P=0.365	P=0.557	P=0.355
Logistic regression tests	P=0.219	P=0.270	P=0.297	P=0.184
Cochran-Armitage test	P=0.174			
Fisher exact test		P=0.243	P=0.346	P=0.159
Thyroid Gland (C-cell): Carcinoma				
Overall rates	1/50 (2%)	3/50 (6%)	1/49 (2%)	3/50 (6%)
Adjusted rates	4.3%	9.0%	2.8%	7.9%
Terminal rates	0/22 (0%)	2/29 (7%)	1/36 (3%)	2/35 (6%)
First incidence (days)	728	592	729 (T)	648
Life table tests	P=0.479	P=0.391	P=0.652N	P=0.467
Logistic regression tests	P=0.371	P=0.331	P=0.663N	P=0.380
Cochran-Armitage test	P=0.333			
Fisher exact test		P=0.309	P=0.747	P=0.309
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	4/50 (8%)	9/50 (18%)	6/49 (12%)	9/50 (18%)
Adjusted rates	13.0%	26.9%	15.2%	24.7%
Terminal rates	1/22 (5%)	6/29 (21%)	4/36 (11%)	8/35 (23%)
First incidence (days)	564	592	620	648
Life table tests	P=0.444	P=0.231	P=0.610	P=0.333
Logistic regression tests	P=0.251	P=0.140	P=0.356	P=0.171
Cochran-Armitage test	P=0.185			
Fisher exact test		P=0.117	P=0.357	P=0.117
Thyroid Gland (Follicular Cell): Carcinoma				
Overall rates	1/50 (2%)	2/50 (4%)	1/49 (2%)	3/50 (6%)
Adjusted rates	4.5%	6.9%	2.8%	8.6%
Terminal rates	1/22 (5%)	2/29 (7%)	1/36 (3%)	3/35 (9%)
First incidence (days)	729 (T)	729 (T)	729 (T)	729 (T)
Life table tests	P=0.387	P=0.597	P=0.648N	P=0.482
Logistic regression tests	P=0.387	P=0.597	P=0.648N	P=0.482
Cochran-Armitage test	P=0.245			
Fisher exact test		P=0.500	P=0.747	P=0.309
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rates	3/50 (6%)	4/50 (8%)	1/49 (2%)	4/50 (8%)
Adjusted rates	11.8%	11.9%	2.8%	11.4%
Terminal rates	2/22 (9%)	2/29 (7%)	1/36 (3%)	4/35 (11%)
First incidence (days)	630	675	729 (T)	729 (T)
Life table tests	P=0.444N	P=0.640	P=0.170N	P=0.582N
Logistic regression tests	P=0.541N	P=0.561	P=0.244N	P=0.651
Cochran-Armitage test	P=0.514			
Fisher exact test		P=0.500	P=0.316N	P=0.500

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
All Organs: Mononuclear Cell Leukemia				
Overall rates	28/50 (56%)	22/50 (44%)	10/50 (20%)	4/50 (8%)
Adjusted rates	63.7%	53.5%	25.3%	10.4%
Terminal rates	8/22 (36%)	11/29 (38%)	7/36 (19%)	3/35 (9%)
First incidence (days)	502	301	617	412
Life table tests	P<0.001N	P=0.072N	P<0.001N	P<0.001N
Logistic regression tests	P<0.001N	P=0.232N	P=0.001N	P<0.001N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.159N	P<0.001N	P<0.001N
All Organs: Mesothelioma (Malignant or NOS)				
Overall rates	4/50 (8%)	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted rates	12.2%	0.0%	7.7%	7.6%
Terminal rates	1/22 (5%)	0/29 (0%)	2/36 (6%)	2/35 (6%)
First incidence (days)	585	–	620	513
Life table tests	P=0.533N	P=0.049N	P=0.324N	P=0.348N
Logistic regression tests	P=0.437	P=0.068N	P=0.578N	P=0.594N
Cochran-Armitage test	P=0.500			
Fisher exact test		P=0.059N	P=0.500N	P=0.500N
All Organs: Benign Tumors				
Overall rates	50/50 (100%)	48/50 (96%)	48/50 (96%)	49/50 (98%)
Adjusted rates	100.0%	100.0%	96.0%	100.0%
Terminal rates	22/22 (100%)	29/29 (100%)	34/36 (94%)	35/35 (100%)
First incidence (days)	448	513	479	513
Life table tests	P=0.003N	P=0.046N	P=0.001N	P=0.002N
Logistic regression tests	P=0.306N	P=0.338N	P=0.352N	P=0.443N
Cochran-Armitage test	P=0.488N			
Fisher exact test		P=0.247N	P=0.247N	P=0.500N
All Organs: Malignant Tumors				
Overall rates	33/50 (66%)	30/50 (60%)	22/50 (44%)	22/50 (44%)
Adjusted rates	71.8%	67.4%	48.4%	51.4%
Terminal rates	10/22 (45%)	15/29 (52%)	13/36 (36%)	15/35 (43%)
First incidence (days)	448	301	479	412
Life table tests	P<0.001N	P=0.132N	P=0.002N	P=0.002N
Logistic regression tests	P=0.034N	P=0.482N	P=0.109N	P=0.086N
Cochran-Armitage test	P=0.010N			
Fisher exact test		P=0.339N	P=0.022N	P=0.022N
All Organs: Benign or Malignant Tumors				
Overall rates	50/50 (100%)	50/50 (100%)	48/50 (96%)	50/50 (100%)
Adjusted rates	100.0%	100.0%	96.0%	100.0%
Terminal rates	22/22 (100%)	29/29 (100%)	34/36 (94%)	35/35 (100%)
First incidence (days)	448	301	479	412
Life table tests	P=0.003N	P=0.087N	P=0.001N	P=0.004N
Logistic regression tests	P=0.659N	–	P=0.352N	–
Cochran-Armitage test	P=0.575N			
Fisher exact test		P=1.000N	P=0.247N	P=1.000N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (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 effective incidence rates. For all tests, a negative trend or a lower incidence in a dosed group is indicated by N.
[e] Tissue was examined microscopically only when it was observed to be abnormal at necropsy; therefore statistical comparisons with the controls are not appropriate.
[f] Not applicable; no tumors in animal group

TABLE A4a
Historical Incidence of Renal Tubule Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Nitrofurantoin	0/50	0/50	0/50
Rhodamine 6G	0/50	0/50	0/50
Roxarsone	1/50	1/50	2/50
Total	1/150 (0.7%)	1/150 (0.7%)	2/150 (1.3%)
Standard deviation	1.2%	1.2%	2.3%
Range	0%-2%	0%-2%	0%-4%
Overall Historical Incidence			
Total	4/499 (0.8%)	2/499 (0.4%)	8/499[b] (1.6%)
Standard deviation	1.9%	0.8%	2.3%
Range	0%-6%	0%-2%	0%-6%

[a] Data as of 17 September 1990
[b] Includes two adenocarcinomas

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

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Nitrofurantoin	23/50
Rhodamine 6G	27/50
Roxarsone	27/50
Total	77/150 (51.3%)
Standard deviation	4.6%
Range	46%-54%
Overall Historical Incidence	
Total	256/500 (51.2%)
Standard deviation	6.61%
Range	40%-62%

[a] Data as of 17 September 1990; includes lymphocytic, monocytic, mononuclear cell, or undifferentiated leukemias

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23[a]

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	9
Early deaths				
Moribund	24	15	11	11
Dead	4	6	3	5
Survivors				
Terminal sacrifice	22	29	36	35
Animals examined microscopically	50	50	50	50[b]
Alimentary System				
Intestine large, cecum	(50)	(1)		(50)
Autolysis	1 (2%)	1 (100%)		4 (8%)
Diverticulum				1 (2%)
Edema	1 (2%)			
Inflammation, acute	2 (4%)			
Parasite metazoan				1 (2%)
Intestine large, colon	(50)	(1)		(50)
Autolysis	1 (2%)			3 (6%)
Hyperplasia, lymphoid	2 (4%)			2 (4%)
Hyperplasia, adenomatous				1 (2%)
Mineralization	1 (2%)			
Parasite metazoan	5 (10%)			9 (18%)
Intestine large, rectum	(50)	(1)		(50)
Autolysis	1 (2%)			3 (6%)
Mineralization	1 (2%)			
Parasite metazoan	7 (14%)			8 (16%)
Intestine small, duodenum	(50)	(1)		(50)
Autolysis	1 (2%)			3 (6%)
Intestine small, ileum	(50)	(7)	(17)	(50)
Autolysis	2 (4%)	1 (14%)		3 (6%)
Hyperplasia, lymphoid	11 (22%)	6 (86%)	15 (88%)	15 (30%)
Inflammation			1 (6%)	
Pigmentation			6 (35%)	4 (8%)
Intestine small, jejunum	(50)	(1)	(5)	(50)
Autolysis	2 (4%)	1 (100%)		4 (8%)
Hyperplasia, lymphoid	5 (10%)		3 (60%)	3 (6%)
Intussusception			1 (20%)	
Pigmentation				3 (6%)
Liver	(50)	(50)	(50)	(50)
Autolysis		2 (4%)		1 (2%)
Basophilic focus, multiple	10 (20%)	2 (4%)	10 (20%)	7 (14%)
Clear cell focus	2 (4%)	1 (2%)	2 (4%)	5 (10%)
Congestion				1 (2%)
Cyst				1 (2%)
Cytoplasmic alteration, focal	1 (2%)			
Ectasia	2 (4%)			1 (2%)
Eosinophilic focus	1 (2%)		1 (2%)	4 (8%)
Eosinophilic focus, multiple	1 (2%)			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 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Alimentary System (continued)				
Liver (continued)				
Hepatodiaphragmatic nodule	6 (12%)	6 (12%)	10 (20%)	6 (12%)
Hyperplasia, focal	3 (6%)	1 (2%)	1 (2%)	5 (10%)
Hypertrophy, focal	1 (2%)	2 (4%)		4 (8%)
Hypertrophy, multifocal				1 (2%)
Infarct		1 (2%)		
Inflammation, acute				1 (2%)
Inflammation, granulomatous	1 (2%)		1 (2%)	4 (8%)
Leukocytosis	1 (2%)	7 (14%)		
Necrosis	1 (2%)			
Thrombus	2 (4%)			
Vacuolization cytoplasmic		5 (10%)	3 (6%)	1 (2%)
Bile duct, hyperplasia	10 (20%)	14 (28%)	22 (44%)	17 (34%)
Centrilobular, necrosis	2 (4%)		1 (2%)	2 (4%)
Centrilobular, vacuolization cytoplasmic				2 (4%)
Hepatocyte, degeneration, cystic		3 (6%)	6 (12%)	9 (18%)
Mesentery	(11)	(5)	(7)	(11)
Autolysis	1 (9%)			
Hemorrhage		1 (20%)		
Inflammation, acute	1 (9%)			
Inflammation, chronic		2 (40%)		1 (9%)
Necrosis, focal		1 (20%)	3 (43%)	
Artery, inflammation, chronic				1 (9%)
Fat, necrosis	5 (45%)	1 (20%)		6 (55%)
Pancreas	(50)		(2)	(49)
Atrophy, diffuse				1 (2%)
Atrophy, focal	23 (46%)			21 (43%)
Autolysis	2 (4%)			1 (2%)
Cytoplasmic alteration				1 (2%)
Hyperplasia				1 (2%)
Inflammation, chronic				1 (2%)
Artery, hypertrophy			1 (50%)	
Artery, inflammation, chronic	2 (4%)			3 (6%)
Duct, cyst				1 (2%)
Salivary glands	(49)	(1)		(50)
Atrophy	2 (4%)			1 (2%)
Inflammation, chronic	1 (2%)			
Vacuolization cytoplasmic				1 (2%)
Acinar cell, cytoplasmic alteration				1 (2%)
Stomach, forestomach	(50)	(1)		(50)
Hyperkeratosis	1 (2%)			
Hyperplasia	1 (2%)			3 (6%)
Inflammation, acute				2 (4%)
Mineralization	1 (2%)			
Ulcer	1 (2%)			
Stomach, glandular	(50)	(1)		(50)
Autolysis	1 (2%)			
Mineralization	3 (6%)			5 (10%)
Ulcer	1 (2%)			
Mucosa, cyst				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 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Cardiovascular System				
Blood vessel	(1)			
Aorta, mineralization	1 (100%)			
Heart	(50)	(3)	(5)	(50)
Inflammation, chronic	43 (86%)	1 (33%)		50 (100%)
Mineralization	2 (4%)			
Atrium left, thrombus	1 (2%)	2 (67%)	5 (100%)	10 (20%)
Valve, inflammation, acute	1 (2%)			
Endocrine System				
Adrenal gland, cortex	(48)	(2)		(50)
Accessory adrenal cortical nodule				1 (2%)
Cyst	1 (2%)			
Hyperplasia	12 (25%)	1 (50%)		18 (36%)
Hypertrophy	4 (8%)			1 (2%)
Vacuolization cytoplasmic	7 (15%)	1 (50%)		8 (16%)
Adrenal gland, medulla	(48)	(6)	(5)	(50)
Hyperplasia	6 (13%)			15 (30%)
Thrombus			1 (20%)	
Bilateral, hyperplasia	1 (2%)			2 (4%)
Islets, pancreatic	(50)		(2)	(49)
Autolysis				1 (2%)
Hyperplasia	1 (2%)			1 (2%)
Parathyroid gland	(49)	(1)	(1)	(49)
Hyperplasia	1 (2%)		1 (100%)	2 (4%)
Pituitary gland	(50)	(16)	(9)	(49)
Pars distalis, cyst	7 (14%)		1 (11%)	5 (10%)
Pars distalis, ectasia		1 (6%)		
Pars distalis, hemorrhage	1 (2%)	1 (6%)		1 (2%)
Pars distalis, hyperplasia	14 (28%)	2 (13%)		8 (16%)
Pars distalis, hypertrophy	9 (18%)			5 (10%)
Pars distalis, pigmentation			1 (11%)	
Pars intermedia, hyperplasia	2 (4%)			
Pars nervosa, cyst				1 (2%)
Thyroid gland	(50)	(50)	(49)	(50)
Ultimobranchial cyst				1 (2%)
C-cell, hyperplasia	17 (34%)	19 (38%)	19 (39%)	13 (26%)
Follicle, cyst		2 (4%)	2 (4%)	
Follicle, dilatation	2 (4%)	1 (2%)	3 (6%)	4 (8%)
Follicular cell, hyperplasia	1 (2%)	1 (2%)		
Follicular cell, hyperplasia, cystic	1 (2%)	5 (10%)		1 (2%)
Follicular cell, hypertrophy				1 (2%)
General Body System				
Tissue NOS	(4)	(1)		
Inflammation, chronic active	1 (25%)			

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Genital System				
Epididymis	(50)	(2)		(48)
Granuloma sperm	1 (2%)			1 (2%)
Inflammation, chronic	1 (2%)			
Preputial gland	(49)	(9)	(8)	(49)
Cyst		1 (11%)		
Hyperplasia				1 (2%)
Inflammation, acute	9 (18%)	1 (11%)		3 (6%)
Inflammation, chronic	14 (29%)	1 (11%)		14 (29%)
Inflammation, chronic active		1 (11%)		
Prostate	(50)	(3)	(2)	(49)
Cyst				1 (2%)
Hyperplasia	1 (2%)			
Inflammation, acute	8 (16%)	1 (33%)	2 (100%)	4 (8%)
Inflammation, chronic	20 (40%)	1 (33%)		23 (47%)
Seminal vesicle	(50)	(2)		(49)
Dilatation	1 (2%)	1 (50%)		2 (4%)
Inflammation, acute		1 (50%)		
Epithelium, degeneration				1 (2%)
Testes	(50)	(44)	(44)	(49)
Atrophy	1 (2%)		2 (5%)	
Hemorrhage	1 (2%)			
Bilateral, interstitial cell, hyperplasia	2 (4%)			1 (2%)
Interstitial cell, hyperplasia		1 (2%)		1 (2%)
Hematopoietic System				
Blood	(5)			
Anemia	2 (40%)			
Bone marrow	(50)	(2)		(50)
Autolysis	2 (4%)			1 (2%)
Hemorrhage				1 (2%)
Hypoplasia				3 (6%)
Myelofibrosis				1 (2%)
Myeloid cell, hyperplasia	1 (2%)	1 (50%)		2 (4%)
Lymph node	(49)	(7)	(9)	(48)
Axillary, hyperplasia, RE cell				1 (2%)
Inguinal, hyperplasia, RE cell			1 (11%)	
Mediastinal, hemorrhage		1 (14%)	1 (11%)	1 (2%)
Mediastinal, hyperplasia, RE cell				1 (2%)
Mesenteric, autolysis	1 (2%)			
Mesenteric, congestion				2 (4%)
Mesenteric, ectasia			1 (11%)	
Mesenteric, hemorrhage	1 (2%)		1 (11%)	
Mesenteric, hyperplasia, RE cell				1 (2%)
Mesenteric, pigmentation			4 (44%)	10 (21%)
Mesenteric, lymphocyte, depletion	1 (2%)			
Pancreatic, congestion	1 (2%)			
Pancreatic, ectasia	2 (4%)			
Pancreatic, hyperplasia	1 (2%)			1 (2%)
Pancreatic, hyperplasia, RE cell		1 (14%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Hematopoietic System (continued)				
Lymph node, mandibular	(49)	(2)	(3)	(48)
Congestion				1 (2%)
Ectasia	1 (2%)		1 (33%)	1 (2%)
Hemorrhage	1 (2%)			1 (2%)
Hyperplasia	1 (2%)		1 (33%)	4 (8%)
Hyperplasia, RE cell	1 (2%)			
Spleen	(50)	(50)	(48)	(50)
Atrophy				1 (2%)
Autolysis		1 (2%)		1 (2%)
Congestion	4 (8%)	1 (2%)		1 (2%)
Fibrosis	4 (8%)	3 (6%)	1 (2%)	1 (2%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)		
Hematopoietic cell proliferation granulocytic	1 (2%)	2 (4%)	3 (6%)	1 (2%)
Hematopoietic cell proliferation erythrocytic		1 (2%)		
Infarct		1 (2%)		
Necrosis	1 (2%)			
Pigmentation				1 (2%)
Thymus	(49)	(1)		(46)
Angiectasis	1 (2%)			
Congestion	1 (2%)			
Integumentary System				
Mammary gland	(49)	(46)	(44)	(43)
Cyst		1 (2%)		
Galactocele	1 (2%)	1 (2%)		
Hemorrhage			1 (2%)	
Hyperplasia	4 (8%)	7 (15%)	9 (20%)	6 (14%)
Inflammation, chronic	1 (2%)	1 (2%)		
Duct, ectasia	3 (6%)	12 (26%)	7 (16%)	5 (12%)
Skin	(50)	(14)	(13)	(50)
Acanthosis		1 (7%)	1 (8%)	
Congestion	1 (2%)			
Cyst epithelial inclusion			1 (8%)	
Hyperkeratosis			1 (8%)	1 (2%)
Inflammation, chronic active	1 (2%)			1 (2%)
Face, inflammation, chronic				1 (2%)
Subcutaneous tissue, abscess				1 (2%)
Subcutaneous tissue, cyst		1 (7%)		
Subcutaneous tissue, fibrosis		1 (7%)		
Subcutaneous tissue, inflammation, chronic	1 (2%)	1 (7%)	1 (8%)	
Tail, acanthosis		4 (29%)		
Tail, cyst epithelial inclusion				2 (4%)
Tail, hyperkeratosis		4 (29%)	1 (8%)	1 (2%)
Tail, inflammation, acute		1 (7%)		
Musculoskeletal System				
Bone	(50)	(1)		(50)
Fibrous osteodystrophy	1 (2%)			3 (6%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Nervous System				
Brain	(50)	(3)	(4)	(50)
Compression	2 (4%)	1 (33%)	1 (25%)	5 (10%)
Hydrocephalus	1 (2%)			
Inflammation, acute, multifocal	1 (2%)			
Choroid plexus, infiltration cellular, lymphocytic				1 (2%)
Respiratory System				
Lung	(50)	(6)	(3)	(50)
Autolysis				1 (2%)
Congestion	1 (2%)		1 (33%)	1 (2%)
Hemorrhage	1 (2%)	1 (17%)		
Hyperplasia, lymphoid				5 (10%)
Inflammation, chronic	2 (4%)			2 (4%)
Inflammation, granulomatous				1 (2%)
Mineralization	1 (2%)			
Thrombus	1 (2%)			
Alveolar epithelium, hyperplasia	1 (2%)			
Alveolus, infiltration cellular, histiocytic	5 (10%)			1 (2%)
Perivascular, infiltration cellular, lymphocytic	1 (2%)			1 (2%)
Nose	(50)	(1)	(1)	(49)
Autolysis				1 (2%)
Foreign body	5 (10%)			5 (10%)
Fungus	4 (8%)			2 (4%)
Hyperkeratosis			1 (100%)	
Inflammation, chronic	4 (8%)			4 (8%)
Inflammation, chronic active			1 (100%)	
Metaplasia, squamous			1 (100%)	
Mucosa, inflammation, chronic active	9 (18%)			9 (18%)
Mucosa, glands, exudate				1 (2%)
Nasolacrimal duct, inflammation, acute		1 (100%)		
Nasolacrimal duct, inflammation, chronic	5 (10%)			11 (22%)
Respiratory epithelium, hyperplasia	3 (6%)			1 (2%)
Special Senses System				
Eye	(1)	(1)		(2)
Bilateral, lens, cataract				1 (50%)
Bilateral, retina, degeneration				1 (50%)
Cornea, inflammation, chronic				1 (50%)
Lens, cataract	1 (100%)	1 (100%)		
Retina, degeneration	1 (100%)			
Retina, inflammation, chronic		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 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Urinary System				
Kidney	(50)	(48)	(50)	(50)
Autolysis		1 (2%)		1 (2%)
Congestion		1 (2%)	2 (4%)	1 (2%)
Inflammation, acute, multifocal	1 (2%)			
Mineralization				1 (2%)
Nephropathy	49 (98%)	48 (100%)	49 (98%)	49 (98%)
Cortex, cyst			2 (4%)	2 (4%)
Renal tubule, degeneration	1 (2%)			
Renal tubule, hyperplasia	3 (6%)	6 (13%)	5 (10%)	8 (16%)
Renal tubule, hypertrophy, focal			1 (2%)	
Renal tubule, epithelium, hypertrophy, focal	1 (2%)			
Urinary bladder	(50)	(1)		(49)
Mineralization				1 (2%)

[a] Number of animals examined microscopically at site and the number of animals with lesion.
[b] Does not include one early death that occurred prior to scheduled sacrifice.

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR FEED STUDY OF C.I. PIGMENT RED 23

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	18	11	14	8
Dead	3	5	3	2
Survivors				
Terminal sacrifice	29	34	33	40
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)		(1)	(50)
Fibrosarcoma, metastatic, uterus			1 (100%)	
Liver	(50)	(50)	(50)	(50)
Adenoma	1 (2%)		1 (2%)	1 (2%)
Fibrosarcoma, metastatic, uterus			1 (2%)	
Mesentery	(4)	(2)	(7)	(5)
Carcinoma				1 (20%)
Carcinoma, metastatic, ovary			1 (14%)	
Fibrosarcoma, metastatic, uterus			1 (14%)	
Sarcoma	1 (25%)			1 (20%)
Pancreas	(50)	(50)	(50)	(50)
Acinar cell, adenoma		2 (4%)		
Stomach, forestomach	(50)	(2)		(50)
Leiomyosarcoma				1 (2%)
Tongue		(1)		(1)
Papilloma squamous		1 (100%)		
Cardiovascular System				
None				
Endocrine System				
Adrenal gland, cortex	(50)	(1)		(50)
Adenoma	2 (4%)			2 (4%)
Carcinoma		1 (100%)		
Adrenal gland, medulla	(49)	(1)	(1)	(50)
Pheochromocytoma malignant	1 (2%)	1 (100%)	1 (100%)	
Pheochromocytoma benign	1 (2%)			6 (12%)
Bilateral, pheochromocytoma benign	3 (6%)			
Islets, pancreatic	(50)	(49)	(49)	(50)
Adenoma		2 (4%)	1 (2%)	3 (6%)
Carcinoma				1 (2%)
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, adenoma	29 (58%)	23 (46%)	28 (56%)	18 (36%)
Pars distalis, carcinoma		2 (4%)		

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Endocrine System (continued)				
Thyroid gland	(50)	(50)	(50)	(50)
Bilateral, C-cell, adenoma		1 (2%)	1 (2%)	
C-cell, adenoma	5 (10%)	4 (8%)	4 (8%)	2 (4%)
C-cell, carcinoma	1 (2%)		4 (8%)	3 (6%)
Follicular cell, adenoma		1 (2%)		3 (6%)
Follicular cell, carcinoma	1 (2%)			1 (2%)
General Body System				
Tissue NOS			(1)	
Mediastinum, myxoma			1 (100%)	
Genital System				
Clitoral gland	(47)	(48)	(47)	(49)
Adenoma	5 (11%)	4 (8%)	3 (6%)	2 (4%)
Carcinoma	3 (6%)		1 (2%)	
Ovary	(50)	(4)	(1)	(50)
Carcinoma			1 (100%)	
Granulosa cell tumor NOS		1 (25%)		
Granulosa cell tumor benign				1 (2%)
Thecoma NOS		2 (50%)		
Uterus	(50)	(50)	(50)	(50)
Carcinoma, metastatic, ovary			1 (2%)	
Fibrosarcoma			1 (2%)	
Leiomyoma			1 (2%)	
Cervix, sarcoma stromal		1 (2%)		
Cervix, endometrium, polyp stromal			1 (2%)	
Endometrium, polyp stromal	7 (14%)	4 (8%)	7 (14%)	13 (26%)
Endometrium, sarcoma stromal	1 (2%)	1 (2%)	1 (2%)	
Vagina	(8)		(1)	(4)
Fibrosarcoma	1 (13%)			
Leiomyosarcoma	1 (13%)			
Sarcoma			1 (100%)	
Schwannoma malignant	1 (13%)			
Hematopoietic System				
Bone marrow	(50)	(1)	(1)	(50)
Lymph node	(50)	(2)	(2)	(50)
Lumbar, carcinoma, metastatic, ovary			1 (50%)	
Renal, carcinoma, metastatic, ovary			1 (50%)	
Lymph node, mandibular	(50)		(1)	(50)
Spleen	(50)	(50)	(49)	(50)
Fibrosarcoma, metastatic, uterus			1 (2%)	
Hemangioma				1 (2%)
Thymus	(49)			(48)
Thymoma benign	1 (2%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Integumentary System				
Mammary gland	(50)	(38)	(32)	(50)
Adenoma		2 (5%)	2 (6%)	1 (2%)
Carcinoma	1 (2%)	2 (5%)		
Fibroadenoma	23 (46%)	24 (63%)	14 (44%)	19 (38%)
Skin	(50)	(8)	(2)	(49)
Basal cell carcinoma		1 (13%)		
Keratoacanthoma	1 (2%)			1 (2%)
Sebaceous gland, carcinoma			1 (50%)	
Subcutaneous tissue, fibroma		1 (13%)		
Subcutaneous tissue, fibrosarcoma	1 (2%)			1 (2%)
Subcutaneous tissue, lipoma	1 (2%)			
Tail, hemangiosarcoma		1 (13%)		
Tail, papilloma squamous		2 (25%)		
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(5)	(3)	(50)
Astrocytoma NOS		1 (20%)		3 (6%)
Glioma NOS	1 (2%)	1 (20%)		
Meningioma malignant				1 (2%)
Oligodendroglioma NOS	1 (2%)			
Choroid plexus, meningioma malignant, metastatic, brain				1 (2%)
Meninges, granular cell tumor benign	1 (2%)			
Respiratory System				
Lung	(50)	(4)	(8)	(50)
Alveolar/bronchiolar adenoma		1 (25%)	1 (13%)	
Alveolar/bronchiolar carcinoma	1 (2%)	1 (25%)		
Carcinoma, metastatic, ovary			1 (13%)	
Carcinoma, metastatic, skin			1 (13%)	
Fibrosarcoma, metastatic, uterus			1 (13%)	
Special Senses System				
Ear			(1)	
Pinna, papilloma squamous			1 (100%)	
Zymbal's gland		(2)	(1)	
Adenoma		2 (100%)	1 (100%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Urinary System				
Kidney	(50)	(45)	(44)	(50)
Renal tubule, adenoma				1 (2%)
Urinary bladder	(50)	(2)		(50)
Papilloma		1 (50%)		
Systemic Lesions				
Multiple organs[a]	(50)	(50)	(50)	(50)
Leukemia mononuclear	14 (28%)	7 (14%)	3 (6%)	3 (6%)
Neoplasm Summary				
Total animals with primary neoplasms[b]	48	48	44	44
Total primary neoplasms	110	98	81	90
Total animals with benign neoplasms	43	43	41	41
Total benign neoplasms	80	75	67	74
Total animals with malignant neoplasms	22	15	14	10
Total malignant neoplasms	28	18	14	13
Total animals with metastatic neoplasms			3	1
Total metastatic neoplasms			11	1
Total animals with neoplasms uncertain-benign or malignant	2	5		3
Total uncertain neoplasms	2	5		3

[a] Number of animals examined microscopically at site and the number of animals with lesion.
[b] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm

Number of Days on Study	2 4 9	3 7 8	4 1 2	4 9 4	5 0 7	5 3 3	5 7 8	5 8 2	5 9 1	5 9 1	5 9 6	6 0 1	6 1 6	6 4 8	6 5 5	6 7 5	6 7 6	6 8 1	6 8 7	6 9 3	6 9 6	7 1 8	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	5 0 1	5 4 1	5 6 1	5 3 1	4 9 1	5 8 1	5 0 2	5 3 2	5 2 1	5 2 2	5 5 1	5 9 2	5 0 3	5 2 3	5 2 3	5 0 4	5 9 3	5 3 3	5 5 2	5 6 2	5 1 1	5 4 2	4 9 4	4 9 5	5 0 5	5 1 2
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Mesentery		+												+			+									
Sarcoma																	X									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Blood vessel																						+				
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																										
Pheochromocytoma benign																										
Bilateral, pheochromocytoma benign		X						X																X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X			X	X			X	X	X	X	X	X	X	X		X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma											X												X	X		
C-cell, carcinoma																								X		
Follicular cell, carcinoma																										

+: 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 23: 0 ppm
(continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	
Carcass ID Number	51 3	51 4	51 5	52 4	52 5	53 4	53 5	53 3	54 4	54 5	55 3	55 4	55 5	56 3	56 4	56 5	57 1	57 2	57 3	57 4	57 5	58 2	58 3	58 4	58 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X								1
Mesentery		+																								4
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X			X										2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant														X												1
Pheochromocytoma benign																							X			1
Bilateral, pheochromocytoma benign																										3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X			X	X	X	X	X			X	X		X		X	X	X	X		X	X		X	X	29
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma				X																				X		5
C-cell, carcinoma																										1
Follicular cell, carcinoma			X																							1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm (continued)

Number of Days on Study	2 4 9	3 7 8	4 1 2	4 9 4	5 0 7	5 3 3	5 7 8	5 8 2	5 9 1	5 9 1	6 0 6	6 1 8	6 4 8	6 5 5	6 7 5	6 7 6	6 8 1	6 8 7	6 9 3	6 9 6	7 1 8	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	5 0 1	5 4 1	5 6 1	5 3 1	4 9 1	5 8 1	5 0 2	5 3 2	5 2 1	5 2 2	5 5 1	4 9 2	5 0 3	5 2 3	5 0 3	5 9 4	5 3 3	5 5 2	5 6 2	5 1 1	5 4 2	4 9 4	4 9 5	5 0 5	5 1 2
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	
Adenoma													X												
Carcinoma							X							X											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrium, polyp stromal														X						X		X			
Endometrium, sarcoma stromal																					X				
Vagina				+		+										+				+		+			
Fibrosarcoma						X																			
Leiomyosarcoma				X																					
Schwannoma malignant																X									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma					X			X	X	X								X			X	X	X		X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma														X											
Subcutaneous tissue, fibrosarcoma																			X						
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 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 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 1 3	5 1 4	5 1 5	5 2 4	5 2 5	5 3 4	5 3 5	5 4 3	5 4 4	5 4 5	5 5 3	5 5 4	5 5 5	5 6 3	5 6 4	5 6 5	5 7 1	5 7 2	5 7 3	5 7 4	5 7 5	5 8 2	5 8 3	5 8 4	5 8 5	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma		X												X	X		X									5
Carcinoma															X											3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrium, polyp stromal		X					X						X				X									7
Endometrium, sarcoma stromal																										1
Vagina				+																		+	+			8
Fibrosarcoma																										1
Leiomyosarcoma																										1
Schwannoma malignant																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymoma benign							X																			1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																						X				1
Fibroadenoma	X		X	X				X	X			X	X	X	X			X		X		X	X	X		23
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, lipoma																						X				1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm
(continued)

Number of Days on Study	2 4 9	3 7 8	4 1 2	4 9 4	5 0 7	5 3 3	5 7 8	5 8 2	5 9 1	5 9 1	6 0 6	6 1 8	6 4 8	6 5 5	6 7 5	6 7 6	6 8 1	6 8 7	6 9 3	6 9 6	7 1 8	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	5 0 1	5 4 1	5 6 1	5 3 1	4 9 1	5 8 1	5 0 2	5 3 2	5 2 1	5 2 2	5 5 1	4 9 2	5 0 3	5 2 3	5 0 4	5 9 3	4 3 3	5 3 2	5 5 2	5 6 2	5 1 1	5 4 2	4 9 4	4 9 5	5 0 5	5 1 2
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma NOS													X												
Oligodendroglioma NOS	X																								
Meninges, granular cell tumor benign																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																						+			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter																					+				
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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 23: 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 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 1 3	5 1 4	5 1 5	5 2 4	5 2 5	5 3 4	5 3 5	5 4 3	5 4 4	5 4 5	5 5 3	5 5 4	5 5 5	5 6 3	5 6 4	5 6 5	5 7 1	5 7 2	5 7 3	5 7 4	5 7 5	5 8 2	5 8 3	5 8 4	5 8 5	**Total Tissues/ Tumors**
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma NOS																										1
Oligodendroglioma NOS																										1
Meninges, granular cell tumor benign																		X								1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																						X				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X			X		X		X					X				X			X				14

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm

Number of Days on Study	2 4 2	4 0 7	5 1 4	5 9 2	6 1 2	6 4 5	6 5 1	6 7 3	6 7 3	6 7 3	6 7 3	6 8 6	6 9 3	6 9 7	7 0 3	7 2 7	7 2 9	7 2 9	7 2 9	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	8 8 1	8 6 1	9 4 1	8 7 1	8 8 2	9 2 1	8 7 2	8 8 3	9 0 1	9 3 1	9 4 2	9 3 2	8 5 1	9 2 2	8 9 1	8 9 2	8 5 2	8 6 2	8 7 3	8 9 3	8 5 3	8 5 4	8 5 5	8 6 3	8 6 4
Alimentary System																									
Intestine small	+													+			+	+		+		+			+
Intestine small, ileum	+													+			+	+				+			+
Intestine small, jejunum																				+					+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																		+							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell, adenoma																							X		
Stomach		+										+													
Stomach, forestomach		+										+													
Stomach, glandular		+																							
Tongue																						+			
Papilloma squamous																						X			
Cardiovascular System																									
None																									
Endocrine System																									
Adrenal gland																					+				
Adrenal gland, cortex																					+				
Carcinoma																					X				
Adrenal gland, medulla																									
Pheochromocytoma malignant																									
Islets, pancreatic	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland												+													
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X	X	X		X	X	X								X						
Pars distalis, carcinoma				X														X							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma													X												
C-cell, adenoma																									
Follicular cell, adenoma																				X					
General Body System																									
None																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm (continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	8 6 5	8 7 4	8 7 5	8 8 4	8 8 5	8 9 4	8 9 5	9 0 2	9 0 3	9 0 4	9 0 5	9 1 1	9 1 2	9 1 3	9 1 4	9 1 5	9 2 3	9 2 4	9 2 5	9 3 3	9 3 4	9 3 5	9 4 3	9 4 4	9 4 5	**Total Tissues/ Tumors**
Alimentary System																										
Intestine small	+		+	+							+		+	+				+	+		+			+	+	18
Intestine small, ileum	+		+	+							+		+	+					+		+		+			15
Intestine small, jejunum			+															+					+	+		6
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery										+																	2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell, adenoma																								X			2
Stomach																											2
Stomach, forestomach																											2
Stomach, glandular																											1
Tongue																											1
Papilloma squamous																											1
Cardiovascular System																											
None																											
Endocrine System																											
Adrenal gland					+																						2
Adrenal gland, cortex																											1
Carcinoma																											1
Adrenal gland, medulla					+																						1
Pheochromocytoma malignant					X																						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																			X				X				2
Parathyroid gland																											1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X		X	X	X	X	X		X	X			X			X		X	X	X	X		X			23
Pars distalis, carcinoma																											2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																											1
C-cell, adenoma								X	X			X														X	4
Follicular cell, adenoma																											1
General Body System																											
None																											

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm (continued)

Number of Days on Study	2 4 5 5 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7
	4 0 1 9 1 4 5 7 7 7 7 8 9 9 0 2 2 2 2 2 3 3 3 3 3
	2 7 4 2 2 5 1 3 3 3 3 6 3 7 3 7 9 9 9 9 5 5 5 5 5
Carcass ID Number	8 8 9 8 8 9 8 8 9 9 9 9 8 9 8 8 8 8 8 8 8 8 8 8 8
	8 6 4 7 8 2 7 8 0 3 4 3 5 2 9 9 5 6 7 9 5 5 5 6 6
	1 1 1 1 2 1 2 3 1 1 2 2 1 2 1 2 2 2 3 3 3 4 5 3 4
Genital System	
Clitoral gland	+ +
Adenoma	X
Ovary	+ + + +
Granulosa cell tumor NOS	X
Thecoma NOS	X
Uterus	+ +
Cervix, sarcoma stromal	X
Endometrium, polyp stromal	X X X
Endometrium, sarcoma stromal	X
Hematopoietic System	
Bone marrow	+
Lymph node	+ +
Spleen	+ +
Integumentary System	
Mammary gland	+ + + + + + + + + + + + + + + + + + + +
Adenoma	
Carcinoma	X
Fibroadenoma	X X X X X X X X X X
Skin	+ + + + + + +
Basal cell carcinoma	X
Subcutaneous tissue, fibroma	X
Tail, hemangiosarcoma	X
Tail, papilloma squamous	X
Musculoskeletal System	
Bone	+ + +
Nervous System	
Brain	+ + + + + +
Astrocytoma NOS	X
Glioma NOS	X
Respiratory System	
Lung	+ + + +
Alveolar/bronchiolar adenoma	
Alveolar/bronchiolar carcinoma	X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm (continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	8 6 5	8 7 4	8 7 5	8 8 4	8 8 5	8 9 4	8 9 5	9 0 2	9 0 3	9 0 4	9 0 5	9 1 1	9 1 2	9 1 3	9 1 4	9 1 5	9 2 3	9 2 4	9 2 5	9 3 3	9 3 4	9 3 5	9 4 3	9 4 4	9 4 5	**Total Tissues/ Tumors**
Genital System																										
Clitoral gland	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma			X				X						X													4
Ovary								+																		4
Granulosa cell tumor NOS																										1
Thecoma NOS								X																		2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cervix, sarcoma stromal																										1
Endometrium, polyp stromal					X																					4
Endometrium, sarcoma stromal																										1
Hematopoietic System																										
Bone marrow																										1
Lymph node																										2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland		+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+		38
Adenoma																						X	X			2
Carcinoma				X																						2
Fibroadenoma		X	X		X	X	X		X				X	X	X		X	X		X	X	X		X		24
Skin	+				+				+																	8
Basal cell carcinoma																										1
Subcutaneous tissue, fibroma																										1
Tail, hemangiosarcoma																										1
Tail, papilloma squamous	X																									2
Musculoskeletal System																										
Bone										+						+										5
Nervous System																										
Brain																										5
Astrocytoma NOS																										1
Glioma NOS																										1
Respiratory System																										
Lung		+																								4
Alveolar/bronchiolar adenoma		X																								1
Alveolar/bronchiolar carcinoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm (continued)

Number of Days on Study	2	4	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	
	4	0	1	9	1	4	5	7	7	7	7	8	9	9	0	2	2	2	2	2	3	3	3	3	
	2	7	4	2	2	5	1	3	3	3	3	6	3	7	3	7	9	9	9	9	5	5	5	5	
Carcass ID Number	8	8	9	8	8	9	8	8	9	9	9	9	8	9	8	8	8	8	8	8	8	8	8	8	
	8	6	4	7	8	2	7	8	0	3	4	3	5	2	9	9	5	6	7	9	5	5	5	6	
	1	1	1	1	2	1	2	3	1	1	2	2	1	2	1	2	2	2	3	3	3	4	5	3	
Special Senses System																									
Eye																		+						+	
Zymbal's gland					+																				
Adenoma					X																				
Urinary System																									
Kidney		+		+	+	+	+	+	+	+	+	+	+		+	+	+	+	+		+	+	+	+	+	
Urinary bladder						+													+						
Papilloma						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 23: 10,000 ppm (continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	8 6 5	8 7 4	8 7 5	8 8 4	8 8 5	8 9 4	8 9 5	9 0 2	9 0 3	9 0 4	9 0 5	9 1 1	9 1 2	9 1 3	9 1 4	9 1 5	9 2 3	9 2 4	9 2 5	9 3 3	9 3 4	9 3 5	9 4 3	9 4 4	9 4 5	**Total Tissues/ Tumors**
Special Senses System																										
Eye																										2
Zymbal's gland			+																							2
Adenoma			X																							2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	45
Urinary bladder																										2
Papilloma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																							X			7

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 ppm

Number of Days on Study	3 2 5	4 5 7	4 9 1	5 0 1	5 4 6	5 6 4	5 7 2	5 9 5	6 1 2	6 1 8	6 3 1	6 5 1	6 5 5	6 6 2	6 8 8	6 8 8	6 9 3	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	7 3 2	7 5 1	7 6 1	7 5 2	8 2 1	7 4 1	7 3 3	7 4 2	8 2 2	8 1 1	7 8 1	7 6 2	7 9 1	7 4 3	7 4 4	7 1 1	8 2 2	7 1 3	7 3 4	7 3 5	7 4 5	7 5 3	7 5 4	7 5 5	7 5 3	7 6 3
Alimentary System																										
Intestine large		+																								
Intestine large, colon		+																								
Fibrosarcoma, metastatic, uterus		X																								
Intestine small				+					+		+	+						+	+	+	+		+		+	
Intestine small, ileum				+					+		+	+						+	+	+	+		+			
Intestine small, jejunum																		+	+							+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Fibrosarcoma, metastatic, uterus		X																								
Mesentery		+				+																				
Carcinoma, metastatic, ovary						X																				
Fibrosarcoma, metastatic, uterus		X																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
None																										
Endocrine System																										
Adrenal gland								+																		
Adrenal gland, medulla								+																		
Pheochromocytoma malignant								X																		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X							
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X			X	X	X			X	X	X	X	X		X	X	X			X	X		X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																										
C-cell, adenoma												X				X	X									
C-cell, carcinoma																										
General Body System																										
Tissue NOS	+																									
Mediastinum, myxoma	X																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 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 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	7 6 4	7 6 5	7 7 2	7 7 3	7 7 4	7 7 5	7 9 2	7 9 3	8 2 3	7 8 2	7 8 3	7 8 4	7 8 5	7 9 4	7 9 5	8 0 1	8 0 2	8 0 3	8 0 4	8 0 5	8 1 3	8 1 4	8 1 5	8 2 4	8 2 5	**Total Tissues/ Tumors**
Alimentary System																										
Intestine large																										1
Intestine large, colon																										1
Fibrosarcoma, metastatic, uterus																										1
Intestine small	+		+	+		+	+		+			+		+		+	+	+		+		+	+		+	25
Intestine small, ileum	+		+	+		+	+		+			+		+		+	+	+		+		+	+		+	24
Intestine small, jejunum																									+	4
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																					X					1
Fibrosarcoma, metastatic, uterus																										1
Mesentery	+					+										+			+					+		7
Carcinoma, metastatic, ovary																										1
Fibrosarcoma, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
None																										
Endocrine System																										
Adrenal gland																										1
Adrenal gland, medulla																										1
Pheochromocytoma malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X	X		X	X		X		X	X	X				X		X	X			X	X		28
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma	X																									1
C-cell, adenoma												X														4
C-cell, carcinoma												X				X	X			X						4
General Body System																										
Tissue NOS																										1
Mediastinum, myxoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 ppm (continued)

Number of Days on Study	3 2 5	4 5 7	4 9 1	5 0 1	5 4 6	5 6 4	5 7 2	5 9 5	6 1 2	6 1 8	6 3 1	6 5 1	6 5 5	6 6 2	6 8 8	6 8 8	6 9 3	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	7 3 2	7 5 1	7 6 1	7 5 2	8 2 1	7 4 1	7 3 3	7 4 2	8 2 2	8 1 1	7 8 1	7 6 2	7 9 1	7 4 3	7 4 4	7 7 1	8 1 2	7 3 1	7 3 4	7 3 5	7 4 5	7 5 3	7 5 4	7 5 5	7 6 3
Genital System																									
Clitoral gland	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Ovary						+																			
Carcinoma						X																			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, ovary						X																			
Fibrosarcoma		X																							
Leiomyoma																									
Cervix, endometrium, polyp stromal																	X								
Endometrium, polyp stromal					X																				X
Endometrium, sarcoma stromal																									
Vagina																									
Sarcoma																									
Hematopoietic System																									
Blood						+																			
Bone marrow							+																		
Lymph node						+																			
Lumbar, carcinoma, metastatic, ovary						X																			
Renal, carcinoma, metastatic, ovary						X																			
Lymph node, mandibular																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, uterus		X																							
Integumentary System																									
Mammary gland			+	+	+			+		+	+	+	+		+	+	+	+	+	+		+	+	+	
Adenoma																									
Fibroadenoma			X		X					X					X	X	X	X				X			
Skin	+																								
Sebaceous gland, carcinoma	X																								
Musculoskeletal System																									
Bone												+			+							+			
Skeletal muscle																									
Nervous System																									
Brain													+		+	+									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 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 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	7 6 4	7 6 5	7 7 2	7 7 3	7 7 4	7 7 5	7 9 2	7 9 3	8 2 3	7 8 2	7 8 3	7 8 4	7 8 5	7 9 4	7 9 5	8 0 1	8 0 2	8 0 3	8 0 4	8 0 5	8 1 3	8 1 4	8 1 5	8 2 4	8 2 5	**Total Tissues/ Tumors**
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma			X							X						X										3
Carcinoma					X																					1
Ovary																										1
Carcinoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, ovary																										1
Fibrosarcoma																										1
Leiomyoma																		X								1
Cervix, endometrium, polyp stromal																										1
Endometrium, polyp stromal									X								X			X	X			X		7
Endometrium, sarcoma stromal																					X					1
Vagina									+																	1
Sarcoma									X																	1
Hematopoietic System																										
Blood																										1
Bone marrow																										1
Lymph node								+																		2
Lumbar, carcinoma, metastatic, ovary																										1
Renal, carcinoma, metastatic, ovary																										1
Lymph node, mandibular								+																		1
Spleen	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic, uterus																										1
Integumentary System																										
Mammary gland		+	+	+		+	+			+	+		+	+			+	+	+	+	+			+		32
Adenoma		X									X															2
Fibroadenoma			X								X						X	X	X					X		14
Skin															+											2
Sebaceous gland, carcinoma																										1
Musculoskeletal System																										
Bone		+				+	+										+	+			+	+				10
Skeletal muscle			+																							1
Nervous System																										
Brain																										3

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 ppm (continued)

Number of Days on Study	3 2 5	4 5 7	4 9 1	5 0 1	5 4 6	5 6 4	5 7 2	5 9 5	6 1 2	6 1 8	6 3 1	6 5 1	6 5 5	6 6 2	6 8 8	6 8 8	6 9 3	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	7 3 2	7 5 1	7 6 1	7 5 2	8 2 1	7 4 1	7 3 3	7 4 2	8 2 2	8 1 1	7 8 1	7 6 2	7 9 1	7 4 3	7 4 4	7 7 1	8 1 2	7 3 1	7 3 4	7 3 5	7 4 5	7 5 3	7 5 4	7 5 5	7 6 3
Respiratory System																									
Lung	+	+				+		+			+														
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, ovary						X																			
Carcinoma, metastatic, skin	X																								
Fibrosarcoma, metastatic, uterus		X																							
Special Senses System																									
Ear																									
Pinna, papilloma squamous																									
Eye	+																								
Zymbal's gland																									
Adenoma																									
Urinary System																									
Kidney		+		+		+	+	+	+	+		+	+		+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X							X											

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 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 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	7 6 4	7 6 5	7 7 2	7 7 3	7 7 4	7 7 5	7 9 2	7 9 3	8 2 3	7 8 2	7 8 3	7 8 4	7 8 5	7 9 4	7 9 5	8 0 1	8 0 2	8 0 3	8 0 4	8 0 5	8 1 3	8 1 4	8 1 5	8 2 4	8 2 5	**Total Tissues/ Tumors**
Respiratory System																										
Lung		+				+						+														8
Alveolar/bronchiolar adenoma												X														1
Carcinoma, metastatic, ovary																										1
Carcinoma, metastatic, skin																										1
Fibrosarcoma, metastatic, uterus																										1
Special Senses System																										
Ear															+											1
Pinna, papilloma squamous															X											1
Eye																										1
Zymbal's gland																								+		1
Adenoma																								X		1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	44
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X															3

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 ppm

Number of Days on Study	5 0 5	5 3 5	5 9 2	5 9 2	6 1 0	6 1 8	6 2 4	6 2 7	6 2 7	6 7 7	7 0 0	7 3 0	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
Carcass ID Number	6 1 1	6 1 1	6 1 2	6 5 1	6 9 1	7 0 1	6 6 2	6 3 1	6 8 1	6 3 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 3	6 3 4	6 3 5	6 4 1	6 4 2	6 4 3	6 4 4
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Mesentery										+											+			
Carcinoma																					X			
Sarcoma										X														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																X								
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																								
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign												X								X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Carcinoma																X								
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X		X			X					X	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 23: 50,000 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 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	6 4 5	6 5 2	6 5 3	6 5 4	6 5 5	6 6 3	6 6 4	6 6 5	6 7 1	6 7 2	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 2	7 0 3	7 0 4	7 0 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X																								1
Mesentery	+										+					+										5
Carcinoma																										1
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue				+																						1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X																									2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																X	X						X	X		6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X					X						X												3
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X							X	X		X	X	X									X		X		18

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 ppm (continued)

Number of Days on Study	5	5	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	3	9	9	1	1	2	2	2	0	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	5	5	2	2	0	8	4	7	7	7	0	0	0	0	0	0	0	1	1	1	1	1	1	1
Carcass ID Number	6	6	6	6	6	7	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
	1	6	1	5	9	0	6	3	8	3	1	1	1	2	2	2	2	2	3	3	3	4	4	4
	1	1	2	1	1	1	2	1	1	2	3	4	5	1	2	3	4	5	3	4	5	1	2	3	4
Endocrine System (continued)																								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma										X														
C-cell, carcinoma																								
Follicular cell, adenoma						X																		
Follicular cell, carcinoma																							X	
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenoma																				X				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrium, polyp stromal		X					X			X		X				X				X			X	
Vagina										+					+									
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma			X																					
Thymus	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Fibroadenoma		X	X		X	X	X							X	X	X		X	X			X	X	X	X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma	X																							
Subcutaneous tissue, fibrosarcoma															X									
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																								+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 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 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	6 4 5	6 5 2	6 5 3	6 5 4	6 5 5	6 6 3	6 6 4	6 6 5	6 7 1	6 7 2	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 2	7 0 3	7 0 4	7 0 5	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma								X																		2
C-cell, carcinoma	X								X											X						3
Follicular cell, adenoma																					X				X	3
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma			X																							2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																				X						1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrium, polyp stromal	X			X		X										X					X	X				13
Vagina				+			+																			4
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X														1
Fibroadenoma					X	X															X	X			X	19
Skin	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Keratoacanthoma																										1
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 ppm (continued)

Number of Days on Study	5 0 5	5 3 5	5 9 2	5 9 2	6 1 0	6 1 8	6 2 4	6 2 7	6 2 7	6 2 7	7 0 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 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	6 1 1	6 1 1	6 1 2	6 5 1	6 9 1	7 0 1	6 6 2	6 3 1	6 8 1	6 3 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 3	6 3 4	6 3 5	6 4 1	6 4 2	6 4 3	6 4 4
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma NOS								X																		
Meningioma malignant																										
Choroid plexus, meningioma malignant, metastatic, brain																										
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye													+													
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X						X															

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 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 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	6 4 5	6 5 2	6 5 3	6 5 4	6 5 5	6 6 3	6 6 4	6 6 5	6 7 1	6 7 2	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 2	7 0 3	7 0 4	7 0 5	**Total Tissues/ Tumors**
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma NOS	X																		X							3
Meningioma malignant	X																									1
Choroid plexus, meningioma malignant, metastatic, brain	X																									1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																					+					2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma													X													1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X																			3

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	4/49 (8%)	0/1 (0%)[e]	0/1 (0%)[e]	6/50 (12%)
Adjusted rates[b]	10.9%			15.0%
Terminal rates[c]	2/29 (7%)			6/40 (15%)
First incidence (days)	378			729 (T)
Life table tests[d]				P=0.545
Logistic regression tests[d]				P=0.356
Fisher exact test[d]				P=0.383
Adrenal Medulla: Pheochromocytoma (Benign or Malignant)				
Overall rates	5/49 (10%)	1/1 (100%)[e]	1/1 (100%)[e]	6/50 (12%)
Adjusted rates	14.2%			15.0%
Terminal rates	3/29 (10%)			6/40 (15%)
First incidence (days)	378			729 (T)
Life table tests				P=0.564N
Logistic regression tests				P=0.503
Fisher exact test				P=0.514
Brain: Astrocytoma NOS				
Overall rates	0/50 (0%)	1/5 (20%)[e]	0/3 (0%)[e]	3/50 (6%)
Adjusted rates	0.0%			7.2%
Terminal rates	0/29 (0%)			2/40 (5%)
First incidence (days)	–[f]			627
Life table tests				P=0.172
Logistic regression tests				P=0.124
Fisher exact test				P=0.121
Clitoral Gland: Adenoma				
Overall rates	5/47 (11%)	4/48 (8%)	3/47 (6%)	2/49 (4%)
Adjusted rates	17.6%	11.2%	9.4%	5.1%
Terminal rates	4/26 (15%)	3/33 (9%)	3/32 (9%)	2/39 (5%)
First incidence (days)	648	673	729 (T)	729 (T)
Life table tests	P=0.074N	P=0.364N	P=0.259N	P=0.099N
Logistic regression tests	P=0.099N	P=0.397N	P=0.294N	P=0.132N
Cochran-Armitage test[d]	P=0.141N			
Fisher exact test		P=0.486N	P=0.357N	P=0.201N
Clitoral Gland: Carcinoma				
Overall rates	3/47 (6%)	0/48 (0%)	1/47 (2%)	0/49 (0%)
Adjusted rates	8.6%	0.0%	3.1%	0.0%
Terminal rates	1/26 (4%)	0/33 (0%)	1/32 (3%)	0/39 (0%)
First incidence (days)	578	–	729 (T)	–
Life table tests	P=0.081N	P=0.099N	P=0.271N	P=0.091N
Logistic regression tests	P=0.101N	P=0.125N	P=0.305N	P=0.130N
Cochran-Armitage test	P=0.098N			
Fisher exact test		P=0.117N	P=0.308N	P=0.113N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Clitoral Gland: Adenoma or Carcinoma				
Overall rates	7/47 (15%)	4/48 (8%)	4/47 (9%)	2/49 (4%)
Adjusted rates	21.7%	11.2%	12.5%	5.1%
Terminal rates	4/26 (15%)	3/33 (9%)	4/32 (13%)	2/39 (5%)
First incidence (days)	578	673	729 (T)	729 (T)
Life table tests	P=0.031N	P=0.165N	P=0.184N	P=0.032N
Logistic regression tests	P=0.049N	P=0.215N	P=0.227N	P=0.056N
Cochran-Armitage test	P=0.065N			
Fisher exact test		P=0.249N	P=0.261N	P=0.070N
Mammary Gland: Fibroadenoma				
Overall rates	23/50 (46%)	24/50 (48%)	14/50 (28%)	19/50 (38%)
Adjusted rates	64.7%	62.8%	35.1%	41.7%
Terminal rates	17/29 (59%)	20/34 (59%)	8/33 (24%)	14/40 (35%)
First incidence (days)	507	651	491	535
Life table tests	P=0.022N	P=0.373N	P=0.028N	P=0.048N
Logistic regression tests	P=0.083N	P=0.474N	P=0.039N	P=0.199N
Cochran-Armitage test	P=0.129N			
Fisher exact test		P=0.500	P=0.048N	P=0.272N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rates	23/50 (46%)	25/50 (50%)	15/50 (30%)	20/50 (40%)
Adjusted rates	64.7%	65.5%	37.7%	44.0%
Terminal rates	17/29 (59%)	21/34 (62%)	9/33 (27%)	15/40 (38%)
First incidence (days)	507	651	491	535
Life table tests	P=0.028N	P=0.444N	P=0.042N	P=0.066N
Logistic regression tests	P=0.107N	P=0.551N	P=0.060N	P=0.255N
Cochran-Armitage test	P=0.168N			
Fisher exact test		P=0.421	P=0.074N	P=0.343N
Mammary Gland: Adenoma or Carcinoma				
Overall rates	1/50 (2%)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted rates	3.4%	10.7%	6.1%	2.5%
Terminal rates	1/29 (3%)	3/34 (9%)	2/33 (6%)	1/40 (3%)
First incidence (days)	729 (T)	514	729 (T)	729 (T)
Life table tests	P=0.273N	P=0.225	P=0.545	P=0.688N
Logistic regression tests	P=0.345N	P=0.182	P=0.545	P=0.688N
Cochran-Armitage test	P=0.369N			
Fisher exact test		P=0.181	P=0.500	P=0.753N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rates	23/50 (46%)	27/50 (54%)	15/50 (30%)	20/50 (40%)
Adjusted rates	64.7%	68.8%	37.7%	44.0%
Terminal rates	17/29 (59%)	22/34 (65%)	9/33 (27%)	15/40 (38%)
First incidence (days)	507	514	491	535
Life table tests	P=0.020N	P=0.564	P=0.042N	P=0.066N
Logistic regression tests	P=0.083N	P=0.424	P=0.060N	P=0.255N
Cochran-Armitage test	P=0.129N			
Fisher exact test		P=0.274	P=0.074N	P=0.343N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Pancreatic Islets: Adenoma				
Overall rates	0/50 (0%)	2/49 (4%)	1/49 (2%)	3/50 (6%)
Adjusted rates	0.0%	5.9%	3.1%	7.5%
Terminal rates	0/29 (0%)	2/34 (6%)	1/32 (3%)	3/40 (8%)
First incidence (days)	–	729 (T)	729 (T)	729 (T)
Life table tests	P=0.177	P=0.274	P=0.520	P=0.183
Logistic regression tests	P=0.177	P=0.274	P=0.520	P=0.183
Cochran-Armitage test	P=0.115			
Fisher exact test		P=0.242	P=0.495	P=0.121
Pancreatic Islets: Adenoma or Carcinoma				
Overall rates	0/50 (0%)	2/49 (4%)	1/49 (2%)	4/50 (8%)
Adjusted rates	0.0%	5.9%	3.1%	10.0%
Terminal rates	0/29 (0%)	2/34 (6%)	1/32 (3%)	4/40 (10%)
First incidence (days)	–	729 (T)	729 (T)	729 (T)
Life table tests	P=0.081	P=0.274	P=0.520	P=0.111
Logistic regression tests	P=0.081	P=0.274	P=0.520	P=0.111
Cochran-Armitage test	P=0.045			
Fisher exact test		P=0.242	P=0.495	P=0.059
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	29/50 (58%)	23/50 (46%)	28/50 (56%)	18/50 (36%)
Adjusted rates	74.2%	56.5%	66.3%	41.6%
Terminal rates	19/29 (66%)	17/34 (50%)	19/33 (58%)	15/40 (38%)
First incidence (days)	582	612	501	592
Life table tests	P=0.004N	P=0.053N	P=0.306N	P=0.001N
Logistic regression tests	P=0.014N	P=0.062N	P=0.426N	P=0.005N
Cochran-Armitage test	P=0.036N			
Fisher exact test		P=0.158N	P=0.500N	P=0.022N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	29/50 (58%)	25/50 (50%)	28/50 (56%)	18/50 (36%)
Adjusted rates	74.2%	59.9%	66.3%	41.6%
Terminal rates	19/29 (66%)	18/34 (53%)	19/33 (58%)	15/40 (38%)
First incidence (days)	582	592	501	592
Life table tests	P=0.002N	P=0.102N	P=0.306N	P=0.001N
Logistic regression tests	P=0.009N	P=0.138N	P=0.426N	P=0.005N
Cochran-Armitage test	P=0.024N			
Fisher exact test		P=0.274N	P=0.500N	P=0.022N
Thyroid Gland (C-cell): Adenoma				
Overall rates	5/50 (10%)	5/50 (10%)	5/50 (10%)	2/50 (4%)
Adjusted rates	15.9%	14.1%	13.6%	4.9%
Terminal rates	4/29 (14%)	4/34 (12%)	2/33 (6%)	1/40 (3%)
First incidence (days)	606	693	651	707
Life table tests	P=0.091N	P=0.528N	P=0.561N	P=0.119N
Logistic regression tests	P=0.129N	P=0.559N	P=0.611N	P=0.172N
Cochran-Armitage test	P=0.160N			
Fisher exact test		P=0.630N	P=0.630N	P=0.218N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Thyroid Gland (C-cell): Carcinoma				
Overall rates	1/50 (2%)	0/50 (0%)	4/50 (8%)	3/50 (6%)
Adjusted rates	3.4%	0.0%	12.1%	7.5%
Terminal rates	1/29 (3%)	0/34 (0%)	4/33 (12%)	3/40 (8%)
First incidence (days)	729 (T)	–	729 (T)	729 (T)
Life table tests	P=0.166	P=0.468N	P=0.218	P=0.426
Logistic regression tests	P=0.166	P=0.468N	P=0.218	P=0.426
Cochran-Armitage test	P=0.098			
Fisher exact test		P=0.500N	P=0.181	P=0.309
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	5/50 (10%)	5/50 (10%)	8/50 (16%)	5/50 (10%)
Adjusted rates	15.9%	14.1%	22.0%	12.2%
Terminal rates	4/29 (14%)	4/34 (12%)	5/33 (15%)	4/40 (10%)
First incidence (days)	606	693	651	707
Life table tests	P=0.420N	P=0.528N	P=0.355	P=0.434N
Logistic regression tests	P=0.531N	P=0.559N	P=0.300	P=0.538N
Cochran-Armitage test	P=0.506			
Fisher exact test		P=0.630N	P=0.277	P=0.630N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rates	0/50 (0%)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted rates	0.0%	2.9%	0.0%	7.1%
Terminal rates	0/29 (0%)	1/34 (3%)	0/33 (0%)	2/40 (5%)
First incidence (days)	–	729 (T)	–	618
Life table tests	P=0.072	P=0.532	–	P=0.173
Logistic regression tests	P=0.051	P=0.532	–	P=0.121
Cochran-Armitage test	P=0.047			
Fisher exact test		P=0.500	–	P=0.121
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rates	1/50 (2%)	1/50 (2%)	0/50 (0%)	4/50 (8%)
Adjusted rates	3.4%	2.9%	0.0%	9.6%
Terminal rates	1/29 (3%)	1/34 (3%)	0/33 (0%)	3/40 (8%)
First incidence (days)	729 (T)	729 (T)	–	618
Life table tests	P=0.101	P=0.726N	P=0.474N	P=0.276
Logistic regression tests	P=0.073	P=0.726N	P=0.474N	P=0.209
Cochran-Armitage test	P=0.062			
Fisher exact test		P=0.753N	P=0.500N	P=0.181
Uterus: Stromal Polyp				
Overall rates	7/50 (14%)	4/50 (8%)	8/50 (16%)	13/50 (26%)
Adjusted rates	22.1%	10.2%	22.3%	30.0%
Terminal rates	5/29 (17%)	2/34 (6%)	6/33 (18%)	10/40 (25%)
First incidence (days)	655	592	546	535
Life table tests	P=0.082	P=0.184N	P=0.588	P=0.300
Logistic regression tests	P=0.030	P=0.221N	P=0.533	P=0.158
Cochran-Armitage test	P=0.022			
Fisher exact test		P=0.262N	P=0.500	P=0.105

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rates	8/50 (16%)	6/50 (12%)	8/50 (16%)	13/50 (26%)
Adjusted rates	24.7%	15.5%	22.3%	30.0%
Terminal rates	5/29 (17%)	3/34 (9%)	6/33 (18%)	10/40 (25%)
First incidence (days)	655	592	546	535
Life table tests	P=0.193	P=0.277N	P=0.515N	P=0.406
Logistic regression tests	P=0.087	P=0.323N	P=0.575N	P=0.237
Cochran-Armitage test	P=0.064			
Fisher exact test		P=0.387N	P=0.607N	P=0.163
All Organs: Mononuclear Cell Leukemia				
Overall rates	14/50 (28%)	7/50 (14%)	3/50 (6%)	3/50 (6%)
Adjusted rates	41.2%	18.3%	7.8%	6.9%
Terminal rates	10/29 (34%)	4/34 (12%)	1/33 (3%)	1/40 (3%)
First incidence (days)	507	242	572	610
Life table tests	P<0.001N	P=0.038N	P=0.003N	P<0.001N
Logistic regression tests	P=0.002N	P=0.065N	P=0.003N	P=0.002N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.070N	P=0.003N	P=0.003N
All Organs: Benign Tumors				
Overall rates	43/50 (86%)	43/50 (86%)	41/50 (82%)	41/50 (82%)
Adjusted rates	95.5%	93.4%	87.2%	83.6%
Terminal rates	27/29 (93%)	31/34 (91%)	27/33 (82%)	32/40 (80%)
First incidence (days)	378	592	325	505
Life table tests	P=0.018N	P=0.162N	P=0.199N	P=0.016N
Logistic regression tests	P=0.146N	P=0.348N	P=0.315N	P=0.195N
Cochran-Armitage test	P=0.295N			
Fisher exact test		P=0.613N	P=0.393N	P=0.393N
All Organs: Malignant Tumors				
Overall rates	22/50 (44%)	15/50 (30%)	14/50 (28%)	10/50 (20%)
Adjusted rates	53.9%	36.1%	34.0%	23.6%
Terminal rates	11/29 (38%)	9/34 (26%)	8/33 (24%)	8/40 (20%)
First incidence (days)	494	242	325	610
Life table tests	P=0.003N	P=0.063N	P=0.061N	P=0.002N
Logistic regression tests	P=0.017N	P=0.134N	P=0.079N	P=0.007N
Cochran-Armitage test	P=0.010N			
Fisher exact test		P=0.107N	P=0.072N	P=0.009N
All Organs: Benign or Malignant Tumors				
Overall rates	48/50 (96%)	48/50 (96%)	44/50 (88%)	44/50 (88%)
Adjusted rates	98.0%	96.0%	89.7%	88.0%
Terminal rates	28/29 (97%)	32/34 (94%)	28/33 (85%)	34/40 (85%)
First incidence (days)	249	242	325	505
Life table tests	P=0.006N	P=0.169N	P=0.128N	P=0.006N
Logistic regression tests	P=0.063N	P=0.672N	P=0.135N	P=0.135N
Cochran-Armitage test	P=0.052N			
Fisher exact test		P=0.691N	P=0.134N	P=0.134N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (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; therefore statistical comparisons with the controls are not appropriate.
[f] Not applicable; no tumors in animal group

TABLE B4a
Historical Incidence of Renal Tubule Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Nitrofurantoin	0/50	0/50	0/50
Rhodamine 6G	0/50	0/50	0/50
Roxarsone	0/50	0/50	0/50
Total	0/150	0/150	0/150
Overall Historical Incidence			
Total	1/499 (0.2%)	0/499 (0.0%)	1/499 (0.2%)
Standard deviation	0.6%		0.6%
Range	0%-2%		0%-2%

[a] Data as of 17 September 1990

TABLE B4b
Historical Incidence of Pituitary Gland Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma, Cystadenocarcinoma, Adenocarcinoma, or Carcinoma
Historical Incidence at Southern Research Institute			
Nitrofurantoin	23/50	3/50	26/50
Rhodamine 6G	31/49	0/49	31/50
Roxarsone	27/50	1/50	28/50
Total	81/149 (54.4%)	4/149 (2.7%)	85/149 (57.0%)
Standard deviation	8.5%	3.1%	5.6%
Range	46%-63%	0%-6%	52%-63%
Overall Historical Incidence			
Total	254/496 (51.2%)	8/496 (1.6%)	262/496 (52.8%)
Standard deviation	8.5%	2.1%	8.7%
Range	38%-63%	0%-6%	38%-64%

[a] Data as of 17 September 1990. Includes data for all lesions of the pars distalis or NOS.

TABLE B4c
Historical Incidence of Leukemias in Untreated Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
Nitrofurantoin	13/50
Rhodamine 6G	11/50
Roxarsone	14/50
Total	38/150 (25.3%)
Standard deviation	3.1%
Range	22%-28%
Overall Historical Incidence	
Total	124/500 (24.8%)
Standard deviation	6.12%
Range	14%-36%

[a] Data as of 17 September 1990; includes lymphocytic, monocytic, mononuclear cell, or undifferentiated leukemias

TABLE B4d
Historical Incidence of Brain Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls			
	Astrocytoma	Glioma	Oligodendroglioma[b]	Astrocytoma, Glioma, or Oligodendroglioma
Historical Incidence at Southern Research Institute				
Nitrofurantoin	0/50	0/50	0/50	0/50
Rhodamine 6G	0/50	0/50	0/50	0/50
Roxarsone	0/50	0/50	0/50	0/50
Overall Historical Incidence				
Total	3/499 (0.6%)[c]	0/499 (0%)	0/499 (0%)	3/499 (0.6%)
Standard deviation	1.4%			1.4%
Range	0%-4%			0%-4%

[a] Data as of 17 September 1990. Historical incidences for benign and malignant lesions, as well as lesions of unspecified site (NOS)
[b] Data for benign and malignant neoplasms; data for oligodendroglioma NOS not available
[c] Represents three malignant astrocytomas

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23[a]

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	18	11	14	8
Dead	3	5	3	2
Survivors				
Terminal sacrifice	29	34	33	40
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(50)			(50)
Autolysis	2 (4%)			2 (4%)
Intestine large, colon	(50)		(1)	(50)
Autolysis	1 (2%)			2 (4%)
Parasite metazoan	6 (12%)			1 (2%)
Intestine large, rectum	(50)			(50)
Autolysis				2 (4%)
Parasite metazoan	12 (24%)			8 (16%)
Intestine small, duodenum	(50)			(50)
Autolysis	1 (2%)			2 (4%)
Inflammation, acute	1 (2%)			
Intestine small, ileum	(50)	(15)	(24)	(50)
Autolysis	1 (2%)			2 (4%)
Hyperplasia, lymphoid	10 (20%)	14 (93%)	24 (100%)	26 (52%)
Inflammation		1 (7%)		
Pigmentation		1 (7%)	6 (25%)	10 (20%)
Intestine small, jejunum	(50)	(6)	(4)	(50)
Autolysis	2 (4%)			2 (4%)
Hyperplasia, lymphoid		5 (83%)	3 (75%)	4 (8%)
Necrosis, focal				1 (2%)
Pigmentation		1 (17%)	2 (50%)	2 (4%)
Liver	(50)	(50)	(50)	(50)
Basophilic focus, multiple	34 (68%)	35 (70%)	37 (74%)	43 (86%)
Bile stasis	1 (2%)			
Clear cell focus	2 (4%)	3 (6%)		1 (2%)
Congestion	2 (4%)			
Ectasia			1 (2%)	
Hematopoietic cell proliferation	3 (6%)			1 (2%)
Hepatodiaphragmatic nodule	7 (14%)	8 (16%)	8 (16%)	9 (18%)
Hyperplasia	3 (6%)	4 (8%)		2 (4%)
Hypertrophy, focal	1 (2%)			
Infiltration cellular, lymphocytic	1 (2%)			1 (2%)
Inflammation, acute	1 (2%)	1 (2%)		2 (4%)
Inflammation, chronic	1 (2%)		2 (4%)	1 (2%)
Inflammation, granulomatous	14 (28%)	13 (26%)	11 (22%)	16 (32%)
Leukocytosis		2 (4%)	1 (2%)	
Necrosis	1 (2%)			2 (4%)
Vacuolization cytoplasmic	8 (16%)	4 (8%)	6 (12%)	5 (10%)
Bile duct, hyperplasia	2 (4%)	6 (12%)		3 (6%)
Centrilobular, necrosis		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 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Alimentary System (continued)				
Mesentery	(4)	(2)	(7)	(5)
Fat, necrosis, focal	3 (75%)	1 (50%)	5 (71%)	3 (60%)
Pancreas	(50)	(50)	(50)	(50)
Atrophy			2 (4%)	
Atrophy, focal	13 (26%)	8 (16%)	11 (22%)	19 (38%)
Autolysis	1 (2%)			2 (4%)
Ectopic liver			1 (2%)	
Inflammation, acute				1 (2%)
Inflammation, chronic	2 (4%)			
Duct, ectasia	1 (2%)			
Salivary glands	(50)			(50)
Atrophy				1 (2%)
Duct, inflammation, chronic	1 (2%)			
Stomach, forestomach	(50)	(2)		(50)
Hyperplasia	3 (6%)	1 (50%)		1 (2%)
Inflammation, acute	1 (2%)			
Inflammation, chronic	3 (6%)			1 (2%)
Mineralization	1 (2%)			2 (4%)
Ulcer	1 (2%)	1 (50%)		
Stomach, glandular	(50)	(1)		(50)
Autolysis				1 (2%)
Inflammation, acute	1 (2%)			
Inflammation, chronic	1 (2%)			
Mineralization	16 (32%)			22 (44%)
Necrosis		1 (100%)		
Tongue		(1)		(1)
Epithelium, hyperplasia, focal				1 (100%)
Cardiovascular System				
Blood vessel	(1)			
Mineralization	1 (100%)			
Heart	(50)			(50)
Inflammation, chronic	42 (84%)			46 (92%)
Mineralization	1 (2%)			
Endocrine System				
Adrenal gland, cortex	(50)	(1)		(50)
Congestion				3 (6%)
Cyst	1 (2%)			
Ectasia	3 (6%)			5 (10%)
Hyperplasia	13 (26%)			18 (36%)
Hypertrophy	10 (20%)			10 (20%)
Vacuolization cytoplasmic	14 (28%)			7 (14%)
Adrenal gland, medulla	(49)	(1)	(1)	(50)
Angiectasis				1 (2%)
Hyperplasia	7 (14%)			3 (6%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Endocrine System (continued)				
Islets, pancreatic	(50)	(49)	(49)	(50)
Atrophy		1 (2%)		
Atypical cells			2 (4%)	2 (4%)
Autolysis				1 (2%)
Hyperplasia	1 (2%)	1 (2%)		
Parathyroid gland	(50)	(1)		(50)
Hyperplasia		1 (100%)		
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, angiectasis	1 (2%)			1 (2%)
Pars distalis, cyst	17 (34%)	15 (30%)	7 (14%)	22 (44%)
Pars distalis, ectasia	5 (10%)	8 (16%)	3 (6%)	5 (10%)
Pars distalis, hemorrhage				1 (2%)
Pars distalis, hyperplasia	9 (18%)	10 (20%)	11 (22%)	11 (22%)
Pars distalis, hypertrophy	3 (6%)	1 (2%)		1 (2%)
Pars intermedia, cyst	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, hyperplasia	33 (66%)	26 (52%)	32 (64%)	24 (48%)
Follicle, cyst			2 (4%)	
Follicle, dilatation		1 (2%)		
Follicular cell, hyperplasia		2 (4%)	1 (2%)	
Follicular cell, hyperplasia, cystic		1 (2%)		
General Body System				
None				
Genital System				
Clitoral gland	(47)	(48)	(47)	(49)
Atrophy			1 (2%)	
Hyperplasia	5 (11%)	3 (6%)	1 (2%)	1 (2%)
Inflammation, acute	5 (11%)	1 (2%)	5 (11%)	3 (6%)
Inflammation, chronic	3 (6%)	3 (6%)	2 (4%)	7 (14%)
Duct, cyst				1 (2%)
Duct, dilatation		1 (2%)		
Duct, ectasia	1 (2%)		1 (2%)	
Ovary	(50)	(4)	(1)	(50)
Follicle, cyst	2 (4%)	1 (25%)		1 (2%)
Uterus	(50)	(50)	(50)	(50)
Cyst		2 (4%)	1 (2%)	
Dilatation	4 (8%)	3 (6%)	2 (4%)	4 (8%)
Hemorrhage		1 (2%)		
Inflammation, acute	1 (2%)			
Necrosis	1 (2%)			
Cervix, cyst		2 (4%)		
Cervix, inflammation, acute	1 (2%)			
Endometrium, hyperplasia, cystic	2 (4%)			
Vagina	(8)		(1)	(4)
Inflammation, acute	1 (13%)			
Inflammation, chronic				1 (25%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Hematopoietic System				
Blood			(1)	
Polychromasia			1 (100%)	
Bone marrow	(50)	(1)	(1)	(50)
Autolysis				1 (2%)
Hyperplasia	1 (2%)			
Hypoplasia	2 (4%)	1 (100%)		
Myelofibrosis	2 (4%)			
Myeloid cell, hyperplasia	1 (2%)			3 (6%)
Lymph node	(50)	(2)	(2)	(50)
Inguinal, hyperplasia				1 (2%)
Mediastinal, congestion				1 (2%)
Mesenteric, congestion	1 (2%)			1 (2%)
Mesenteric, pigmentation				9 (18%)
Pancreatic, ectasia				1 (2%)
Pancreatic, hyperplasia				1 (2%)
Lymph node, mandibular	(50)		(1)	(50)
Congestion	4 (8%)			2 (4%)
Hemorrhage			1 (100%)	
Hyperplasia	3 (6%)			
Hyperplasia, RE cell				1 (2%)
Spleen	(50)	(50)	(49)	(50)
Atrophy, focal				1 (2%)
Congestion	1 (2%)			
Ectasia	1 (2%)			
Fibrosis				1(2%)
Hematopoietic cell proliferation		1 (2%)	2 (4%)	1 (2%)
Hematopoietic cell proliferation granulocytic	4 (8%)	3 (6%)	1 (2%)	3 (6%)
Hematopoietic cell proliferation erythrocytic		1 (2%)	3 (6%)	
Hemorrhage, focal		1 (2%)		
Infarct		1 (2%)		
Thymus	(49)			(48)
Cyst	3 (6%)			1 (2%)
Medulla, hyperplasia				1 (2%)
Integumentary System				
Mammary gland	(50)	(38)	(32)	(50)
Galactocele	1 (2%)			
Hyperplasia	4 (8%)	4 (11%)	5 (16%)	4 (8%)
Inflammation, acute		1 (3%)		
Duct, ectasia	30 (60%)	20 (53%)	22 (69%)	18 (36%)
Duct, hyperplasia		1 (3%)		
Skin	(50)	(8)	(2)	(49)
Acanthosis		2 (25%)		
Hyperkeratosis		2 (25%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Musculoskeletal System				
Bone	(50)	(5)	(10)	(50)
Osteopetrosis	3 (6%)	5 (100%)	10 (100%)	7 (14%)
Skeletal muscle			(1)	(1)
Cyst			1 (100%)	
Foreign body				1 (100%)
Inflammation, chronic				1 (100%)
Nervous System				
Brain	(50)	(5)	(3)	(50)
Compression	13 (26%)	3 (60%)	3 (100%)	7 (14%)
Gliosis, focal			1 (33%)	
Meninges, infiltration cellular, lymphocytic				1 (2%)
Respiratory System				
Lung	(50)	(4)	(8)	(50)
Congestion	3 (6%)		2 (25%)	
Foreign body	1 (2%)			
Hemorrhage			2 (25%)	
Hyperplasia, lymphoid				1 (2%)
Inflammation, acute	1 (2%)			
Alveolus, infiltration cellular, histiocytic	4 (8%)			6 (12%)
Alveolus, mineralization	1 (2%)			
Epithelium, alveolus, hyperplasia	1 (2%)			1 (2%)
Nose	(50)			(50)
Foreign body	1 (2%)			3 (6%)
Fungus	1 (2%)			2 (4%)
Mucosa, inflammation, chronic active	4 (8%)			5 (10%)
Nasolacrimal duct, cyst	1 (2%)			
Nasolacrimal duct, inflammation, acute	1 (2%)			
Nasolacrimal duct, inflammation, chronic	5 (10%)		1 (2%)	
Special Senses System				
Eye	(1)	(2)	(1)	(2)
Lens, cataract	1 (100%)	2 (100%)	1 (100%)	1 (50%)
Retina, degeneration			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 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Urinary System				
Kidney	(50)	(45)	(44)	(50)
Autolysis	1 (2%)			2 (4%)
Congestion			3 (7%)	
Hydronephrosis	2 (4%)		1 (2%)	
Infarct	1 (2%)			1 (2%)
Inflammation, chronic		1 (2%)		
Mineralization	6 (12%)			7 (14%)
Nephropathy	48 (96%)	44 (98%)	43 (98%)	46 (92%)
Cortex, cyst				1 (2%)
Renal tubule, hyperplasia	2 (4%)	2 (4%)		2 (4%)
Renal tubule, epithelium, degeneration				1 (2%)
Ureter	(1)			
Inflammation, chronic	1 (100%)			
Urinary bladder	(50)	(2)		(50)
Hyperplasia		1 (50%)		
Inflammation, chronic	1 (2%)			
Inflammation, chronic active		1 (50%)		
Metaplasia, squamous		1 (50%)		
Mineralization		1 (50%)		

[a] Number of animals examined microscopically at site and the number of animals with lesion.

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR FEED STUDY OF C.I. PIGMENT RED 23

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	9	7	8	9
Early deaths				
Dead	10	22	8	6
Moribund	12	14	17	15
Survivors				
Terminal sacrifice	29	17	27	30
Animals examined microscopically[a]	50	50	50	50
Alimentary System				
Intestine small, duodenum	(43)	(36)	(46)	(45)
Polyp		1 (3%)		
Intestine small, jejunum	(42)	(37)	(47)	(45)
Adenocarcinoma	1 (2%)			
Lymphoid tissue, histiocytic sarcoma		2 (5%)		
Liver	(49)	(50)	(50)	(49)
Fibrosarcoma, metastatic, skin			1 (2%)	
Hemangiosarcoma			4 (8%)	
Hepatocellular carcinoma	9 (18%)	6 (12%)	9 (18%)	11 (22%)
Hepatocellular carcinoma, multiple	3 (6%)	1 (2%)	1 (2%)	4 (8%)
Hepatocellular adenoma	2 (4%)	1 (2%)	3 (6%)	6 (12%)
Hepatocellular adenoma, multiple	1 (2%)		1 (2%)	2 (4%)
Histiocytic sarcoma		2 (4%)	2 (4%)	
Mesentery			(3)	(2)
Pancreas	(49)	(31)	(25)	(47)
Salivary glands	(49)	(32)	(22)	(48)
Fibrosarcoma, metastatic, skin				1 (2%)
Stomach, forestomach	(49)	(48)	(50)	(48)
Mast cell tumor malignant	1 (2%)			
Papilloma squamous				1 (2%)
Stomach, glandular	(49)	(48)	(50)	(44)
Cardiovascular System				
None				
Endocrine System				
Adrenal gland	(48)	(32)	(23)	(48)
Adrenal gland, cortex	(48)	(32)	(23)	(48)
Adenoma	2 (4%)			3 (6%)
Histiocytic sarcoma		1 (3%)		
Adrenal gland, medulla	(48)	(32)	(23)	(48)
Pheochromocytoma malignant	1 (2%)			
Pheochromocytoma benign				1 (2%)
Pituitary gland	(41)	(29)	(22)	(48)
Pars distalis, adenoma				2 (4%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Endocrine System (continued)				
Thyroid gland	(49)	(30)	(23)	(50)
Follicular cell, adenoma	2 (4%)	2 (7%)		2 (4%)
Follicular cell, carcinoma	1 (2%)		1 (4%)	1 (2%)
General Body System				
Tissue NOS	(1)	(1)	(2)	
Mediastinum, hepatocellular carcinoma, metastatic, liver	1 (100%)			
Genital System				
Seminal vesicle	(49)	(32)	(25)	(48)
Histiocytic sarcoma			1 (4%)	
Testes	(49)	(32)	(23)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Interstitial cell, adenoma				1 (2%)
Hematopoietic System				
Bone marrow	(49)	(31)	(22)	(48)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Hemangiosarcoma	1 (2%)		2 (9%)	
Mast cell tumor malignant	1 (2%)			
Lymph node	(49)	(50)	(49)	(48)
Axillary, sarcoma, metastatic, skin		1 (2%)		
Inguinal, sarcoma, metastatic, skin	1 (2%)			
Mesenteric, histiocytic sarcoma		2 (4%)	2 (4%)	
Pancreatic, histiocytic sarcoma			1 (2%)	
Lymph node, mandibular	(48)	(27)	(21)	(48)
Fibrosarcoma, metastatic, skin				1 (2%)
Mast cell tumor malignant	1 (2%)			
Spleen	(49)	(31)	(26)	(47)
Hemangiosarcoma	1 (2%)	1 (3%)	1 (4%)	
Histiocytic sarcoma		2 (6%)	1 (4%)	
Thymus	(39)	(18)	(14)	(32)
Integumentary System				
Skin	(49)	(50)	(48)	(50)
Fibroma	4 (8%)	1 (2%)	2 (4%)	1 (2%)
Fibroma, multiple				1 (2%)
Fibrosarcoma	3 (6%)	5 (10%)	5 (10%)	4 (8%)
Fibrosarcoma, multiple	2 (4%)			1 (2%)
Hemangiosarcoma	1 (2%)			
Papilloma squamous			1 (2%)	1 (2%)
Sarcoma	5 (10%)	7 (14%)	5 (10%)	5 (10%)
Sarcoma, multiple				1 (2%)
Schwannoma malignant			1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(32)	(23)	(49)
Third ventricle, lipoma	1 (2%)			
Respiratory System				
Lung	(49)	(49)	(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	5 (10%)	6 (12%)	2 (4%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	1 (2%)		1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)		2 (4%)	4 (8%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)		
Fibrosarcoma, metastatic, skin		1 (2%)	1 (2%)	
Hepatocellular carcinoma, metastatic, liver	2 (4%)	1 (2%)	2 (4%)	3 (6%)
Histiocytic sarcoma		2 (4%)	1 (2%)	
Sarcoma, metastatic, skin	1 (2%)			
Nose	(49)	(32)	(23)	(49)
Special Senses System				
Harderian gland	(2)	(1)	(1)	(1)
Adenoma	2 (100%)	1 (100%)	1 (100%)	1 (100%)
Urinary System				
Kidney	(49)	(33)	(23)	(50)
Hepatocellular carcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma		1 (3%)	1 (4%)	
Bilateral, alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Cortex, renal tubule, adenoma				1 (2%)
Renal tubule, adenoma		1 (3%)		
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		3 (6%)	2 (4%)	
Leukemia granulocytic	1 (2%)			
Lymphoma malignant				1 (2%)
Lymphoma malignant mixed	2 (4%)		1 (2%)	3 (6%)
Lymphoma malignant undifferentiated cell				2 (4%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]	35	27	33	41
Total primary neoplasms	54	37	48	63
Total animals with benign neoplasms	17	13	12	20
Total benign neoplasms	18	13	14	26
Total animals with malignant neoplasms	27	22	28	31
Total malignant neoplasms	36	24	34	37
Total animals with metastatic neoplasms	5	3	3	4
Total metastatic neoplasms	9	3	4	5

[a] Does not include early deaths that occurred prior to interim evaluation.
[b] Incidences are expressed as number of animals examined microscopically at site and the number of animals with lesion.
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm

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

+: 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 23: 0 ppm
(continued)

Number of Days on Study	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 2 3	0 2 4	0 2 5	0 3 1	0 3 3	0 3 2	0 4 1	0 4 3	0 4 4	0 4 5	0 5 3	0 6 2	0 6 3	0 6 4	0 7 2	0 7 1	0 7 3	0 7 4	0 8 1	0 8 2	0 8 3	0 8 5	0 9 2	0 9 5	1 0 5	**Total Tissues/ Tumors**
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+			+	+	+	+	+	+	+	40
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Adenocarcinoma	X																									1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma	X			X								X								X			X		X	9
Hepatocellular carcinoma, multiple																										3
Hepatocellular adenoma												X			X											2
Hepatocellular adenoma, multiple																									X	1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mast cell tumor malignant																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth			+			+																				3
Cardiovascular System																										
Blood vessel												+														1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma malignant				X																						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	M	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	M	M	+	+	+	41
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma						X																				2
Follicular cell, carcinoma									X																	1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm
(continued)

Number of Days on Study	0 2 7	1 4 0	4 1 8	4 5 5	4 6 3	5 1 1	5 1 8	5 3 6	6 0 4	6 1 0	6 1 8	6 4 4	6 4 4	6 4 4	6 4 4	6 4 7	6 4 7	6 8 7	6 9 4	7 1 1	7 2 2	7 2 3	7 2 3	7 2 3	7 2 3
Carcass ID Number	0 5 1	0 1 1	1 0 1	0 1 3	0 6 1	0 9 3	0 5 2	1 0 3	0 8 4	1 0 2	0 5 4	0 3 5	0 4 2	0 7 5	0 9 1	0 9 4	1 0 4	0 3 4	0 2 2	0 6 5	0 5 5	0 1 2	0 1 4	0 1 5	0 2 1
General Body System																									
Tissue NOS							+																		
Mediastinum, hepatocellular carcinoma, metastatic, liver							X																		
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Penis			+																						
Preputial gland	M			+				+								+									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Hemangiosarcoma																									
Mast cell tumor malignant																								X	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Inguinal, sarcoma, metastatic, skin									X																
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Mast cell tumor malignant																								X	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	M	+	+	+	+	+	M	+	+	M	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma																		X							
Fibrosarcoma, multiple																				X					
Hemangiosarcoma											X														
Sarcoma					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 23: 0 ppm
(continued)

Number of Days on Study	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 2 3	0 2 4	0 2 5	0 3 1	0 3 3	0 3 2	0 4 1	0 4 3	0 4 4	0 4 5	0 5 3	0 6 2	0 6 3	0 6 4	0 7 2	0 7 1	0 7 3	0 7 4	0 8 1	0 8 2	0 8 3	0 8 5	0 9 2	0 9 5	1 0 5	**Total Tissues/ Tumors**
General Body System																									
Tissue NOS																									1
Mediastinum, hepatocellular carcinoma, metastatic, liver																									1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Penis																									1
Preputial gland				+			+					+			+		+		+						9
Prostate	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung									X																1
Hematopoietic System																									
Blood																		+							1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung									X																1
Hemangiosarcoma																						X			1
Mast cell tumor malignant																									1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Inguinal, sarcoma, metastatic, skin																									1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	48
Mast cell tumor malignant																									1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																						X			1
Thymus	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	39
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
Fibroma											X			X									X	X		4
Fibrosarcoma	X													X												3
Fibrosarcoma, multiple															X											2
Hemangiosarcoma																										1
Sarcoma																										5

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm
(continued)

Number of Days on Study	0 2 7	1 4 0	4 1 8	4 5 5	4 6 3	5 1 1	5 1 8	5 3 6	6 0 4	6 1 0	6 1 8	6 4 4	6 4 4	6 4 4	6 4 4	6 4 7	6 4 7	6 8 7	6 9 4	7 1 1	7 2 2	7 2 3	7 2 3	7 2 3	7 2 3
Carcass ID Number	0 5 1	0 1 1	1 0 1	0 1 3	0 6 1	0 9 3	0 5 2	1 0 3	0 8 4	1 0 2	0 5 4	0 3 5	0 4 2	0 7 5	0 9 1	0 9 4	1 0 4	0 3 4	0 2 2	0 6 5	0 5 5	0 1 2	0 1 4	0 1 5	0 2 1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Third ventricle, lipoma																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X																					
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver							X						X												
Sarcoma, metastatic, skin					X																				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Special Senses System																									
Eye																									+
Harderian gland													+												+
Adenoma													X												X
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver							X																		
Bilateral, alveolar/bronchiolar carcinoma, metastatic, lung																									
Urethra			+	+		+		+																	
Urinary bladder	A	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia granulocytic																			X						
Lymphoma malignant mixed													X												

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm
(continued)

Number of Days on Study	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 2 3	0 2 4	0 2 5	0 3 1	0 3 3	0 3 2	0 4 1	0 4 3	0 4 4	0 4 5	0 5 3	0 6 2	0 6 3	0 6 4	0 7 2	0 7 1	0 7 3	0 7 4	0 8 1	0 8 2	0 8 3	0 8 5	0 9 2	0 9 5	1 0 5	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Third ventricle, lipoma																		X								1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma					X														X							3
Alveolar/bronchiolar adenoma, multiple									X																	1
Alveolar/bronchiolar carcinoma									X												X					2
Hepatocellular carcinoma, metastatic, liver																										2
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																										1
Harderian gland																										2
Adenoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic, liver																										1
Bilateral, alveolar/bronchiolar carcinoma, metastatic, lung									X																	1
Urethra																										4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia granulocytic																										1
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 23: 10,000 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm (continued)

Number of Days on Study	6 8 7	7 1 9	7 2 1	7 2 1	7 2 1	7 2 2	7 2 2	7 2 2	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	
Carcass ID Number	4 0 2	4 2 2	3 7 4	4 3 5	4 6 5	4 0 3	4 3 1	4 5 5	3 7 3	3 7 5	3 8 3	3 8 4	3 8 5	3 9 3	4 0 4	4 1 3	4 1 4	4 1 5	4 2 1	4 2 4	4 3 4	4 5 2	4 5 4	4 5 1	4 6 4		**Total Tissues/ Tumors**
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+																			32
Gallbladder	M	A	+	+	A	A	+	A																			20
Intestine large	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		43
Intestine large, cecum	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		42
Intestine large, colon	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		42
Intestine large, rectum	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		41
Intestine small	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		42
Intestine small, duodenum	+	A	+	A	A	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		36
Polyp	X																										1
Intestine small, ileum	+	M	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		39
Intestine small, jejunum	+	A	+	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		37
Lymphoid tissue, histiocytic sarcoma														X													2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hepatocellular carcinoma		X							X	X	X																6
Hepatocellular carcinoma, multiple					X																						1
Hepatocellular adenoma																											1
Histiocytic sarcoma																											2
Pancreas	+	+	+	+	+	+	+	+																			31
Salivary glands	+	+	+	+	+	+	+	+																			32
Stomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Stomach, forestomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Stomach, glandular	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Tooth								+																			3
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+																			32
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+																			32
Adrenal gland, cortex	+	+	+	+	+	+	+	+																			32
Histiocytic sarcoma																											1
Adrenal gland, medulla	+	+	+	+	+	+	+	+																			32
Islets, pancreatic	+	+	+	+	+	+	+	+																			30
Parathyroid gland	+	+	+	+	+	+	M	+																			26
Pituitary gland	+	M	+	+	+	+	+	+																			29
Thyroid gland	+	+	+	+	+	+	+	+																			30
Follicular cell, adenoma					X	X																					2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm (continued)

Number of Days on Study	0 3 5	0 7 3	0 7 9	0 8 7	1 1 5	1 2 2	1 2 5	1 6 8	3 2 7	3 8 0	3 8 8	4 2 1	4 2 2	4 3 6	4 7 2	5 1 5	5 2 4	5 8 1	5 9 8	6 0 3	6 1 7	6 4 4	6 4 7	6 7 8	6 7 3
Carcass ID Number	3 8 1	4 1 1	4 6 2	4 6 1	4 4 1	4 1 2	4 4 2	3 8 2	3 7 1	4 2 3	3 7 2	4 4 3	4 4 4	3 9 2	4 0 1	4 6 3	3 9 4	4 3 2	3 9 5	4 3 3	3 9 1	4 2 5	4 0 5	4 5 3	4 4 5
General Body System																									
Tissue NOS					+																				
Genital System																									
Epididymis	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis											+														
Preputial gland													+	+										+	
Prostate	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+		+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, sarcoma, metastatic, skin																							X		
Mesenteric, histiocytic sarcoma														X			X								
Lymph node, mandibular	+	+	+	+	+	+	M	M		+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	M	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																			X						
Histiocytic sarcoma														X			X								
Thymus	+	+	M	+	+	+	+	+		+	M	M	+	M	M	+	M	M	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
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma																X									X
Sarcoma															X			X		X	X		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 23: 10,000 ppm (continued)

Number of Days on Study	6 8 7	7 1 9	7 2 1	7 2 1	7 2 1	7 2 2	7 2 2	7 2 2	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	
Carcass ID Number	4 0 2	4 2 2	3 7 4	4 3 5	4 6 5	4 0 3	4 3 1	4 5 5	3 7 3	3 7 5	3 8 3	3 8 4	3 8 5	3 9 3	4 0 4	4 1 3	4 1 4	4 1 5	4 2 1	4 2 4	4 3 4	4 5 2	4 5 4	4 5 1	4 6 4	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS																										1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+																		32
Penis																										1
Preputial gland													+					+		+						6
Prostate	+	+	+	+	+	+	+	+																		32
Seminal vesicle	+	+	+	+	+	+	+	+																		32
Testes	+	+	+	+	+	+	+	+																		32
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+																		31
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Axillary, sarcoma, metastatic, skin																										1
Mesenteric, histiocytic sarcoma																										2
Lymph node, mandibular	+	M	+	+	+	+	+	+																		27
Spleen	+	+	+	+	+	+	+	+																		31
Hemangiosarcoma																										1
Histiocytic sarcoma																										2
Thymus	M	+	M	+	+	M	+	+																		18
Integumentary System																										
Mammary gland	M	M	M	M	A	M	M	M																		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																					X					1
Fibrosarcoma								X							X							X			5
Sarcoma			X			X																				7
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+																		32
Nervous System																										
Brain	+	+	+	+	+	+	+	+																		32

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm (continued)

Number of Days on Study	6 8 7	7 1 9	7 2 1	7 2 1	7 2 1	7 2 2	7 2 2	7 2 2	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	
Carcass ID Number	4 0 2	4 2 2	3 7 4	4 3 5	4 6 5	4 0 3	4 3 1	4 5 5	3 7 3	3 7 5	3 8 3	3 8 4	3 8 5	3 9 3	4 0 4	4 1 3	4 1 4	4 1 5	4 2 1	4 2 4	4 3 4	4 5 2	4 5 4	4 5 1	4 5 4	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	49
Alveolar/bronchiolar adenoma			X										X	X												5
Alveolar/bronchiolar adenoma, multiple								X																		1
Alveolar/bronchiolar carcinoma, multiple					X																					1
Fibrosarcoma, metastatic, skin								X																		1
Hepatocellular carcinoma, metastatic, liver		X																								1
Histiocytic sarcoma																										2
Nose	+	+	+	+	+	+	+	+																		32
Trachea	+	+	+	+	+	+	+	+																		32
Special Senses System																										
Harderian gland															+											1
Adenoma															X											1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+			+															33
Histiocytic sarcoma																										1
Renal tubule, adenoma							X																			1
Urethra																										1
Urinary bladder	+	A	+	+	A	+	+	+																		28
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma														X												3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 ppm

Number of Days on Study	0 8 7	0 8 7	0 8 7	3 3 9	4 5 2	5 0 5	5 2 0	5 2 9	5 8 3	5 8 5	5 9 0	6 0 3	6 1 7	6 1 8	6 2 2	6 4 7	6 4 7	6 4 8	6 4 8	6 8 7	7 1 9	7 2 1	7 2 1	7 2 3	7 2 3
Carcass ID Number	2 9 3	2 9 4	2 9 5	3 0 1	3 0 3	2 6 3	2 8 1	3 2 1	3 3 3	2 8 2	2 7 3	2 6 5	3 8 4	4 3 3	2 5 5	3 6 4	3 3 2	2 8 5	3 8 5	3 0 5	3 7 5	3 5 4	2 6 3	2 5 2	2 5 1	2 5 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+		
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	A	+	+	+
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																X									
Hemangiosarcoma											X		X				X								
Hepatocellular carcinoma									X			X						X					X		
Hepatocellular carcinoma, multiple								X																	
Hepatocellular adenoma																									X
Hepatocellular adenoma, multiple																									
Histiocytic sarcoma					X															X					
Mesentery								+																	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M		
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth							+																		
Cardiovascular System																									
Blood vessel										+															
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, carcinoma					X																				

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 ppm (continued)

Number of Days on Study	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	
Carcass ID Number	2 5 4	2 6 1	2 7 2	2 7 1	2 7 4	2 8 3	2 9 1	2 9 2	3 0 2	3 0 4	3 1 1	3 1 4	3 1 5	3 1 2	3 1 3	3 2 3	3 2 4	3 2 5	3 2 2	3 3 1	3 3 5	3 4 1	3 4 2	3 4 4	3 4 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus																										23
Gallbladder																										20
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Hemangiosarcoma															X											4
Hepatocellular carcinoma								X									X		X	X					X	9
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma				X					X																	3
Hepatocellular adenoma, multiple													X													1
Histiocytic sarcoma																										2
Mesentery																	+		+							3
Pancreas	+																									25
Salivary glands																										22
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Blood vessel																										1
Heart																										23
Endocrine System																										
Adrenal gland																										23
Adrenal gland, cortex																										23
Adrenal gland, medulla																										23
Islets, pancreatic																										23
Parathyroid gland																										20
Pituitary gland																										22
Thyroid gland																										23
Follicular cell, carcinoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 ppm (continued)

Number of Days on Study	0 8 7	0 8 7	0 8 7	3 3 9	4 5 2	5 0 5	5 2 0	5 2 9	5 8 3	5 8 5	5 8 0	6 9 3	6 0 7	6 1 8	6 1 2	6 2 7	6 4 7	6 4 8	6 4 8	6 8 7	7 1 9	7 2 1	7 2 1	7 2 3	7 2 3
Carcass ID Number	2 9 3	2 9 4	2 9 5	3 0 1	3 0 3	2 6 3	2 8 1	2 2 1	3 3 3	2 8 2	2 2 3	2 6 5	2 8 4	3 4 3	2 5 5	2 6 4	3 3 2	2 8 5	3 0 5	2 7 5	3 3 4	2 5 3	2 6 2	2 5 1	2 5 2
General Body System																									
Tissue NOS									+																+
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Penis						+																			
Preputial gland											+			+											
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Histiocytic sarcoma																				X					
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+		
Hemangiosarcoma											X		X												
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Mesenteric, histiocytic sarcoma					X															X					
Pancreatic, histiocytic sarcoma																				X					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Hemangiosarcoma											X														
Histiocytic sarcoma					X																				
Thymus	+	+	M	+	M	+	+	M	M	+	+	M	+	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		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma												X													
Fibrosarcoma												X				X			X			X		X
Papilloma squamous												X													
Sarcoma																	X				X	X			
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 23: 25,000 ppm (continued)

Number of Days on Study	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	
Carcass ID Number	2 5 4	2 6 1	2 7 2	2 7 1	2 7 4	2 8 3	2 9 1	2 9 2	3 0 2	3 0 4	3 1 1	3 1 4	3 1 5	3 1 2	3 1 3	3 2 3	3 2 4	3 2 5	3 2 1	3 3 1	3 3 5	3 4 1	3 4 2	3 4 4	3 4 5	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS																										2
Genital System																										
Epididymis																										23
Penis																										1
Preputial gland		+						+			+	+			+	+					+					9
Prostate																										23
Seminal vesicle																			+							25
Histiocytic sarcoma																										1
Testes																										23
Hematopoietic System																										
Bone marrow																										22
Hemangiosarcoma																										2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesenteric, histiocytic sarcoma																										2
Pancreatic, histiocytic sarcoma																										1
Lymph node, mandibular																										21
Spleen																+								+		26
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Thymus																										14
Integumentary System																										
Mammary gland																										
Skin	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	48
Fibroma																				X						2
Fibrosarcoma																										5
Papilloma squamous																										1
Sarcoma																X								X		5
Schwannoma malignant																										1
Musculoskeletal System																										
Bone																										23
Nervous System																										
Brain																										23

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 ppm (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 ppm (continued)

Number of Days on Study	723	723	723	724	724	724	724	724	725	725	725	725	725	728	728	728	728	728	729	729	729	729	729	730	730	
Carcass ID Number	25414	26161	26272	27721	27744	27883	28991	29012	30022	30044	31121	31144	31145	31252	31263	32233	32244	32245	32252	33321	33515	34121	34412	34444	34445	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X																							X		6
Alveolar/bronchiolar carcinoma											X												X			2
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver																										2
Histiocytic sarcoma																										1
Nose																										23
Trachea																										23
Special Senses System																										
Harderian gland																										1
Adenoma																										1
Urinary System																										
Kidney																										23
Histiocytic sarcoma																										1
Urethra															+											1
Urinary bladder																										22
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant mixed																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 ppm (continued)

Number of Days on Study	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	
Carcass ID Number	1 4 2	1 4 5	1 5 2	1 6 2	1 6 3	1 6 1	1 6 5	1 7 1	1 7 3	1 7 4	1 7 5	1 8 2	1 8 3	1 8 4	1 8 5	1 9 1	1 9 2	1 9 3	1 9 5	2 0 2	2 0 3	2 0 4	2 0 5	2 1 1	2 1 2	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma												X														11
Hepatocellular carcinoma, multiple					X																					4
Hepatocellular adenoma									X									X			X		X			6
Hepatocellular adenoma, multiple						X																				2
Mesentery																		+								2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma, metastatic, skin																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papilloma squamous								X																		1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Tooth	+			+									+											+		4
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma		X					X				X															3
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma														X								X				2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										2
Follicular cell, carcinoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 ppm (continued)

Number of Days on Study	1 5 1	4 6 9	5 4 2	5 5 9	5 7 1	5 9 6	6 0 3	6 0 6	6 3 8	6 4 7	6 4 8	6 4 8	6 4 8	6 7 2	6 7 2	6 7 2	6 7 2	6 7 3	6 7 0	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3
Carcass ID Number	1 3 3	1 7 2	2 2 2	1 3 5	1 3 1	1 8 1	1 5 1	2 1 5	2 2 1	1 6 4	1 5 4	2 1 3	2 1 4	1 5 3	1 9 4	2 0 1	2 2 3	2 2 5	1 5 5	1 4 3	1 3 2	1 3 4	1 4 1	1 4 4	2 2 4
General Body System																									
None																									
Genital System																									
Coagulating gland				+																					
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland		+			+						+	+				+			+						
Prostate	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																		X							
Hematopoietic System																									
Blood																									
Bone marrow	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin										X															
Spleen	A	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	M	+	+	A	+	+	+	M	+	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
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibroma, multiple																									
Fibrosarcoma			X							X										X					X
Fibrosarcoma, multiple																									
Papilloma squamous																									
Sarcoma																									
Sarcoma, multiple							X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 ppm (continued)

Number of Days on Study	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	
Carcass ID Number	1 4 2	1 4 5	1 5 2	1 6 2	1 6 3	1 6 1	1 6 5	1 7 1	1 7 3	1 7 4	1 7 5	1 8 2	1 8 3	1 8 4	1 8 5	1 9 1	1 9 2	1 9 3	1 9 5	2 0 2	2 0 3	2 0 4	2 0 5	2 1 1	2 1 2	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+							+							+				+						+	11
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell, adenoma																										1
Hematopoietic System																										
Blood																				+						1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma, metastatic, skin																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	M	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	M	+	M	M	+	+	M	M	M	32
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	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma				X																						1
Fibroma, multiple			X																							1
Fibrosarcoma																										4
Fibrosarcoma, multiple											X															1
Papilloma squamous			X																							1
Sarcoma							X			X			X		X				X							5
Sarcoma, multiple																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 ppm (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 ppm (continued)

Number of Days on Study	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	
Carcass ID Number	1 4 2	1 4 5	1 5 2	1 6 2	1 6 3	1 6 1	1 6 5	1 7 1	1 7 3	1 7 4	1 7 5	1 8 2	1 8 3	1 8 4	1 8 5	1 9 1	1 9 2	1 9 3	1 9 5	2 0 2	2 0 3	2 0 4	2 0 5	2 1 1	2 1 2	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X															X		2
Alveolar/bronchiolar adenoma, multiple													X													1
Alveolar/bronchiolar carcinoma	X					X																				4
Hepatocellular carcinoma, metastatic, liver																										3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye																										1
Harderian gland																							+			1
Adenoma																							X			1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortex, renal tubule, adenoma																										1
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																										1
Lymphoma malignant mixed															X			X								3
Lymphoma malignant undifferentiated cell type																										2

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Adrenal Cortex: Adenoma				
Overall rates[a]	2/48 (4%)	0/32 (0%)[e]	0/23 (0%)	3/48 (6%)
Adjusted rates[b]	6.2%			10.0%
Terminal rates[c]	1/29 (3%)			3/30 (10%)
First incidence (days)	647			723 (T)
Life table tests[d]				P=0.527
Logistic regression tests[d]				P=0.521
Fisher exact test[d]				P=0.500
Liver: Hepatocellular Adenoma				
Overall rates	3/49 (6%)	1/50 (2%)	4/50 (8%)	8/49 (16%)
Adjusted rates	10.3%	2.6%	14.8%	23.9%
Terminal rates	3/29 (10%)	0/17 (0%)	4/27 (15%)	6/30 (20%)
First incidence (days)	723 (T)	422	723 (T)	638
Life table tests	P=0.037	P=0.477N	P=0.460	P=0.117
Logistic regression tests	P=0.027	P=0.337N	P=0.460	P=0.118
Cochran-Armitage test[d]	P=0.014			
Fisher exact test		P=0.301N	P=0.511	P=0.100
Liver: Hepatocellular Carcinoma				
Overall rates	12/49 (24%)	7/50 (14%)	10/50 (20%)	15/49 (31%)
Adjusted rates	32.2%	29.4%	29.9%	36.5%
Terminal rates	6/29 (21%)	3/17 (18%)	6/27 (22%)	5/30 (17%)
First incidence (days)	518	515	529	571
Life table tests	P=0.313	P=0.465N	P=0.470N	P=0.414
Logistic regression tests	P=0.200	P=0.260N	P=0.401N	P=0.342
Cochran-Armitage test	P=0.129			
Fisher exact test		P=0.142N	P=0.384N	P=0.326
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	13/49 (27%)	8/50 (16%)	14/50 (28%)	21/49 (43%)
Adjusted rates	35.1%	31.2%	43.3%	50.4%
Terminal rates	7/29 (24%)	3/17 (18%)	10/27 (37%)	10/30 (33%)
First incidence (days)	518	422	529	571
Life table tests	P=0.071	P=0.501N	P=0.428	P=0.135
Logistic regression tests	P=0.023	P=0.260N	P=0.497	P=0.083
Cochran-Armitage test	P=0.009			
Fisher exact test		P=0.150N	P=0.525	P=0.068
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	4/49 (8%)	6/49 (12%)	6/50 (12%)	3/50 (6%)
Adjusted rates	12.3%	25.5%	17.8%	10.0%
Terminal rates	3/29 (10%)	2/16 (13%)	2/27 (7%)	3/30 (10%)
First incidence (days)	455	598	618	723 (T)
Life table tests	P=0.247N	P=0.144	P=0.338	P=0.481N
Logistic regression tests	P=0.266N	P=0.256	P=0.372	P=0.470N
Cochran-Armitage test	P=0.330N			
Fisher exact test		P=0.370	P=0.383	P=0.489N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Lung: Alveolar/bronchiolar Carcinoma				
Overall rates	2/49 (4%)	1/49 (2%)	2/50 (4%)	4/50 (8%)
Adjusted rates	6.9%	4.3%	7.4%	12.4%
Terminal rates	2/29 (7%)	0/16 (0%)	2/27 (7%)	3/30 (10%)
First incidence (days)	723 (T)	721	723 (T)	672
Life table tests	P=0.230	P=0.665N	P=0.670	P=0.359
Logistic regression tests	P=0.202	P=0.609N	P=0.670	P=0.358
Cochran-Armitage test	P=0.161			
Fisher exact test		P=0.500N	P=0.684N	P=0.349
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	5/49 (10%)	7/49 (14%)	8/50 (16%)	7/50 (14%)
Adjusted rates	15.6%	28.8%	24.4%	22.2%
Terminal rates	4/29 (14%)	2/16 (13%)	4/27 (15%)	6/30 (20%)
First incidence (days)	455	598	618	672
Life table tests	P=0.517	P=0.135	P=0.244	P=0.408
Logistic regression tests	P=0.483	P=0.239	P=0.273	P=0.427
Cochran-Armitage test	P=0.374			
Fisher exact test		P=0.380	P=0.290	P=0.394
Skin: Fibroma				
Overall rates	4/50 (8%)	1/50 (2%)	2/50 (4%)	2/50 (4%)
Adjusted rates	13.8%	5.9%	6.2%	6.7%
Terminal rates	4/29 (14%)	1/17 (6%)	1/27 (4%)	2/30 (7%)
First incidence (days)	723 (T)	723 (T)	603	723 (T)
Life table tests	P=0.289N	P=0.368N	P=0.370N	P=0.319N
Logistic regression tests	P=0.314N	P=0.368N	P=0.354N	P=0.319N
Cochran-Armitage test	P=0.367N			
Fisher exact test		P=0.181N	P=0.339N	P=0.339N
Skin: Fibrosarcoma				
Overall rates	5/50 (10%)	5/50 (10%)	5/50 (10%)	5/50 (10%)
Adjusted rates	15.9%	21.7%	14.7%	13.7%
Terminal rates	3/29 (10%)	2/17 (12%)	1/27 (4%)	2/30 (7%)
First incidence (days)	687	515	603	542
Life table tests	P=0.442N	P=0.370	P=0.595	P=0.604N
Logistic regression tests	P=0.488N	P=0.482	P=0.612	P=0.606N
Cochran-Armitage test	P=0.562			
Fisher exact test		P=0.630N	P=0.630N	P=0.630N
Skin: Sarcoma				
Overall rates	5/50 (10%)	7/50 (14%)	5/50 (10%)	6/50 (12%)
Adjusted rates	12.5%	22.7%	16.0%	18.6%
Terminal rates	0/29 (0%)	0/17 (0%)	2/27 (7%)	5/30 (17%)
First incidence (days)	463	472	647	603
Life table tests	P=0.459N	P=0.213	P=0.595	P=0.530
Logistic regression tests	P=0.539N	P=0.349	P=0.625	P=0.497
Cochran-Armitage test	P=0.529			
Fisher exact test		P=0.380	P=0.630N	P=0.500

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rates	3/49 (6%)	2/30 (7%)	1/23 (4%)	3/50 (6%)
Adjusted rates	10.0%			7.8%
Terminal rates	2/29 (7%)			0/30 (0%)
First incidence (days)	722			648
Life table tests				P=0.622N
Logistic regression tests				P=0.633N
Fisher exact test				P=0.651N
All Organs: Hemangiosarcoma				
Overall rates	2/50 (4%)	1/50 (2%)	4/50 (8%)	0/50 (0%)
Adjusted rates	5.9%	3.1%	11.2%	0.0%
Terminal rates	1/29 (3%)	0/17 (0%)	1/27 (4%)	0/30 (0%)
First incidence (days)	618	598	590	–[f]
Life table tests	P=0.246N	P=0.628N	P=0.317	P=0.231N
Logistic regression tests	P=0.284N	P=0.540N	P=0.334	P=0.234N
Cochran-Armitage test	P=0.296N			
Fisher exact test		P=0.500N	P=0.339	P=0.247N
All Organs: Malignant Lymphoma (Mixed, NOS, or Undifferentiated Cell Type)				
Overall rates	2/50 (4%)	0/50 (0%)	1/50 (2%)	6/50 (12%)
Adjusted rates	5.9%	0.0%	2.8%	16.1%
Terminal rates	1/29 (3%)	0/17 (0%)	0/27 (0%)	2/30 (7%)
First incidence (days)	644	–	622	606
Life table tests	P=0.030	P=0.334N	P=0.530N	P=0.158
Logistic regression tests	P=0.019	P=0.283N	P=0.505N	P=0.140
Cochran-Armitage test	P=0.014			
Fisher exact test		P=0.247N	P=0.500N	P=0.134
All Organs: Benign Tumors				
Overall rates	17/50 (34%)	13/50 (26%)	12/50 (24%)	20/50 (40%)
Adjusted rates	50.6%	48.0%	36.0%	58.0%
Terminal rates	13/29 (45%)	4/17 (24%)	7/27 (26%)	16/30 (53%)
First incidence (days)	455	422	603	638
Life table tests	P=0.456	P=0.383	P=0.260N	P=0.406
Logistic regression tests	P=0.371	P=0.530N	P=0.213N	P=0.411
Cochran-Armitage test	P=0.208			
Fisher exact test		P=0.257N	P=0.189N	P=0.339
All Organs: Malignant Tumors				
Overall rates	27/50 (54%)	22/50 (44%)	28/50 (56%)	31/50 (62%)
Adjusted rates	62.4%	64.3%	65.0%	67.1%
Terminal rates	13/29 (45%)	6/17 (35%)	12/27 (44%)	15/30 (50%)
First incidence (days)	463	436	452	542
Life table tests	P=0.459	P=0.312	P=0.405	P=0.418
Logistic regression tests	P=0.224	P=0.480N	P=0.458	P=0.315
Cochran-Armitage test	P=0.110			
Fisher exact test		P=0.212N	P=0.500	P=0.272

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
All Organs: Benign or Malignant Tumors				
Overall rates	35/50 (70%)	27/50 (54%)	33/50 (66%)	41/50 (82%)
Adjusted rates	79.3%	74.2%	76.7%	89.0%
Terminal rates	20/29 (69%)	8/17 (47%)	17/27 (63%)	25/30 (83%)
First incidence (days)	455	422	452	542
Life table tests	P=0.373	P=0.324	P=0.558	P=0.316
Logistic regression tests	P=0.100	P=0.325N	P=0.479N	P=0.185
Cochran-Armitage test	P=0.025			
Fisher exact test		P=0.074N	P=0.415N	P=0.121

(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; therefore statistical comparisons with the controls are not appropriate.
[f] Not applicable; no tumors in animal group

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23[a]

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	9	7	8	9
Early deaths				
Dead	10	22	8	6
Moribund	12	14	17	15
Survivors				
Terminal sacrifice	29	17	27	30
Animals examined microscopically[b]	50	50	50	50
Alimentary System				
Gallbladder	(40)	(20)	(20)	(43)
Inflammation, chronic active	2 (5%)			
Epithelium, cytoplasmic alteration				2 (5%)
Wall, mucocele				1 (2%)
Intestine large, cecum	(42)	(42)	(48)	(46)
Lymphoid tissue, hyperplasia, lymphoid		1 (2%)		
Lymphoid tissue, pigmentation				1 (2%)
Intestine large, colon	(45)	(42)	(50)	(46)
Inflammation, chronic		1 (2%)		
Intestine large, rectum	(44)	(41)	(50)	(46)
Inflammation, acute		1 (2%)		
Intestine small, duodenum	(43)	(36)	(46)	(45)
Lymphoid tissue, hyperplasia, lymphoid				1 (2%)
Intestine small, ileum	(42)	(39)	(47)	(45)
Inflammation, acute	1 (2%)			
Lymphoid tissue, hyperplasia				1 (2%)
Lymphoid tissue, pigmentation			2 (4%)	
Intestine small, jejunum	(42)	(37)	(47)	(45)
Lymphoid tissue, hyperplasia			1 (2%)	
Lymphoid tissue, hyperplasia, lymphoid	2 (5%)	2 (5%)	7 (15%)	7 (16%)
Lymphoid tissue, inflammation, chronic	1 (2%)		1 (2%)	
Lymphoid tissue, pigmentation		4 (11%)	14 (30%)	10 (22%)
Liver	(49)	(50)	(50)	(49)
Basophilic focus	2 (4%)			1 (2%)
Clear cell focus			1 (2%)	
Hematopoietic cell proliferation	3 (6%)	7 (14%)	2 (4%)	1 (2%)
Inflammation, acute				1 (2%)
Inflammation, chronic		2 (4%)		1 (2%)
Hepatocyte, necrosis	3 (6%)	8 (16%)	6 (12%)	3 (6%)
Hepatocyte, vacuolization cytoplasmic			1 (2%)	
Serosa, fibrosis				1 (2%)
Sinusoid, dilatation	1 (2%)	1 (2%)		
Mesentery			(3)	(2)
Fat, congestion			1 (33%)	
Fat, necrosis			2 (67%)	
Pancreas	(49)	(31)	(25)	(47)
Inflammation, chronic		1 (3%)	1 (4%)	
Acinar cell, atrophy	1 (2%)			1 (2%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Alimentary System (continued)				
Salivary glands	(49)	(32)	(22)	(48)
Duct, ectasia				1 (2%)
Duct, submandibular gland, hyperplasia	1 (2%)			
Stomach, forestomach	(49)	(48)	(50)	(48)
Hyperkeratosis		1 (2%)	3 (6%)	5 (10%)
Infiltration cellular, mast cell		1 (2%)		
Inflammation, acute			1 (2%)	3 (6%)
Ulcer			1 (2%)	
Epithelium, hyperplasia		1 (2%)	1 (2%)	7 (15%)
Stomach, glandular	(49)	(48)	(50)	(44)
Inflammation, acute		1 (2%)	1 (2%)	
Inflammation, chronic			2 (4%)	
Mineralization	9 (18%)	7 (15%)	4 (8%)	7 (16%)
Ulcer, focal	1 (2%)			
Mucosa, granuloma				1 (2%)
Mucosa, hyperplasia	4 (8%)	2 (4%)		3 (7%)
Tooth	(3)	(3)	(1)	(4)
Incisor, developmental malformation	3 (100%)	3 (100%)	1 (100%)	3 (75%)
Incisor, inflammation, chronic active				1 (25%)
Cardiovascular System				
Blood vessel	(1)		(1)	
Aorta, inflammation, chronic	1 (100%)			
Carotid artery, aneurysm			1 (100%)	
Heart	(49)	(32)	(23)	(50)
Inflammation, acute		2 (6%)		1 (2%)
Inflammation, chronic	2 (4%)			
Artery, polyarteritis, chronic	1 (2%)			
Atrioventricular valve, inflammation, chronic				1 (2%)
Atrium, thrombus		1 (3%)		
Endocardium, inflammation, acute		1 (3%)		
Interstitium, fibrosis	7 (14%)	3 (9%)	2 (9%)	7 (14%)
Myocardium, degeneration	1 (2%)	1 (3%)	2 (9%)	2 (4%)
Myocardium, mineralization		1 (3%)		
Endocrine System				
Adrenal gland, cortex	(48)	(32)	(23)	(48)
Clear cell focus	3 (6%)			1 (2%)
Clear cell focus, focal				1 (2%)
Cyst	1 (2%)			
Hematocyst				1 (2%)
Hemorrhage, focal				1 (2%)
Hyperplasia, focal	1 (2%)		1 (4%)	2 (4%)
Hypertrophy, focal	8 (17%)	2 (6%)	4 (17%)	9 (19%)
Necrosis			1 (4%)	
Extra adrenal tissue, accessory adrenal cortical nodule	1 (2%)			2 (4%)
Spindle cell, hyperplasia	41 (85%)	21 (66%)	15 (65%)	41 (85%)
Unilateral, atrophy			1 (4%)	

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Endocrine System (continued)				
Adrenal gland, medulla	(48)	(32)	(23)	(48)
Hyperplasia	2 (4%)	3 (9%)		2 (4%)
Hyperplasia, focal			1 (4%)	
Unilateral, necrosis			1 (4%)	
Islets, pancreatic	(49)	(30)	(23)	(47)
Cyst				1 (2%)
Hyperplasia	1 (2%)			
Parathyroid gland	(46)	(26)	(20)	(47)
Cyst	2 (4%)	2 (8%)	1 (5%)	1 (2%)
Ectopic thymus				1 (2%)
Pituitary gland	(41)	(29)	(22)	(48)
Pars distalis, congestion		1 (3%)		
Pars distalis, cyst	1 (2%)	1 (3%)		3 (6%)
Pars distalis, hyperplasia	1 (2%)			1 (2%)
Thyroid gland	(49)	(30)	(23)	(50)
Inflammation, acute			1 (4%)	
Inflammation, chronic	1 (2%)			
Ultimobranchial cyst	1 (2%)	1 (3%)		
Follicle, cyst	4 (8%)			3 (6%)
Follicular cell, hyperplasia	2 (4%)	1 (3%)	1 (4%)	2 (4%)
General Body System				
None				
Genital System				
Coagulating gland				(1)
Lumen, dilatation				1 (100%)
Epididymis	(49)	(32)	(23)	(50)
Fibrosis	1 (2%)			
Granuloma sperm				2 (4%)
Hemorrhage				1 (2%)
Hypospermia	2 (4%)			1 (2%)
Inflammation, chronic	1 (2%)		2 (9%)	1 (2%)
Inflammation, subacute				1 (2%)
Spermatocele	1 (2%)			
Unilateral, necrosis			1 (4%)	
Penis	(1)	(1)	(1)	
Cyst		1 (100%)		
Inflammation, acute	1 (100%)		1 (100%)	
Preputial gland	(9)	(6)	(9)	(11)
Abscess	1 (11%)	1 (17%)	1 (11%)	1 (9%)
Inflammation, acute				3 (27%)
Inflammation, chronic	6 (67%)	3 (50%)		4 (36%)
Duct, ectasia	6 (67%)	4 (67%)	7 (78%)	8 (73%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Genital System (continued)				
Prostate	(48)	(32)	(23)	(48)
Hemorrhage	1 (2%)			
Inflammation, acute	2 (4%)	5 (16%)	1 (4%)	1 (2%)
Inflammation, chronic	1 (2%)	2 (6%)	1 (4%)	
Inflammation, chronic active	2 (4%)			
Seminal vesicle	(49)	(32)	(25)	(48)
Depletion	1 (2%)	1 (3%)	1 (4%)	
Inflammation, acute		2 (6%)	1 (4%)	
Inflammation, chronic	2 (4%)	2 (6%)	1 (4%)	1 (2%)
Lumen, dilatation				1 (2%)
Testes	(49)	(32)	(23)	(49)
Polyarteritis, chronic	1 (2%)		1 (4%)	
Interstitial cell, hyperplasia	1 (2%)			
Interstitium, pigmentation				1 (2%)
Seminiferous tubule, atrophy	4 (8%)		2 (9%)	4 (8%)
Seminiferous tubule, degeneration	1 (2%)			
Seminiferous tubule, dilatation				1 (2%)
Seminiferous tubule, giant cell	3 (6%)		1 (4%)	1 (2%)
Seminiferous tubule, mineralization				1 (2%)
Unilateral, necrosis			1 (4%)	
Hematopoietic System				
Bone marrow	(49)	(31)	(22)	(48)
Erythroid cell, hyperplasia				3 (6%)
Myeloid cell, hyperplasia	13 (27%)	1 (3%)	2 (9%)	12 (25%)
Lymph node	(49)	(50)	(49)	(48)
Iliac, hyperplasia, lymphoid	1 (2%)			
Iliac, hyperplasia, plasma cell			1 (2%)	
Inguinal, autolysis		1 (2%)		
Inguinal, hematopoietic cell proliferation		1 (2%)		
Inguinal, hyperplasia, lymphoid	3 (6%)			
Inguinal, hyperplasia, plasma cell	1 (2%)	2 (4%)		
Inguinal, lymphocyte, necrosis		2 (4%)	2 (4%)	
Mesenteric, angiectasis	10 (20%)	8 (16%)	9 (18%)	13 (27%)
Mesenteric, autolysis		2 (4%)		
Mesenteric, congestion			1 (2%)	1 (2%)
Mesenteric, hematopoietic cell proliferation	14 (29%)	10 (20%)	8 (16%)	9 (19%)
Mesenteric, hyperplasia, lymphoid	16 (33%)	10 (20%)	16 (33%)	22 (46%)
Mesenteric, inflammation, acute	4 (8%)	4 (8%)	1 (2%)	6 (13%)
Mesenteric, inflammation, chronic			1 (2%)	
Mesenteric, pigmentation		8 (16%)	14 (29%)	16 (33%)
Mesenteric, thrombus	1 (2%)	2 (4%)		
Mesenteric, lymphocyte, necrosis	2 (4%)	2 (4%)	3 (6%)	
Renal, lymphocyte, hyperplasia		1 (2%)		
Renal, lymphocyte, necrosis		1 (2%)		

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Hematopoietic System (continued)				
Lymph node, mandibular	(48)	(27)	(21)	(48)
Hyperplasia, lymphoid		1 (4%)	1 (5%)	2 (4%)
Hyperplasia, plasma cell	1 (2%)			
Hyperplasia, RE cell	1 (2%)			
Pigmentation			1 (5%)	
Lymphocyte, necrosis			1 (5%)	
Spleen	(49)	(31)	(26)	(47)
Angiectasis		1 (3%)	1 (4%)	
Hematopoietic cell proliferation	20 (41%)	15 (48%)	13 (50%)	16 (34%)
Hyperplasia, lymphoid	5 (10%)	2 (6%)	3 (12%)	6 (13%)
Hyperplasia, RE cell	1 (2%)			
Capsule, inflammation, chronic				1 (2%)
Lymphocyte, depletion		1 (3%)		
Lymphocyte, necrosis	2 (4%)	3 (10%)	2 (8%)	1 (2%)
Red pulp, depletion		1 (3%)		
Thymus	(39)	(18)	(14)	(32)
Atrophy	7 (18%)	10 (56%)	3 (21%)	7 (22%)
Cyst	12 (31%)	2 (11%)	3 (21%)	13 (41%)
Inflammation, acute	1 (3%)			
Cortex, necrosis	4 (10%)	2 (11%)		3 (9%)
Medulla, atrophy				1 (3%)
Integumentary System				
Mammary gland				(1)
Acinus, duct, dilatation				1 (100%)
Skin	(49)	(50)	(48)	(50)
Parakeratosis	1 (2%)			
Ulcer	4 (8%)	4 (8%)	3 (6%)	2 (4%)
Dermis, fibrosis	1 (2%)			4 (8%)
Dermis, inflammation, acute	1 (2%)			
Dermis, inflammation, chronic	19 (39%)	16 (32%)	13 (27%)	12 (24%)
Dermis, mineralization		1 (2%)		2 (4%)
Epidermis, hyperkeratosis				1 (2%)
Epithelium, hyperplasia	3 (6%)		2 (4%)	3 (6%)
Prepuce, inflammation, chronic	1 (2%)		1 (2%)	
Musculoskeletal System				
Bone	(50)	(32)	(23)	(50)
Joint, arthrosis				1 (2%)
Nervous System				
Brain	(50)	(32)	(23)	(49)
Perivascular, fibrosis, focal				1 (2%)
Thalamus, mineralization	39 (78%)	14 (44%)	9 (39%)	34 (69%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Respiratory System				
Lung	(49)	(49)	(50)	(50)
Congestion	2 (4%)	3 (6%)	3 (6%)	2 (4%)
Hemorrhage	2 (4%)			2 (4%)
Inflammation, acute	2 (4%)	2 (4%)		
Alveolar epithelium, hyperplasia	1 (2%)	1 (2%)		1 (2%)
Peribronchial, glands, exudate	1 (2%)			
Peribronchiolar, cyst			1 (2%)	
Perivascular, inflammation, chronic	1 (2%)			
Pleura, fibrosis	1 (2%)			
Pleura, inflammation, chronic			1 (2%)	
Nose	(49)	(32)	(23)	(49)
Exudate, purulent	3 (6%)		1 (4%)	1 (2%)
Foreign body	1 (2%)			
Inflammation, acute	2 (4%)			1 (2%)
Inflammation, chronic active	1 (2%)			
Lumen, hemorrhage	1 (2%)			
Nasolacrimal duct, exudate				1 (2%)
Nasolacrimal duct, foreign body	1 (2%)			
Nasolacrimal duct, inflammation, acute	1 (2%)			
Submucosa, cyst	1 (2%)			
Vomeronasal organ, exudate, purulent	1 (2%)			
Vomeronasal organ, foreign body	1 (2%)			
Special Senses System				
Eye	(1)			(1)
Phthisis bulbi	1 (100%)			1 (100%)
Urinary System				
Kidney	(49)	(33)	(23)	(50)
Cyst	2 (4%)	1 (3%)		
Infarct, chronic	1 (2%)	2 (6%)	3 (13%)	
Inflammation, acute	1 (2%)			
Nephropathy	37 (76%)	12 (36%)	12 (52%)	37 (74%)
Artery, polyarteritis, chronic	1 (2%)			
Cortex, metaplasia, osseous			1 (4%)	1 (2%)
Cortex, renal tubule, necrosis, acute	1 (2%)			
Medulla, congestion	1 (2%)	1 (3%)	2 (9%)	
Papilla, necrosis		1 (3%)		
Pelvis, inflammation, acute	1 (2%)	2 (6%)		
Proximal convoluted renal tubule, degeneration, hyaline	1 (2%)			
Renal tubule, dilatation	2 (4%)	2 (6%)	1 (4%)	5 (10%)
Renal tubule, hypertrophy	1 (2%)	1 (3%)		1 (2%)
Renal tubule, mineralization	11 (22%)	3 (9%)	1 (4%)	10 (20%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Urinary System (continued)				
Urethra	(4)	(1)	(1)	(1)
Calculus micro observation only		1 (100%)		
Inflammation, acute	3 (75%)			1 (100%)
Bulbourethral gland, ectasia	1 (25%)		1 (100%)	
Bulbourethral gland, inflammation, acute	1 (25%)			1 (100%)
Urinary bladder	(44)	(28)	(22)	(46)
Inflammation, acute		1 (4%)		
Inflammation, chronic	1 (2%)	1 (4%)	1 (5%)	1 (2%)
Transitional epithelium, hyperplasia		2 (7%)	1 (5%)	

[a] Number of animals examined microscopically at site and the number of animals with lesion.
[b] Does not include early deaths that occurred prior to scheduled sacrifice.

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR FEED STUDY OF C.I. PIGMENT RED 23

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	11	7	11	10
Dead	4	8	3	4
Survivors				
Terminal sacrifice	35	34	36	35
Accidental deaths		1		
Missing				1
Animals examined microscopically	50	50	50	49
Alimentary System				
Esophagus	(50)	(15)	(14)	(48)
Gallbladder	(46)	(12)	(12)	(46)
Intestine large, cecum	(47)	(47)	(48)	(46)
Leiomyoma		1 (2%)		
Intestine large, colon	(47)	(47)	(48)	(46)
Intestine large, rectum	(46)	(48)	(48)	(46)
Intestine small, duodenum	(46)	(46)	(47)	(46)
Histiocytic sarcoma	1 (2%)			
Intestine small, ileum	(46)	(45)	(48)	(46)
Histiocytic sarcoma	1 (2%)			
Intestine small, jejunum	(46)	(46)	(48)	(47)
Histiocytic sarcoma	1 (2%)			
Liver	(49)	(49)	(50)	(48)
Granulosa cell tumor malignant, metastatic, ovary	1 (2%)			
Hemangiosarcoma		1 (2%)		
Hepatocellular carcinoma	3 (6%)	4 (8%)	5 (10%)	2 (4%)
Hepatocellular carcinoma, multiple	1 (2%)			1 (2%)
Hepatocellular adenoma	1 (2%)	5 (10%)	4 (8%)	1 (2%)
Hepatocellular adenoma, multiple			1 (2%)	
Histiocytic sarcoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Plasma cell tumor malignant		1 (2%)		
Mesentery	(7)		(4)	(3)
Pheochromocytoma malignant, metastatic, adrenal gland				1 (33%)
Pancreas	(49)	(14)	(15)	(47)
Histiocytic sarcoma			1 (7%)	
Plasma cell tumor malignant		1 (7%)		
Salivary glands	(49)	(16)	(14)	(49)
Stomach, forestomach	(49)	(49)	(50)	(49)
Papilloma squamous		1 (2%)		1 (2%)
Plasma cell tumor malignant		1 (2%)		
Stomach, glandular	(48)	(48)	(50)	(45)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Cardiovascular System				
Heart	(50)	(16)	(14)	(49)
Histiocytic sarcoma			1 (7%)	
Endocrine System				
Adrenal gland	(49)	(15)	(14)	(48)
Adrenal gland, cortex	(49)	(15)	(14)	(48)
Adenoma		1 (7%)		1 (2%)
Adrenal gland, medulla	(49)	(15)	(14)	(47)
Pheochromocytoma malignant				1 (2%)
Pheochromocytoma benign	1 (2%)			
Islets, pancreatic	(49)	(15)	(15)	(47)
Adenoma	1 (2%)	1 (7%)	1 (7%)	
Pituitary gland	(50)	(23)	(16)	(47)
Pars distalis, adenoma	16 (32%)	7 (30%)	6 (38%)	11 (23%)
Pars distalis, carcinoma	2 (4%)		1 (6%)	2 (4%)
Thyroid gland	(50)	(15)	(14)	(49)
Granulosa cell tumor malignant, metastatic, ovary	1 (2%)			
Follicular cell, adenoma	2 (4%)	1 (7%)		3 (6%)
Follicular cell, adenoma, minimal			1 (7%)	
General Body System				
None				
Genital System				
Ovary	(47)	(20)	(28)	(48)
Cystadenocarcinoma				1 (2%)
Cystadenoma		1 (5%)		
Granulosa-theca tumor benign		1 (5%)		
Histiocytic sarcoma	1 (2%)		1 (4%)	
Luteoma				1 (2%)
Mixed tumor malignant				1 (2%)
Plasma cell tumor malignant		1 (5%)		
Bilateral, granulosa cell tumor malignant	1 (2%)			
Bilateral, granulosa cell tumor benign	1 (2%)			
Uterus	(49)	(41)	(39)	(49)
Histiocytic sarcoma	1 (2%)			
Leiomyoma			1 (3%)	
Leiomyosarcoma				1 (2%)
Polyp stromal	1 (2%)	4 (10%)		4 (8%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Hematopoietic System				
Bone marrow	(49)	(49)	(49)	(49)
Hemangiosarcoma			2 (4%)	2 (4%)
Histiocytic sarcoma	1 (2%)			1 (2%)
Lymph node	(50)	(48)	(50)	(49)
Iliac, histiocytic sarcoma	1 (2%)			
Inguinal, sarcoma, metastatic, skin		1 (2%)		
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)		
Mediastinal, histiocytic sarcoma	1 (2%)			1 (2%)
Mediastinal, pheochromocytoma malignant, metastatic, adrenal gland				1 (2%)
Mediastinal, plasma cell tumor malignant		1 (2%)		
Mesenteric, histiocytic sarcoma	2 (4%)			
Mesenteric, plasma cell tumor malignant		1 (2%)		
Mesenteric, sarcoma, metastatic, skin		1 (2%)		
Renal, hemangiosarcoma		1 (2%)		
Renal, histiocytic sarcoma	1 (2%)			
Renal, plasma cell tumor malignant		1 (2%)		
Renal, sarcoma, metastatic, skin		1 (2%)		
Lymph node, mandibular	(49)	(18)	(15)	(49)
Histiocytic sarcoma	1 (2%)			
Plasma cell tumor malignant		1 (6%)		
Spleen	(50)	(21)	(25)	(48)
Hemangiosarcoma			2 (8%)	
Histiocytic sarcoma	1 (2%)		1 (4%)	1 (2%)
Plasma cell tumor malignant		1 (5%)		
Thymus	(18)	(7)	(14)	(39)
Integumentary System				
Mammary gland	(49)	(15)	(15)	(48)
Adenocarcinoma	1 (2%)	1 (7%)		
Skin	(49)	(48)	(48)	(49)
Fibrosarcoma	1 (2%)			1 (2%)
Hemangiosarcoma			1 (2%)	
Sarcoma		2 (4%)		1 (2%)
Schwannoma malignant			1 (2%)	
Musculoskeletal System				
Bone	(50)	(16)	(14)	(49)
Pelvis, osteosarcoma		1 (6%)		
Vertebra, granulosa cell tumor malignant, metastatic, ovary	1 (2%)			
Nervous System				
Brain	(50)	(15)	(14)	(49)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Respiratory System				
Lung	(50)	(50)	(49)	(49)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)	2 (4%)	4 (8%)
Alveolar/bronchiolar carcinoma				1 (2%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)		
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Histiocytic sarcoma	1 (2%)		1 (2%)	1 (2%)
Osteosarcoma, metastatic, bone		1 (2%)		
Pheochromocytoma malignant, metastatic, adrenal gland				1 (2%)
Plasma cell tumor malignant		1 (2%)		
Sarcoma, metastatic, skin		2 (4%)		1 (2%)
Nose	(50)	(15)	(14)	(49)
Vomeronasal organ, histiocytic sarcoma				1 (2%)
Special Senses System				
Harderian gland		(2)	(4)	
Adenoma		2 (100%)	3 (75%)	
Carcinoma			1 (25%)	
Urinary System				
Kidney	(49)	(17)	(15)	(49)
Histiocytic sarcoma	1 (2%)		1 (7%)	1 (2%)
Plasma cell tumor malignant		1 (6%)		
Urinary bladder	(47)	(15)	(12)	(46)
Systemic Lesions				
Multiple organs[a]	(50)	(50)	(50)	(49)
Histiocytic sarcoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Lymphoma malignant	1 (2%)			
Lymphoma malignant lymphocytic		2 (4%)		2 (4%)
Lymphoma malignant mixed	5 (10%)	4 (8%)	8 (16%)	7 (14%)
Lymphoma malignant undifferentiated cell		3 (6%)	1 (2%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[b]	27	31	31	32
Total primary neoplasms	41	58	42	51
Total animals with benign neoplasms	19	19	17	18
Total benign neoplasms	24	26	19	26
Total animals with malignant neoplasms	14	20	21	18
Total malignant neoplasms	17	32	23	25
Total animals with metastatic neoplasms	1	4	1	2
Total metastatic neoplasms	3	7	1	4

[a] Number of animals examined microscopically at site and the number of animals with lesion.
[b] Primary neoplasms: all tumors except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm

Number of Days on Study	5 0 1	5 5 9	5 8 5	6 0 3	6 1 0	6 1 6	6 1 8	6 3 4	6 5 5	6 5 5	6 6 1	6 7 3	6 8 7	6 9 4	7 1 0	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4
Carcass ID Number	5 8 1	5 4 5	5 4 1	5 1 1	5 8 4	5 4 4	5 5 2	5 8 5	4 9 5	5 6 2	5 7 5	4 9 3	5 1 3	4 9 4	5 2 2	4 9 1	4 9 2	5 0 1	5 0 2	5 0 3	5 0 4	5 0 5	5 1 2	5 1 4	5 1 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	A	+	+	+	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+
Intestine large	A	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small	A	+	+	+	+	A	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	A	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Intestine small, ileum	A	+	+	+	+	A	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Intestine small, jejunum	A	+	+	+	+	A	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant, metastatic, ovary										X															
Hepatocellular carcinoma																									
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma																				X					
Histiocytic sarcoma								X				X													
Mesentery	+	+	+		+	+																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel															+										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									

+: 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 23: 0 ppm (continued)

Number of Days on Study	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	5 2 1	5 2 3	5 2 4	5 2 5	5 3 1	5 3 2	5 3 3	5 3 4	5 3 5	5 4 2	5 4 3	5 5 1	5 5 3	5 5 4	5 5 5	5 6 1	5 6 3	5 6 4	5 6 5	5 7 1	5 7 2	5 7 3	5 7 4	5 8 2	5 8 3	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell tumor malignant, metastatic, ovary																										1
Hepatocellular carcinoma					X							X		X												3
Hepatocellular carcinoma, multiple																					X					1
Hepatocellular adenoma																										1
Histiocytic sarcoma																										2
Mesentery									+									+								7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	48
Tooth							+																		+	2
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign			X																							1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm (continued)

Number of Days on Study	5 0 1	5 5 9	5 8 5	6 0 3	6 1 0	6 1 6	6 1 8	6 3 4	6 5 5	6 5 5	6 6 1	6 7 3	6 8 7	6 9 4	7 1 0	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4
Carcass ID Number	5 8 1	5 4 5	5 4 1	5 1 1	5 8 4	5 4 4	5 5 2	5 8 5	4 9 5	5 6 2	5 7 5	4 9 3	5 1 3	4 9 4	5 2 2	4 9 1	4 9 2	5 0 1	5 0 2	5 0 3	5 0 4	5 0 5	5 1 2	5 1 4	5 1 5
Endocrine System (continued)																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X	X				X						X	X					
Pars distalis, carcinoma														X											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant, metastatic, ovary										X															
Follicular cell, adenoma																				X					
General Body System																									
None																									
Genital System																									
Ovary	+	+	+	+	+	+	I	+	+	+	I	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Bilateral, granulosa cell tumor malignant										X															
Bilateral, granulosa cell tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, histiocytic sarcoma								X																	
Mediastinal, histiocytic sarcoma												X													
Mesenteric, histiocytic sarcoma								X				X													
Renal, histiocytic sarcoma								X																	
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Thymus	+	A	M	M	M	M	+	M	A	M	M	M	+	+	M	+	+	M	M	+	+	M	M	M	M

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm (continued)

Number of Days on Study	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	5 2 1	5 2 3	5 2 4	5 2 5	5 3 1	5 3 2	5 3 3	5 3 4	5 3 5	5 4 2	5 4 3	5 5 1	5 5 3	5 5 4	5 5 5	5 6 1	5 6 3	5 6 4	5 6 5	5 7 1	5 7 2	5 7 3	5 7 4	5 8 2	5 8 3	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X		X		X	X	X			X	X	X	X							X				16
Pars distalis, carcinoma																								X		2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor malignant, metastatic, ovary																										1
Follicular cell, adenoma			X																							2
General Body System																										
None																										
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Bilateral, granulosa cell tumor malignant																										1
Bilateral, granulosa cell tumor benign																	X									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Polyp stromal																								X		1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Iliac, histiocytic sarcoma																										1
Mediastinal, histiocytic sarcoma																										1
Mesenteric, histiocytic sarcoma																										2
Renal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	M	+	M	+	M	+	M	M	M	M	M	+	+	+	+	M	M	+	+	M	M	M	M	M	+	18

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm (continued)

Number of Days on Study	5 0 1	5 5 9	5 8 5	6 0 3	6 1 0	6 1 6	6 1 8	6 3 4	6 5 5	6 5 5	6 6 1	6 7 3	6 8 7	6 9 4	7 1 0	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4
Carcass ID Number	5 8 1	5 4 5	4 4 1	5 1 1	5 8 4	5 4 4	5 5 2	4 8 5	4 9 5	5 6 2	5 7 5	4 9 3	5 1 3	4 9 4	5 2 2	4 9 1	4 9 2	5 0 1	5 0 2	5 0 3	5 0 4	5 0 5	5 1 2	5 1 4	5 1 5
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma							X																	
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vertebra, granulosa cell tumor malignant, metastatic, ovary										X														
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord									+															
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X																		
Histiocytic sarcoma								X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																
Urinary bladder	+	+	+	+	+	A	+	+	+	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X				X												
Lymphoma malignant														X										
Lymphoma malignant mixed											X					X								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 0 ppm (continued)

Number of Days on Study	7 2 4	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	5 2 1	5 2 3	5 2 4	5 2 5	5 3 1	5 3 2	5 3 3	5 3 4	5 3 5	5 4 2	5 4 3	5 5 1	5 5 3	5 5 4	5 5 5	5 6 1	5 6 3	5 6 4	5 6 5	5 7 1	5 7 2	5 7 3	5 7 4	5 8 2	5 8 3	**Total Tissues/ Tumors**
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Vertebra, granulosa cell tumor malignant, metastatic, ovary																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye												+														1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant																										1
Lymphoma malignant mixed																				X	X			X		5

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm

Number of Days on Study	0 7 7	0 8 0	4 2 0	4 4 5	4 6 9	4 8 7	5 1 6	5 7 1	6 1 3	6 1 9	6 4 7	6 6 5	6 8 3	7 0 3	7 1 0	7 2 2	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4
Carcass ID Number	8 5 1	8 5 2	9 3 1	8 7 1	8 8 1	9 1 1	9 4 1	9 1 5	9 0 4	9 2 4	9 3 2	9 4 4	9 9 5	8 9 1	8 8 3	8 6 5	8 5 3	8 5 4	8 5 5	8 6 1	8 6 2	8 6 3	8 6 4	8 7 2	8 7 3
Alimentary System																									
Esophagus	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+									
Gallbladder	+	A	A	+	+	+	+	+	+	+	+	A	+	+	A	+									
Intestine large	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma															X										
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+		+	
Intestine small, ileum	+	+	A	+	+	+	A	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+		+	
Intestine small, jejunum	+	+	A	+	+	+	A	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Liver	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X																		
Hepatocellular carcinoma																						X			
Hepatocellular adenoma									X																X
Histiocytic sarcoma																									
Plasma cell tumor malignant															X										
Pancreas	+	+	A	+	+	+	+	+	+	+	+	M	+	+	+	+									
Plasma cell tumor malignant															X										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Stomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																						X			
Plasma cell tumor malignant															X										
Stomach, glandular	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Endocrine System																									
Adrenal gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+									
Adrenal gland, cortex	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+									
Adenoma									X																
Adrenal gland, medulla	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+									
Islets, pancreatic	+	+	A	+	+	+	+	+	+	+	+	M	+	+	+	+									
Adenoma																									
Parathyroid gland	M	+	M	+	+	M	+	+	M	+	M	+	+	+	M	+									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm
(continued)

Number of Days on Study	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	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	
Carcass ID Number	8 7 4	8 7 5	8 8 2	8 8 4	8 8 5	8 9 2	8 9 3	8 9 4	9 0 1	9 0 2	9 0 3	9 0 5	9 1 2	9 1 3	9 1 4	9 2 1	9 2 2	9 2 3	9 2 5	9 3 3	9 3 4	9 3 5	9 4 2	9 4 3	9 4 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus																										15
Gallbladder																										12
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leiomyoma																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Hepatocellular carcinoma												X			X						X					4
Hepatocellular adenoma								X							X		X									5
Histiocytic sarcoma					X																					1
Plasma cell tumor malignant																										1
Pancreas																										14
Plasma cell tumor malignant																										1
Salivary glands																										16
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous																										1
Plasma cell tumor malignant																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Heart																										16
Endocrine System																										
Adrenal gland																										15
Adrenal gland, cortex																										15
Adenoma																										1
Adrenal gland, medulla																										15
Islets, pancreatic																					+					15
Adenoma																					X					1
Parathyroid gland																										10

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm
(continued)

Number of Days on Study	0	0	4	4	4	4	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7
	7	8	2	4	6	8	1	7	1	1	4	6	8	0	1	2	2	2	2	2	2	2	2	2	2
	7	0	0	5	9	7	6	1	3	9	7	5	3	3	0	2	3	3	3	3	3	4	4	4	4
Carcass ID Number	8	8	9	8	8	9	9	9	9	9	9	9	8	8	8	8	8	8	8	8	8	8	8	8	8
	5	5	3	7	8	1	4	1	0	2	3	4	9	9	8	6	5	5	5	6	6	6	6	7	7
	1	2	1	1	1	1	1	5	4	4	2	4	5	1	3	5	3	4	5	1	2	3	4	2	3
Endocrine System (continued)																									
Pituitary gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+								+	
Pars distalis, adenoma																								X	
Thyroid gland	+		A	+	+	+	+	+	+	+	+	+	+	+	+	+									
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Ovary	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+				+					
Cystadenoma																									
Granulosa-theca tumor benign																									
Plasma cell tumor malignant															X										
Uterus	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	
Polyp stromal																								X	
Hematopoietic System																									
Bone marrow	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, sarcoma, metastatic, skin											X														
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung										X															
Mediastinal, plasma cell tumor malignant															X										
Mesenteric, plasma cell tumor malignant															X										
Mesenteric, sarcoma, metastatic, skin											X														
Renal, hemangiosarcoma								X																	
Renal, plasma cell tumor malignant															X										
Renal, sarcoma, metastatic, skin											X														
Lymph node, mandibular	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+		+							
Plasma cell tumor malignant															X										
Spleen	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+		+							
Plasma cell tumor malignant															X										
Thymus	+	M	M	M	+	M	M	+	M	M	M	M	M	+	M	+									
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+									
Adenocarcinoma													X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Sarcoma			X								X														

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm
(continued)

Number of Days on Study	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	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	
Carcass ID Number	8 7 4	8 7 5	8 8 2	8 8 4	8 8 5	8 9 2	8 9 3	8 9 4	9 0 1	9 0 2	9 0 3	9 0 5	9 1 2	9 1 3	9 1 4	9 2 1	9 2 2	9 2 3	9 2 5	9 3 3	9 3 4	9 3 5	9 4 2	9 4 3	9 4 5	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Pituitary gland	+				+	+				+			+					+					+		23
Pars distalis, adenoma	X				X	X							X					X					X			7
Thyroid gland									+																	15
Follicular cell, adenoma									X																	1
General Body System																										
None																										
Genital System																										
Ovary			+								+		+								+					20
Cystadenoma											X															1
Granulosa-theca tumor benign																					X					1
Plasma cell tumor malignant																										1
Uterus	+	+	+	+		+		+	+	+	+	+	+	+		+	+	+	+	+			+	+		41
Polyp stromal	X					X			X																	4
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Inguinal, sarcoma, metastatic, skin																										1
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinal, plasma cell tumor malignant																										1
Mesenteric, plasma cell tumor malignant																										1
Mesenteric, sarcoma, metastatic, skin																										1
Renal, hemangiosarcoma																										1
Renal, plasma cell tumor malignant																										1
Renal, sarcoma, metastatic, skin																										1
Lymph node, mandibular						+									+								+			18
Plasma cell tumor malignant																										1
Spleen						+						+	+										+		+	21
Plasma cell tumor malignant																										1
Thymus												+											+			7
Integumentary System																										
Mammary gland																										15
Adenocarcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma																										2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm
(continued)

Number of Days on Study	0	0	4	4	4	4	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
	7	8	2	4	6	8	1	7	1	1	4	6	8	0	1	2	2	2	2	2	2	2	2	2	2	2
	7	0	0	5	9	7	6	1	3	9	7	5	3	3	0	2	3	3	3	3	3	4	4	4	4	4
Carcass ID Number	8	8	9	8	8	9	9	9	9	9	9	9	8	8	8	8	8	8	8	8	8	8	8	8	8	8
	5	5	3	7	8	1	4	1	0	2	3	4	9	9	8	6	5	5	5	6	6	6	6	7	7	7
	1	2	1	1	1	1	1	5	4	4	2	4	5	1	3	5	3	4	5	1	2	3	4	2	3	3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Pelvis, osteosarcoma									X																	
Nervous System																										
Brain	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+										
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																										
Alveolar/bronchiolar carcinoma, multiple										X																
Osteosarcoma, metastatic, bone									X																	
Plasma cell tumor malignant															X											
Sarcoma, metastatic, skin			X								X															
Nose	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+										
Trachea	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+										
Special Senses System																										
Eye																+										
Harderian gland																+										
Adenoma																X										
Urinary System																										
Kidney	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		+								
Plasma cell tumor malignant															X											
Urinary bladder	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+										
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Lymphoma malignant lymphocytic																										
Lymphoma malignant mixed													X				X	X								
Lymphoma malignant undifferentiated cell type														X		X										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 10,000 ppm
(continued)

Number of Days on Study	7 2 4	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	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	
Carcass ID Number	8 7 4	8 7 5	8 8 2	8 8 4	8 8 5	8 9 2	8 9 3	8 9 4	9 0 1	9 0 2	9 0 3	9 0 5	9 1 2	9 1 3	9 1 4	9 2 1	9 2 2	9 2 3	9 2 5	9 3 3	9 3 4	9 3 5	9 4 2	9 4 3	9 4 5	**Total Tissues/ Tumors**
Musculoskeletal System																										
Bone																										16
Pelvis, osteosarcoma																										1
Nervous System																										
Brain																										15
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																			X							1
Alveolar/bronchiolar carcinoma, multiple																										1
Osteosarcoma, metastatic, bone																										1
Plasma cell tumor malignant																										1
Sarcoma, metastatic, skin																										2
Nose																										15
Trachea																										15
Special Senses System																										
Eye												+														2
Harderian gland												+														2
Adenoma												X														2
Urinary System																										
Kidney					+																					17
Plasma cell tumor malignant																										1
Urinary bladder																										15
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma					X																					1
Lymphoma malignant lymphocytic												X												X		2
Lymphoma malignant mixed																					X					4
Lymphoma malignant undifferentiated cell type																									X	3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 ppm
(continued)

Number of Days on Study	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	
Carcass ID Number	7 6 3	7 6 5	7 7 1	7 7 2	7 8 1	7 7 3	7 7 4	7 7 5	7 8 2	7 8 4	7 8 5	7 9 2	7 9 3	7 9 4	8 0 3	8 0 5	8 1 1	8 1 2	8 1 3	8 1 4	8 1 5	8 2 1	8 2 2	8 2 3	8 2 4	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus																										14
Gallbladder														+												12
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma												X														5
Hepatocellular adenoma							X											X			X					4
Hepatocellular adenoma, multiple													X													1
Histiocytic sarcoma																										1
Mesentery																+				+						4
Pancreas			+																							15
Histiocytic sarcoma																										1
Salivary glands																										14
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart																										14
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal gland																										14
Adrenal gland, cortex																										14
Adrenal gland, medulla																										14
Islets, pancreatic																										15
Adenoma																										1
Parathyroid gland																										14
Pituitary gland										+					+											16
Pars distalis, adenoma										X					X											6
Pars distalis, carcinoma																										1
Thyroid gland																										14
Follicular cell, adenoma, minimal																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 ppm
(continued)

Number of Days on Study	4 5 2	4 7 2	5 1 6	5 2 1	5 8 5	6 0 6	6 3 1	6 4 5	6 6 1	6 6 7	7 0 7	7 1 0	7 2 1	7 2 1	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5
Carcass ID Number	7 3 1	7 9 1	8 0 1	8 0 2	7 6 2	7 8 3	8 0 4	7 6 4	7 5 1	7 9 5	7 5 5	8 2 5	7 4 1	7 6 1	7 3 2	7 3 3	7 3 4	7 3 5	7 4 2	7 4 3	7 4 4	7 4 5	7 5 2	7 5 3	7 5 4
General Body System																									
None																									
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+			+	+	+		+	
Histiocytic sarcoma					X																				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+		+
Leiomyoma					X																				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X																							
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+								
Hemangiosarcoma			X																						
Histiocytic sarcoma					X																				
Thymus	+	+	+	+	+	+	+	I	M	M	+	+	+	M	+		+								
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Schwannoma malignant										X															
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X			X								
Hepatocellular carcinoma, metastatic, liver								X																	
Histiocytic sarcoma					X																				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+											

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 ppm
(continued)

Number of Days on Study	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	
Carcass ID Number	7 6 3	7 6 5	7 7 1	7 7 2	7 8 1	7 7 3	7 7 4	7 7 5	7 8 2	7 8 4	7 8 5	7 9 2	7 9 3	7 9 4	8 0 3	8 0 5	8 1 1	8 1 2	8 1 3	8 1 4	8 1 5	8 2 1	8 2 2	8 2 3	8 2 4	**Total Tissues/ Tumors**
General Body System																									
None																									
Genital System																									
Ovary			+	+			+			+	+						+	+			+			+	28
Histiocytic sarcoma																									1
Uterus			+	+		+		+	+		+		+	+	+		+		+	+	+		+	+	+	39
Leiomyoma																									1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma					X																				2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular										+															15
Spleen		+			+	+				+		+				+		+			+		+		25
Hemangiosarcoma					X																				2
Histiocytic sarcoma																									1
Thymus		+								+															14
Integumentary System																									
Mammary gland										+															15
Skin	+	+	+	+	+		+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																						X			1
Schwannoma malignant																									1
Musculoskeletal System																									
Bone																									14
Nervous System																									
Brain																									14
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																									2
Hepatocellular carcinoma, metastatic, liver																									1
Histiocytic sarcoma																									1
Nose																									14
Trachea																									14

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 25,000 ppm
(continued)

Number of Days on Study	4 5 2	4 7 2	5 1 6	5 2 1	5 8 5	6 0 6	6 3 1	6 4 5	6 6 1	6 6 7	7 0 7	7 1 0	7 2 1	7 2 1	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4	7 2 5
Carcass ID Number	7 3 1	7 9 1	8 0 1	8 0 2	7 6 2	7 8 3	8 0 4	7 6 4	7 5 1	7 9 5	7 5 5	8 2 5	7 4 1	7 6 1	7 3 2	7 3 3	7 3 4	7 3 5	7 4 2	7 4 3	7 4 4	7 4 5	7 5 2	7 5 3	7 5 4
Special Senses System																									
Eye																							+		
Harderian gland	+																				+				
Adenoma																					X				
Carcinoma	X																								
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+											
Histiocytic sarcoma					X																				
Urinary bladder	+	+	A	+	+	+	+	+	+	+	A	+	+	+											
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Lymphoma malignant mixed													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 23: 25,000 ppm
(continued)

Number of Days on Study	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	
Carcass ID Number	7 6 3	7 6 5	7 7 1	7 7 2	7 8 1	7 7 3	7 7 4	7 7 5	7 8 2	7 8 4	7 8 5	7 9 2	7 9 3	7 9 4	8 0 3	8 0 5	8 1 1	8 1 2	8 1 3	8 1 4	8 1 5	8 2 1	8 2 2	8 2 3	8 2 4	**Total Tissues/ Tumors**
Special Senses System																										
Eye								+																		2
Harderian gland								+														+				4
Adenoma								X														X				3
Carcinoma																										1
Urinary System																										
Kidney		+																								15
Histiocytic sarcoma																										1
Urinary bladder																										12
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant mixed		X	X				X			X													X			8
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 23: 50,000 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 ppm
(continued)

Number of Days on Study	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	
Carcass ID Number	6 3 5	6 4 1	6 4 4	6 4 5	6 5 1	6 5 2	6 5 5	6 6 3	6 6 4	6 6 5	6 7 1	6 7 2	6 8 1	6 8 2	6 8 3	6 8 4	6 9 1	6 9 2	6 9 3	6 9 4	6 9 5	7 0 1	7 0 2	7 0 3	7 0 4	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma										X							X								2
Hepatocellular carcinoma, multiple								X																		1
Hepatocellular adenoma					X																					1
Histiocytic sarcoma																										1
Mesentery																										3
Pheochromocytoma malignant, metastatic, adrenal gland																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous																										1
Stomach, glandular	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Tongue																										1
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Pheochromocytoma malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 ppm
(continued)

Number of Days on Study	2 9 7	5 1 5	5 5 3	5 8 3	5 8 5	5 8 8	5 9 9	6 1 8	6 2 7	6 3 3	6 4 5	6 5 2	6 5 8	6 6 7	7 2 3	7 2 3	7 2 3	7 2 3	7 2 4	7 2 4	7 2 4	7 2 4	7 2 4
Carcass ID Number	6 3 1	6 6 2	6 5 4	6 3 3	6 7 4	6 4 2	6 4 3	6 1 4	6 2 3	6 7 5	7 0 5	6 5 3	6 7 3	6 8 5	6 1 1	6 1 2	6 1 3	6 1 5	6 2 2	6 2 1	6 2 4	6 2 5	6 3 2	6 3 4
Endocrine System (continued)																								
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Pars distalis, adenoma										X							X					X		
Pars distalis, carcinoma																								
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma						X																		
General Body System																								
None																								
Genital System																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+
Cystadenocarcinoma													X											
Luteoma																								
Mixed tumor malignant																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																		X						
Polyp stromal																								X
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Histiocytic sarcoma		X																						
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, histiocytic sarcoma		X																						
Mediastinal, pheochromocytoma malignant, metastatic, adrenal gland			X																					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																						
Thymus	+	+	M	+	+	+	M	M	+	M	+	+	+	+	+	M	+	+	M	+	+	+	M	M
Integumentary System																								
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma									X															
Sarcoma										X														

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 ppm
(continued)

Number of Days on Study	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	
Carcass ID Number	6 3 5	6 4 1	6 4 4	6 4 5	6 5 1	6 5 2	6 5 5	6 6 3	6 6 4	6 6 5	6 7 1	6 7 2	6 8 1	6 8 2	6 8 3	6 8 4	6 9 1	6 9 2	6 9 3	6 9 4	6 9 5	7 0 1	7 0 2	7 0 3	7 0 4	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Pars distalis, adenoma			X	X	X	X	X					X		X									X			11
Pars distalis, carcinoma										X										X						2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma					X									X												3
General Body System																										
None																										
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cystadenocarcinoma																										1
Luteoma																								X		1
Mixed tumor malignant																						X				1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyosarcoma																										1
Polyp stromal						X			X					X												4
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma			X																	X						2
Histiocytic sarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mediastinal, histiocytic sarcoma																										1
Mediastinal, pheochromocytoma malignant, metastatic, adrenal gland																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	39
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma																										1
Sarcoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 ppm
(continued)

Number of Days on Study	2	5	5	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	
	9	1	5	8	8	8	9	1	2	3	4	5	5	6	2	2	2	2	2	2	2	2	2	2	
	7	5	3	3	5	8	9	8	7	3	5	2	8	7	3	3	3	3	3	4	4	4	4	4	
Carcass ID Number	6	6	6	6	6	6	6	6	6	6	7	6	6	6	6	6	6	6	6	6	6	6	6	6	
	3	6	5	3	7	4	4	1	2	7	0	5	7	8	1	1	1	1	2	2	2	2	3	3	
	1	2	4	3	4	2	3	4	3	5	5	3	3	5	1	2	3	5	2	1	4	5	2	4	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma						X																	X		
Alveolar/bronchiolar carcinoma																									
Histiocytic sarcoma		X																							
Pheochromocytoma malignant, metastatic, adrenal gland			X																						
Sarcoma, metastatic, skin										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Vomeronasal organ, histiocytic sarcoma		X																							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma		X																							
Urinary bladder	+	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma		X																							
Lymphoma malignant lymphocytic				X																					
Lymphoma malignant mixed				X				X				X						X							
Lymphoma malignant undifferentiated cell type																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23: 50,000 ppm
(continued)

Number of Days on Study	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	
Carcass ID Number	6 3 5	6 4 1	6 4 4	6 4 5	6 5 1	6 5 2	6 5 5	6 6 3	6 6 4	6 6 5	6 7 1	6 7 2	6 8 1	6 8 2	6 8 3	6 8 4	6 9 1	6 9 2	6 9 3	6 9 4	6 9 5	7 0 1	7 0 2	7 0 3	7 0 4	**Total Tissues/ Tumors**
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma			X																X							4
Alveolar/bronchiolar carcinoma																X										1
Histiocytic sarcoma																										1
Pheochromocytoma malignant, metastatic, adrenal gland																										1
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Vomeronasal organ, histiocytic sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymphoma malignant lymphocytic											X															2
Lymphoma malignant mixed							X										X			X					7
Lymphoma malignant undifferentiated cell type										X																1

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Harderian Gland: Adenoma				
Overall rates[a]	0/50 (0%)	2/50 (4%)	3/50 (6%)	0/49 (0%)
Adjusted rates[b]	0.0%	5.9%	8.3%	0.0%
Terminal rates[c]	0/35 (0%)	2/34 (6%)	3/36 (8%)	0/35 (0%)
First incidence (days)	–[e]	723 (T)	723 (T)	–
Life table tests[d]	P=0.507N	P=0.232	P=0.126	–
Logistic regression tests[d]	P=0.507N	P=0.232	P=0.126	–
Cochran-Armitage test[d]	P=0.519N			
Fisher exact test[d]		P=0.247	P=0.121	–
Harderian Gland: Adenoma or Carcinoma				
Overall rates	0/50 (0%)	2/50 (4%)	4/50 (8%)	0/49 (0%)
Adjusted rates	0.0%	5.9%	10.2%	0.0%
Terminal rates	0/35 (0%)	2/34 (6%)	3/36 (8%)	0/35 (0%)
First incidence (days)	–	723 (T)	452	–
Life table tests	P=0.540N	P=0.232	P=0.067	–
Logistic regression tests	P=0.552N	P=0.232	P=0.070	–
Cochran-Armitage test	P=0.552N			
Fisher exact test		P=0.247	P=0.059	–
Liver: Hepatocellular Adenoma				
Overall rates	1/49 (2%)	5/49 (10%)	5/50 (10%)	1/48 (2%)
Adjusted rates	2.9%	13.9%	13.1%	2.9%
Terminal rates	1/35 (3%)	4/34 (12%)	4/36 (11%)	1/35 (3%)
First incidence (days)	723 (T)	613	631	723 (T)
Life table tests	P=0.388N	P=0.097	P=0.111	P=0.762
Logistic regression tests	P=0.401N	P=0.093	P=0.108	P=0.762
Cochran-Armitage test	P=0.400N			
Fisher exact test		P=0.102	P=0.107	P=0.747
Liver: Hepatocellular Carcinoma				
Overall rates	4/49 (8%)	4/49 (8%)	5/50 (10%)	3/48 (6%)
Adjusted rates	11.4%	11.8%	12.4%	8.6%
Terminal rates	4/35 (11%)	4/34 (12%)	3/36 (8%)	3/35 (9%)
First incidence (days)	723 (T)	723 (T)	521	723 (T)
Life table tests	P=0.425N	P=0.629	P=0.512	P=0.500N
Logistic regression tests	P=0.444N	P=0.629	P=0.514	P=0.500N
Cochran-Armitage test	P=0.442N			
Fisher exact test		P=0.643N	P=0.513	P=0.512N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	5/49 (10%)	8/49 (16%)	10/50 (20%)	4/48 (8%)
Adjusted rates	14.3%	22.5%	24.7%	11.4%
Terminal rates	5/35 (14%)	7/34 (21%)	7/36 (19%)	4/35 (11%)
First incidence (days)	723 (T)	613	521	723 (T)
Life table tests	P=0.359N	P=0.253	P=0.145	P=0.500N
Logistic regression tests	P=0.381N	P=0.253	P=0.139	P=0.500N
Cochran-Armitage test	P=0.379N			
Fisher exact test		P=0.276	P=0.140	P=0.513N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	1/50 (2%)	1/50 (2%)	2/49 (4%)	4/49 (8%)
Adjusted rates	2.2%	2.9%	5.4%	10.6%
Terminal rates	0/35 (0%)	1/34 (3%)	1/35 (3%)	3/35 (9%)
First incidence (days)	616	723 (T)	721	588
Life table tests	P=0.071	P=0.747	P=0.507	P=0.175
Logistic regression tests	P=0.066	P=0.761N	P=0.496	P=0.184
Cochran-Armitage test	P=0.065			
Fisher exact test		P=0.753N	P=0.492	P=0.175
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	1/50 (2%)	2/50 (4%)	2/49 (4%)	5/49 (10%)
Adjusted rates	2.2%	5.3%	5.4%	13.4%
Terminal rates	0/35 (0%)	1/34 (3%)	1/35 (3%)	4/35 (11%)
First incidence (days)	616	619	721	588
Life table tests	P=0.053	P=0.480	P=0.507	P=0.102
Logistic regression tests	P=0.048	P=0.529	P=0.496	P=0.102
Cochran-Armitage test	P=0.048			
Fisher exact test		P=0.500	P=0.492	P=0.098
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	16/50 (32%)	7/23 (30%)[f]	6/16 (38%)	11/47 (23%)
Adjusted rates	41.6%			32.0%
Terminal rates	13/35 (37%)			10/33 (30%)
First incidence (days)	634			633
Life table tests				P=0.239N
Logistic regression tests				P=0.278N
Fisher exact test				P=0.237N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	18/50 (36%)	7/23 (30%)	7/16 (44%)	13/47 (28%)
Adjusted rates	45.8%			38.0%
Terminal rates	14/35 (40%)			12/33 (36%)
First incidence (days)	634			633
Life table tests				P=0.256N
Logistic regression tests				P=0.302N
Fisher exact test				P=0.254N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rates	2/50 (4%)	1/15 (7%)	1/14 (7%)	3/49 (6%)
Adjusted rates	5.7%			7.9%
Terminal rates	2/35 (6%)			2/35 (6%)
First incidence (days)	723 (T)			588
Life table tests				P=0.494
Logistic regression tests				P=0.484
Fisher exact test				P=0.490

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Uterus: Stromal Polyp				
Overall rates	1/50 (2%)	4/50 (8%)	0/50 (0%)	4/49 (8%)
Adjusted rates	2.9%	11.8%	0.0%	11.4%
Terminal rates	1/35 (3%)	4/34 (12%)	0/36 (0%)	4/35 (11%)
First incidence (days)	723 (T)	723 (T)	–	723 (T)
Life table tests	P=0.260	P=0.170	P=0.494N	P=0.178
Logistic regression tests	P=0.260	P=0.170	P=0.494N	P=0.178
Cochran-Armitage test	P=0.247			
Fisher exact test		P=0.181	P=0.500N	P=0.175
All Organs: Hemangiosarcoma				
Overall rates	0/50 (0%)	2/50 (4%)	4/50 (8%)	2/49 (4%)
Adjusted rates	0.0%	4.5%	9.4%	5.7%
Terminal rates	0/35 (0%)	0/34 (0%)	2/36 (6%)	2/35 (6%)
First incidence (days)	–	516	472	723 (T)
Life table tests	P=0.242	P=0.216	P=0.067	P=0.238
Logistic regression tests	P=0.206	P=0.327	P=0.086	P=0.238
Cochran-Armitage test	P=0.229			
Fisher exact test		P=0.247	P=0.059	P=0.242
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, NOS, or Undifferentiated Cell Type)				
Overall rates	6/50 (12%)	9/50 (18%)	9/50 (18%)	9/49 (18%)
Adjusted rates	16.0%	24.2%	23.3%	23.0%
Terminal rates	4/35 (11%)	6/34 (18%)	7/36 (19%)	6/35 (17%)
First incidence (days)	661	683	606	583
Life table tests	P=0.307	P=0.281	P=0.316	P=0.278
Logistic regression tests	P=0.280	P=0.248	P=0.291	P=0.263
Cochran-Armitage test	P=0.285			
Fisher exact test		P=0.288	P=0.288	P=0.274
All Organs: Benign Tumors				
Overall rates	19/50 (38%)	19/50 (38%)	17/50 (34%)	18/49 (37%)
Adjusted rates	48.1%	52.5%	40.2%	47.0%
Terminal rates	15/35 (43%)	17/34 (50%)	11/36 (31%)	15/35 (43%)
First incidence (days)	616	613	585	588
Life table tests	P=0.421N	P=0.530	P=0.382N	P=0.524N
Logistic regression tests	P=0.472N	P=0.488	P=0.415N	P=0.584N
Cochran-Armitage test	P=0.459N			
Fisher exact test		P=0.582N	P=0.418N	P=0.531N
All Organs: Malignant Tumors				
Overall rates	14/50 (28%)	20/50 (40%)	21/50 (42%)	18/49 (37%)
Adjusted rates	33.6%	45.2%	44.6%	41.1%
Terminal rates	8/35 (23%)	10/34 (29%)	11/36 (31%)	10/35 (29%)
First incidence (days)	618	420	452	515
Life table tests	P=0.329	P=0.151	P=0.152	P=0.253
Logistic regression tests	P=0.282	P=0.135	P=0.103	P=0.261
Cochran-Armitage test	P=0.287			
Fisher exact test		P=0.146	P=0.104	P=0.238

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
All Organs: Benign or Malignant Tumors				
Overall rates	27/50 (54%)	31/50 (62%)	31/50 (62%)	32/49 (65%)
Adjusted rates	61.1%	70.3%	62.0%	72.4%
Terminal rates	18/35 (51%)	21/34 (62%)	17/36 (47%)	23/35 (66%)
First incidence (days)	616	420	452	515
Life table tests	P=0.265	P=0.253	P=0.363	P=0.216
Logistic regression tests	P=0.181	P=0.179	P=0.273	P=0.155
Cochran-Armitage test	P=0.179			
Fisher exact test		P=0.272	P=0.272	P=0.173

(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; therefore statistical comparisons with the controls are not appropriate.

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23[a]

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
Scheduled sacrifice	10	10	10	10
Early deaths				
Moribund	11	7	11	10
Dead	4	8	3	4
Survivors				
Terminal sacrifice	35	34	36	35
Accidental deaths		1		
Missing				1
Animals examined microscopically	50	50	50	49
Alimentary System				
Esophagus	(50)	(15)	(14)	(48)
Inflammation, chronic		2 (13%)		
Gallbladder	(46)	(12)	(12)	(46)
Epithelium, cytoplasmic alteration				1 (2%)
Wall, mucocele	3 (7%)			1 (2%)
Intestine large, cecum	(47)	(47)	(48)	(46)
Lymphoid tissue, hyperplasia, lymphoid	3 (6%)	5 (11%)	3 (6%)	2 (4%)
Lymphoid tissue, pigmentation			2 (4%)	5 (11%)
Submucosa, edema	1 (2%)			
Intestine large, rectum	(46)	(48)	(48)	(46)
Inflammation, chronic	1 (2%)	1 (2%)		
Polyarteritis		1 (2%)		
Intestine small, duodenum	(46)	(46)	(47)	(46)
Erosion			1 (2%)	
Polyarteritis		1 (2%)		
Submucosa, inflammation, acute				1 (2%)
Intestine small, ileum	(46)	(45)	(48)	(46)
Lymphoid tissue, pigmentation			1 (2%)	1 (2%)
Intestine small, jejunum	(46)	(46)	(48)	(47)
Lymphoid tissue, hyperplasia, lymphoid	2 (4%)	1 (2%)		
Lymphoid tissue, hyperplasia, plasma cell				1 (2%)
Lymphoid tissue, hyperplasia, RE cell				1 (2%)
Lymphoid tissue, pigmentation		12 (26%)	25 (52%)	31 (66%)
Liver	(49)	(49)	(50)	(48)
Clear cell focus				1 (2%)
Fibrosis, focal	1 (2%)			
Hematopoietic cell proliferation	9 (18%)	4 (8%)	7 (14%)	3 (6%)
Inflammation, acute	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Inflammation, chronic	4 (8%)	2 (4%)		
Mitotic alteration			1 (2%)	
Polyarteritis		1 (2%)		
Hepatocyte, cytomegaly, focal	2 (4%)			
Hepatocyte, necrosis	2 (4%)		1 (2%)	
Hepatocyte, vacuolization cytoplasmic	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Kupffer cell, hyperplasia				1 (2%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Alimentary System (continued)				
Mesentery	(7)		(4)	(3)
Inflammation, acute	2 (29%)			
Inflammation, chronic	2 (29%)			
Fat, necrosis	3 (43%)		2 (50%)	2 (67%)
Pancreas	(49)	(14)	(15)	(47)
Cytoplasmic alteration				1 (2%)
Inflammation, acute	3 (6%)	1 (7%)		
Inflammation, chronic			1 (7%)	
Polyarteritis		1 (7%)		
Acinar cell, atrophy	2 (4%)	3 (21%)	1 (7%)	
Duct, ectasia	3 (6%)	1 (7%)	1 (7%)	1 (2%)
Perivascular, inflammation, chronic	1 (2%)			
Salivary glands	(49)	(16)	(14)	(49)
Inflammation, acute		1 (6%)		
Stomach, forestomach	(49)	(49)	(50)	(49)
Abscess	4 (8%)	5 (10%)	28 (56%)	32 (65%)
Angiectasis	1 (2%)			
Hyperkeratosis	2 (4%)	1 (2%)	3 (6%)	18 (37%)
Inflammation, chronic			2 (4%)	3 (6%)
Ulcer	2 (4%)	6 (12%)	30 (60%)	38 (78%)
Epithelium, cyst				1 (2%)
Epithelium, hyperplasia	4 (8%)	9 (18%)	27 (54%)	20 (41%)
Epithelium, hyperplasia, multiple	2 (4%)	5 (10%)	16 (32%)	27 (55%)
Submucosa, edema				1 (2%)
Stomach, glandular	(48)	(48)	(50)	(45)
Inflammation, acute	1 (2%)	1 (2%)		
Inflammation, chronic		1 (2%)		
Mineralization	9 (19%)	4 (8%)	6 (12%)	10 (22%)
Ulcer				1 (2%)
Mucosa, cyst		1 (2%)		
Mucosa, hyperplasia	2 (4%)			
Submucosa, edema				1 (2%)
Tongue				(1)
Angiectasis				1 (100%)
Tooth	(2)			
Incisor, abscess	1 (50%)			
Incisor, developmental malformation	1 (50%)			
Cardiovascular System				
Blood vessel	(1)			(1)
Aorta, polyarteritis				1 (100%)
Pulmonary artery, inflammation, acute	1 (100%)			
Heart	(50)	(16)	(14)	(49)
Inflammation, acute	1 (2%)			
Inflammation, chronic	4 (8%)	1 (6%)	1 (7%)	2 (4%)
Atrioventricular valve, thrombus	1 (2%)			
Epicardium, fibrosis	1 (2%)			
Interstitium, fibrosis	4 (8%)			3 (6%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Cardiovascular System (continued)				
Heart (continued)				
Myocardium, degeneration				2 (4%)
Myocardium, inflammation		1 (6%)		
Myocardium, inflammation, acute		1 (6%)		
Myocardium, mineralization	1 (2%)	1 (6%)		
Endocrine System				
Adrenal gland, cortex	(49)	(15)	(14)	(48)
Congestion		1 (7%)		
Hematopoietic cell proliferation	2 (4%)			
Hyperplasia, focal				1 (2%)
Hypertrophy, diffuse			1 (7%)	
Hypertrophy, focal	1 (2%)			2 (4%)
Inflammation, acute	1 (2%)	1 (7%)		
Corticomedullary junction, pigmentation	46 (94%)		3 (21%)	45 (94%)
Extra adrenal tissue, accessory adrenal cortical nodule	1 (2%)		1 (7%)	
Spindle cell, hyperplasia	49 (100%)	14 (93%)	14 (100%)	47 (98%)
Adrenal gland, medulla	(49)	(15)	(14)	(47)
Hyperplasia	2 (4%)		1 (7%)	3 (6%)
Parathyroid gland	(49)	(10)	(14)	(49)
Cyst	4 (8%)			3 (6%)
Ectopic thymus	1 (2%)			1 (2%)
Pituitary gland	(50)	(23)	(16)	(47)
Pars distalis, angiectasis	1 (2%)	2 (9%)		2 (4%)
Pars distalis, cyst	1 (2%)			
Pars distalis, degeneration, cystic	2 (4%)			3 (6%)
Pars distalis, hyperplasia	10 (20%)	3 (13%)	2 (13%)	11 (23%)
Pars intermedia, hyperplasia				1 (2%)
Thyroid gland	(50)	(15)	(14)	(49)
Inflammation, acute	2 (4%)			1 (2%)
Ultimobranchial cyst		1 (7%)	1 (7%)	2 (4%)
Follicle, cyst	5 (10%)			7 (14%)
Follicular cell, hyperplasia	6 (12%)	1 (7%)	1 (7%)	11 (22%)
General Body System				
None				
Genital System				
Ovary	(47)	(20)	(28)	(48)
Abscess	8 (17%)	4 (20%)	2 (7%)	2 (4%)
Atrophy	24 (51%)	6 (30%)	6 (21%)	28 (58%)
Cyst	1 (2%)		2 (7%)	
Hyperplasia, tubular				1 (2%)
Inflammation, acute	1 (2%)			
Mineralization	1 (2%)			

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Genital System (continued)				
Ovary (continued)				
Pigmentation, ceroid	35 (74%)	9 (45%)	14 (50%)	43 (90%)
Polyarteritis		1 (5%)		
Follicle, cyst	11 (23%)	1 (5%)	10 (36%)	13 (27%)
Follicle, hemorrhage	1 (2%)		1 (4%)	1 (2%)
Periovarian tissue, cyst	1 (2%)		1 (4%)	
Periovarian tissue, inflammation, acute	2 (4%)			
Periovarian tissue, inflammation, chronic	2 (4%)			1 (2%)
Uterus	(49)	(41)	(39)	(49)
Abscess	1 (2%)	1 (2%)		
Exudate, purulent	6 (12%)	1 (2%)		4 (8%)
Hemorrhage	1 (2%)	1 (2%)		1 (2%)
Hydrometra	5 (10%)	1 (2%)	3 (8%)	1 (2%)
Polyarteritis		1 (2%)		
Endometrium, cyst		1 (2%)	3 (8%)	
Endometrium, hyperplasia, cystic	41 (84%)	28 (68%)	29 (74%)	43 (88%)
Endometrium, inflammation, acute	2 (4%)	1 (2%)		1 (2%)
Endometrium, inflammation, chronic	1 (2%)			
Hematopoietic System				
Bone marrow	(49)	(49)	(49)	(49)
Hypocellularity	4 (8%)	2 (4%)		
Myelofibrosis	21 (43%)	14 (29%)	27 (55%)	26 (53%)
Erythroid cell, hyperplasia	1 (2%)			
Myeloid cell, hyperplasia	13 (27%)	7 (14%)	5 (10%)	7 (14%)
Lymph node	(50)	(48)	(50)	(49)
Hyperplasia, lymphoid	1 (2%)			
Hyperplasia, plasma cell	1 (2%)			
Iliac, edema		1 (2%)		
Iliac, hyperplasia, plasma cell	1 (2%)	1 (2%)		2 (4%)
Iliac, inflammation, chronic	1 (2%)			
Mediastinal, abscess		1 (2%)		
Mediastinal, edema				1 (2%)
Mediastinal, hematopoietic cell proliferation	1 (2%)			
Mediastinal, hyperplasia, lymphoid	1 (2%)			1 (2%)
Mediastinal, hyperplasia, plasma cell	3 (6%)	1 (2%)		
Mediastinal, inflammation, acute	1 (2%)	1 (2%)		
Mediastinal, inflammation, chronic	2 (4%)			
Mesenteric, abscess			1 (2%)	
Mesenteric, angiectasis	1 (2%)		2 (4%)	
Mesenteric, autolysis	1 (2%)			2 (4%)
Mesenteric, hematopoietic cell proliferation	1 (2%)	2 (4%)	1 (2%)	
Mesenteric, hyperplasia, lymphoid	11 (22%)	14 (29%)	8 (16%)	9 (18%)
Mesenteric, hyperplasia, plasma cell	2 (4%)	1 (2%)		
Mesenteric, inflammation, acute	3 (6%)		1 (2%)	1 (2%)
Mesenteric, inflammation, chronic	2 (4%)		1 (2%)	
Mesenteric, pigmentation		4 (8%)	26 (52%)	29 (59%)
Mesenteric, lymphocyte, necrosis		1 (2%)		

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Hematopoietic System *(continued)*				
Lymph node (continued)				
Pancreatic, hyperplasia, lymphoid			1 (2%)	1 (2%)
Pancreatic, inflammation, granulomatous			1 (2%)	
Renal, abscess		1 (2%)		
Renal, hyperplasia, lymphoid	1 (2%)			
Renal, hyperplasia, plasma cell	2 (4%)	1 (2%)		2 (4%)
Renal, inflammation, acute	1 (2%)			
Renal, lymphocyte, necrosis				1 (2%)
Lymph node, mandibular	(49)	(18)	(15)	(49)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia, lymphoid	4 (8%)			
Inflammation, acute		1 (6%)		1 (2%)
Inflammation, granulomatous				1 (2%)
Arteriole, amyloid deposition				1 (2%)
Spleen	(50)	(21)	(25)	(48)
Angiectasis				1 (2%)
Hematopoietic cell proliferation	23 (46%)	7 (33%)	15 (60%)	17 (35%)
Hyperplasia, lymphoid	6 (12%)		2 (8%)	9 (19%)
Red pulp, depletion				1 (2%)
Thymus	(18)	(7)	(14)	(39)
Atrophy	1 (6%)	2 (29%)	2 (14%)	4 (10%)
Cyst	3 (17%)		2 (14%)	4 (10%)
Hyperplasia, lymphoid			1 (7%)	2 (5%)
Cortex, necrosis	1 (6%)			
Integumentary System				
Mammary gland	(49)	(15)	(15)	(48)
Inflammation, chronic	2 (4%)			
Acinus, hyperplasia			1 (7%)	3 (6%)
Duct, dilatation	1 (2%)		1 (7%)	3 (6%)
Duct, ectasia			1 (7%)	
Skin	(49)	(48)	(48)	(49)
Dermis, fibrosis	1 (2%)			
Dermis, inflammation, acute	2 (4%)	1 (2%)		
Dermis, inflammation, chronic	25 (51%)	25 (52%)	28 (58%)	21 (43%)
Epidermis, pigmentation				1 (2%)
Subcutaneous tissue, abscess				1 (2%)
Subcutaneous tissue, edema	1 (2%)			
Musculoskeletal System				
None				

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Nervous System				
Brain	(50)	(15)	(14)	(49)
Cerebellum, compression	1 (2%)			
Cerebrum, compression			1 (7%)	2 (4%)
Cerebrum, degeneration				1 (2%)
Meninges, infiltration cellular, lymphocyte	1 (2%)			1 (2%)
Thalamus, mineralization	44 (88%)	12 (80%)	8 (57%)	35 (71%)
Third ventricle, infiltration cellular, lipocyte	1 (2%)			
Spinal cord	(1)			
Nerve, demyelination	1 (100%)			
Respiratory System				
Lung	(50)	(50)	(49)	(49)
Congestion		1 (2%)	1 (2%)	
Infiltration cellular, histiocyte	1 (2%)	1 (2%)		
Inflammation, acute	2 (4%)	2 (4%)		1 (2%)
Inflammation, chronic		1 (2%)	1 (2%)	
Alveolar epithelium, hyperplasia		1 (2%)	1 (2%)	
Alveolus, mineralization		1 (2%)		
Artery, foreign body			1 (2%)	
Artery, mineralization		1 (2%)	1 (2%)	
Pleura, inflammation, acute	1 (2%)			
Pleura, inflammation, chronic	4 (8%)			3 (6%)
Nose	(50)	(15)	(14)	(49)
Exudate, purulent				1 (2%)
Foreign body				1 (2%)
Inflammation, acute				1 (2%)
Inflammation, chronic				1 (2%)
Nasolacrimal duct, exudate, purulent	1 (2%)			
Nasolacrimal duct, inflammation, chronic	1 (2%)			
Sinus, exudate, acute		1 (7%)		
Vomeronasal organ, inflammation, acute				1 (2%)
Special Senses System				
Eye	(1)	(2)	(2)	
Phthisis bulbi	1 (100%)		2 (100%)	
Cornea, inflammation, chronic		2 (100%)		

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23 (continued)

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Urinary System				
Kidney	(49)	(17)	(15)	(49)
Casts protein	7 (14%)			6 (12%)
Infarct, chronic	3 (6%)	1 (6%)		1 (2%)
Nephropathy	24 (49%)	2 (12%)	1 (7%)	26 (53%)
Cortex, metaplasia, osseous	2 (4%)			6 (12%)
Corticomedullary junction, embolus bacterial, focal	1 (2%)			
Glomerulus, amyloid deposition				1 (2%)
Glomerulus, inflammation, membranoproliferative	6 (12%)	1 (6%)	1 (7%)	3 (6%)
Proximal convoluted renal tubule, degeneration, hyaline	1 (2%)			2 (4%)
Proximal convoluted renal tubule, renal tubule, degeneration, hyaline		2 (12%)	1 (7%)	
Proximal convoluted renal tubule, renal tubule, pigmentation			1 (7%)	
Renal tubule, dilatation	1 (2%)			3 (6%)
Renal tubule, hypertrophy		1 (6%)		
Renal tubule, mineralization		1 (6%)	1 (7%)	
Renal tubule, pigmentation			1 (7%)	
Urinary bladder	(47)	(15)	(12)	(46)
Polyarteritis		2 (13%)		
Transitional epithelium, hyperplasia	1 (2%)			

[a] Number of animals examined microscopically at site and the number of animals with lesion.

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA PROTOCOL

Testing was performed as reported by Mortelmans *et al.* (1986). C.I. Pigment Red 23 was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). C.I. Pigment Red 23 was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) both in buffer and in 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 23. High dose was limited by toxicity or solubility. All trials were repeated.

A positive response in this assay 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 response is considered negative 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 23 was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). C.I. Pigment Red 23 was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) 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 test consisted of concurrent solvent and positive controls and of at least three doses of C.I. Pigment Red 23. The high dose in the SCE test was limited by toxicity; in the assay for Abs, the high dose was 100 μg/mL.

In the SCE test without S9, CHO cells were incubated for 26 hours (31.5 hours in the case of an extended harvest) with C.I. Pigment Red 23 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 23 was removed and replaced with fresh medium containing 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 23, 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 23 and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining procedures were the same as for cells treated without S9.

In the Abs test without S9, cells were incubated in McCoy's 5A medium with C.I. Pigment Red 23 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 23 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 hours. Cells were harvested

in the same manner as for the treatment without S9. For the SCE test, if significant chemical-induced cell-cycle delay was seen, incubation time was lengthened to ensure the presence of a sufficient number of scorable cells. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test; if cell cycle delay was anticipated, the incubation period was extended.

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, usually 50 second-division metaphase cells were scored for frequency of SCEs per cell from each dose level; 200 first-division metaphase cells were scored at each dose level for the Abs test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

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

RESULTS

C.I. Pigment Red 23 (10 to 3,333 μg/plate) was positive for induction of gene mutations in *Salmonella typhimurium* strains TA100, TA1537, and TA98 when tested in a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9; it was negative in strain TA1535 with and without S9 (Table E1; Mortelmans *et al.*, 1986).

In cytogenetic tests with CHO cells, C.I. Pigment Red 23 induced SCE over a concentration range of 5 to 50 μg/mL in the absence of S9 in an initial trial; the second trial performed without S9 also demonstrated an increase in SCEs, but only at a higher dose than was evaluated in the first trial (Table E2). At this dose (50 μg/mL) a delayed harvest protocol was employed to offset the toxic effect of the pigment on cell cycle progression. No induction of SCEs was observed in CHO cells in the presence of liver S9 from Aroclor 1254-induced male Sprague-Dawley rats.

C.I. Pigment Red 23 (30 to 100 μg/mL) was negative for induction of Abs in CHO cells, with and without S9 (Table E3).

TABLE E1
Mutagenicity of C.I. Pigment Red 23 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	172 ± 4.7	169 ± 6.7	167 ± 4.9	163 ± 2.6	161 ± 9.4	138 ± 7.2
	10		133 ± 19.0		166 ± 7.8		156 ± 10.2
	33	208 ± 14.2	189 ± 8.0[c]	165 ± 7.2	183 ± 17.7[c]	195 ± 5.7	162 ± 8.5[c]
	100	309 ± 1.0[c]	171 ± 12.9[c]	167 ± 10.5[c]	174 ± 3.8[c]	211 ± 4.2[c]	168 ± 5.5[c]
	333	459 ± 10.4[c]	250 ± 9.5[c]	201 ± 10.8[c]	196 ± 18.6[c]	252 ± 5.2[c]	211 ± 5.2[c]
	1,000	615 ± 29.3[c]	306 ± 18.6[c]	313 ± 4.5[c]	223 ± 6.9[c]	386 ± 24.6[c]	215 ± 32.8[c]
	3,333	672 ± 26.0[c]		403 ± 6.4[c]		430 ± 55.5[c]	
Trial summary		Positive	Positive	Positive	Weakly Positive	Positive	Positive
Positive control[d]		421 ± 4.7	365 ± 4.7	1,307 ± 20.1	1,603 ± 66.1	764 ± 16.7	682 ± 17.3
TA1535	0	26 ± 6.1		37 ± 3.4		41 ± 1.5	
	10						
	33	33 ± 4.5[c]		22 ± 3.3		37 ± 3.8	
	100	33 ± 5.9[c]		18 ± 4.5[c]		19 ± 3.2[c]	
	333	38 ± 3.8[c]		11 ± 1.0[c]		12 ± 1.8[c]	
	1,000	37 ± 2.3[c]		20 ± 2.1[c]		14 ± 3.5[c]	
	3,333	43 ± 3.0[c]		27 ± 2.2[c]		27 ± 1.2[c]	
Trial summary		Negative		Negative		Negative	
Positive control		394 ± 2.3		486 ± 14.9		307 ± 5.5	
TA1537	0	13 ± 2.0	8 ± 2.2	8 ± 2.1	7 ± 2.4	9 ± 1.5	6 ± 1.2
	10		9 ± 1.7		8 ± 0.3		10 ± 2.4
	33	28 ± 2.5	34 ± 4.5[c]	9 ± 0.0	13 ± 3.4[c]	14 ± 2.7	14 ± 1.8[c]
	100	40 ± 4.4[c]	50 ± 8.4[c]	20 ± 2.0[c]	9 ± 2.2[c]	21 ± 1.5[c]	16 ± 1.3[c]
	333	113 ± 2.3[c]	66 ± 5.5[c]	24 ± 2.7[c]	14 ± 1.5[c]	23 ± 3.3[c]	14 ± 6.1[c]
	1,000	113 ± 17.4[c]	88 ± 5.8[c]	49 ± 8.3[c]	27 ± 1.9[c]	50 ± 6.1[c]	30 ± 0.3[c]
	3,333	100 ± 6.7[c]		76 ± 1.9[c]		62 ± 4.3[c]	
Trial summary		Positive	Positive	Positive	Equivocal	Positive	Positive
Positive control		242 ± 23.5	147 ± 18.7	424 ± 22.5	574 ± 16.1	304 ± 2.9	161 ± 15.3
TA98							
	0	24 ± 2.8	20 ± 0.7	44 ± 1.3	32 ± 2.6	33 ± 2.0	38 ± 5.7
	10		25 ± 2.6		33 ± 6.5		41 ± 3.7
	33	99 ± 3.8	115 ± 10.9[c]	49 ± 1.9	65 ± 2.7[c]	54 ± 1.5	43 ± 6.3[c]
	100	148 ± 4.4[c]	167 ± 16.4[c]	68 ± 2.1[c]	62 ± 4.9[c]	66 ± 4.1[c]	52 ± 6.1[c]
	333	343 ± 27.9[c]	283 ± 11.9[c]	149 ± 6.5[c]	115 ± 17.0[c]	179 ± 9.2[c]	120 ± 1.5[c]
	1,000	396 ± 22.0[c]	333 ± 7.8[c]	363 ± 13.9[c]	180 ± 21.0[c]	327 ± 13.7[c]	70 ± 24.0[e]
	3,333	292 ± 18.5[c]		336 ± 7.2[c]		407 ± 46.2[c]	
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control		687 ± 40.0	591 ± 76.8	1,219 ± 34.6	1,171 ± 136.5	571 ± 22.3	502 ± 49.5

[a] Study performed at SRI, International. The detailed protocol and these data are presented in Mortelmans *et al.* (1986).
[b] Revertants are presented as mean ± the 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.
[e] Slight toxicity

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by C.I. Pigment Red 23[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosomes	SCEs/ Cell	Hrs in BrdU	Relative SCEs/Chromosome (%)[b]
-S9								
Trial 1								
Summary: Positive								
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 23	5	50	1,049	486	0.46	9.7	26.0	21.31*
	10	50	1,049	474	0.45	9.5	26.0	18.32
	16	50	1,046	513	0.49	10.3	26.0	28.42*
	30	50	1,047	560	0.53	11.2	26.0	40.05*
								P<0.001[c]
Trial 2								
Summary: Weak Positive								
Dimethylsulfoxide		50	1,050	432	0.41	8.6	26.0	
Mitomycin-C	0.0005	50	1,049	520	0.49	10.4	26.0	20.49
	0.0050	10	210	307	1.46	30.7	26.0	255.33
C.I. Pigment Red 23	10	50	1,050	441	0.42	8.8	26.0	2.09
	16	50	1,049	462	0.44	9.2	26.0	7.05
	30	50	1,048	515	0.49	10.3	26.0	19.44
	50	26[d]	546	271	0.49	10.4	31.5[e]	20.64*
								P<0.001
+S9								
Trial 1								
Summary: Negative								
Dimethylsulfoxide		50	1,048	444	0.42	8.9	26.0	
Cyclophosphamide	0.1	50	1,049	610	0.58	12.2	26.0	37.26
	0.6	10	210	325	1.54	32.5	26.0	265.30
C.I. Pigment Red 23	16	50	1,049	445	0.42	8.9	26.0	0.13
	30	50	1,048	500	0.47	10.0	26.0	12.61
	50	50	1,049	487	0.46	9.7	26.0	9.58
	100	50	1,049	506	0.48	10.1	26.0	13.86
								P=0.008

* Positive (≥20% increase over solvent control)

[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).

[b] Percent increase in SCEs/chromosome of culture exposed to C.I. Pigment Red 23 relative to those of culture exposed to solvent. Values at least 20% above control levels are considered positive.

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

[d] Only 26 metaphases could be evaluated at this dose level due to the cytostatic nature of C.I. Pigment Red 23.

[e] Because the pigment induced a delay in the cell division cycle, the harvest time was extended to maximize the proportion of second division cells available for analysis.

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by C.I. Pigment Red 23[a]

-S9					+S9				
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	3	0.02	1.5		200	2	0.01	1.0
Mitomycin-C					Cyclophosphamide				
0.0625	200	31	0.16	13.5	2.5	200	26	0.13	12.5
0.2500	50	21	0.42	34.0	7.5	50	26	0.52	34.0
C.I. Pigment Red 23					C.I. Pigment Red 23				
30	200	2	0.01	1.0	30	200	1	0.01	0.5
50	200	2	0.01	1.0	50	200	4	0.02	2.0
100	200	3	0.02	1.0	100	200	4	0.02	2.0
				P=0.672[b]					P=0.118

[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).

[b] Differences in percent cells with aberrations between solvent and C.I. Pigment Red 23 are not significant by 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 17-Day Feed Studies of C.I. Pigment Red 23[a]

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm	100,000 ppm
n	5	5	5	5	5	5
Male						
Necropsy body wt	229 ± 5	232 ± 6	237 ± 3	225 ± 4	220 ± 3	223 ± 8
Brain						
Absolute	1.79 ± 0.03	1.86 ± 0.02	1.80 ± 0.02	1.83 ± 0.01	1.81 ± 0.03	1.75 ± 0.06
Relative	7.81 ± 0.16	8.02 ± 0.20	7.58 ± 0.09	8.11 ± 0.14	8.26 ± 0.20	7.85 ± 0.31
Heart						
Absolute	0.74 ± 0.02	0.84 ± 0.04	0.75 ± 0.01	0.76 ± 0.03	0.74 ± 0.03	0.73 ± 0.03
Relative	3.21 ± 0.06	3.60 ± 0.16	3.16 ± 0.06	3.40 ± 0.15	3.39 ± 0.11	3.28 ± 0.05
Liver						
Absolute	9.69 ± 0.35	9.73 ± 0.63[b]	9.97 ± 0.24	9.26 ± 0.32	9.47 ± 0.33	10.07 ± 0.26
Relative	42.3 ± 1.8	42.4 ± 2.1[b]	42.1 ± 0.6	41.1 ± 0.8	43.1 ± 1.1	45.2 ± 0.8
Lung						
Absolute	1.12 ± 0.06	1.14 ± 0.08	1.00 ± 0.03	1.16 ± 0.17	1.02 ± 0.04	0.99 ± 0.03
Relative	4.88 ± 0.26	4.93 ± 0.32	4.21 ± 0.10	5.19 ± 0.84	4.65 ± 0.16	4.44 ± 0.14
R. Kidney						
Absolute	0.88 ± 0.02	0.88 ± 0.02	0.90 ± 0.04	0.89 ± 0.02	0.86 ± 0.02	0.89 ± 0.04
Relative	3.86 ± 0.09	3.78 ± 0.07	3.77 ± 0.12	3.93 ± 0.06	3.90 ± 0.11	4.00 ± 0.14
R. Testis						
Absolute	1.25 ± 0.02	1.28 ± 0.02	1.29 ± 0.02	1.24 ± 0.01	1.21 ± 0.02	1.24 ± 0.04
Relative	5.47 ± 0.04	5.53 ± 0.10	5.43 ± 0.06	5.52 ± 0.12	5.51 ± 0.03	5.56 ± 0.18
Thymus						
Absolute	0.50 ± 0.03	0.47 ± 0.04	0.45 ± 0.03	0.43 ± 0.02	0.46 ± 0.04	0.51 ± 0.04
Relative	2.19 ± 0.12	2.01 ± 0.12	1.89 ± 0.16	1.89 ± 0.08	2.10 ± 0.17	2.30 ± 0.12
Female						
Necropsy body wt	155 ± 2	160 ± 2	155 ± 3	152 ± 3	156 ± 2	153 ± 3
Brain						
Absolute	1.75 ± 0.03	1.74 ± 0.02	1.72 ± 0.02	1.71 ± 0.02	1.75 ± 0.01	1.66 ± 0.03*
Relative	11.3 ± 0.2	10.9 ± 0.1	11.1 ± 0.3	11.2 ± 0.2	11.3 ± 0.2	10.9 ± 0.3
Heart						
Absolute	0.51 ± 0.01	0.56 ± 0.02	0.55 ± 0.01	0.51 ± 0.02	0.54 ± 0.01	0.53 ± 0.02
Relative	3.27 ± 0.01	3.51 ± 0.10	3.53 ± 0.08	3.37 ± 0.10	3.49 ± 0.09	3.43 ± 0.15
Liver						
Absolute	5.77 ± 0.19	6.18 ± 0.08	6.05 ± 0.25	5.98 ± 0.16	6.18 ± 0.09	6.20 ± 0.31
Relative	37.2 ± 1.3	38.6 ± 0.2	39.0 ± 1.6	39.3 ± 0.8	39.7 ± 0.5	40.4 ± 1.5
Lung						
Absolute	0.80 ± 0.01	0.93 ± 0.05*	0.84 ± 0.04	0.76 ± 0.01	0.84 ± 0.03	0.76 ± 0.03
Relative	5.14 ± 0.09	5.83 ± 0.26	5.42 ± 0.25	5.01 ± 0.07	5.41 ± 0.23	4.97 ± 0.12
R. Kidney						
Absolute	0.60 ± 0.01	0.64 ± 0.03	0.60 ± 0.01	0.60 ± 0.01	0.59 ± 0.01	0.63 ± 0.02
Relative	3.84 ± 0.06	4.02 ± 0.15	3.87 ± 0.12	3.96 ± 0.08	3.80 ± 0.10	4.13 ± 0.12
Thymus						
Absolute	0.35 ± 0.04	0.41 ± 0.02	0.31 ± 0.03	0.35 ± 0.02	0.33 ± 0.01	0.34 ± 0.03
Relative	2.26 ± 0.26	2.59 ± 0.14	2.03 ± 0.21	2.30 ± 0.10	2.14 ± 0.06	2.22 ± 0.19

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
[a] Organ 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 23[a]

	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
n	10	10	10	10	10	10
Male						
Necropsy body wt	338 ± 9	352 ± 8	347 ± 10	344 ± 9	341 ± 9	349 ± 10
Brain						
Absolute	2.00 ± 0.01	2.02 ± 0.03	1.91 ± 0.02*	1.94 ± 0.02	1.94 ± 0.04	1.97 ± 0.01
Relative	5.97 ± 0.17	5.74 ± 0.12	5.55 ± 0.17	5.67 ± 0.13	5.72 ± 0.16	5.67 ± 0.14
Heart						
Absolute	0.95 ± 0.02	0.95 ± 0.03	0.87 ± 0.03	0.89 ± 0.03	0.92 ± 0.02	0.88 ± 0.03
Relative	2.81 ± 0.08	2.70 ± 0.06	2.50 ± 0.06*	2.57 ± 0.04*	2.70 ± 0.07*	2.53 ± 0.06**
Liver						
Absolute	9.55 ± 0.49	11.57 ± 0.44**	11.16 ± 0.32*	11.88 ± 0.27**	9.45 ± 0.23	10.97 ± 0.45*
Relative	28.1 ± 1.0	32.8 ± 0.7**	32.2 ± 0.7**	34.6 ± 0.4**	27.7 ± 0.2	31.4 ± 0.9**
Lung						
Absolute	1.23 ± 0.03	1.33 ± 0.06	1.15 ± 0.03	1.15 ± 0.03	1.31 ± 0.05	1.26 ± 0.08
Relative	3.67 ± 0.13	3.78 ± 0.16	3.30 ± 0.05	3.34 ± 0.05	3.88 ± 0.23	3.62 ± 0.21
R. Kidney						
Absolute	1.07 ± 0.04	1.16 ± 0.05	1.08 ± 0.03	1.11 ± 0.04	1.09 ± 0.03	1.10 ± 0.04
Relative	3.17 ± 0.05	3.27 ± 0.09	3.11 ± 0.05	3.22 ± 0.06	3.20 ± 0.04	3.17 ± 0.10
R. Testis						
Absolute	1.42 ± 0.02	1.50 ± 0.04	1.41 ± 0.04	1.41 ± 0.04	1.43 ± 0.03	1.47 ± 0.04[b]
Relative	4.21 ± 0.08	4.26 ± 0.05	4.06 ± 0.08	4.10 ± 0.07	4.19 ± 0.05	4.17 ± 0.10[b]
Thymus						
Absolute	0.35 ± 0.03	0.39 ± 0.03	0.35 ± 0.05	0.34 ± 0.01	0.34 ± 0.03	0.38 ± 0.04
Relative	1.03 ± 0.08	1.09 ± 0.08	1.01 ± 0.13	0.98 ± 0.06	1.00 ± 0.09	1.07 ± 0.10
Female						
Necropsy body wt	204 ± 4	208 ± 4	207 ± 3	204 ± 3	197 ± 3	200 ± 6
Brain						
Absolute	1.84 ± 0.01	1.84 ± 0.01	1.80 ± 0.01	1.84 ± 0.01	1.85 ± 0.01	1.84 ± 0.01
Relative	9.05 ± 0.17	8.90 ± 0.14	8.71 ± 0.14	9.03 ± 0.15	9.41 ± 0.13	9.28 ± 0.26
Heart						
Absolute	0.64 ± 0.01	0.63 ± 0.02	0.61 ± 0.01	0.59 ± 0.02	0.64 ± 0.01	0.60 ± 0.02
Relative	3.14 ± 0.04	3.03 ± 0.08	2.94 ± 0.08	2.91 ± 0.10	3.26 ± 0.06	3.01 ± 0.10
Liver						
Absolute	6.00 ± 0.29	6.69 ± 0.21	6.32 ± 0.16	6.62 ± 0.16	5.38 ± 0.08	6.06 ± 0.23
Relative	29.4 ± 1.1	32.2 ± 0.7*	30.6 ± 0.5	32.5 ± 0.6*	27.4 ± 0.3	30.3 ± 0.7
Lung						
Absolute	0.97 ± 0.05	0.98 ± 0.07	0.90 ± 0.02	0.89 ± 0.03	0.99 ± 0.05	0.96 ± 0.04
Relative	4.75 ± 0.20	4.70 ± 0.30	4.39 ± 0.13	4.36 ± 0.11	5.02 ± 0.18	4.81 ± 0.22
R. Kidney						
Absolute	0.68 ± 0.02	0.68 ± 0.02	0.66 ± 0.01	0.66 ± 0.02	0.68 ± 0.02	0.66 ± 0.01
Relative	3.36 ± 0.06	3.26 ± 0.07	3.19 ± 0.06	3.24 ± 0.07	3.46 ± 0.06	3.32 ± 0.08
Thymus						
Absolute	0.26 ± 0.02	0.28 ± 0.03	0.26 ± 0.02	0.23 ± 0.02	0.27 ± 0.01	0.28 ± 0.02
Relative	1.28 ± 0.08	1.36 ± 0.14	1.27 ± 0.09	1.12 ± 0.08	1.37 ± 0.07	1.41 ± 0.10

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ 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 Evaluations in the 2-Year Feed Studies of C.I. Pigment Red 23[a]

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male				
n	10	10	10	9
Necropsy body wt	464 ± 16	436 ± 14	449 ± 12	459 ± 13
Brain				
Absolute	2.08 ± 0.02	2.11 ± 0.02	2.15 ± 0.02	2.11 ± 0.03
Relative	4.55 ± 0.18	4.87 ± 0.13	4.81 ± 0.14	4.62 ± 0.14
Liver				
Absolute	11.87 ± 0.24	10.90 ± 0.46	11.80 ± 0.32	11.72 ± 0.32
Relative	25.8 ± 0.6	25.0 ± 0.5	26.3 ± 0.2	25.6 ± 0.3
R. Kidney				
Absolute	1.35 ± 0.01	1.36 ± 0.04	1.41 ± 0.05	1.38 ± 0.03
Relative	2.94 ± 0.10	3.13 ± 0.06	3.13 ± 0.08	3.02 ± 0.05
Female				
n	10	10	10	10
Necropsy body wt	309 ± 5	314 ± 7	285 ± 5**	276 ± 5**
Brain				
Absolute	1.91 ± 0.02	1.88 ± 0.03	1.94 ± 0.02	1.92 ± 0.02
Relative	6.22 ± 0.10	5.99 ± 0.11	6.81 ± 0.17**	6.98 ± 0.16**
Liver				
Absolute	6.97 ± 0.14	7.15 ± 0.23	6.89 ± 0.17	6.71 ± 0.12
Relative	22.6 ± 0.3	22.7 ± 0.3	24.2 ± 0.6**	24.3 ± 0.3**
R. Kidney				
Absolute	0.81 ± 0.02	0.86 ± 0.03	0.85 ± 0.02	0.84 ± 0.02
Relative	2.64 ± 0.05	2.74 ± 0.08	2.98 ± 0.07**	3.04 ± 0.05**

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test
[a] Organ 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 17-Day Feed Studies of C.I. Pigment Red 23[a]

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm	100,000 ppm
n	5	5	5	5	5	5
Male						
Necropsy body wt	25.2 ± 0.7	25.2 ± 1.0	25.4 ± 0.2	23.6 ± 1.0	24.6 ± 0.4	23.2 ± 0.9
Brain						
Absolute	0.40 ± 0.04	0.45 ± 0.00	0.47 ± 0.02	0.43 ± 0.01	0.44 ± 0.01	0.44 ± 0.01
Relative	16.0 ± 1.7	17.9 ± 0.8	18.5 ± 0.7	18.3 ± 0.8	17.7 ± 0.3	18.9 ± 0.6
Heart[b]						
Absolute	119.0 ± 6.6	124.0 ± 6.2	137.0 ± 5.4	112.0 ± 7.3	125.0 ± 4.2	125.0 ± 11.0
Relative	4.72 ± 0.18	4.92 ± 0.11	5.39 ± 0.16	4.73 ± 0.14	5.08 ± 0.14	5.39 ± 0.41
Liver						
Absolute	1.19 ± 0.04	1.25 ± 0.12	1.34 ± 0.05	1.14 ± 0.08	1.30 ± 0.01	1.27 ± 0.07
Relative	47.2 ± 1.6	49.1 ± 2.9	52.9 ± 1.9	48.1 ± 2.0	52.7 ± 0.7	54.4 ± 1.3*
Lung						
Absolute	0.17 ± 0.03	0.15 ± 0.01	0.16 ± 0.01	0.13 ± 0.00	0.15 ± 0.00	0.14 ± 0.01
Relative	6.86 ± 1.17	6.15 ± 0.39	6.26 ± 0.32	5.69 ± 0.37	6.02 ± 0.16	6.15 ± 0.32
R. Kidney						
Absolute	0.19 ± 0.01	0.22 ± 0.01	0.21 ± 0.03	0.20 ± 0.01	0.20 ± 0.01	0.20 ± 0.01
Relative	7.72 ± 0.33	8.80 ± 0.07	8.17 ± 0.95	8.28 ± 0.27	8.09 ± 0.19	8.39 ± 0.12
R. Testis[b]						
Absolute	94.00 ± 5.79	115.00 ± 5.00*	101.00 ± 6.78	97.00 ± 4.06	98.00 ± 3.39	98.00 ± 3.74
Relative	3.72 ± 0.16	4.57 ± 0.15**	3.98 ± 0.28	4.12 ± 0.11	3.98 ± 0.11	4.23 ± 0.10
Thymus[b]						
Absolute	45.00 ± 5.48	39.00 ± 4.30	40.00 ± 3.54	40.00 ± 2.74	43.00 ± 2.55	83.00 ± 42.27
Relative	1.80 ± 0.23	1.57 ± 0.19	1.58 ± 0.14	1.71 ± 0.14	1.74 ± 0.08	3.59 ± 1.84
Female						
Necropsy body wt	20.4 ± 0.4	19.8 ± 0.2	21.4 ± 1.4	19.2 ± 0.4	19.8 ± 0.5	19.6 ± 0.6
Brain						
Absolute	0.47 ± 0.01	0.46 ± 0.01	0.45 ± 0.01	0.45 ± 0.01	0.45 ± 0.01	0.43 ± 0.01**
Relative	23.0 ± 0.3	23.2 ± 0.4	21.5 ± 1.4	23.4 ± 0.5	22.9 ± 0.8	22.1 ± 0.1
Heart[b]						
Absolute	97.00 ± 3.00	104.00 ± 3.32	98.00 ± 4.06	88.00 ± 8.75	98.00 ± 6.44	99.00 ± 2.45
Relative	4.75 ± 0.08	5.26 ± 0.18	4.61 ± 0.16	4.62 ± 0.52	4.93 ± 0.23	5.07 ± 0.17
Liver						
Absolute	0.86 ± 0.04	0.85 ± 0.02	0.88 ± 0.03	0.81 ± 0.02	0.97 ± 0.06	0.89 ± 0.02
Relative	41.9 ± 1.1	42.9 ± 1.1	41.6 ± 2.5	42.3 ± 0.5	49.0 ± 2.2*	45.5 ± 1.3*
Lung						
Absolute	0.14 ± 0.01	0.15 ± 0.02	0.13 ± 0.01	0.14 ± 0.01	0.15 ± 0.00	0.14 ± 0.00
Relative	6.97 ± 0.36	7.47 ± 0.77	6.34 ± 0.56	7.37 ± 0.47	7.40 ± 0.29	6.91 ± 0.28
R. Kidney						
Absolute	0.17 ± 0.02	0.16 ± 0.00	0.15 ± 0.01	0.14 ± 0.00	0.16 ± 0.01	0.15 ± 0.01
Relative	8.16 ± 0.97	8.14 ± 0.19	6.87 ± 0.44	7.47 ± 0.32	8.05 ± 0.33	7.60 ± 0.14
Thymus[b]						
Absolute	61.00 ± 3.32	55.00 ± 3.87	59.00 ± 4.58	56.00 ± 1.87	58.00 ± 4.06	56.00 ± 4.00
Relative	3.00 ± 0.19	2.78 ± 0.21	2.83 ± 0.34	2.93 ± 0.15	2.92 ± 0.16	2.86 ± 0.19

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

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight-Ratios for Mice in the 13-Week Feed Studies of C.I. Pigment Red 23[a]

	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
n	10	10	10	10	10	10
Male						
Necropsy body wt	31.4 ± 0.6	30.7 ± 0.7	30.0 ± 1.0	32.0 ± 1.1	30.0 ± 0.9	30.1 ± 0.6
Brain						
Absolute	0.46 ± 0.01	0.45 ± 0.01	0.44 ± 0.01	0.44 ± 0.01	0.45 ± 0.01	0.43 ± 0.01
Relative	14.8 ± 0.5	14.5 ± 0.3	14.6 ± 0.4	13.8 ± 0.3	15.1 ± 0.5	14.2 ± 0.4
Heart[b]						
Absolute	144.0 ± 4.8	138.0 ± 6.3	138.0 ± 8.3	150.0 ± 4.9	143.0 ± 5.6	142.0 ± 9.2
Relative	4.59 ± 0.14	4.49 ± 0.18	4.57 ± 0.18	4.72 ± 0.18	4.77 ± 0.14	4.71 ± 0.28
Liver						
Absolute	1.44 ± 0.05	1.64 ± 0.07	1.55 ± 0.10	1.75 ± 0.05*	1.49 ± 0.06	1.46 ± 0.09
Relative	45.7 ± 1.0	53.1 ± 1.3**	51.1 ± 1.8	55.0 ± 1.8**	49.6 ± 1.2	48.1 ± 2.0
Lung						
Absolute	0.19 ± 0.02	0.17 ± 0.01	0.17 ± 0.01	0.19 ± 0.01	0.17 ± 0.01	0.15 ± 0.01
Relative	6.00 ± 0.55	5.46 ± 0.15	5.65 ± 0.24	5.81 ± 0.36	5.78 ± 0.37	5.11 ± 0.45
R. Kidney						
Absolute	0.25 ± 0.01	0.24 ± 0.01	0.25 ± 0.01	0.26 ± 0.01	0.25 ± 0.01	0.24 ± 0.02
Relative	8.01 ± 0.32	7.76 ± 0.13	8.23 ± 0.18	8.15 ± 0.22	8.31 ± 0.27	7.98 ± 0.37
R. Testis[b]						
Absolute	111.11 ± 5.12[c]	92.00 ± 5.54	97.78 ± 4.34[c]	97.00 ± 7.75	112.00 ± 3.89	109.00 ± 13.78
Relative	3.53 ± 0.17[c]	3.00 ± 0.17	3.18 ± 0.14[c]	2.99 ± 0.18	3.74 ± 0.11	3.61 ± 0.45
Thymus[b]						
Absolute	41.00 ± 6.40	37.00 ± 3.35	38.00 ± 4.67	46.00 ± 6.53	42.00 ± 4.16	39.00 ± 6.90
Relative	1.30 ± 0.19	1.21 ± 0.12	1.28 ± 0.15	1.42 ± 0.19	1.41 ± 0.15	1.27 ± 0.20
Female						
Necropsy body wt	23.4 ± 0.7	22.2 ± 0.5	22.6 ± 0.4	23.0 ± 0.7	22.4 ± 0.5	23.6 ± 0.7
Brain						
Absolute	0.47 ± 0.01	0.45 ± 0.01	0.45 ± 0.00	0.45 ± 0.01	0.45 ± 0.01	0.46 ± 0.01
Relative	20.0 ± 0.5	20.3 ± 0.5	20.0 ± 0.4	19.8 ± 0.6	20.3 ± 0.5	19.6 ± 0.5
Heart[b]						
Absolute	115.00 ± 6.54	89.00 ± 6.57*	96.00 ± 4.76	105.00 ± 4.77	103.00 ± 4.48	95.00 ± 7.92
Relative	4.93 ± 0.29	4.02 ± 0.28	4.25 ± 0.21	4.58 ± 0.20	4.59 ± 0.15	4.04 ± 0.34
Liver						
Absolute	1.09 ± 0.05	0.95 ± 0.03	1.06 ± 0.03	1.13 ± 0.04	1.04 ± 0.03	1.12 ± 0.04
Relative	46.3 ± 1.2	42.7 ± 1.0	46.8 ± 1.2	48.9 ± 0.7	46.4 ± 0.6	47.4 ± 1.4
Lung						
Absolute	0.16 ± 0.01	0.14 ± 0.01	0.14 ± 0.01	0.15 ± 0.01	0.14 ± 0.01	0.15 ± 0.01
Relative	6.96 ± 0.35	6.41 ± 0.35	6.29 ± 0.24	6.58 ± 0.31	6.37 ± 0.24	6.56 ± 0.51
R. Kidney						
Absolute	0.16 ± 0.01	0.13 ± 0.01	0.16 ± 0.01	0.16 ± 0.01	0.15 ± 0.01	0.16 ± 0.01
Relative	6.86 ± 0.14	5.97 ± 0.20	6.88 ± 0.27	7.04 ± 0.25	6.76 ± 0.30	6.79 ± 0.35
Thymus[b]						
Absolute	53.00 ± 4.48	33.00 ± 3.35*	40.00 ± 2.58*	50.00 ± 4.71	39.00 ± 2.77*	35.00 ± 5.82**
Relative	2.26 ± 0.17	1.50 ± 0.16**	1.78 ± 0.13*	2.17 ± 0.18	1.74 ± 0.12*	1.49 ± 0.25**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ and body weights are given in grams unless otherwise noted; organ-weight-to-body weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] Weights are given in milligrams.
[c] n=9

TABLE F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluations in the 2-Year Feed Studies of C.I. Pigment Red 23[a]

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male				
n	8	7	8	9
Necropsy body wt	35.6 ± 1.4	35.0 ± 1.5	33.8 ± 1.2	32.9 ± 1.4
Brain				
Absolute	0.47 ± 0.01	0.48 ± 0.01	0.47 ± 0.01	0.47 ± 0.01
Relative	13.3 ± 0.5	13.8 ± 0.7	14.0 ± 0.4	14.4 ± 0.6
Liver				
Absolute	1.82 ± 0.20	1.43 ± 0.04	1.85 ± 0.33	1.53 ± 0.08
Relative	51.6 ± 5.8	41.2 ± 1.0	55.3 ± 10.7	46.9 ± 2.4
R. Kidney				
Absolute	0.30 ± 0.01	0.36 ± 0.01*	0.33 ± 0.02	0.34 ± 0.01
Relative	8.53 ± 0.36	10.19 ± 0.25**	9.64 ± 0.28**	10.37 ± 0.32**
Female				
n	10	10	10	10
Necropsy body wt	35.2 ± 1.5	39.7 ± 1.3	35.9 ± 1.5	34.5 ± 1.4
Brain				
Absolute	0.49 ± 0.01	0.49 ± 0.01	0.48 ± 0.01	0.50 ± 0.01
Relative	14.1 ± 0.8	12.5 ± 0.5	13.5 ± 0.5	14.6 ± 0.7
Liver				
Absolute	1.30 ± 0.04	1.44 ± 0.03*	1.46 ± 0.05*	1.40 ± 0.04
Relative	37.3 ± 1.0	36.5 ± 1.1	41.1 ± 1.7	40.9 ± 1.4
R. Kidney				
Absolute	0.23 ± 0.01	0.24 ± 0.01	0.23 ± 0.01	0.23 ± 0.01
Relative	6.46 ± 0.31	5.99 ± 0.31	6.49 ± 0.20	6.82 ± 0.39

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ 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).

APPENDIX G
HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 17-Day Feed Studies of C.I. Pigment Red 23[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
Hematology						
Hematocrit (%)	42.8 ± 2.2	42.8 ± 0.7	43.2 ± 0.9	44.6 ± 2.0	42.6 ± 0.7	38.2 ± 1.4
Hemoglobin (g/dL)	17.5 ± 0.2	17.1 ± 0.6	15.9 ± 0.4*	16.5 ± 0.5	16.6 ± 0.5	14.8 ± 0.8**
Erythrocytes ($10^6/\mu L$)	9.48 ± 0.19	8.45 ± 0.29*	8.14 ± 0.19**	8.85 ± 0.26*	8.25 ± 0.20**	7.55 ± 0.36**
Platelets ($10^3/\mu L$)	186.8 ± 30.7	289.6 ± 16.5	332.2 ± 8.9**	179.2 ± 22.5	220.0 ± 27.9	214.0 ± 30.0
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.1 ± 0.0	0.1 ± 0.0**	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	7.98 ± 0.33	6.58 ± 0.54	7.68 ± 0.57	6.80 ± 0.57	7.86 ± 0.48	5.78 ± 1.02
Segmented neutrophils ($10^3/\mu L$)	0.74 ± 0.09	1.04 ± 0.23	1.16 ± 0.09	0.90 ± 0.16	1.29 ± 0.15	0.83 ± 0.14
Lymphocytes ($10^3/\mu L$)	7.18 ± 0.40	5.47 ± 0.44	6.49 ± 0.64	5.83 ± 0.41	6.48 ± 0.48	4.88 ± 0.93
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.04 ± 0.03*	0.04 ± 0.03
Eosinophils ($10^3/\mu L$)	0.06 ± 0.03	0.07 ± 0.02	0.03 ± 0.02	0.07 ± 0.03	0.05 ± 0.02	0.02 ± 0.02
Clinical chemistry						
Blood urea nitrogen (mg/dL)	21.0 ± 0.6	25.8 ± 1.5	19.4 ± 1.2	20.4 ± 0.9	22.6 ± 1.8	20.8 ± 1.4
Creatinine (mg/dL)	0.82 ± 0.02	0.62 ± 0.04**	0.56 ± 0.07**	0.78 ± 0.02*	0.58 ± 0.04**	0.60 ± 0.03**
Sodium (meq/L)	143 ± 1	140 ± 1	143 ± 1	140 ± 1	155 ± 3	161 ± 2*
Potassium (meq/L)	6.01 ± 0.21	5.28 ± 0.50	5.09 ± 0.23	7.43 ± 1.08	6.53 ± 0.47	6.25 ± 0.55
Chloride (meq/L)	106 ± 1	101 ± 1**	103 ± 1	102 ± 2	102 ± 1	102 ± 1
Calcium (mg/dL)	11.4 ± 0.3	11.4 ± 0.2	11.5 ± 0.3	11.5 ± 0.3	12.1 ± 0.3	11.8 ± 0.3
Phosphorus (mg/dL)	9.54 ± 0.60	9.12 ± 0.57	8.44 ± 0.19	9.46 ± 1.00	9.56 ± 0.43	9.68 ± 0.26
Total protein (g/dL)	6.1 ± 0.1	5.6 ± 0.1	5.4 ± 0.1*	6.3 ± 0.1	5.9 ± 0.1	5.8 ± 0.1
Albumin (g/dL)	3.9 ± 0.1	3.9 ± 0.1	3.9 ± 0.0	4.0 ± 0.1	3.9 ± 0.1	3.8 ± 0.1
Albumin/globulin ratio	1.9 ± 0.1	2.4 ± 0.1*	2.5 ± 0.2*	1.8 ± 0.1	2.0 ± 0.1	1.9 ± 0.0

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 17-Day Feed Studies of C.I. Pigment Red 23 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm	100,000 ppm
Male (continued)						
n	5	5	5	5	5	5
Clinical chemistry (continued)						
Total bilirubin (mg/dL)	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.1 ± 0.0
Alanine aminotransferase (IU/L)	36 ± 3	23 ± 3	21 ± 3	73 ± 33	19 ± 2*	40 ± 11
Aspartate aminotransferase (IU/L)	69 ± 3	73 ± 6	74 ± 4	120 ± 41	58 ± 4	87 ± 25
Lactate dehydrogenase (IU/L)	600 ± 66	739 ± 89	864 ± 111	915 ± 247	422 ± 60	717 ± 81
Cholinesterase (IU/L)	597.4 ± 22.2	638.4 ± 12.0	621.8 ± 14.3	617.6 ± 25.5	566.0 ± 12.5	591.8 ± 27.0[b]
pH	7.10 ± 0.02	7.16 ± 0.04	7.11 ± 0.03	7.11 ± 0.05	7.10 ± 0.03	7.16 ± 0.02[b]
Female						
Hematology						
Hematocrit (%)	42.0 ± 1.3	44.0 ± 1.1	41.0 ± 0.8	40.0 ± 0.6	38.6 ± 1.5	40.2 ± 0.6
Hemoglobin (g/dL)	16.1 ± 0.6	17.2 ± 0.7	16.1 ± 0.4	16.2 ± 0.4	14.6 ± 0.6	15.5 ± 0.1
Erythrocytes ($10^6/\mu L$)	8.44 ± 0.38	8.35 ± 0.31	8.17 ± 0.25	8.27 ± 0.20	7.12 ± 0.28*	7.50 ± 0.03*
Platelets ($10^3/\mu L$)	198.4 ± 16.8	242.8 ± 51.2	335.6 ± 12.2**	278.8 ± 34.8	267.8 ± 32.6	234.0 ± 25.1
Reticulocytes ($10^6/\mu L$)	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Leukocytes ($10^3/\mu L$)	6.72 ± 0.57	6.68 ± 0.45	5.66 ± 0.46	7.50 ± 0.47	7.50 ± 0.15	8.04 ± 0.65
Segmented neutrophils ($10^3/\mu L$)	0.98 ± 0.23	0.83 ± 0.11	1.06 ± 0.19	1.17 ± 0.21	1.07 ± 0.09	1.19 ± 0.28
Lymphocytes ($10^3/\mu L$)	5.67 ± 0.54	5.68 ± 0.36	4.45 ± 0.44	6.27 ± 0.33	6.29 ± 0.25	6.77 ± 0.46
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	0.00 ± 0.00	0.05 ± 0.03	0.05 ± 0.02*
Eosinophils ($10^3/\mu L$)	0.07 ± 0.04	0.14 ± 0.05	0.14 ± 0.04	0.078 ± 0.04	0.09 ± 0.04	0.04 ± 0.04
Clinical chemistry						
Blood urea nitrogen (mg/dL)	23.2 ± 1.6	21.8 ± 0.9	22.8 ± 1.6	22.4 ± 1.4	23.8 ± 0.6	22.4 ± 0.8
Creatinine (mg/dL)	0.72 ± 0.09	0.56 ± 0.02	0.58 ± 0.02	0.76 ± 0.04	0.60 ± 0.05	0.60 ± 0.03

TABLE G1
Hematology and Clinical Chemistry Data for Rats in the 17-Day Feed Studies of C.I. Pigment Red 23 (continued)

	0 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm	100,000 ppm
Female (continued)						
n	5	5	5	5	5	5
Clinical chemistry (continued)						
Sodium (meq/L)	141 ± 1	142 ± 1	138 ± 0	140 ± 1	166 ± 4*	161 ± 2*
Potassium (meq/L)	5.22 ± 0.17	5.12 ± 0.12	6.15 ± 0.28*	5.42 ± 0.10	6.72 ± 0.77	6.21 ± 0.31*
Chloride (meq/L)	107 ± 0	103 ± 0**	105 ± 1	108 ± 1	104 ± 0	105 ± 0
Calcium (mg/dL)	11.5 ± 0.2	11.5 ± 0.1	11.6 ± 0.2	11.8 ± 0.2	12.0 ± 0.1	12.2 ± 0.2*
Phosphorus (mg/dL)	7.44 ± 0.37	7.42 ± 0.28	8.10 ± 0.43	7.64 ± 0.24	8.50 ± 0.45*	8.14 ± 0.40
Total protein (g/dL)	6.0 ± 0.1	5.5 ± 0.2	5.5 ± 0.2	6.1 ± 0.1	5.7 ± 0.0	6.0 ± 0.1
Albumin (g/dL)	4.1 ± 0.0	3.9 ± 0.0**	4.0 ± 0.1	4.1 ± 0.1	3.9 ± 0.0	4.1 ± 0.1
Albumin/globulin ratio	2.2 ± 0.1	2.5 ± 0.2	2.8 ± 0.4	2.0 ± 0.0	2.2 ± 0.0	2.2 ± 0.1
Total bilirubin (mg/dL)	0.1 ± 0.1	0.1 ± 0.1	0.2 ± 0.1	0.0 ± 0.0	0.1 ± 0.1	0.1 ± 0.1
Alanine aminotransferase (IU/L)	37 ± 3	24 ± 3	39 ± 12	41 ± 11	25 ± 4	34 ± 10
Aspartate aminotransferase (IU/L)	82 ± 5	68 ± 4*	74 ± 7	69 ± 2	59 ± 4**	75 ± 9*
Lactate dehydrogenase (IU/L)	744 ± 62	663 ± 53	715 ± 87	714 ± 36	400 ± 83**	617 ± 63
Cholinesterase (IU/L)	2,628 ± 56	2,540 ± 108	2,651 ± 92	2,650 ± 140	2,408 ± 179[c]	2,679 ± 210
pH	7.15 ± 0.04	7.10 ± 0.02	7.07 ± 0.01	7.15 ± 0.02	7.13 ± 0.02[c]	7.22 ± 0.05[b]

* 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=4
[c] n=3

TABLE G2
Hematology and Clinical Chemistry Data for Rats in the 13-Week Feed Studies of C.I. Pigment Red 23[a]

	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male						
n	7	10	10	10	10	8
Hematology						
Hematocrit (%)	46.4 ± 0.6	47.2 ± 0.5	47.0 ± 0.4	47.7 ± 0.3	46.1 ± 0.3	44.6 ± 0.4*
Hemoglobin (g/dL)	16.6 ± 0.2	16.8 ± 0.2	16.6 ± 0.2	16.6 ± 0.1	16.3 ± 0.1	16.1 ± 0.1*
Erythrocytes ($10^6/\mu L$)	8.65 ± 0.10	8.70 ± 0.10	8.51 ± 0.14	8.70 ± 0.04	8.68 ± 0.04	8.39 ± 0.05*
Platelets ($10^3/\mu L$)	167.1 ± 5.1	147.3 ± 5.1	155.7 ± 5.7	145.8 ± 5.4	173.5 ± 2.8	167.1 ± 2.7
Reticulocytes (%)	2.0 ± 0.3	1.3 ± 0.1	1.5 ± 0.1	1.5 ± 0.2	2.1 ± 0.1	1.9 ± 0.3
Leukocytes ($10^3/\mu L$)	4.61 ± 0.29	5.88 ± 0.21	5.92 ± 0.43*	5.93 ± 0.24	5.23 ± 0.17	5.80 ± 0.56
Segmented neutrophils ($10^3/\mu L$)	0.88 ± 0.10	0.89 ± 0.04	1.02 ± 0.08	1.05 ± 0.07	1.19 ± 0.12	1.06 ± 0.15
Lymphocytes ($10^3/\mu L$)	3.68 ± 0.23	4.92 ± 0.23*	4.87 ± 0.36*	4.79 ± 0.18*	3.95 ± 0.17	4.68 ± 0.49
Eosinophils ($10^3/\mu L$)	0.04 ± 0.02	0.03 ± 0.01	0.04 ± 0.01	0.07 ± 0.02	0.11 ± 0.02	0.03 ± 0.01
n	10	10	10	9	10	9
Clinical chemistry						
Total bilirubin (mg/dL)	0.3 ± 0.1	0.3 ± 0.0	0.6 ± 0.1	0.5 ± 0.1[b]	0.3 ± 0.0	0.2 ± 0.0
Alanine aminotransferase (IU/L)	36 ± 6	37 ± 2	41 ± 6	55 ± 8*	27 ± 2	31 ± 2[b]
Aspartate aminotransferase (IU/L)	66 ± 9	57 ± 3	64 ± 5[c]	71 ± 7	56 ± 3	53 ± 6*[b]
Lactate dehydrogenase (IU/L)	130 ± 27	119 ± 36	178 ± 30[c]	133 ± 17	151 ± 21	79 ± 12
Sorbitol dehydrogenase (IU/L)	19 ± 1	16 ± 1	17 ± 3[d]	20 ± 3	20 ± 1	17 ± 1

TABLE G2
Hematology and Clinical Chemistry Data for Rats in the 13-Week Feed Studies of C.I. Pigment Red 23 (continued)

	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Female						
n	8	6	9	7	9	8
Hematology						
Hematocrit (%)	44.0 ± 0.5	44.5 ± 0.4	45.1 ± 0.3	44.8 ± 0.4	45.9 ± 0.2*	42.8 ± 0.3
Hemoglobin (g/dL)	15.6 ± 0.2	15.8 ± 0.2	15.9 ± 0.1	15.6 ± 0.2	16.2 ± 0.1*	15.5 ± 0.1
Erythrocytes ($10^6/\mu L$)	7.66 ± 0.09	7.64 ± 0.06	7.70 ± 0.03	7.62 ± 0.07	7.95 ± 0.03	7.51 ± 0.06
Platelets ($10^3/\mu L$)	171.0 ± 5.5	169.0 ± 6.7	168.2 ± 7.4	175.7 ± 3.5	186.0 ± 6.1	182.3 ± 3.4
Reticulocytes (%)	1.8 ± 0.2	1.2 ± 0.2	1.7 ± 0.1	1.6 ± 0.2	1.7 ± 0.3	1.8 ± 0.2
Leukocytes ($10^3/\mu L$)	2.61 ± 0.23	4.27 ± 0.15**	3.59 ± 0.28	3.01 ± 0.12	3.57 ± 0.27	3.60 ± 0.27
Segmented neutrophils ($10^3/\mu L$)	0.52 ± 0.09	0.72 ± 0.03	0.56 ± 0.07	0.54 ± 0.10	0.61 ± 0.05	0.47 ± 0.05
Lymphocytes ($10^3/\mu L$)	2.03 ± 0.19	3.50 ± 0.15**	2.99 ± 0.24*	2.44 ± 0.13	2.90 ± 0.22	3.11 ± 0.27*
Eosinophils ($10^3/\mu L$)	0.03 ± 0.01	0.04 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.05 ± 0.02	0.02 ± 0.01
n	10	10	8	10	9	9
Clinical chemistry						
Total bilirubin (mg/dL)	0.3 ± 0.1	0.6 ± 0.1[c]	0.7 ± 0.2[c]	1.0 ± 0.3	0.3 ± 0.0	0.3 ± 0.0
Alanine aminotransferase (IU/L)	26 ± 4	28 ± 2	28 ± 2	36 ± 2*	21 ± 1	23 ± 5
Aspartate aminotransferase (IU/L)	48 ± 4	50 ± 2	55 ± 3	61 ± 3*	47 ± 3	58 ± 8
Lactate dehydrogenase (IU/L)	77 ± 12	174 ± 25**	178 ± 35**	247 ± 46**	81 ± 7*	353 ± 38**
Sorbitol dehydrogenase (IU/L)	14 ± 1	13 ± 1	16 ± 1	9 ± 1**	12 ± 1*	11 ± 2

* 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=10
[c] n=9
[d] n=8

TABLE G3
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Studies of C.I. Pigment Red 23[a]

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male				
n	10	10	10	9
Hematology				
Hematocrit (%)	38.7 ± 0.7	39.4 ± 0.8	38.3 ± 0.5	37.1 ± 0.6
Hemoglobin (g/dL)	15.7 ± 0.2	16.0 ± 0.4	15.5 ± 0.2	15.1 ± 0.2
Erythrocytes ($10^6/\mu L$)	8.41 ± 0.14	8.64 ± 0.16	8.36 ± 0.05	8.11 ± 0.09
Platelets ($10^3/\mu L$)	3.0 ± 0.0	2.9 ± 0.1	3.2 ± 0.1	3.3 ± 0.0**
Leukocytes ($10^3/\mu L$)	3.46 ± 0.16	2.92 ± 0.26	2.95 ± 0.21	3.92 ± 0.28
Clinical chemistry				
Total bilirubin (mg/dL)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Female				
n	9	10	10	10
Hematology				
Hematocrit (%)	35.3 ± 0.5	34.6 ± 0.6	34.5 ± 0.4	33.4 ± 0.4**
Hemoglobin (g/dL)	15.3 ± 0.4	15.1 ± 0.7	14.9 ± 0.4	14.3 ± 0.2*
Erythrocytes ($10^6/\mu L$)	7.32 ± 0.09	7.19 ± 0.12	7.17 ± 0.08	6.92 ± 0.09**
Platelets ($10^3/\mu L$)	2.5 ± 0.1	2.4 ± 0.1	2.6 ± 0.2	2.7 ± 0.1
Leukocytes ($10^3/\mu L$)	1.71 ± 0.07	1.64 ± 0.10	1.63 ± 0.17	1.50 ± 0.18
n	10	10	10	10
Clinical chemistry				
Total bilirubin (mg/dL)	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.3 ± 0.0*

* 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

TABLE G4
Hematology and Clinical Chemistry Data for Mice in the 17-Day Feed Studies of C.I. Pigment Red 23[a]

	0 ppm	6,000 ppm	25,000 ppm	50,000 ppm	100,000 ppm
Male					
n	5	5	4	4	5
Hematology					
Hematocrit (%)	34.6 ± 1.2	33.9 ± 0.5	33.5 ± 0.7[b]	36.6 ± 0.4	34.4 ± 1.4
Hemoglobin (g/dL)	12.6 ± 0.4	13.4 ± 0.2	14.5 ± 0.7	14.7 ± 0.4*	12.9 ± 0.4
Erythrocytes ($10^6/\mu L$)	7.24 ± 0.26	7.91 ± 0.12*	8.84 ± 0.40**	8.51 ± 0.25**	7.81 ± 0.41*
Platelets ($10^3/\mu L$)	322.4 ± 51.4	516.0 ± 37.8	241.5 ± 46.1	467.3 ± 62.8	386.2 ± 108
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.1 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	2.06 ± 0.38	3.08 ± 0.30	3.98 ± 0.81*	4.45 ± 0.31**	4.38 ± 0.50**
Segmented neutrophils ($10^3/\mu L$)	1.04 ± 0.21	1.27 ± 0.22	0.73 ± 0.17	1.47 ± 0.11	1.30 ± 0.41
Lymphocytes ($10^3/\mu L$)	1.02 ± 0.17	1.79 ± 0.22*	3.23 ± 0.74**	2.90 ± 0.25**	2.99 ± 0.43**
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.03 ± 0.03	0.02 ± 0.01
Eosinophils ($10^3/\mu L$)	0.00 ± 0.00	0.02 ± 0.01	0.01 ± 0.01	0.05 ± 0.02*	0.07 ± 0.04*
n	4	4	3	3	5
Clinical chemistry					
Potassium (meq/L)	6.76 ± 1.03	6.27[c]	5.96 ± 1.13	–[d]	–
Partial carbon dioxide (mmHg)	56.90 ± 4.03	59.08 ± 6.44	57.46 ± 5.90[b]	58.83 ± 11.48	58.56 ± 8.24
Total bilirubin (mg/dL)	0.5 ± 0.3[e]	–	0.2 ± 0.1	–	–
Alanine aminotransferase (IU/L)	44 ± 9	38 ± 16	31 ± 12	29[c]	43[c]
Lactate dehydrogenase (IU/L)	570 ± 47[b]	757 ± 179[b]	761 ± 390[f]	1,001 ± 231	731 ± 50
Sorbitol dehydrogenase (IU/L)	99 ± 9[g]	129 ± 50[e]	250[c]	127 ± 39	98 ± 28[f]
pH	7.26 ± 0.00	7.23 ± 0.02	7.23 ± 0.02[b]	7.19 ± 0.02	7.27 ± 0.03

TABLE G4
Hematology and Clinical Chemistry Data for Mice in the 17-Day Feed Studies of C.I. Pigment Red 23 (continued)

	0 ppm	6,000 ppm	25,000 ppm	50,000 ppm	100,000 ppm
Female					
n	4	2	3	4	5
Hematology					
Hematocrit (%)	38.3 ± 2.8	33.8 ± 2.7[f]	34.5 ± 1.2[b]	35.2 ± 1.2[b]	37.0 ± 1.3
Hemoglobin (g/dL)	13.2 ± 0.2	14.6 ± 0.1	14.1 ± 0.2*	14.6 ± 0.3*	14.4 ± 0.4*
Erythrocytes ($10^6/\mu L$)	7.85 ± 0.10	8.50 ± 0.09	8.59 ± 0.11	8.56 ± 0.16	8.34 ± 0.26
Platelets ($10^3/\mu L$)	344.0 ± 37.1	232.3 ± 126[f]	217.6 ± 20.1[b]	319.4 ± 60.7[b]	431.6 ± 46.2
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.2 ± 0.1	0.2 ± 0.0	0.3 ± 0.1	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	2.63 ± 0.42	3.15 ± 0.35	2.40 ± 0.32	4.03 ± 0.21*	3.32 ± 0.07
Segmented neutrophils ($10^3/\mu L$)	0.82 ± 0.20	0.95 ± 0.28	0.29 ± 0.01	1.05 ± 0.19	0.46 ± 0.07
Lymphocytes ($10^3/\mu L$)	1.81 ± 0.23	2.18 ± 0.62	2.11 ± 0.33	2.94 ± 0.34*	2.82 ± 0.07*
Monocytes ($10/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.02	0.02 ± 0.01
Eosinophils ($10/\mu L$)	0.00 ± 0.00	0.02 ± 0.02	0.00 ± 0.00	0.02 ± 0.02	0.02 ± 0.01
n	3	5	4	5	2
Clinical chemistry					
Potassium (meq/L)	4.46 ± 0.28[g]	–	4.05 ± 0.34	5.98[c]	5.54 ± 0.42
Partial carbon dioxide (mmHg)	56.34 ± 7.51[b]	54.38 ± 4.35	56.18 ± 3.24[b]	58.38 ± 3.64	60.14 ± 5.94[b]
Total bilirubin	0.1 ± 0.1	–	–	0.3[c]	–
Alanine aminotransferase (IU/L)	14 ± 8	–	23 ± 4[e]	15 ± 4[g]	21 ± 2
Lactate dehydrogenase (IU/L)	690 ± 130[f]	1,648[c]	849 ± 175	572 ± 140[e]	332 ± 28
Sorbitol dehydrogenase (IU/L)	69 ± 8	–	88 ± 16	59 ± 9[g]	50 ± 2
pH	7.28 ± 0.03[b]	7.28 ± 0.03	7.25 ± 0.02[b]	7.26 ± 0.04	7.25 ± 0.03[b]

* 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=5
[c] n=1; no standard error calculated due to insufficient measurements
[d] n=0; no data calculated due to insufficient measurements
[e] n=3
[f] n=4
[g] n=2

TABLE G5
Hematology and Clinical Chemistry Data for Mice in the 13-Week Feed Studies of C.I. Pigment Red 23[a]

	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Male						
n	7	8	8	6	4	9
Hematology						
Hematocrit (%)	38.6 ± 0.9	37.8 ± 0.6	36.9 ± 1.3	38.8 ± 0.9	40.5 ± 1.8	40.0 ± 0.8
Hemoglobin (g/dL)	12.8 ± 0.3	13.0 ± 0.2	12.6 ± 0.4	13.2 ± 0.3	13.9 ± 0.7	13.3 ± 0.2
Erythrocytes (10^6/μL)	7.81 ± 0.17	7.58 ± 0.13	7.32 ± 0.30	7.84 ± 0.20	8.33 ± 0.33	7.99 ± 0.15
Platelets (10^3/μL)	160.6 ± 11.1	174.6 ± 15.3	163.0 ± 21.8	144.2 ± 12.6	110.8 ± 22.5	166.7 ± 14.3
Reticulocytes (%)	2.9 ± 0.2	3.2 ± 0.3	4.9 ± 0.9	2.2 ± 0.3	2.4 ± 0.3	3.1 ± 0.2
Leukocytes (10^3/μL)	3.17 ± 0.60	3.68 ± 0.45	3.03 ± 0.25	3.87 ± 0.39	2.45 ± 0.29	3.23 ± 0.54[b]
Segmented neutrophils (10^3/μL)	0.65 ± 0.14	0.99 ± 0.18	0.72 ± 0.14	0.91 ± 0.18	0.53 ± 0.05	1.08 ± 0.25[b]
Lymphocytes (10^3/μL)	2.52 ± 0.47	2.67 ± 0.43	2.30 ± 0.14	2.95 ± 0.30	1.91 ± 0.30	2.10 ± 0.43[b]
n	5	8	8	8	8	2
Clinical chemistry						
Alanine aminotransferase (IU/L)	42 ± 10	32 ± 2	35 ± 8	37 ± 4	50 ± 5	62 ± 32
Aspartate aminotransferase (IU/L)	212 ± 40[c]	117 ± 16	134 ± 51[d]	216 ± 51	289 ± 47[d]	209 ± 78

TABLE G5
Hematology and Clinical Chemistry Data for Mice in the 13-Week Feed Studies of C.I. Pigment Red 23 (continued)

	0 ppm	3,000 ppm	6,000 ppm	12,500 ppm	25,000 ppm	50,000 ppm
Female						
n	6	8	7	9	7	9
Hematology						
Hematocrit (%)	43.6 ± 0.5	41.6 ± 0.4	40.7 ± 0.6*	41.8 ± 0.7	41.5 ± 0.9	41.9 ± 0.5
Hemoglobin (g/dL)	14.3 ± 0.1	14.3 ± 0.1	13.7 ± 0.2*	14.1 ± 0.2	14.0 ± 0.3	13.8 ± 0.1
Erythrocytes ($10^6/\mu L$)	8.63 ± 0.08	8.31 ± 0.09	8.16 ± 0.13	8.43 ± 0.15	8.43 ± 0.18	8.36 ± 0.11
Platelets ($10^3/\mu L$)	159.5 ± 12.8	122.3 ± 17.9	138.4 ± 39.6	118.0 ± 16.3	117.7 ± 9.5	144.1 ± 7.7
Reticulocytes (%)	2.2 ± 0.3	2.5 ± 0.2	2.8 ± 0.3	2.5 ± 0.2	2.5 ± 0.3	2.9 ± 0.3
Leukocytes ($10^3/\mu L$)	2.55 ± 0.43	2.53 ± 0.25	3.36 ± 0.55	2.28 ± 0.18	2.13 ± 0.36	2.73 ± 0.44
Segmented neutrophils ($10^3/\mu L$)	0.72 ± 0.21	0.61 ± 0.09	0.62 ± 0.12	0.55 ± 0.07	0.46 ± 0.07	0.65 ± 0.11
Lymphocytes ($10^3/\mu L$)	1.82 ± 0.28	1.92 ± 0.20	2.73 ± 0.45	1.72 ± 0.13	1.66 ± 0.30	2.08 ± 0.35
n	5	7	7	7	8	3
Clinical chemistry						
Alanine aminotransferase (IU/L)	31 ± 6	35 ± 3	37 ± 4[e]	45 ± 7	43 ± 5	38 ± 5
Aspartate aminotransferase (IU/L)	197 ± 45	175 ± 22	315 ± 91	309 ± 48	240 ± 70	122 ± 13

* 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=8
[c] n=4
[d] n=9
[e] n=6

TABLE G6
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Studies of C.I. Pigment Red 23[a]

	0 ppm	10,000 ppm	25,000 ppm	50,000 ppm
Male				
n	8	7	8	9
Hematology				
Hematocrit (%)	37.8 ± 1.5	39.4 ± 0.5	38.3 ± 1.1	39.2 ± 0.6
Hemoglobin (g/dL)	13.2 ± 0.6	13.8 ± 0.2	13.3 ± 0.3	13.5 ± 0.3
Erythrocytes ($10^6/\mu L$)	7.57 ± 0.39	7.46 ± 0.11	7.42 ± 0.18	7.72 ± 0.18
Platelets ($10^3/\mu L$)	7.3 ± 0.7	7.7 ± 0.4	9.6 ± 0.5*	8.7 ± 0.3
Leukocytes ($10^3/\mu L$)	1.74 ± 0.31	1.11 ± 0.26	1.46 ± 0.19	1.47 ± 0.28
Clinical chemistry				
Total bilirubin (mg/dL)	0.9 ± 0.2	0.8 ± 0.1	0.9 ± 0.1	0.7 ± 0.1
Female				
n	10	10	8	10
Hematology				
Hematocrit (%)	39.3 ± 0.5	39.4 ± 0.5	38.4 ± 0.5	39.0 ± 0.5
Hemoglobin (g/dL)	13.5 ± 0.2	13.4 ± 0.1	13.3 ± 0.2	13.6 ± 0.2
Erythrocytes ($10^6/\mu L$)	7.74 ± 0.11	7.63 ± 0.07	7.54 ± 0.12	7.60 ± 0.06
Platelets ($10^3/\mu L$)	6.0 ± 0.1	5.7 ± 0.1	5.8 ± 0.4	5.9 ± 0.1
Leukocytes ($10^3/\mu L$)	1.09 ± 0.09[b]	1.09 ± 0.15	1.54 ± 0.25	1.10 ± 0.11
n	10	10	9	10
Clinical chemistry				
Total bilirubin (mg/dL)	0.9 ± 0.1	0.9 ± 0.1	1.1 ± 0.2	0.8 ± 0.1

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error
[b] n=9

APPENDIX H
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

C.I. Pigment Red 23 was obtained in two lots. Lot G1723 was manufactured by American Cyanamid Co. (Wayne, NJ). This lot was used throughout the 17-day and 13-week studies and for part of the 2-year studies. Lot UB2158 was manufactured by Sun Chemical Co. (New York, NY) and was used to complete the 2-year studies. Purity and identity analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (MRI; Kansas City, MO). Reports from MRI on the analyses performed in support of the C.I. Pigment Red 23 studies are on file at the National Institute of Environmental Health Sciences.

Both lots of the dye, a bluish red solid, were identified as C.I. Pigment Red 23 by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra of C.I. Pigment Red 23 (*Sadtler Standard Spectra*), as shown in Figures H1 and H2.

The purity of both lots was determined by elemental analyses, Karl Fischer water analysis, potentiometric titration, thin-layer chromatography, and high-performance liquid chromatography (HPLC). Potentiometric titration of the phenol group was performed in anhydrous ethylene diamine with 0.06N tetrabutylammonium hydroxide in methanol:isopropanol (1:9), using a glass electrode and a calomel reference electrode filled with 1M tetrabutyl ammonium chloride in methanol. Thin-layer chromatography was performed on silica gel plates with two solvent systems: 1) chloroform:xylenes:methanol (75:24:1) and 2) methylene chloride:acetonitrile (100:0.5). Visualization was accomplished by measuring absorbance from 700 nm to 300 nm against an *o*-dichlorobenzene reference. High-performance liquid chromatography was performed with a μBondapak CN column with a mobile phase of hexane:methylene chloride (80:20, isocratic) at a flow rate of 2 mL/min. Ultraviolet detection was at 546 nm.

For lot G1723, elemental analysis for carbon was slightly higher, for nitrogen was lower, and hydrogen values were in agreement with theoretical values. In addition, elemental analyses indicated 0.45% chlorine and traces of sulfur and phosphorus. Water content was 0.35% by Karl Fischer analysis. Titration of the phenol group indicated a purity of 110%. Thin-layer chromatography indicated a major spot, a trace, and a minor spot with system 1, and a major spot with trace spots above and below the major spot with a minor spot at the origin in a system 2. Two impurities with areas of 1.5% and 2.1% eluting before the major peak were indicated by HPLC. The first impurity found by HPLC was tentatively identified by mass spectroscopy as 3-hydroxy-4-((2-methoxy-5-nitrosophenyl)azo)-N-(3-aminophenyl)-2-naphthalenecarboxamide. The second HPLC impurity was found to consist of two components tentatively identified as 3-hydroxy-4-((2-methoxy-5-nitrophenyl)azo)-N-phenyl-2-naphthalenecarboxamide and 3-hydroxy-N-(3-aminophenyl)-2-naphthalenecarboxamide. Overall purity of the lot was 99.6%.

For lot UB2158, elemental analyses were low for carbon and nitrogen but consistent with theoretical values for hydrogen. Elemental analyses also indicated 0.52% chlorine and 0.28% sodium with a trace of potassium. Water content was 0.57% by Karl Fischer analysis. Purity based on titration of the phenol group was 110%. Thin-layer chromatography by systems 1 and 2 indicated a major spot, and one trace and one minor impurity. A major peak with no impurities greater than 0.5% was indicated by HPLC. Overall purity of the lot was 99.7%. Major peak comparison by HPLC showed both lots to be identical within experimental error.

Bulk chemical stability studies performed by the analytical chemistry laboratory indicated the chemical to be stable when protected from light for 2 weeks at temperatures up to 60° C. A sample of the bulk chemical was frozen and used as a reference for comparison to the bulk chemical during the 2-year studies. The bulk chemical was analyzed by the study laboratory at approximately 4-month intervals and no degradation was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by mixing appropriate quantities of C.I. Pigment Red 23 with feed (NIH-07 Rat and Mouse Ration) to form a premix, then the remaining feed was added and mixed in a twin-shell blender equipped with an intensifier bar (Table H1). Studies conducted by the analytical chemistry laboratory to determine stability and homogeneity of the dosed feed formulations indicated that the formulations were homogeneous and stable for at least 2 weeks at temperatures up to 45° C when stored in the dark. The preparations protected from light were stored at 5° C prior to use and at room temperature during use. Storage time was not more than 14 days. Periodic analyses of the dosed-feed formulations were conducted at the study laboratory and at the analytical chemistry laboratory throughout the studies (Tables H2-H4). The original method used the extraction solvent nitrobenzene; the solvent was changed to a solution of 10 g potassium hydroxide in 500 mL methanol diluted to 1,000 mL with tetrahydrofuran because of inconsistent recoveries. Dose levels were determined using visible spectroscopy at 478 nm. Homogeneity of the formulations was confirmed by the study laboratory. For the 2-year studies, a total of 142 samples were analyzed and five were remixed in order to be within acceptable limits (Table H4). Periodically, the dose formulations were sent for referee analyses by MRI. The results from the study laboratory and from the referee analytical chemistry laboratory were generally in good agreement, with all value differences less than 13% (Table H3).

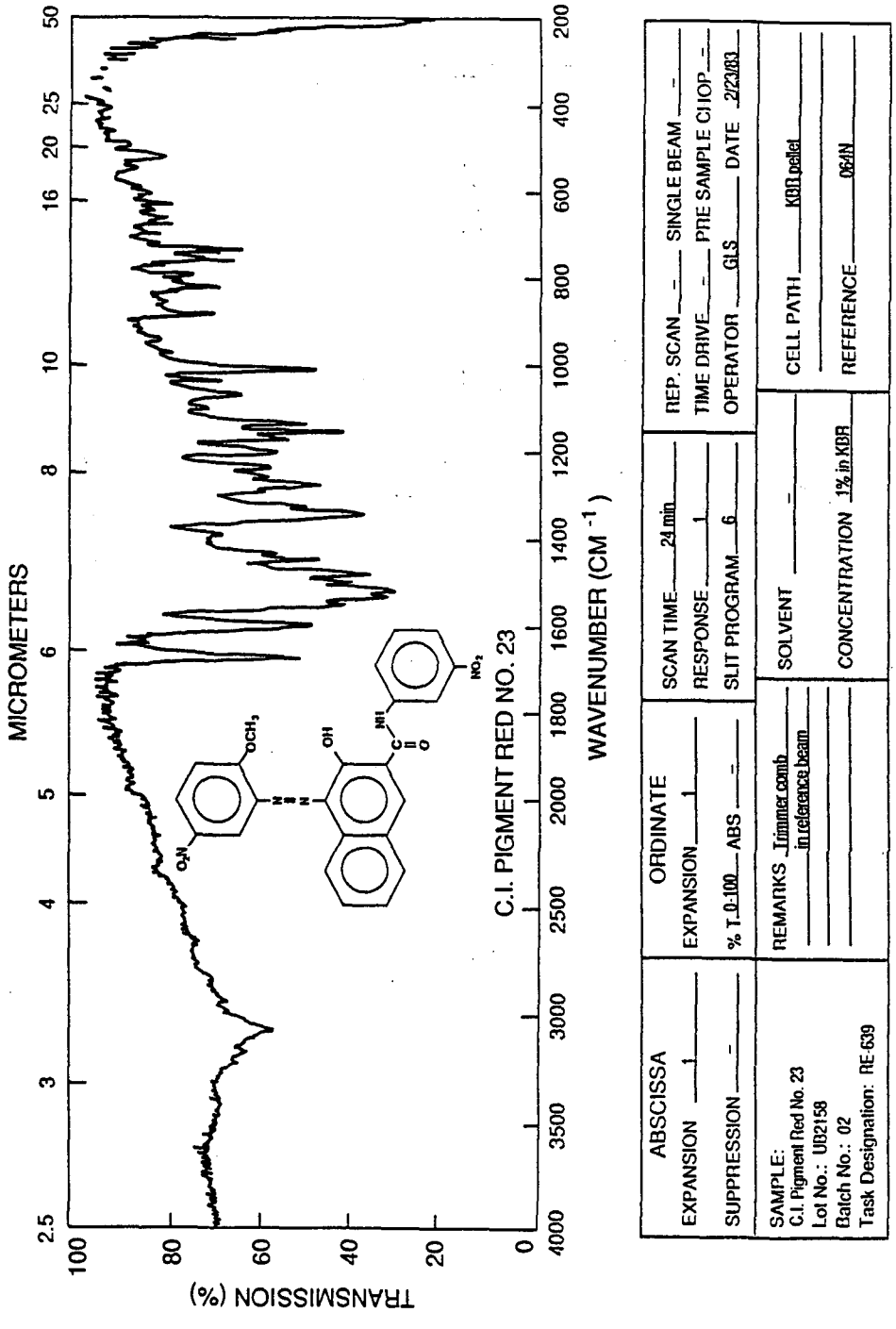

FIGURE H1
Infrared Absorption Spectrum of C.I. Pigment Red 23

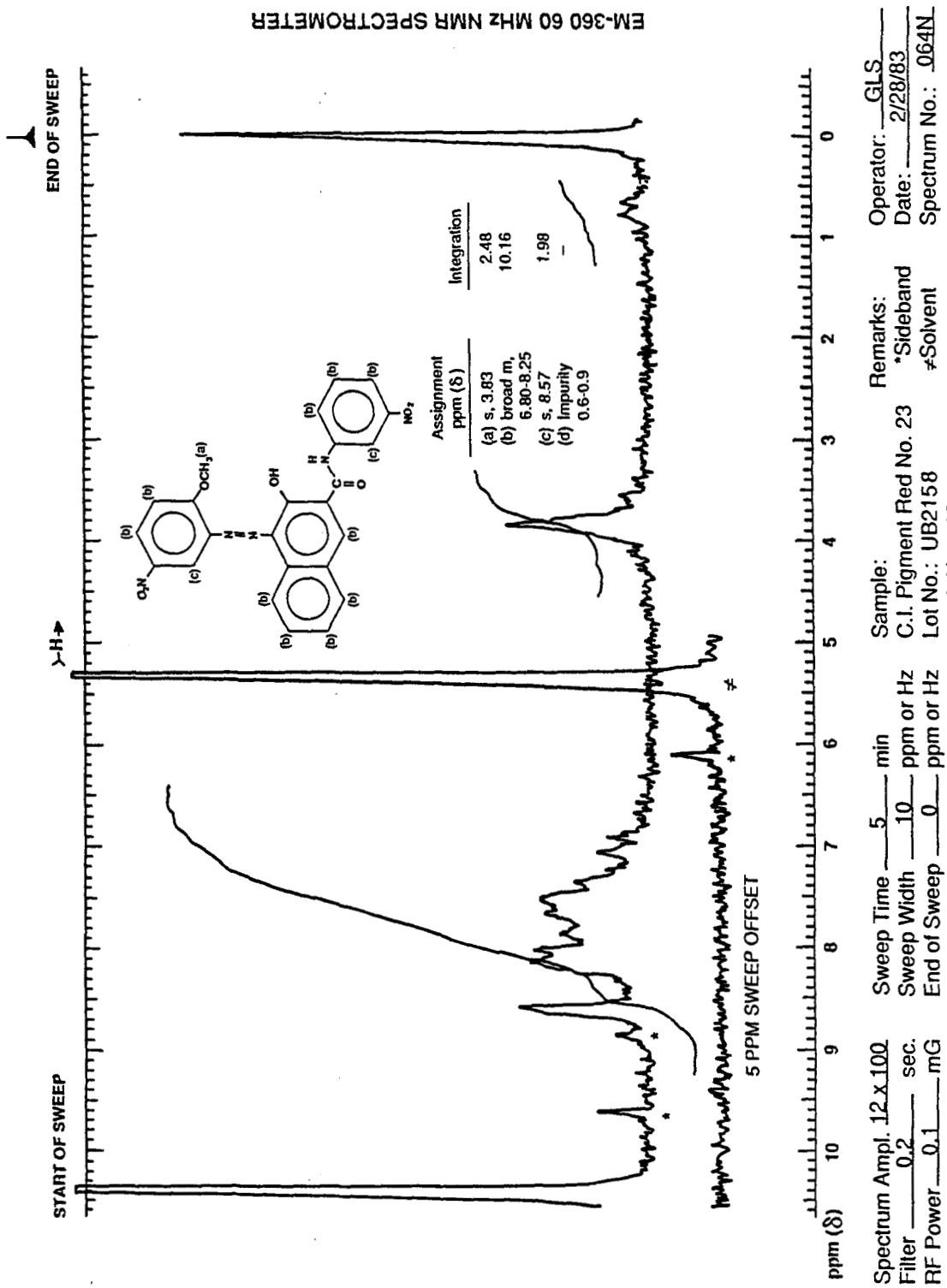

FIGURE H2
Nuclear Magnetic Resonance Spectrum of C.I. Pigment Red 23

TABLE H1
Preparation and Storage of Dose Formulations in the Feed Studies of C.I. Pigment Red 23

17-Day Studies	13-Week Studies	2-Year Studies
Preparation		
Dosed feed was prepared three times. The appropriate amount of C.I. Pigment Red 23 was premixed with NIH-07 Rat and Mouse Ration. The remaining feed was blended with the dosed-premix for 15 minutes using a twin-shell blender with an intensifier bar. The intensifier bar was on for 5 minutes during blending.	Same as 17-day studies, except dosed-feed was prepared weekly.	Same as 13-week studies
Chemical Lot Number		
G1723	G1723	G1723 UB2158
Maximum Storage Time		
14 days from date of preparation	Same as 17-day studies	Same as 17-day studies
Storage Conditions		
Protected from light in a cold room at 5° C prior to use, then at animal room temperature during use.	Same as 17-day studies	Same as 17-day studies

TABLE H2
Results of Analysis of Dose Formulations for Rats and Mice in the 17-Day Feed Studies of C.I. Pigment Red 23

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Percent Difference from Target
11 June 1981	16-19 June 1981	6,000	6,000	0
		12,500	10,600	-15[b]
		25,000	10,100	-60[b]
		50,000	13,600	-73[b]
		100,000	101,000	+1[c]

[a] Results of duplicate analyses.
[b] The low results of the 12,500, 25,000, and 50,000 ppm dose levels were due to the analytical procedure, rather than a mixing error.
[c] The extraction method was modified for the analysis of the 100,000 ppm dose level, and the results were within acceptable limits.

TABLE H3
Results of Analysis of Dose Formulations for Rats and Mice in the 13-Week Feed Studies of C.I. Pigment Red 23

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Percent Difference from Target
7 December 1981	15 December 1981	3,000	3,280	+9
		3,000	3,620	+21[b]
		3,000	3,080	+3
		6,000	6,020	0
		12,500	12,000	–4
		25,000	24,400	–2
		50,000	49,200	–2
		50,000	48,700	–3
		50,000	49,200	–2
1 February 1982[c]	11 February 1982	3,000	8,380	+179
		6,000	15,500	+158
		12,500	28,800	+130
		25,000	28,200	+13
		50,000	38,200	–24
15 March 1982	17 March 1982	3,000	2,960	–1
		6,000	5,800	–3
		12,500	12,500	0
		25,000	23,800	–5
		50,000	45,100	–10

[a] Results of duplicate analyses.
[b] This sample was used for dosing prior to analysis; however, overall results of the 3,000 ppm dose level were acceptable.
[c] Data and results not reliable due to problem with extraction procedure.

TABLE H4
Results of Analysis of Dose Formulations for Rats and Mice in the 2-Year Feed Studies of C.I. Pigment Red 23

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Percent Difference from Target
3 December 1982[b]	6 December 1982	10,000	9,390	–6
		25,000	15,000	–40[c]
		50,000	48,600	–3
9 December 1982[d]	9 December 1982	25,000	24,200	–3
28 January 1983	2 February 1983	10,000	9,810	–2
		10,000	10,100	+1
		10,000	9,770	–2
		25,000	25,200	+1
		25,000	24,500	–2
		25,000	25,100	0
		50,000	50,200	0
		50,000	49,800	0
		50,000	50,800	+2
22 March 1983	24 March 1983	10,000	9,820	–2
		10,000	10,300	+3
		10,000	9,780	–2
		25,000	26,200	+5
		25,000	26,000	+4
		25,000	27,300	+9
		50,000	51,300	+3
		50,000	54,900	+10
		50,000	52,800	+6
		50,000	53,600	+7
17 May 1983	17 May 1983	10,000	11,000	+10
		10,000	10,000	0
		10,000	10,200	+2
		25,000	27,500	+10
		25,000	27,400	+10
		25,000	28,800	+15[c]
		50,000	56,000	+12[c]
		50,000	56,600	+13[c]
		50,000	57,200	+14[c]
		50,000	57,500	+15[c]
	20 May 1983[d]	25,000	27,500	+10
		50,000	54,800	+10
		50,000	54,800	+10
		50,000	54,300	+9
		50,000	54,600	+9

TABLE H4
Results of Analysis of Dose Formulations for Rats and Mice in the 2-Year Feed Studies of C.I. Pigment Red 23 (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Percent Difference from Target
26 July 1983	29 July 1983	10,000	9,240	–8
		10,000	9,300	–7
		10,000	9,020	–10
		25,000	25,200	+1
		25,000	25,200	+1
		25,000	25,000	0
		50,000	51,600	+3
		50,000	52,500	+5
		50,000	51,800	+4
		50,000	51,400	+3
6 September 1983	7 September 1983	10,000	9,920	–1
		10,000	9,980	0
		10,000	9,740	–3
		25,000	25,300	+1
		25,000	24,400	–2
		25,000	25,400	+2
		50,000	49,000	–2
		50,000	49,900	0
		50,000	48,800	–2
		50,000	49,600	–1
1 November 1983	2 November 1983	10,000	9,540	–5
		10,000	9,810	–2
		10,000	9,660	–3
		25,000	24,900	0
		25,000	24,200	–3
		25,000	24,400	–2
		50,000	48,400	–3
		50,000	49,000	–2
		50,000	50,000	0
		50,000	49,300	–1
27 December 1983	28 December 1983	10,000	10,100	+1
		10,000	10,100	+1
		10,000	10,000	0
		25,000	25,400	+2
		25,000	25,200	+1
		25,000	24,800	–1
		50,000	51,400	+3
		50,000	49,500	–1
		50,000	51,400	+3
		50,000	49,400	–1

TABLE H4
Results of Analysis of Dose Formulations for Rats and Mice in the 2-Year Feed Studies of C.I. Pigment Red 23 (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Percent Difference from Target
28 February 1984	28-29 February 1984	10,000	9,860	–1
		10,000	9,740	–3
		10,000	10,100	+1
		25,000	25,000	0
		25,000	24,800	–1
		25,000	25,100	0
		50,000	50,000	0
		50,000	50,000	0
		50,000	49,600	–1
		50,000	50,000	0
24 April 1984	25 April 1984	10,000	10,200	+2
		10,000	9,960	0
		10,000	10,000	0
		10,000	10,200	+2
		25,000	25,000	0
		25,000	24,900	0
		25,000	25,200	+1
		25,000	25,800	+3
		50,000	51,200	+2
		50,000	49,700	–1
		50,000	49,400	–1
		50,000	49,100	–2
5 June 1984	6 June 1984	10,000	10,800	+8
		10,000	10,200	+2
		10,000	10,100	+1
		25,000	25,200	+1
		25,000	24,500	–2
		25,000	24,800	–1
		25,000	24,600	–2
		50,000	49,000	–2
		50,000	52,400	+5
		50,000	48,800	–2
		50,000	51,600	+3
17 July 1984	18 July 1984	10,000	9,880	–1
		10,000	9,890	–1
		10,000	9,780	–2
		25,000	25,200	+1
		25,000	25,400	+2
		25,000	24,800	–1
		25,000	25,100	0
		50,000	51,100	+2
		50,000	51,400	+3
		50,000	51,200	+2
		50,000	49,000	–2

TABLE H4
Results of Analysis of Dose Formulations for Rats and Mice in the 2-Year Feed Studies of C.I. Pigment Red 23 (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Percent Difference from Target
18 September 1984	18-19 September 1984	10,000	10,300	+3
		10,000	9,480	–5
		10,000	9,460	–5
		25,000	24,000	–4
		25,000	23,900	–4
		25,000	24,200	–3
		25,000	24,000	–4
		50,000	47,800	–4
		50,000	48,500	–3
		50,000	47,300	–5
		50,000	47,300	–5
20 November 1984	20-21 November 1984	10,000	9,540	–5
		10,000	9,480	–5
		10,000	9,940	–1
		25,000	24,400	–2
		25,000	24,700	–1
		25,000	24,900	0
		50,000	51,800	+4
		50,000	51,200	+2
		50,000	50,600	+1

[a] Results of duplicate analyses
[b] Samples prepared on 3 and 9 December 1982 used for dosing mice only
[c] Sample remixed
[d] Results of remix

TABLE H5
Results of Referee Analysis of Dose Formulations in the 13-Week and 2-Year Feed Studies of C.I. Pigment Red 23

Date Prepared	Target Concentration	Determined Concentration (ppm)	
		Study Laboratory[a]	Referee Laboratory[b]
13-Week Studies			
7 December 1981	50,000	49,033	56,400
2-Year Studies			
3 December 1982	10,000	9,390	10,800
22 March 1983	50,000	53,150	50,500
6 September 1983	25,000	25,033	23,900
28 February 1984	50,000	49,900	51,100
17 July 1984	10,000	9,850	11,200
20 November 1984	10,000	9,653	10,200

[a] Results of duplicate analyses
[b] Results of triplicate analyses

APPENDIX I
FEED AND COMPOUND CONSUMPTION

TABLE I1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of C.I. Pigment Red 23

	0 ppm		10,000 ppm			25,000 ppm			50,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b]	Feed (g/day)	Body Weight (g)	Dose/ Day	Feed (g/day)	Body Weight (g)	Dose/ Day
2	16.9	208	18.7	209	895	19.2	211	2,272	18.1	207	4,380
3	18.9	233	19.0	233	815	19.0	235	2,030	18.8	232	4,048
5	17.9	269	19.3	263	734	18.5	268	1,728	18.0	266	3,391
6	18.1	284	19.5	284	685	18.6	286	1,629	19.5	282	3,463
9	17.7	326	17.8	321	553	18.3	323	1,413	17.5	319	2,744
10	17.3	334	17.0	333	512	17.5	333	1,311	17.9	330	2,715
13	18.9	364	19.0	360	528	18.8	359	1,313	18.6	356	2,617
17	20.3	388	18.5	390	475	17.6	390	1,132	17.8	382	2,326
21	17.7	401	21.2	391	542	21.6	390	1,382	18.0	388	2,316
25	18.3	421	19.3	411	470	19.1	408	1,167	19.8	407	2,433
29	17.9	434	18.2	431	423	17.9	430	1,044	17.2	423	2,031
33	19.2	442	18.7	440	425	18.3	436	1,049	18.7	431	2,174
37	19.8	447	19.8	450	440	18.6	443	1,051	19.0	433	2,196
41	19.1	455	18.5	455	406	18.7	453	1,031	18.8	444	2,113
45	19.8	459	20.2	462	437	19.8	456	1,083	18.5	452	2,044
49	19.9	463	19.9	465	428	20.2	461	1,092	18.4	454	2,031
53	18.5	475	20.1	473	424	19.5	469	1,038	19.2	458	2,100
57	13.2	452	13.0	456	286	12.6	453	694	12.7	448	1,419
61	18.7	482	18.7	482	388	18.3	478	959	18.1	468	1,934
65	17.7	483	16.7	480	347	17.4	478	911	17.0	472	1,799
69	17.9	478	17.5	485	360	17.4	479	911	17.9	469	1,906
73	16.2	479	15.6	481	325	16.7	480	870	16.8	473	1,780
77	15.1	467	14.8	467	318	15.1	463	817	14.9	458	1,624
81	14.9	456	15.0	459	327	14.8	454	816	15.1	443	1,702
85	15.4	463	15.7	456	345	15.8	447	882	15.2	439	1,736
89	14.2	456	15.3	447	342	15.0	444	847	16.0	435	1,843
93	15.3	445	15.3	437	350	14.6	435	837	17.3	429	2,022
97	13.9	425	14.0	422	332	14.5	423	856	14.3	418	1,710
101	14.5	431	13.9	415	335	14.5	416	871	14.8	408	1,813
Mean for weeks											
1-13	18.0	288	18.6	286	675	18.6	288	1,671	18.4	285	3,337
14-52	19.1	434	19.4	433	450	19.1	430	1,115	18.5	424	2,185
53-101	15.8	461	15.8	459	345	15.9	455	870	16.1	448	1,799

[a] Grams of feed consumed per animal per day
[b] Estimated milligrams of C.I. Pigment Red 23 consumed per day per kilogram of body weight

TABLE I2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of C.I. Pigment Red 23

	0 ppm		10,000 ppm			25,000 ppm			50,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b]	Feed (g/day)	Body Weight (g)	Dose/ Day	Feed (g/day)	Body Weight (g)	Dose/ Day
2	14.7	147	14.5	145	1,001	14.0	145	2,430	13.2	144	4,561
3	17.7	158	17.0	155	1,097	17.2	155	2,774	15.6	154	5,041
5	12.8	171	13.6	168	805	13.7	169	2,030	12.4	167	3,711
6	16.8	178	16.0	177	903	18.7	176	2,643	17.7	174	5,086
9	13.8	194	13.5	192	704	13.6	189	1,801	13.3	189	3,513
10	16.0	196	13.8	197	699	15.7	196	2,007	16.7	193	4,338
13	14.4	208	14.5	205	709	14.1	203	1,741	13.9	202	3,437
17	13.6	219	13.2	217	607	13.2	214	1,540	12.8	211	3,025
21	12.9	221	13.2	220	604	13.0	215	1,509	12.9	211	3,060
25	12.3	231	12.2	224	544	12.1	221	1,369	12.2	220	2,773
29	12.3	241	13.3	233	573	12.8	228	1,401	12.5	226	2,772
33	12.1	246	12.6	236	535	12.5	232	1,345	12.0	229	2,621
37	12.8	255	13.0	247	524	12.7	239	1,325	12.5	235	2,667
41	13.2	260	13.2	253	522	12.8	245	1,310	12.9	239	2,691
45	13.3	268	13.2	260	507	13.3	251	1,329	12.7	245	2,587
49	13.6	277	13.4	265	506	13.1	255	1,280	13.2	250	2,642
53	13.3	291	15.0	284	530	15.0	271	1,380	13.9	265	2,619
57	13.6	306	12.9	296	436	13.4	283	1,183	13.1	277	2,364
61	14.3	319	14.1	312	452	13.8	295	1,167	13.8	288	2,391
65	13.1	327	12.6	319	396	12.4	303	1,022	12.6	295	2,138
69	13.3	339	13.3	326	407	13.3	316	1,055	13.1	308	2,129
73	12.9	341	12.6	332	379	12.2	323	942	12.8	315	2,034
77	12.4	348	13.0	335	388	12.7	325	978	13.2	316	2,098
81	12.4	349	12.7	335	380	12.3	329	935	12.9	319	2,018
85	12.9	357	11.9	343	348	12.6	333	950	12.6	324	1,940
89	12.8	358	12.6	344	367	12.0	334	899	12.0	328	1,827
93	12.0	357	12.6	343	366	12.8	332	964	12.2	325	1,876
97	11.3	354	11.4	344	331	11.1	330	838	11.6	325	1,778
101	12.3	355	11.9	343	348	12.4	333	931	12.8	328	1,946
Mean for weeks											
1-13	15.2	179	14.7	177	846	15.3	176	2,204	14.7	175	4,241
14-52	12.9	247	13.0	239	547	12.8	233	1,379	12.6	229	2,760
53-101	12.8	338	12.8	327	395	12.8	316	1,019	12.8	309	2,089

[a] Grams of feed consumed per animal per day
[b] Estimated milligrams of C.I. Pigment Red 23 consumed per day per kilogram of body weight

TABLE I3
Feed and Compound Consumption by Male Mice in the 2-Year Feed Studies of C.I. Pigment Red 23

	0 ppm		10,000 ppm			25,000 ppm			50,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b]	Feed (g/day)	Body Weight (g)	Dose/ Day	Feed (g/day)	Body Weight (g)	Dose/ Day
2	5.5	27.6	6.0	27.9	2,142	6.1	28.1	5,407	6.4	28.0	11,419
3	7.3	28.1	7.0	28.3	2,463	7.6	28.5	6,672	7.4	28.5	13,034
6	8.0	29.9	9.2	29.9	3,081	8.3	30.1	6,920	8.9	31.2	14,214
7	9.1	29.4	8.8	30.9	2,861	8.9	30.9	7,173	8.4	31.2	13,478
10	8.4	32.6	8.8	32.0	2,738	8.5	32.7	6,511	9.2	33.0	13,958
12	7.6	32.6	8.6	32.6	2,635	8.2	32.3	6,344	8.4	32.8	12,791
16	6.8	33.9	7.5	33.3	2,239	7.2	33.9	5,322	8.0	33.8	11,774
20	7.8	35.9	9.6	35.3	2,707	8.1	35.9	5,647	8.8	34.9	12,618
25	7.6	36.8	8.6	35.8	2,404	7.5	36.6	5,114	8.1	35.9	11,350
28	9.1	37.2	11.3	36.7	3,085	10.2	37.3	6,808	11.2	36.8	15,278
32	9.3	38.1	11.1	37.7	2,952	9.8	38.5	6,343	11.1	37.8	14,651
36	8.6	39.3	11.3	38.2	2,965	9.3	39.2	5,947	11.0	37.4	14,732
40	6.0	38.8	6.2	37.7	1,656	6.1	38.0	3,984	7.1	37.6	9,433
44	5.3	38.9	5.9	37.8	1,562	5.3	38.3	3,481	5.9	37.5	7,915
48	5.4	38.5	5.6	38.6	1,444	5.6	38.4	3,644	5.6	37.8	7,343
52	5.5	38.2	6.1	38.5	1,583	5.3	38.9	3,389	6.2	38.2	8,123
56	6.2	37.7	6.4	38.3	1,681	6.3	37.2	4,232	6.3	37.7	8,371
60	6.3	39.7	6.9	39.1	1,768	7.0	38.9	4,498	6.1	38.7	7,866
64	6.1	40.6	6.9	41.2	1,679	5.7	40.1	3,582	5.8	39.1	7,367
68	5.6	39.6	6.7	40.3	1,653	5.0	39.5	3,179	5.4	39.4	6,903
72	4.2	39.5	4.5	40.0	1,137	4.3	39.2	2,770	4.6	39.2	5,844
77	4.7	40.1	4.7	40.3	1,154	4.9	40.1	3,044	4.9	39.2	6,262
80	4.4	40.2	4.7	39.3	1,197	4.8	39.2	3,079	4.6	39.0	5,929
84	4.5	39.6	4.6	40.0	1,156	4.9	39.8	3,058	4.9	38.7	6,379
88	4.7	39.5	4.8	38.6	1,255	4.8	38.7	3,090	4.9	38.0	6,436
92	4.5	38.8	4.7	38.2	1,237	4.6	38.2	2,992	4.9	37.4	6,528
96	4.3	38.5	4.6	37.8	1,224	4.6	37.5	3,045	4.4	37.0	6,002
100	3.7	37.5	4.3	37.3	1,144	4.6	37.0	3,100	4.5	36.6	6,158
Mean for weeks											
1-13	7.7	30.0	8.1	30.3	2,653	7.9	30.4	6,505	8.1	30.8	13,149
14-52	7.1	37.6	8.3	37.0	2,260	7.4	37.5	4,968	8.3	36.8	11,322
53-104	4.9	39.3	5.3	39.2	1,357	5.1	38.8	3,306	5.1	38.3	6,670

[a] Grams of feed consumed per animal per day
[b] Estimated milligrams of C.I. Pigment Red 23 consumed per day per kilogram of body weight

TABLE I4
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of C.I. Pigment Red 23

	0 ppm		10,000 ppm			25,000 ppm			50,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b]	Feed (g/day)	Body Weight (g)	Dose/ Day	Feed (g/day)	Body Weight (g)	Dose/ Day
2	5.8	20.8	6.4	20.6	3,099	6.2	20.4	7,561	6.7	20.6	16,141
3	7.2	20.9	7.4	21.3	3,467	7.8	21.2	9,245	8.2	21.2	19,369
6	8.6	23.4	9.7	23.6	4,123	9.0	23.4	9,648	9.7	23.7	20,457
7	7.7	23.4	7.7	23.6	3,248	7.8	23.4	8,314	7.7	23.0	16,754
10	8.4	24.1	8.6	24.8	3,484	8.5	24.1	8,831	8.8	24.7	17,769
11	7.7	25.2	11.1	25.0	4,447	12.4	24.8	12,548	8.7	25.1	17,303
12	6.7	25.3	7.7	25.6	3,000	7.4	25.3	7,278	7.0	25.2	13,982
16	5.8	27.2	5.8	27.1	2,156	5.7	26.7	5,362	5.0	26.5	9,507
20	6.1	28.9	7.4	28.5	2,592	7.0	28.0	6,216	6.7	28.1	11,833
25	6.7	29.7	6.9	28.6	2,406	6.3	28.9	5,481	6.7	28.1	11,930
28	7.6	30.5	7.6	30.2	2,509	6.8	29.8	5,744	8.1	29.7	13,599
32	7.1	32.8	8.0	33.1	2,428	7.7	31.7	6,050	8.6	31.5	13,584
36	6.8	34.3	7.2	33.4	2,148	6.6	32.2	5,150	8.0	32.2	12,472
40	7.2	33.6	7.0	34.5	2,019	6.5	33.9	4,761	7.2	32.7	10,960
44	5.2	35.0	5.4	34.7	1,550	5.3	34.0	3,874	5.5	33.7	8,199
48	5.5	36.4	5.3	37.8	1,403	5.6	35.6	3,930	5.9	34.5	8,560
52	6.0	38.5	6.1	38.6	1,568	6.0	37.4	4,043	7.7	36.9	10,396
56	7.1	37.8	7.0	38.7	1,798	5.9	37.0	3,995	7.4	36.8	10,076
60	5.6	39.1	6.8	39.7	1,706	6.1	38.7	3,919	6.4	38.3	8,292
64	6.8	41.8	7.2	42.4	1,701	6.4	40.9	3,919	7.9	40.5	9,703
68	5.0	42.8	6.1	42.7	1,420	5.3	42.0	3,179	6.0	41.1	7,317
72	3.8	41.7	3.8	41.4	920	3.9	41.7	2,330	3.8	39.8	4,785
77	4.4	41.4	4.5	40.7	1,115	4.7	41.3	2,816	4.5	39.3	5,728
80	4.6	42.0	4.7	40.4	1,176	4.8	40.9	2,911	4.6	39.1	5,922
88	5.6	43.5	5.6	42.4	1,327	6.2	42.2	3,666	5.8	40.9	7,070
92	6.1	43.6	6.7	42.5	1,581	6.7	41.7	4,011	6.2	41.1	7,536
96	5.3	42.1	5.6	41.1	1,359	5.6	39.9	3,497	5.8	39.7	7,341
100	4.9	40.7	5.3	39.4	1,335	5.2	38.9	3,320	5.1	38.9	6,620
Mean for weeks											
1-13	7.4	23.3	8.4	23.5	3,553	8.4	23.2	9,060	8.1	23.4	17,397
14-52	6.4	32.7	6.7	32.7	2,078	6.4	31.8	5,061	6.9	31.4	11,104
53-104	5.4	41.5	5.8	41.0	1,403	5.5	40.5	3,415	5.8	39.6	7,308

[a] Grams of feed consumed per animal per day
[b] Estimated milligrams of C.I. Pigment Red 23 consumed per day per kilogram of 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	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

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

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

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

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

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

Nutrient	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
Phenylalinine	0.987 ± 0.140	0.665–1.110	8
Threonine	0.877 ± 0.042	0.824–0.940	8
Tryptophan	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 ± 9.406	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 (%)	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

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

	Mean ± Standard Deviation[a]	Range	Number of Samples
Contaminants			
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	3.00–2,400	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-Nitrosodimethylamine (ppb)[f]	5.39 ± 5.96	0.50–30.00	25
N-Nitrosopyrrolidine (ppb)[f]	0.66 ± 0.71	0.30–2.70	25
Pesticides (ppm)			
α-BHC[g]	<0.01		25
β-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

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

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] Four batches, milled 22 February 1984, 14 March 1984, 9 May 1984, and 13 June 1984, 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 = 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. Under this program, the disease state of the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals are untreated, and these animals and the study animals are subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Rats

During the 13-week studies, five F344 rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. At the termination of the 13-week studies, the animals were bled. Blood collected from each animal was allowed to clot, and the sera were separated, cooled on ice, and shipped to Microbiological Associates, Inc. (Bethesda, MD) for determination of the antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
PVM (pneumonia 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 rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Samples for viral screening at 24 months were collected from five diet control animals of each sex. Blood collected from each animal was allowed to clot, and the sera were separated, cooled on ice, and shipped to Microbiological Associates, Inc. (Bethesda, MD) for determination of the antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
PVM	6, 12, and 18 months
Sendai	6, 12, and 18 months
KRV	6, 12, 18, and 24 months
H-1	6, 12, 18, and 24 months
ELISA	
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
PVM	24 months
Sendai	24 months

Test results are presented in Table K1.

Mice

During the 13-week studies, five B6C3F$_1$ mice of each sex were selected at the time of randomization and allocation of the animals to the various study groups. At the termination of the 13-week studies, the male animals were bled. Female mice were reserved for a special disease screening performed as a result of health problems occurring in other studies. Blood collected from each animal was allowed to clot, and the serum were separated, cooled on ice, and shipped to Microbiological Associates, Inc. (Bethesda, MD) for determination of the 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 of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Samples for viral screening at 24 months were collected from five diet control animals of each sex. Blood collected from each animal was allowed to clot, and the sera were separated, cooled on ice, and shipped to Microbiological Associates, Inc. (Bethesda, MD) for determination of the antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
PVM	6, 12, and 18 months
Reovirus 3	6, 12, and 18 months
GDVII	6 and 12 months
Polyoma virus	6, 12, 18, and 24 months
Sendai	6, 12, and 18 months
MVM	6, 12, 18, and 24 months
Ectromelia virus	6, 12, and 18 months

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

Test results are presented in Table K1.

TABLE K1
Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Feed Studies of C.I. Pigment Red 23

	Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-Week Studies			
Rats	13 weeks	0/4	–
Mice	13 weeks	0/5	–
2-Year Studies			
Rats	6 months	0/10	–
	12 months	0/10	–
	18 months	0/10	–
	24 months	0/10	–
Mice	6 months	0/10	–[a]
	12 months	0/8	–
	18 months	0/9	–
	24 months	1/10	*M. arthritidis*[b]

[a] One serum reacted with the control antigen in the LCM test, and was unreadable at a 20-fold dilution but negative at a 40-fold dilution. The serum was equivocal for *Mycoplasma pulmonis*; further evaluation of this assay indicated that it was not specific for *M. pulmonis*, and these results were considered to be false positive.

[b] Possible *Mycoplasma arthritidis*. Three sera in the Reovirus 3 test and one serum in the MHV test reacted with the control antigen.

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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	Trichlorethylene (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)
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) phosponium 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 Pariffins (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

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TR No.	CHEMICAL
336	Penicillin VK
337	Nitrofurazone
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	α-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
385	Methyl Bromide
386	Tetranitromethane
387	Amphetamine Sulfate
388	Ethylene Thiourea
389	Sodium Azide
390	3,3′-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
392	Chlorinated Water and Chloraminated Water
393	Sodium Fluoride
395	Probenecid
396	Monochloroacetic Acid
397	C.I. Direct Blue 15
399	Titanocene Dichloride
401	2,4-Diaminophenol Dihydrochloride
403	Resorcinol
405	C.I. Acid Red 114
406	γ-Butyrolactone
407	C.I. Pigment Red 3
409	Quercetin
410	Naphthalene
412	4,4-Diamino-2,2-Stilbenedisulfonic Acid
415	Polysorbate 80
419	HC Hellow 4

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