NATIONAL TOXICOLOGY PROGRAM Technical Report Series No. 419



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# TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

HC YELLOW 4

(CAS NO. 59820-43-8)

IN F344/N RATS AND B6C3F1 MICE

(FEED STUDIES)

U.S. DEPARTMIENT OF HIEALTH 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

## $\mathbb{ON} \ \mathbb{THE}$

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

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# CONTENTS

ABSTRACT	• • • • • • • • • • • • • • • • • • • •	5
EXPLANATION	OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY	8
technical r	EPORTS REVIEW SUBCOMMITTEE	Ð
summary of	TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS	10
INTRODUCTIO	DN	11
materials a	ND METHODS	13
RESULTS	· · · · · · · · · · · · · · · · · · ·	21
DISCUSSION A	AND CONCLUSIONS	45
REFERENCES		49
Appendix A	Summary of Lesions in Male Rats in the 2-Year Feed Study of HC Yellow 4	53
Appendix B	Summary of Lesions in Female Rats in the 2-Year Feed Study of HC Yellow 4	85
Appendix C	Summary of Lesions in Male Mice in the 2-Year Feed Study of HC Yellow 4	117
Appendix D	Summary of Lesions in Female Mice in the 2-Year Feed Study of HC Yellow 4	147
Appendix E	Genetic Toxicology	175
Appendix F	Organ Weights and Organ-Weight-to-Body-Weight Ratios	183
Appendix G	Hematology and Clinical Chemistry Results	191
Appendix H	Chemical Characterization and Dose Formulation Studies	199
Appendix I	Feed and Compound Consumption in the 2-Year Feed Studies	211
Appendix J	Ingredients, Nutrient Composition, and Contaminant Levels in NIH-07 Rat and Mouse Ration	217
Appendix K	Sentinel Animal Program	223

3

## ABSTRACT



CAS No. 59820-43-8

Chemical Formula:  $C_{10}H_{14}N_2O_5$  Molecular Weight: 242.2

Synonym: N,O-di(2-hydroxyethyl)-2-amino-5-nitrophenol

HC Yellow 4 is used in semipermanent hair dyes. Toxicology and carcinogenesis studies were conducted by administering HC Yellow 4 (greater than 93% pure) in feed to groups of F344/N rats and B6C3F<sub>1</sub> mice of each sex for 14 days, 13 weeks, and 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, and *Drosophila melanogaster*.

14-Day Studies: Groups of five rats of each sex were given 0, 5,000, 10,000, 20,000, 40,000, or 80,000 ppm and groups of five mice of each sex were given 0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm HC Yellow 4 in feed for 14 days. All animals survived to the end of the studies. Final mean body weights of male rats that received 20,000 ppm or more, female rats that received 10,000 ppm or more, and female mice that received 20,000 ppm were significantly lower than those of the controls. The mean body weights of exposed and control groups of male mice were similar. No chemical-related decrease in feed consumption was observed. No chemical-related clinical findings or changes in absolute or relative organ weights occurred in rats or mice. No gross or microscopic changes were related to HC Yellow 4 administration in rats or mice.

13-Week Studies: Groups of 10 rats of each sex were fed diets containing 0, 2,500, 5,000, 10,000, 20,000, or 40,000 ppm and groups of 10 mice of each sex were fed diets containing 0, 5,000, 10,000, 20,000, 40,000, or 80,000 ppm HC Yellow 4 for 13 weeks. All rats survived to study termination. Chemical-related deaths occurred at the two highest dose levels in male and female mice. Final mean body weights of male rats that received 10,000 ppm or greater, female rats that received 20,000 or 40,000 ppm, and mice that received 10,000 ppm or greater were significantly lower than those of the controls. There were no biologically significant changes in absolute or relative organ weights. Mineralization of the renal papilla occurred in all male rats in the 40,000 ppm group. Thyroid pigmentation occurred in rats receiving 40,000 ppm and in mice at all dose levels. Uterine atrophy occurred in female rats in the 20,000 and 40,000 ppm groups and female mice in the 40,000 and 80,000 ppm groups. Lymphoid depletion and atrophy of the spleen occurred in male mice that received 40,000 or 80,000 ppm and female mice that received 80,000 ppm. Atrophy of the thymus occurred in male and female mice that received 40,000 or 80,000 ppm.

2-Year Studies: Groups of 70 male rats were fed diets containing 0, 2,500, or 5,000 ppm and groups of 70 female rats and 70 mice of each sex were fed diets containing 0, 5,000, or 10,000 ppm HC Yellow 4 for up to 2 years. Interim evaluations were performed on 10 rats and 10 mice from each dose group at 6 and 15 months. No biologically significant changes in absolute or relative organ weight or hematology or clinical chemistry values were found in these rats or mice. No compoundrelated lesions were seen in exposed rats. In exposed mice, pigmentation of the thyroid gland was observed at the 6-month interim evaluations; pigmentation and hyperplasia of the thyroid gland were seen at the 15-month interim evaluations.

Body Weight, Survival, and Feed Consumption in the 2-Year Studies: The mean body weight of female rats that received 10,000 ppm was significantly lower than that of the controls. The mean body weights of mice receiving 10,000 ppm were 20% to 30% lower than those of the controls during the second year of the studies. The survival of exposed rats and mice was similar to that of the controls.

Neoplasms and Nonneoplastic Lesions in the 2-Year Studies: Pituitary gland pars distalis adenomas were marginally increased in exposed male rats (0 ppm, 17/45; 2,500 ppm, 20/49; 5,000 ppm, 28/49), and there was a concomitant dose-related increase in the incidence of hyperplasia (8/45, 13/49, 18/49). There was no increase in the incidence of pituitary gland adenomas or carcinomas in female rats (34/49, 35/48, 30/49).

In mice, no neoplasms were considered related to chemical administration. However, a dose-related

increased incidence of thyroid gland pigmentation and follicular cell hyperplasia occurred in both sexes of mice.

Genetic Toxicology: HC Yellow 4 was mutagenic in Salmonella typhimurium strains TA100, TA1537, and TA98 with and without exogenous metabolic activation (S9); the response in strain TA1535 without S9 was equivocal. HC Yellow 4 induced sister chromatid exchanges in Chinese hamster ovary cells in the absence but not the presence of S9 activation; no induction of chromosomal aberrations occurred in Chinese hamster ovary cells, with or without S9. HC Yellow 4 induced sex-linked recessive lethal mutations in germ cells of adult male Drosophila melanogaster when administered by injection; results of a reciprocal translocation test in D. melanogaster were negative.

Conclusions: Under the conditions of these 2-year feed studies, there was equivocal evidence of carcinogenic activity\* of HC Yellow 4 in male F344/N rats based on the increased incidence of pituitary gland adenomas and hyperplasia. The male rats may have been able to tolerate a slightly higher dose of the chemical. There was no evidence of carcinogenic activity of HC Yellow 4 in female F344/N rats given 5,000 or 10,000 ppm. There was no evidence of carcinogenic activity of HC Yellow 4 in male or female B6C3F<sub>1</sub> mice given 5,000 or 10,000 ppm.

There was a chemical-related increase in the incidence of thyroid gland pigmentation and follicular cell hyperplasia in mice.

Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 10.

Male F344/N Rats	Female F344,	/N Rats	Male B6C3F <sub>1</sub> Mice	Female B6C3F <sub>1</sub> Mice	
Doses 0, 2,500, or 5,000 ppm in feed	0, 5,000, or 10 in feed	,000 ррт	0, 5,000, or 10,000 ppm in feed	0, 5,000, or 10,000 ppm in feed	
Body weights Dosed groups similar to controls	High-dose grout than controls	ip lower	Dosed groups lower than controls	Dosed groups lower than controls	
2-Year survival rates 21/50, 29/50, 28/50	27/50, 31/50, 3	4/50	28/50, 29/50, 35/50	43/50, 38/50, 43/50	
Nonneoplastic effects None	None		Thyroid gland: follicular cell pigmentation (0/47, 44/48, 49/49), follicular cell hyperplasia (0/47, 27/48, 41/49)	Thyroid gland: follicular cell pigmentation (0/48, 49/49, 50/50), follicular cell hyperplasia (0/48, 3/49, 13/50)	
Neoplastic effects None	None		None	None	
Uncertain findings Pituitary gland pars distalis: adenoma (17/45, 20/49, 28/49), hyperplasia (8/45, 13/49, 18/49)	None		None	None	
Level of evidence of carcinoger	nic activity		No evidence	No evidence	
Genetic toxicology Salmonella typhimurium gene mutation:		Positive with and without S9 in strains TA100, TA1537, and TA98; equivocal without S9 in strain TA1535			
Chinese hamster ovary cells in vi Chromosomal aberrations	itro:	Negative with S9, p	positive without S9		
Chinese hamster ovary cells in vi Sex-linked recessive lethal mutation	itro: 18	Negative with and	without S9		
Drosophila melanogaster: Reciprocal translations Drosophila melanogaster:		Positive by injection Negative	n; negative by feeding		

Summary of the 2-Year Carcinogenicity and Genetic Toxicology Studies of HC Yellow 4

## **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.

### NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on HC Yellow 4, NTP TR 419 on 9 July 1991 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, panel members have five major responsibilities in reviewing NTP studies:

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

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9

### SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 9 July 1991, the draft Technical Report on the toxicology and carcinogenesis studies of HC Yellow 4 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. J.K. Dunnick, NIEHS, introduced the toxicology and carcinogenesis studies of HC Yellow 4 by discussing the uses, describing the experimental design, reporting on survival and body weight effects, and commenting on neoplastic and nonneoplastic lesions in male rats and in mice. The proposed conclusions were *equivocal evidence of carcinogenic activity* of HC Yellow 4 in male rats and *no evidence of carcinogenic activity* of HC Yellow 4 in female rats and male and female mice.

Dr. Zeise, a principal reviewer, agreed in principle with the proposed conclusions. She thought the conclusions should note that male and female rats could have tolerated significantly higher doses. Dr. Zeise said that the increased incidence of uterine stromal polyps in female rats should be considered "may have been related to chemical administration," unless there are better reasons for discounting them than that the incidence in treated animals falls within the range of overall NTP historical controls. Dr. Dunnick commented that more historical control data would be added and that there were no supporting nonneoplastic effects, providing further evidence that these lesions probably were not chemical related. Dr. J.K. Haseman, NIEHS, added that the rate of uterine polyps in the high-dose group was similar to the historical control mean from previous studies at this laboratory. Further, based on the results of previous NCI/NTP studies, it would be unusual for a chemical to induce only uterine polyps.

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

Dr. Garman, the third principal reviewer, agreed with the proposed conclusions. Because of the prominent chemical-related increased frequency of thyroid follicular cell hyperplasia in the 2-year studies in mice, he thought it appropriate to add frequency figures to the summary table in the Abstract.

Dr. Zeise moved that the Technical Report on HC Yellow 4 be accepted with the revisions discussed and with the conclusions as written, equivocal evidence of carcinogenic activity in male rats and no evidence of carcinogenic activity in female rats and male and female mice, and with the addition of a statement that "male and female rats may have been able to tolerate higher doses." Dr. Garman seconded the motion. Dr. Goodman offered an amendment that the added statement be removed. Dr. Klaassen seconded the amendment, which was accepted by seven yes to three no votes (Drs. Carlson, McKnight, and Zeise). Dr. McKnight offered an amendment to add a statement to the conclusions that "male rats may have been able to tolerate a higher dose." Dr. Zeise seconded the amendment, which was accepted by seven yes to three no votes (Mr. Beliczky and Drs. Goodman and Hayden). Dr. Zeise's amended motion was then accepted unanimously with ten votes.

## INTRODUCTION



HC YELLOW 4

CAS No. 59820-43-8

Chemical Formula: C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>5</sub> Molecular Weight: 242.2

Symomyum: N,O-di(2-hydroxyethyl)-2-amino-5-nitrophenol

## Chemical and Physical Properties, Production, Use, and Exposure

HC Yellow 4, a semipermanent dye, is a fluffy, yellow powder with a melting point of 145° to 147° C. HC Yellow 4 is used as an ingredient in hair dyes at concentrations ranging from 0.1% to 1.0% (USFDA, 1975, 1976). Production of HC Yellow 4 in the United States was estimated to be 2.3 x 10<sup>6</sup> g in 1976. The dye was not produced commercially in the United States in 1979 (HSDB, 1990). Human exposure is believed to occur primarily in department stores and beauty shops. An estimated 4,000 workers were exposed in 1974 (NIOSH, 1990). This estimate does not appear to include the general public and may be low for the cosmetology industry. No more recent information on occupational exposure to this dye was found.

Confusion has existed over the structure of HC Yellow 4. In the second edition of the Cosmetic, Toiletry and Fragrance Association's Cosmetic Ingredient Dictionary, the structure was shown with both hydroxyethyl groups on the amine and an assigned Chemical Abstracts Service number of 52551-67-4 (CTFA, 1977). Subsequently, based on additional analysis, the structure was corrected in the third edition to show one hydroxyethyl group on the amine and the other on the phenol. The Chemical Abstracts Service number for this structure is 59820-43-8. Analysis of the chemical used in these studies confirmed that the chemical has the structure given in the third edition of the Cosmetic Ingredient Dictionary (CTFA, 1982).

## Toxicity and Metabolism in Animals

The oral  $LD_{50}$  for rats is presumed to be greater than 1.2 g/kg, although specific data are not available (Wernick et al., 1975). In eye irritation tests of a composite mixture of hair dyes that included HC Yellow 4, a slight, transient conjunctival erythema was noted in rabbits (Draize, 1959). Percutaneous application of HC Yellow 4 to rabbits caused a mild epidermal irritation but no systemic toxicity (Burnett et al., 1976). In teratology and reproduction studies, a composite mixture of dyes that included HC Yellow 4 was given to rats dermally or as a dietary admixture and was given to rabbits by gavage. The dye mixture did not cause any teratogenic or toxic effects. In a 2-year feed study, a composite dye mixture that contained 0.31% HC Yellow 4 (an equivalent of 0.05 or 0.3 mg HC Yellow 4 per kg body weight per day) was given to purebred beagle dogs. No gross or microscopic changes that could be attributed to dye mixture

administration were observed (Wernick *et al.*, 1975). These studies were considered inadequate to assess the toxicologic or carcinogenic potential of HC Yellow 4 because the doses were low, the tests were not lifetime studies, and mixtures of dyes were used. No information was found on the metabolism of HC Yellow 4.

## TOXICITY AND CARCINOGENICITY IN HUMANS

No information or epidemiological evidence on the toxicity or the carcinogenicity of HC Yellow 4 in humans was found in the literature. Dark urine, indicative of dermal absorption, has been reported occasionally by women using the dye (Wernick *et al.*, 1975).

### **GENETIC TOXICITY**

No genotoxicity data were available for HC Yellow 4 other than the NTP-sponsored tests reported in Appendix E of this report. HC Yellow 4 has been shown to be mutagenic in *Salmonella typhimurium*, with and without S9 activation (Table E1; Mortelmans *et al.*, 1986). Administered by injection, the dye induced sex-linked recessive lethal mutations in germ cells of adult male *Drosophila melanogaster* (Table E4; Woodruff *et al.*, 1985). However, results of a reciprocal translocation test in *D. melanogaster* were negative (Table E5; Woodruff *et al.*, 1985).

#### STUDY RATIONALE

HC Yellow 4 is the last of six semipermanent hair dyes nominated by the Food and Drug Administration for toxicology and carcinogenicity assessment in a class study of hair color materials. The other dyes that have been studied and reported are HC Blue No. 1 (NTP, 1985a), HC Blue No. 2 (NTP, 1985b), C.I. Disperse Blue 1 (NTP, 1986a), HC Red No. 3 (NTP, 1986b), and C.I. Acid Orange 3 (NTP, 1988). HC Yellow 4 was recommended for testing because of the high potential for exposure of cosmetology industry workers and the general population through its use as a hair dye, lack of published toxicology data on this dye, and its possible enzymatic reduction to a potential tumor promoter, an aromatic N-hydroxy derivative. Although human exposure occurs primarily via the dermal route, the oral route was selected to ensure systemic exposure.

## MATERIALS AND MIETHODS

## PROCUREMENT AND CHARACTERIZATION

HC Yellow 4 was obtained from Southland Corporation (lots 0-218 and 3-074) and Prochimie International (lot 81031). Lot 0-218 was used for the 14-day and 13-week studies and for the first 11 months of the 2-year study. Lot 3-074 was used for the next 7 months of the 2-year study, and lot 81031 was used for the final 6 months. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO), and are described in Appendix H. The study chemical, a fluffy, yellow powder, was identified as HC Yellow 4 by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy.

Purity was determined by weight loss on drying, Karl Fischer water analysis, thin-layer chromatography, high-performance liquid chromatography, ultraviolet/ visible spectroscopy, titration, and elemental analysis. Lot 0-218 was greater than 93% pure, lot 3-074 was greater than 97% pure, and lot 81031 was greater than 98% pure. The largest impurity was tentatively N-(2-hydroxyethyl)-2-hydroxy-4identified as nitroaniline. The concentration of the impurity was determined to be 7% in lot 0-218, 2.5% in lot 3-074, and 0.3% in lot 81031. Stability studies performed by high-performance liquid chromatography indicated that HC Yellow 4 was stable as a bulk chemical for 2 weeks at temperatures up to 60° C when protected from light. To ensure stability, the bulk chemical was stored in the dark at 4° C throughout the studies. The stability of the bulk chemical was monitored periodically by highperformance liquid chromatography, titration, and infrared spectroscopy during all phases of the studies. No change in the dye was detected.

## Preparation and Analysis of Dose Formulations

The dose formulations were prepared by mixing HC Yellow 4 with feed (Table H1). Studies were conducted by the analytical chemistry laboratory to determine the homogeneity and stability of

10,000 ppm HC Yellow 4 in feed. Homogeneity was confirmed using an ultraviolet spectroscopic method for sample analysis; stability of the dose formulations for at least 14 days when stored in the dark at temperatures up to 25° C was confirmed using a high-performance liquid chromatographic method. During the 14-day and 13-week studies, the dose formulations were stored in the dark at  $0^{\circ} \pm 5^{\circ}$  C for no longer than 2 weeks. During the 2-year studies, the dose formulations were prepared weekly and stored protected from light at  $0^{\circ} \pm 5^{\circ}$  C for no longer than 2 weeks. The study laboratory conducted periodic analyses of the HC Yellow 4 dose formulations using ultraviolet spectroscopy as described in Appendix H. All dose formulations analyzed for the 14-day and 13-week studies were within 10% of the target concentrations (Tables H2 and H3). In the 2-year studies, the first set of dose formulations and one of every eight subsequent sets were analyzed and all were within 10% of the target concentrations (Table H4). Results of periodic referee analyses of the dose formulations performed by the analytical chemistry laboratory were in agreement with the results from the study laboratory (Table H5).

## 14-Day Studies

Male and female F344/N rats and B6C3F<sub>1</sub> mice were obtained from Charles River Breeding Laboratories (Kingston, NY) and observed for 13 to 15 days (rats) or 14 to 16 days (mice) before the studies began. Rats were 7 weeks old and mice were 8 weeks old when the studies began. Groups of five rats of each sex received feed with 0, 5,000, 10,000, 20,000, 40,000, or 80,000 ppm and groups of five mice of each sex received feed with 0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm HC Yellow 4 (Table 1). All groups received dosed feed for 14 days, followed by a 1-day observation period when the animals were given only undosed feed. Animals were housed five per cage; water and feed were available ad libitum. Animals were observed twice daily for signs of toxicity. Clinical observations were recorded on the day of necropsy. Animals were weighed at the start of the study, on

days 7 and 14, and at necropsy. Feed consumption per cage was determined weekly. Complete necropsies were performed on all animals. The brain, heart, right kidney, liver, lung, right testis, and thymus of survivors were weighed at necropsy. Histopathology was performed on selected tissues from all rats in the 0, 20,000, 40,000, and 80,000 ppm dose groups, and mice in the 20,000 ppm dose groups. Further experimental

## **13-WEEK STUDIES**

details are presented in Table 1.

The 13-week studies were conducted to determine the cumulative toxic effects of repeated exposure to HC Yellow 4 and to determine appropriate concentrations for use in the 2-year studies. The experimental design of the 13-week studies is summarized in Table 1.

Male and female F344/N rats and B6C3F<sub>1</sub> mice were obtained from Frederick Cancer Research Facility (Frederick, MD) and were observed for 13 to 14 days before the studies began. Rats were 7 to 8 weeks old and mice were 8 weeks old when the studies began. Groups of 10 rats of each sex were given 0, 2,500, 5,000, 10,000, 20,000, or 40,000 ppm HC Yellow 4 in feed 7 days a week for 13 weeks. Groups of 10 mice of each sex were given 0, 5,000, 10,000, 20,000, 40,000, or 80,000 ppm HC Yellow 4 in feed for 13 weeks. Animals were housed five per cage; water and feed were available ad libitum. Animals were observed twice each day and clinical observations were recorded daily. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix K). Animals were weighed at the start of the study and weekly Feed consumption per cage was thereafter. measured weekly. Further experimental details are presented in Table 1.

Necropsies were performed on all study animals. The brain, heart, right kidney, liver, lung, right testis, and thymus of survivors were weighed at necropsy. Complete histopathology was performed on all animals that died or were killed moribund prior to the end of the studies, all control animals, all rats that received 40,000 ppm, and all mice that received 80,000 ppm. Tissues examined for rats in the 2,500, 5,000, 10,000 and 20,000 ppm dose groups were the kidney, thyroid gland, and uterus. The thyroid gland was examined for mice in the 5,000, 10,000, 20,000, and 40,000 ppm dose groups. Additional information is provided in Table 1.

# 2-YEAR STUDIES

## Study Design

Groups of 70 rats and 70 mice of each sex were administered HC Yellow 4 in feed 7 days a week for up to 105 weeks. Male rats received doses of 0, 2,500, or 5,000 ppm; female rats and male and female mice received doses of 0, 5,000, or 10,000 ppm. After 6 months and again after 15 months of HC Yellow 4 administration, 10 rats and 10 mice of each sex were randomly selected from each group for interim evaluations.

#### Source and Specification of Animals

Male and female F344/N rats and B6C3F<sub>1</sub> mice were obtained from Frederick Cancer Research Facility for use in the 2-year studies. Rats were quarantined 14 days and mice were quarantined 13 to 14 days. Five rats and five mice of each sex were randomly selected and killed for parasite evaluation and gross observation of disease. Blood samples were collected for viral screens. Rats and mice were approximately 6 weeks old when the studies began. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix K).

#### Animal Maintenance

Rats and mice were initially housed five per cage. Male mice were housed individually beginning 27 July 1984 (15 months after the studies began). Feed and water were available *ad libitum*. Cages were rotated every 2 weeks during the studies. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix J.

#### **Clinical Examinations and Pathology**

All animals were observed twice daily and findings were recorded monthly or as necessary. Animals were weighed at the beginning of the studies, weekly for 13 weeks, and monthly thereafter. Feed consumption per cage was measured once a month (Appendix I).

Ten rats and 10 mice from each group were randomly selected after 6 months and again after 15 months of HC Yellow 4 administration for interim evaluations. Blood was drawn from the tail of rats and mice for hematology evaluations and from the external jugular of anesthetized animals for determining thyroid hormone levels. The brain, right kidney, and liver of each animal selected for the 15-month interim evaluations were weighed at necropsy. Further details of the interim evaluations are presented in Table 1.

Necropsies were performed on all animals. At necropsy, all organs and tissues were examined for gross lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Histopathologic examinations were performed on the thyroid gland of animals from the 6-month interim evaluations. At the 15-month interim evaluations, complete histopathology was performed on male rats that received 0 or 5,000 ppm, female rats that received 0 or 10,000 ppm, and male and female mice that received 0 or 10,000 ppm. Only gross lesions were examined in male rats receiving 2,500 ppm and female rats receiving 5,000 ppm; gross lesions and thyroid glands were examined in male and female mice that received 5,000 ppm. Complete histopathology was performed at the end of the studies on all animals that died or were killed moribund, all rats, and all control and high-dose mice. The thyroid gland and ovary of low-dose mice were examined. Tissues examined are listed in Table 1.

Upon completion of the microscopic evaluation by the study laboratory pathologist, the pathology data were entered into the Toxicology Data Management System. The microscope slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet-tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent pathology quality assessment laboratory. The liver, pancreas, and pituitary gland of male rats, the liver and uterus of female rats, the thyroid gland of male mice, and the thyroid gland and ovary of female mice were reviewed microscopically by the quality assessment pathologist for neoplasms or nonneoplastic lesions. All parathyroid glands of male rats in which hyperplasia or adenoma had been diagnosed were also reviewed.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the selected tissues and

any other tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative histopathology slides of the uterus, liver, male pituitary gland, male pancreas, and male parathyroid gland for rats and thyroid gland, ovary, mammary gland, and epididymis for mice; examples of disagreements in diagnosis between the laboratory and quality assessment pathologists; and lesions of general interest were presented by the chair to the PWG for review. The PWG consisted of 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 opinion of the PWG differed from that of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of contractor pathologists and the PWG. Details of these review procedures have been described by Maronpot and Boorman (1982) and Boorman et al. (1985). For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are evaluated separately or combined according to the guidelines of McConnell et al. (1986).

#### Statistical Methods

#### Survival Analyses

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

#### Calculation of Incidence

The incidence of neoplasms or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions had multiple potential

#### Analysis of Tumor Incidence

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

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

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

#### Historical Control Data

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

#### Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between dosed and control groups in the analysis of continuous vari-Organ and body weight data, which have ables. approximately normal distributions, were analyzed using the multiple comparison procedures of Williams (1971, 1972) and Dunnett (1955). Clinical chemistry and hematology data, which typically have skewed distributions, were analyzed using the multiple comparison methods of Shirley (1977) and Dunn (1964). 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 (Dunnett's or Dunn's test).

## **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 the NTP Technical Report were conducted. Audit procedures and findings 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 discrepancies had been resolved or were otherwise addressed during the preparation of this Technical Report.

#### **GENETIC TOXICITY**

The genetic toxicity of HC Yellow 4 was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells, and sex-linked recessive lethal mutations and reciprocal translocations in *Drosophila melanogaster*. The protocols for these studies and tabular presentations of their findings are in Appendix E.

## TABLE 1

Experimental Design and Materials and Methods in the Feed Studies of HC Yellow 4

14-Day Studies	13-Week Studies	2-Year Studies		
Study Laboratory		· · · · · · · · · · · · · · · · · · ·		
EG&G Mason Research Institute (Worcester, MA)	EG&G Mason Research Institute (Worcester, MA)	EG&G Mason Research Institute (Worcester, MA)		
Strain and Species				
Rats: F344/N	Rats: F344/N	Rats: F344/N		
MICE: BOC3F1	MICE: BOC3P <sub>1</sub>	MICE: BOC3F1		
Animal Source				
Charles River Breeding Laboratories (Kingston, NY)	Frederick Cancer Research Facility (Frederick, MD)	Frederick Cancer Research Facility (Frederick, MD)		
Size of Study Groups				
5 males and 5 females	10 males and 10 females	70 males and 70 females		
Doses				
Rats: 0, 5,000, 10,000, 20,000, 40,000, and 80,000 ppm HC Yellow 4 in feed	Rats: 0, 2,500, 5,000, 10,000, 20,000, and 40,000 ppm HC Yellow 4 in feed	Rats: Male - 0, 2,500, and 5,000 ppm HC Yellow 4 in feed; Female - 0, 5 (90) and 10 (90) ppm HC Yellow		
Mice: 0, 1,250, 2,500, 5,000, 10,000, and	Mice: 0, 5,000, 10,000, 20,000, 40,000,	in feed		
20,000 ppm HC Yellow 4 in feed	and 80,000 ppm HC Yellow 4 in feed	Mice: 0, 5,000, and 10,000 ppm HC Yellow 4 in feed		
Timme Held Refore Study				
Rats: 13-15 days	13-14 davs	Rats: 14 days		
Mice: 14-16 days		Mice: 13-14 days		
Average Age When Placed on Study				
Rats: 7 weeks	Rats: 7-8 weeks	6 weeks		
Mice: 8 weeks	Mice: 8 weeks			
Date of First Dose Date: Mole. 12 July 1981	Pote: Male - 17 February 1082	Pate: Male 12 April 1083		
Female - 15 July 1981	Female - 24 February 1982	Female - 20 April 1983;		
Mice: Male - 21 July 1981	Mice: Male - 10 March 1982	Mice: Male - 16 March 1983.		
Female - 23 July 1981	Female - 3 March 1982	Female - 29 March 1983		
14 days	13 weeks (7 days/week)	104 weeks (7 days/week)		
Normany Markes				
Rate: Male - 28 July 1981	Rats: Male - 19-21 May 1982	6-month interim -		
Female - 30 July 1981	Female - 26-27 May 1982	Male Rats: 3-4 October 1983:		
Mice: Male - 5 August 1981	Mice: Male - 9-10 June 1982	Female Rats: 18-19 October 1983;		
Female - 7 August 1981	Female - 2-5 June 1982	Mice: 20-22 September 1983		
-		15-month interim -		
		Rats: 24-26 July 1984;		
		Male Mice: 12-13 June 1984;		
		remaie Mice: 20 June 1984		
		2-year survies - Male Rats: 0-12 Anril 1085:		
		Female Rats: 17-24 April 1985:		
		Male Mice: 14-18 March 1985;		
		Female Mice: 27-29 March 1985		

#### TABLE 1

## Experimental Design and Materials and Methods in the Feed Studies of HC Yellow 4 (continued)

14-Day Studies	13-Week Studies	2-Year Studies		
Average Age at Necropsy		· · · · · · · · · · · · · · · · · · ·		
Rats: 9 weeks Mice: 10 weeks	Rats: 20-21 weeks Mice: 21 weeks	110-111 weeks		
Method of Animal Distribution Animals assigned to groups by weight, so that cage weights were approximately equal $(\pm 2 \text{ g})$	Same as 14-day studies	Animals of each sex randomized in cage groups, then cages randomized to dose and control groups using random number table		
Animals per Cage				
5	5	5 (male mice housed individually beginning 27 July 1984)		
Method of Animal Identification				
Ear punch	Same as 14-day studies	Same as 14-day studies		
Diet				
NIH-07 Rat and Mouse Ration, Open formula, mash (Zeigler Bros., Inc., Gardners, PA), available ad libitum	Same as 14-day studies	Same as 14-day studies		
Water				
Tap water (Worcester Public Water Supply) via outside-the-cage automatic watering system (Edstrom Industries, Inc., Waterford, WI), available ad libitum	Same as 14-day studies	Same as 14-day studies		
Canas				
Polycarbonate cages (Lab Products, Inc., Rochelle Park, NJ)	Same as 14-day studies	Same as 14-day studies		
Redding				
Aspen Bed, heat-treated hardwood chips (American Excelsior Co., Baltimore, MD), changed twice weekly	Same as 14-day studies	Aspen Bed (American Excelsior Co., Baltimore, MD) or BetaChips (Northeastern Products Corp., Warrensburg, NY); changed twice weekly		
Case Filter				
Non-woven polyester filters (Snow Filtration, Cincinnati, OH)	Non-woven polyester filters (Lab Products, Rochelle Park, NJ or Snow Filtration, Cincinnati, OH)	Same as 13-week studies		

## Table 1

Experimental Design and Materials and Methods in the Feed Studies of HC Yellow 4 (continued)

14-IDay Studies	13-Week Studies	2-Year Studies		
Aminnal Room Environment Average temperature: 22.2° C; Relative humidity: 69% Fluorescent light: 12 hours/day Room air changes: 12-15/hour	Rats: Male - Average temperature 22.2° C; Relative humidity 34%; Female - Average temperature 22.3° C; Relative humidity 35.3% Mice: Male - Average temperature 22.8°-23.6° C; Relative humidity 38.1%-42%; Female - Average temperature 22.3° C; Relative humidity 37.2% Fluorescent light: 12 hours/day Room air changes: >12/hour	Rats: Average temperature $22.5^{\circ} \pm 1.3^{\circ}$ C; Relative humidity $47.5\% \pm 5.7\%$ ; Mice: Average temperature $22.7^{\circ} \pm 2.2^{\circ}$ C; Relative humidity $44.4\% \pm 6.0\%$ Fluorescent light: 12 hours/day		
Type and Frequency of Observation Observed twice/day; weighed initially and once/week; clinical observations recorded at necropsy; feed consumption once/week by cage	Observed twice/day; weighed initially and once/week; clinical observations recorded daily; feed consumption once/week by cage	Observed twice/day; weighed and clinical observations recorded initially, once/week for 13 weeks, once/month thereafter; feed consumption per cage measured once/month		
Necropsy Necropsy performed on all animals. The following organs were weighed: brain, heart, right kidney, liver, lung, right testis, and thymus.	Necropsy performed on all animals. The following organs were weighed for all survivors: brain, heart, right kidney, liver, lung, right testis, and thymus.	Necropsy performed on all animals. The following organs were weighed for all animals at 15-month interim evaluation: brain, right kidney, and liver.		
Clinical Pathology None	None	Clinical pathology studies were performed at 6 months on control and high-dose rats and on mice from each dose group and at 15 months on rats and mice from each dose group. <i>Herradology</i> : None at 6 months. 15 months: hematocrit, hemoglobin, erythrocyte count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, leukocyte count and differential <i>Clinicel chamistry</i> : 6 months: thyroid stimulating hormone (rats), triiodothyronine, and thyroxine. 15 months: blood urea nitrogen, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, sorbitol dehydrogenase, thyroid stimulating hormone (rats), triiodothyronine, and thyroxine.		

TABLE 1

Experimental Design and Materials and Methods in the Feed Studies of HC Yellow 4 (continued)

14-Day Studies	13-Week Studies	2-Year Studies

#### Histopathology

Histopathology performed on all rats that received 0, 20,000, 40,000, or 80,000 ppm. Tissues examined included: bone and marrow, Peyer's patch, spleen, and thymus. Tissues examined only for the 80,000 ppm dose group included: brain, clitoral gland, and kidney. Tissues examined only for the 0, 20,000, and 40,000 ppm dose groups included: mediastinal lymph node and testis. The lung, skin, and urinary bladder were examined from mice that received 20,000 ppm.

Complete histopathology on all animals that died or were killed moribund during study, all rats that received 0 or 40,000 ppm, and all mice that received 0 or 80,000 ppm. Tissues examined included: adrenal gland, bone and marrow (sternum), brain, clitoral or preputial gland (rats), epididymis, esophagus, heart, kidney, large intestine, liver, lung, lymph node (mandibular and mesenteric), mammary gland, nasal cavity, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, seminal vesicle, skin, small intestine, spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. Tissues examined from rats in the 2,500, 5,000, 10,000, and 20,000 ppm dose groups were kidney, thyroid gland, and uterus. Thyroid gland was examined for all mice in the 5,000, 10,000, 20,000, and 40,000 ppm dose groups.

Histopathology of thyroid glands performed on rats and mice at 6-month interim evaluation. Complete histopathology performed at 15-month interim evaluation on all control animals, male rats that received 5,000 ppm, and mice and female rats that received 10,000 ppm. At the 15-month evaluation, only gross lesions were examined in male rats receiving 2,500 ppm and female rats receiving 5,000 ppm, and gross lesions and thyroid gland were examined in male and female mice that received 5,000 ppm. Complete histopathology performed on all animals that died or were killed moribund during 2-year studies, all controls, all rats, and highdose mice at the end of the studies. Tissues examined: adrenal gland, bone, bone marrow, brain, cecum, clitoral or preputial gland (rats), colon, duodenum, epididymis, esophagus, forestomach, gallbladder (mice), glandular stomach, heart, ileum, jejunum, kidney, liver, lung, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, rectum, salivary gland, seminal vesicle, skin, spleen, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. Organs examined from low-dose mice were thyroid gland and ovary.

## RESULTS

## Rats

#### 14-Day Studies

All animals survived to the end of the studies. The final mean body weights and mean body weight changes of males that received doses of 20,000 ppm and above and females that received doses of 10,000 ppm and above were significantly lower than those of the controls (Table 2). Feed consumption by males that received doses of 20,000 ppm or greater and females that received doses of 10,000 ppm or greater was lower than that of the controls during the first week. During the second week, feed consumption by males in the 40,000 ppm dose group was lower than controls; feed consumption by other male and female dose groups was similar to or higher than that of the controls. Because rats that received 40,000 ppm did not gain weight, and the final mean body weights of rats that received 80,000 ppm were decreased approximately 30%, it was concluded that the feed consumption values were high and may have included feed scattered by animals searching for unadulterated feed.

No clinical findings were attributed to HC Yellow 4 administration. Significant changes in absolute and relative organ weights were observed but were considered to be secondary to decreases in body weights (Table F1).

#### Table 2

Survival, Mean Body Weights, and Feed Consumption of Rats in the 14-Day Feed Studies of HC Yellow 4

Concentration	Survival <sup>a</sup>	Survival <sup>a</sup> Mean Body Weight <sup>b</sup> (g)			Final Weight Relative to Controls	Feed Consumption <sup>c</sup>		
(ppm)		Imitial	Final	Change	(%)	Week 1	Week 2	
Male						<u>.</u>		
0	5/5	107 ± 6	178 ± 7	$71 \pm 3$		15.3	16.7	
5,000	5/5	$108 \pm 5$	$173 \pm 6$	$66 \pm 3$	97	15.6	16.7	
10,000	5/5	$107 \pm 5$	$170 \pm 5$	$63 \pm 2$	95	14.9	16.9	
20,000	5/5	$107 \pm 4$	$148 \pm 6^{\circ \circ}$	$40 \pm 5^{\circ \circ}$	83	10.7	14.4	
40,000	5/5	$108 \pm 3$	$107 \pm 4^{\circ \circ}$	$-1 \pm 2^{\circ \circ}$	60	5.9	11.6	
80,000	5/5	$108 \pm 4$	75 ± 3°°	-32 ± 3°°	42	8.7	16.3	
Female								
0	5/5	$101 \pm 3$	$145 \pm 2$	$44 \pm 1$		16.0	11.6	
5,000	5/5	$101 \pm 3$	$138 \pm 5$	$37 \pm 2$	95	15.0	10.4	
10,000	5/5	$101 \pm 3$	$131 \pm 1^{\circ \circ}$	29 ± 3°°	90	12.6	10.1	
20,000	5/5	$101 \pm 2$	$130 \pm 3^{\circ \circ}$	29 ± 4°°	90	7.2	11.7	
40,000	5/5	$101 \pm 2$	$102 \pm 3^{\circ \circ}$	$0 \pm 3^{\circ \circ}$	70	10.6	15.4	
80,000	5/5	$102 \pm 3$	$72 \pm 3^{\circ \circ}$	-29 ± 4**	50	9.4	12.1	

°° Significantly different (P≤0.01) from the control group by Williams' or Dunnett's test

Number of animals surviving at 14 days/number initially in group

<sup>b</sup> Weights and weight changes are given as mean  $\pm$  standard error.

<sup>c</sup> Grams per animal per day, based on average consumption data per group per week for weeks 1 and 2

#### **13-Week Studies**

All rats survived to study termination. Final mean body weights of males that received doses of 10,000 ppm or greater and females that received 20,000 or 40,000 ppm were significantly lower than those of the controls (Table 3). Feed consumption by males in all dose groups was generally higher than that of the controls throughout the study (Table 4). Feed consumption by females that received 40,000 ppm was generally higher than that of the controls; feed consumption by females in other dose groups was lower than that of the controls. The values for feed consumption by rats receiving 40,000 ppm were nearly twice that of other groups and are probably due to spillage of unpalatable diet.

There were no biologically significant clinical findings. Statistically significant changes in absolute and relative organ weights were observed but were considered to reflect the changes in body weights and were not considered to be related to chemical administration (Table F2).

TABLE 3

Survival and Mean Body Weights of Rats in the 13-Week Feed Studies of HC Yellow 4

Concentration	Survival <sup>a</sup>	Mea	n Body Weight	Final Weight Relative to Controls	
(ppm)		Initial	Final	Change	(%)
	·	·····			
0	10/10	144 ± 3	354 ± 7	$210 \pm 5$	
2,500	10/10	$143 \pm 4$	$364 \pm 6$	$221 \pm 6$	103
5,000	10/10	$144 \pm 3$	346 ± 6	$202 \pm 6$	98
10,000	10/10	$143 \pm 3$	$326 \pm 5^{**}$	$183 \pm 6^{**}$	92
20,000	10/10	$143 \pm 3$	287 ± 5**	$144 \pm 8^{**}$	81
40,000	10/10	$143 \pm 3$	$250 \pm 5^{**}$	$108 \pm 5^{**}$	71
female					
0	10/10	135 ± 2	$204 \pm 4$	69 ± 4	
2,500	10/10	$135 \pm 2$	$214 \pm 3$	79 ± 3	105
5,000	10/10	$135 \pm 2$	$203 \pm 3$	$67 \pm 3$	99
10,000	10/10	$135 \pm 2$	$205 \pm 3$	$70 \pm 3$	101
20,000	10/10	$134 \pm 2$	194 ± 2*	$61 \pm 2$	95
40.000	10/10	124 + 2	181 + 2**	17 + 3**	80

\* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test

\*\* P≤0.01

<sup>a</sup> Number of animals surviving at 13 weeks/number initially in group

<sup>b</sup> Weights and weight changes are given as mean  $\pm$  standard error.

TABLE	4
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Week						
of Study	10 maa	2,5TI ppm	5,000 ppm	10,000 ppm	20,010 ppm	<i>4</i> 0,033 ppm
Male			·	·····		
1	91.2	96.4	94.6	96.3	85.8	106.9
2	78.4	81.3	79.0	79.5	89.6	1196
3	71.8	73.0	73.5	81.3	78.7	106.3
4	69.6	73.3	73.4	75.6	78.5	159.6
5	63.0	65.4	66.8	71.3	72.8	147.2
6	57.5	58.7	60.6	64.0	73.7	136.7
7	55.0	60.7	60.1	58.4	67.4	131.0
8	53.9	62.4	58.0	59.1	67.3	127.6
9	59.1	57.3	60.0	60.9	70.4	104.8
10	57.4	55.8	55.2	58.8	65.4	115.6
11	52.9	52.6	55.4	55.5	63.8	108.2
12	44.2	47.7	48.5	49.5	56.7	104.8
13	45.5	45.6	51.5	48.2	55.3	103.8
Mean ± SD	61.5 ± 13.3	$63.9 \pm 14.2$	64.4 ± 12.8	$66.0 \pm 14.0$	$71.2 \pm 10.2$	$120.9 \pm 18.3$
Female						
1	87.1	86.8	85.1	81.6	65.5	99.3
2	84.5	89.5	83.3	74.3	68.4	86.9
3	85.3	87.8	83.7	68.3	66.1	125.5
4	86.2	75.7	75.7	80.4	55.4	117.8
5	82.0	77.0	72.3	79.0	66.8	123.3
6	86.0	75.6	70.3	82.0	87.7	136.5
7	87.6	74.2	77.0	79.0	78.4	152.3
8	81.3	71.7	73.5	69.0	70.2	143.1
9	78.9	76.7	53.3	70.9	61.8	135.2
10	70.4	79.3	68.7	71.6	56.0	143.8
11	72.6	69.6	64.4	65.5	52.8	143.6
12	70.2	64.1	60.3	86.9	54.7	155.3
13	70.7	58.5	58.2	59.4	52.0	174.5
Mean ± SD	$80.2 \pm 6.9$	75.9 ± 8.9	71.2 ± 10.1	74.5 ± 7.8	$64.3 \pm 10.6$	133.6 ± 23.4

Feed	Consumption	oľ	Rats	im	the	13-Week	Feed	Studies	Oſ	$\mathbb{H}\mathbb{C}$	Yellow	4 <sup>a</sup>
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<sup>a</sup> Feed consumption given in grams per kilogram body weight per day

Lesions related to chemical administration were seen in the thyroid gland of males and females, the kidney in males, and the uterus in females (Table 5). The severity of all lesions ranged from minimal to mild except for uterine atrophy in the 40,000 ppm female group which ranged from mild to moderate. Thyroid gland pigmentation was present in males and females in the 40,000 ppm dose groups and appeared as a golden brown, granular pigment scattered within the cytoplasm of follicular epithelial cells; occasionally a sloughed cell containing pigment was seen within the colloid. The nature of the pigment was undetermined. Special histologic stains (Perl's stain and acid fast) showed that the pigment was not hemosiderin or ceroid, and the periodic acid-Schiff method indicated that the pigment was not colloid. Mineralization of the renal papilla was observed in males that received 40,000 ppm. Mineralization consisted of small numbers of minute basophilic crystalline foci diffusely scattered within the renal papilla and usually located within tubule lumens.

Uterine atrophy, observed in females that received 20,000 or 40,000 ppm, was characterized by a decrease in uterine size, a decrease in the myometrium and endometrium, and a decrease in the size and number of endometrial glands as compared with the uteri of control females.

Dose Selection Rationale: The decreases in mean body weights of male rats in the 10,000, 20,000, and 40,000 ppm dose groups were quite dramatic (8%, 19%, and 29%) and suggested that for male rats, 10,000 ppm may exceed an exposure compatible with long-term survival in the 2-year study. There were no significant histological findings in males receiving doses of 20,000 ppm or less in the 13-week study; thus, doses of 2,500 and 5,000 ppm were selected for the males in the 2-year study. In the females, the weight decreases were much less dramatic (20,000 ppm, 5%; 40,000 ppm, 11%), but all females receiving 20,000 ppm or more had uterine atrophy. Thus, doses of 5,000 and 10,000 ppm were selected for the female rats in the 2-year study.

#### TABLE 5

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm	40,000 ppm
Male	· · · ·					<u></u>
Kidney, papilla Mineralization Thyroid gland	0/10	0/10	0/10	0/10	0/10	9/10** (1.3) <sup>b</sup>
Pigmentation	0/10	0/10	0/10	0/10	0/10	8/10** (1.0)
Female						
Thyroid gland Pigmentation Uterus	0/10	0/10	0/10	0/10	0/10	2/10 (1.0)
Atrophy	0/10	0/10	0/10	0/10	10/10** (1.0)	10/10** (2.3)

Incidences of Treatment-Related Lesions in Rats in the 13-Week Feed Studies of HC Yellow 4ª

\*\* Significantly different (P≤0.01) from the control group by the Fisher exact test

Incidences given as number of lesions/number of tissues examined

<sup>o</sup> Average severity grades for affected animals. Minimal = 1, Mild = 2, Moderate = 3

#### 2-Year Studies

#### 6-Month Interim Evaluations

There were no biologically significant changes in thyroid hormone levels (Table G1) or histopathology observations that were related to administration of HC Yellow 4 at 6 months.

### 15-Month Interim Evaluations

There were no biologically significant changes in hematology or clinical chemistry values (Table G2). The apparent increases in blood urea nitrogen reported in the high-dose males and in dosed females may have been an artifact of the assay, caused by the presence of HC Yellow 4 in the urine. Statistically significant changes in absolute and relative organ weights observed in females were considered to reflect differences in body weight (Table F3). Neoplasms were observed in control and dosed rats (Table 6); neoplasms in dosed rats were not attributed to administration of HC Yellow 4.

### Bady Weights, Feed Consumption, and Clinical Findings

Mean body weights of low-dose males and females were similar to those of the controls throughout the studies; mean body weights of dosed males were slightly higher than those of the controls after week 61 (Tables 7 and 8 and Figure 1). Mean body weights of high-dose females were lower than controls after week 29. Feed consumption by high-dose males and dosed females was lower than that of the controls through week 53 and similar to that of the controls thereafter (Tables I1 and I2). Feed consumption by low-dose males was similar to that of the controls throughout the study. No clinical findings were attributed to the administration of HC Yellow 4.

#### TABLE 6

Incidences of Neoplasms in Rats at the 15-Month Interim Evaluations in the 2-Year Feed Studies of HC Yellow 4<sup>a</sup>

0 ppm	2,500 ppm <sup>b</sup>	5,000 ppm
0/9	1/10	0/10
1/9	0/10	0/10
0/9	1/10	0/10
0/9	1/10	0/10
5/9	0/10	4/9
1/9	0/10	0/10
1/9	0/10	1/10
	5 11 0	240
7/9	5/10	3/10
00	040	2/10
0/9	0/10	2/10
0/9	0/10	1/10
0 ppm	5,000 ppm <sup>b</sup>	10,000 ppm
0/10	1/10	0/10
0120	2, 2 2	
1/10	3/10	5/10
	0 ppm 0/9 1/9 0/9 0/9 5/9 1/9 1/9 1/9 7/9 0/9 0/9 0/9 0/9 0/9 0/9 0/9 0	0 ppm 2,500 ppm <sup>b</sup> 0/9 1/10 1/9 0/10 0/9 1/10 0/9 1/10 5/9 0/10 1/9 0/10 1/9 0/10 1/9 5/10 0/9 5/10 0/9 0/10 0/9 0/10 1/0 1/10 1/10 1/10

<sup>a</sup> Incidences given as number of lesions/number of tissues examined

<sup>b</sup> Only gross lesions were examined microscopically. The denominator is the number of tissues examined grossly.

26

Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of HC Yellow 4

Weeks	Weeks 0 ppm			2,500 ppm			5.000 ppm			
on	Av. Wt.	Number of	Av. Wt.	Wt. (% of	Number of	Av. Wt.	Wt. (% of	Number of		
Study	(g)	Survivors	(g)	controls)	Survivors	(g)	controls)	Survivors		
	107	70	102	07	70	104	07	70		
2	150	70	103	97	70	104	97	70		
2	103	70	188	90 07	70	132	90	70		
<u> </u>	222	70	216	97	70	211	95	70		
5	246	70	210	90	70	211	95	70		
6	262	70	242	99	70	257	97	70		
7	278	70	201	100	70	273	90	70		
, 8	291	70	286	98	70	213	98 07	70		
9	308	70	305	90	70	205	08	60		
10	315	70	310	08	70	207	90 07	60		
10	379	70	326	98	70	307	97	60		
12	327	70	320	99	70	323	90	60		
12	242	70	247	100	70	229	98	60		
14	343	70	342	00	70	336	99 00	60		
17	367	70	267	100	70	262	99 00	0 <del>7</del> 40		
21	388	70	394	00	70	390	08	60		
21	406	70	<u> </u>	101	70	405	100	60		
2.) 20 <sup>8</sup>	420	60	410	101	70 60	405	100	50		
33	420	60	420	100	60	421	100	50		
37	439	60	430	100	60	431	98	50		
<i>31</i>	432	60	439	100	60	431	90	59		
45	461	59	458	00	60	454	08	50		
40	465	59	467	101	60	463	100	50		
53	465	59	465	100	60	465	100	59		
57	405	59	405	100	59	403	100	58		
61	472	59	482	100	58	478	100	58		
65	473	59	481	102	58	479	102	56		
69 <sup>a</sup>	472	49	480	102	47	488	103	46		
73	473	48	487	103	46	489	103	46		
75	466	40	479	103	46	481	103	46		
81	464	47	477	103	46	481	104	40		
85	456	46	472	103	45	483	106	42.		
89	445	43	454	102	44	473	106	41		
93	435	38	441	101	39	463	106	41		
97	434	31	439	101	34	445	103	38		
101	416	29	430	104	34	439	106	31		
104	413	24	417	101	33	440	107	28		
Terminal sa	crifice	21			29			28		
Mean for we	eks						-			
1-13	261		257	98		254	97			
14-52	418		418	100		414	99			
53-104	454		463	102		470	104			

<sup>a</sup> Interim evaluations occurred during weeks 25 and 68.

#### Table 8

Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of HC Yellow 4

Weeks	a		5.000 ppm		10.000 ppm			
OM	Av. Wt.	Number of	Av. WL	Wt. (% of	Number of	Av. Wt.	Wt. (% of	Number of
Study	(g)	Survivors	(g)	controls)	Survivors	(g)	controls)	Survivors
	 99	70	 99	100	70			70
2	131	70	134	102	70	128	98	70
3	144	70	150	104	70	143	99	70
4	154	70	162	105	70	156	102	70
5	165	70	171	104	70	165	100	70
6	177	70	180	102	70	174	99	70
7	180	70	185	103	70	179	100	70
8	190	70	191	101	70	184	97	70
9	196	70	197	101	70	189	97	70
10	200	70	202	101	70	196	98	70
11	204	70	206	101	70	199	98	70
12	206	70	208	101	70	200	97	70
13	209	70	212	102	70	204	98	70
14	212	70	216	102	70	208	98	70
17	221	70	225	102	70	217	98	70
21	228	70	229	101	70	222	98	70
25	237	70	238	101	70	230	97	70
29 <sup>a</sup>	247	60	247	100	60	239	97	60
33	254	60	250	99	60	239	94	60
37	264	60	258	98	60	245	93	60
41	276	60	266	96	60	250	91	60
45	277	60	271	98	60	255	92	60
49	292	60	279	95	60	262	<del>90</del>	60
53	300	60	288	96	60	272	91	60
57	315	60	299	95	60	281	89	60
61	317	58	300	95	60	280	88	60
65	334	57	318	95	60	297	89	60
69 <sup>a</sup>	336	47	321	96	49	298	89	50
73	349	47	335	96	49	309	89	49
77	355	46	342	96	49	314	88	48
81	360	46	352	98	47	322	90	46
85	360	45	348	96	47	321	89	46
89	358	43	351	98	45	326	91	46
93	356	41	356	100	43	324	91	43
97	356	36	351	99	39	327	92	40
101	355	31	351	<b>99</b>	37	330	93	38
104	354	29	353	100	31	330	93	35
Terminal se	ocrifice	27			31			34
Mean for w	veelss							
1-13	173		177	102		170	98	
14-52	251		248	<del>9</del> 9		237	94	
53-104	343		333	97		309	90	

<sup>a</sup> Interim evaluations occurred during weeks 26 and 67.



FIGURE 1 Growth Curves for Rats Administered HC Yellow 4 in Feed for 2 Years

#### Survival

Survival of dosed males and females was similar to those of the controls (Table 9 and Figure 2).

Pathology and Statistical Analyses of Results This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplastic or nonneoplastic lesions of the pituitary gland, uterus, and mammary gland in rats. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendixes A for male rats and B for female rats.

TABLE 9

Survival of Rats in the 2-Year Feed Studies of HC Yellow 4

	0 ppm	2,500 ppm	5,010 ppm	
Male				
Animals initially in study	70	70	70	·
6-month interim evaluation <sup>a</sup>	10	10	10	
15-month interim evaluation <sup>a</sup>	9	10	10	
Natural deaths	6	4	3	
Moribund kills	24	17	18	
Missexed <sup>a</sup>	0	0	1	
Animals surviving to study termination	21	29	28	
Percent survival at end of study <sup>b</sup>	41	59	58	
Mean survival (days) <sup>c</sup>	576	580	579	
Survival analyses <sup>d</sup>	P=0.141N	P=0.139N	P=0.174N	
	0 ppm	5,000 ppm	10,000 ppm	
Female				
Animals initially in study	70	70	70	
6-month interim evaluation <sup>a</sup>	10	10	10	
15-month interim evaluation <sup>a</sup>	10	10	10	
Natural deaths	2	4	1	
Moribund kills	21	15	15	
Animals surviving to study termination	27 <sup>e</sup>	31 <sup>e</sup>	34	
Percent survival at end of study <sup>b</sup>	55	62	68	
Mean survival (days) <sup>c</sup>	581	592	593	
Survival analyses <sup>d</sup>	P=0.168N	P=0.453N	P=0.210N	

Censored from survival analyses

<sup>b</sup> Kaplan-Meier determinations. Survival rates adjusted for interim evaluations.

<sup>c</sup> Mean of all deaths (uncensored, censored, terminal sacrifice)

<sup>d</sup> 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.

e Includes one animal that was sacrificed moribund during the last week of study



FIGURE 2 Kaplan-Meier Survival Curves for Rats Administered HC Yellow 4 in Feed for 2 Years

Pituitary Gland: Adenomas of the pars distalis occurred at greater incidences in dosed male rats than in the controls (Table 10). The increased incidence was significant in the high-dose group. The incidences of hyperplasia of the pars distalis, a lesion generally considered to be a precursor to adenoma, were also increased in dosed males, and the increase was significant in the high-dose group. The incidence of adenomas in dosed males was within the range of 12% to 60% for historical control incidences for untreated male F344/N rats from NTP 2-year feed studies (230/785 or 29.3%; Table A4). Because adenomas and hyperplasia were seen in the pituitary gland of male rats at the 15-month interim evaluation, the results of the 15-month evaluation were combined and analyzed with the 2-year study results (Table 10). The low-dose male rat group was not included in the analysis, because no pituitary glands from this group were examined microscopically at the 15-month evaluation. The combined incidence of adenoma in high-dose males was greater than the combined incidence in the control group, but the difference was not significant. The combined incidence of hyperplasia was significantly greater in the high-dose group than in the control group.

Adenomas of the pars distalis were discrete nodular masses which compressed and sometimes replaced adjacent parenchyma. They were composed of palestaining polygonal cells which formed sheets or trabecular patterns and which often contained multiple cystic vascular spaces. Hyperplasias were composed of cells similar to those of adenomas; however, hyperplasias were smaller lesions which blended smoothly with adjacent parenchyma and usually caused no compression. Uterus: Stromal polyps occurred with a positive trend, and the incidence in the high-dose females was significantly greater than that in the controls (0 ppm, 4/48; 5,000 ppm, 8/50; 10,000 ppm, 12/50; Table B3). One low-dose female had a uterine stromal sarcoma. The incidence of stromal polyps in the high-dose group was within the range (8%-30%) of historical control incidences in untreated female F344/N rats from 2-year NTP feed studies (142/800 or 17.8%, Table B4a). It was also similar to the mean historical incidence from three previous feed studies at this laboratory (30/150 or 20%, Table B4a). The incidence in the control group of the present study is at the low end of the historical control range, so the significant difference between the control and high-dose incidences may be due to an unusually low control group incidence. Consequently, the higher incidence of stromal polyps in treated females as compared with controls was not considered to be due to the administration of HC Yellow 4.

Mammary Gland: In females, fibroadenomas occurred with a significant negative trend (28/48, 19/37, 18/47; Table B3). The incidence in the control group was at the upper end of the historical control range, while the incidences in the dosed groups were near the mean historical control incidence for female rats from 2-year feed studies (314/800 or 39.3%, range 8%-58%; Table B4b). Thus, the significance of this negative trend was considered to be due to the high incidence in the control group and is not considered to be related to the administration of HC Yellow 4.

31

#### TABLE 10

Lesions of the Pituitary Gland Pars Distalis in Male Rats in the 2-Year Feed Study of HC Yellow 4<sup>a</sup>

	0 ррт	2,500 ppm	5,000 ppm
Adenoma (2-vear incidence) <sup>a</sup>	·		
Overall rates <sup>b</sup>	17/45 (38%)	20/49 (41%)	28/49 (57%)
Adjusted rates <sup>c</sup>	59.1%	53.0%	67.4%
Terminal rates <sup>d</sup>	10/20 (50%)	12/29 (41%)	15/28 (54%)
First incidence (days)	598	626	367
Logistic regression tests <sup>e</sup>	P=0.034	P=0.489	P=0.047
Adenoma (combined 15-month and 2-w	ear incidence)		
Overall rates	22/54 (41%)	_f	32/58 (55%)
Adjusted rates	62.6%		69.7%
Terminal rates	5/9 (56%)		4/9 (44%)
First incidence (days)	470 (I)		367
Logistic regression tests			P=0.091
Hyperplasia (2-year incidence)			
Overall rates	8/45 (18%)	13/49 (27%)	18/49 (37%)
Logistic regression tests	P=0.026	P=0.209	P=0.035
Hyperplasia (combined 15-month and 2	2-year incidence)		
Overall rates	11/54 (20%)	-	25/58 (43%)
Logistic regression tests			<b>B_0.000</b>

(I) Interim evaluation

<sup>a</sup> Historical incidence for 2-year NTP feed studies of untreated control groups (mean  $\pm$  standard deviation): 230/785 (29.3%  $\pm$  11.5%), range 12%-60%

<sup>b</sup> Number of lesion-bearing animals/number of animals necropsied or examined microscopically for this lesion

Number of lesion-bearing animals/effective number of animals, i.e., number of animals alive at first occurrence of this tumor type in any of the groups

d Observed incidence at terminal kill

<sup>e</sup> 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 tumors in animals dying prior to terminal kill as nonfatal.

f Not examined at the 15-month interim evaluation

### MICE

#### 14-Day Studies

All mice survived to the end of the studies. The final mean body weight and mean body weight change of females and the mean body weight change of males that received 20,000 ppm were significantly lower than those of the controls (Table 11). Final mean body weights and mean body weight changes of other dose groups were similar to those of the controls. Feed consumption by dosed groups was generally similar to that of the controls during the first week of the studies; during the second week, feed consumption by males and females in the 10,000 and 20,000 ppm dose groups was higher than that of the controls.

No clinical findings in mice were related to HC Yellow 4 administration. No biologically significant changes in absolute or relative organ weights were noted (Table F4). No gross or microscopic lesions were related to HC Yellow 4 administration.

#### Table 11

Survival, Mean Body Weights, and Feed Consumption of Mice in the 14-Day Feed Studies of HC Yellow 4

கோசையிரவிக்கா	Smrvival <sup>a</sup>	Survival <sup>a</sup> Mean Bady Weight <sup>b</sup> (g)			Final Weight Relative to Controls	Feed Consumption <sup>c</sup>		
(ppm)		Initial	Final	Change	(%)	Week 1	Week 2	
Male								
0	5/5	$25.4 \pm 0.5$	$27.8 \pm 0.6$	$2.4 \pm 0.3$		4.3	3.3	
1,250	5/5	$24.9 \pm 0.3$	$29.0 \pm 0.4$	$4.1 \pm 0.3$	104	4.1	3.1	
2,500	5/5	$25.7 \pm 0.2$	$29.3 \pm 0.3$	$3.6 \pm 0.3$	106	4.1	3.0	
5,000	5/5	$25.5 \pm 0.4$	$28.3 \pm 0.3$	$2.9 \pm 0.2$	102	4.0	2.6	
10,000	5/5	$25.2 \pm 0.3$	$27.5 \pm 0.3$	$2.3 \pm 0.2$	99	4.5	4.7	
20,000	5/5	$25.2 \pm 0.8$	$26.4 \pm 0.8$	$1.2 \pm 0.3$ °°	95	3.7	4.7	
Female								
0	5/5	$18.4 \pm 0.4$	$21.1 \pm 0.3$	$2.8 \pm 0.2$		8.0	2.3	
1.250	5/5	$18.3 \pm 0.5$	$22.1 \pm 0.4$	$3.7 \pm 0.8$	104	7.8	3.3	
2,500	5/5	$18.2 \pm 0.4$	$20.3 \pm 0.4$	$2.0 \pm 0.1$	96	6.2	2.3	
5.000	5/5	$18.3 \pm 0.3$	$20.3 \pm 0.1$	$2.0 \pm 0.2$	96	7.0	2.1	
10.000	5/5	$18.2 \pm 0.4$	$20.3 \pm 0.4$	$2.1 \pm 0.6$	96	6.6	4.6	
20,000	5/5	$18.3 \pm 0.6$	$19.6 \pm 0.4^{\circ \circ}$	$1.3 \pm 0.4^{\circ}$	93	8.4	5.3	

° Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test

°° P≤0.01

<sup>a</sup> Number of animals surviving at 14 days/number initially in group

<sup>b</sup> Weights and weight changes are given as mean  $\pm$  standard error.

<sup>c</sup> Grams per animal per day, based on average consumption data per group per week for weeks 1 and 2

#### **13-Week Studies**

Eight males and seven females in the 80,000 ppm dose groups died; nine of these deaths occurred during week 1, five occurred during week 2, and one occurred during week 11 (Table 12). One male that received 40,000 ppm died during week 7. Final mean body weights and mean body weight changes of male and female mice that received doses of 10,000 ppm or greater were significantly lower than those of the controls. Feed consumption by dosed and control mice is shown in Table 13. The high feed consumption values for dosed animals, particularly those receiving the three highest dose levels, may be due to spillage of unpalatable feed and therefore might not reflect the actual amount of feed consumed.

No biologically significant clinical findings were observed that were related to HC Yellow 4 administration. Statistically significant changes in absolute and relative organ weights were considered to reflect decreases in body weight (Table F5).

TABLE 12

Survival and Mean Body Weights of Mice in the 13-Week Feed Studies of HC Yellow 4

Concentration	Survival <sup>a</sup>	Mea	n Body Weight <sup>b</sup>	Final Weight Relative to Controls	
(ppm)		Initial	Final	Change	(%)
Male					
0	10/10	$21.8 \pm 0.4$	$32.4 \pm 0.7$	$10.6 \pm 0.5$	
5,000	10/10	$21.7 \pm 0.4$	$32.4 \pm 0.7$	$10.7 \pm 0.8$	100
10,000	10/10	$22.0 \pm 0.5$	$29.2 \pm 0.6^{**}$	$7.2 \pm 0.6^{\bullet \bullet}$	90
20,000	10/10	$22.0 \pm 0.4$	$30.0 \pm 0.5^{**}$	$8.0 \pm 0.4^{**}$	92
40,000	9/10 <sup>c</sup>	$21.8 \pm 0.5$	$27.9 \pm 0.5^{**}$	$6.2 \pm 0.5^{**}$	86
80,000	2/10 <sup>d</sup>	$21.9 \pm 0.5$	$22.5 \pm 1.1^{**}$	$-0.2 \pm 1.6^{**}$	69
Female					
0	10/10	$18.1 \pm 0.1$	$25.1 \pm 0.6$	$6.9 \pm 0.6$	
5,000	10/10	$18.4 \pm 0.3$	$24.6 \pm 0.4$	$6.2 \pm 0.3$	98
10,000	10/10	$18.2 \pm 0.1$	$23.3 \pm 0.3^{**}$	$5.1 \pm 0.4^{**}$	93
20,000	10/10	$18.4 \pm 0.2$	$21.6 \pm 0.3^{**}$	$3.2 \pm 0.2^{**}$	86
40,000	9/10 <sup>e</sup>	$18.4 \pm 0.2$	$19.3 \pm 0.2^{**}$	$0.9 \pm 0.3^{**}$	77
80,000	3/10 <sup>f</sup>	$18.0 \pm 0.2$	$17.6 \pm 0.8^{**}$	$0.2 \pm 0.7^{**}$	70

\*\* Significantly different (P≤0.01) from the control group by Williams' or Dunnett's test

Number of animals surviving at 13 weeks/number initially in group

<sup>b</sup> Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies.

<sup>c</sup> Week of death: 7

<sup>d</sup> Week of death: 1, 1, 1, 1, 1, 1, 2, 11

<sup>e</sup> Week of death: 2. Animal was missing from cage, sacrificed when captured.

<sup>f</sup> Week of death: 1, 1, 1, 2, 2, 2, 2

TABL	e 13											
Feed	Consumption	oľ	Mice	ům	the	13-Week	Feed	Studies	രി	$\mathbb{H}\mathbb{C}$	Yellow	₄a

Week		r"				
of Study	0 ppm	5,010 ppm	10,010 ppm	20,010 ppm	40,010 ppm	80,010 ppm
Male						
1	258	<b>299</b>	273	393	476	845
2	223	275	299	462	520	1,715
3	207	247	280	385	425	1,328
4	232	266	291	372	376	1,654
5	230	255	294	384	393	1,722
6	219	253	326	373	455	1,711
7	198	196	287	343	444	2,122
8	242	205	323	453	568	2,035
9	226	193	296	344	396	1.407
10	208	214	273	290	384	1,523
11	246	194	266	413	545	1.371
12	221	172	280	391	512	1.360
13	200	185	247	327	398	1,114
Mean ± SD	224 ± 18	$227 \pm 40$	287 ± 22	379 ± 48	453 ± 66	1,531 ± 351
Female						
1	205	256	375	462	510	1.100
2	233	327	421	526	697	1.405
3	216	336	399	510	651	998
4	227	312	422	539	555	964
5	246	336	404	470	556	1.007
6	246	337	403	462	576	1.114
7	231	297	409	504	604	1.099
8	251	253	382	471	577	1.066
9	192	285	426	549	732	1.238
10	223	298	375	423	508	925
11	235	280	330	325	460	854
12	203	270	314	559	743	1.229
13	192	268	416	532	704	1,136
Mean ± SD	233 ± 20	297 ± 31	390 ± 35	487 ± 63	606 ± 92	1,087 ± 147

<sup>a</sup> Feed consumption given in grams per kilogram body weight per day
Treatment-related lesions were observed in the thyroid gland, spleen, thymus, and uterus of dosed mice (Table 14). Pigmentation of the thyroid gland was observed in males and females that received doses from 5,000 to 40,000 ppm. Thyroid pigmentation occurred in only one animal that received 80,000 ppm, presumably because most of these animals died within the first 2 weeks of the studies before sufficient time had elapsed for pigmentation to develop. Thyroid pigmentation appeared as a golden brown granular pigment within the cytoplasm of follicular epithelial cells. The severity of the pigmentation increased with dose; average severity was minimal in the 5,000 and 10,000 ppm dose groups, mild in the 20,000 ppm dose groups, and mild to moderate in the 40,000 ppm dose groups. Minimal pigmentation was characterized by scant, faintly visible amounts of pigment within the follicular epithelium, mild pigmentation was characterized by the presence of small but readily observable amounts of pigment, and moderate pigmentation was prominent and easily visible. The nature of the pigment was undetermined. Special histologic

stains (Perl's stain and acid fast) showed the pigment was not hemosiderin or ceroid, and the periodic acid-Schiff method indicated the pigment was not colloid.

Mild to moderate depletion of lymphoid tissue and subsequent atrophy of the spleen and thymus were observed in the high-dose males and females; these findings were considered to be secondary to the decreased body weights in these groups. Minimal to mild uterine atrophy was observed in females in the 40,000 and 80,000 ppm dose groups and was characterized by thinner myometrium and endometrium with a decrease in the size and number of endometrial glands as compared with uteri from control females.

Dose Selection Rationale: A combination of deaths and decreased mean body weights relative to controls precluded the selection of doses above 10,000 ppm. Therefore, doses of 5,000 and 10,000 ppm were selected for mice in the 2-year studies.

### TABLE 14

Incidences of Selected Treatment-Related Lesions in Mice in the 13-Week Feed Studies of HC Yellow 4<sup>a</sup>

							_
	0 ppm	5,000 ppm	10,000 ррт	20,000 ppm	40,000 ppm	80,000 ppm	
Male							-
Thyroid gland Pigmentation	0/10	10/10** (1.0) <sup>b</sup>	9/10** (1.2)	10/10** (1.6)	10/10** (2.0)	1/6 (1.0)	
Spleen	0/10	c	_	_	1/10 (2.0)	5/6** (2.0)	
Thymus	0/10	-	_	-	1/10 (2.0)	5/0** (5.0)	
Lymphoid depletion/atrophy	0/10	-	-	-	1/10 (3.0)	3/6** (2.7)	
Female							
Thyroid gland							
Pigmentation	0/10	4/10* (1.0)	5/10* (1.0)	10/10** (1.1)	7/9** (1.9)	0/5	
Spleen	0.70				070		
Lymphoid depletion/atrophy	0/10		-	-	0/10	5/5** (3.0)	
Lymphoid depletion/atrophy	0/10	-	-	-	1/10 (2.0)	4/5** (3.0)	
Uterus	-					~ /	
Atrophy	0/10	-	-	. –	5/10* (1.2)	4/5** (1.8)	

\* Significantly different (P≤0.05) from the control group by the Fisher exact test

\*\* P≤0.01

<sup>a</sup> Incidences given as number of lesions/number of tissues examined

<sup>b</sup> Average severity grades for affected animals. Minimal = 1, Mild = 2, Moderate = 3

<sup>c</sup> Not examined at this dose level

### 2-Year Studies

### 6-Month Interim Evaluations

Although statistically significant changes in thyroid hormone levels were observed, the biological significance of these findings was uncertain (Table G3).

Fine golden brown granular pigmentation was observed within follicular epithelial cells in the thyroid glands of all mice in the 5,000 and 10,000 ppm dose groups. The severity of pigmentation increased with dose, and pigmentation was more severe in males than in females. The pigmentation severity was mild in males that received 5,000 ppm and moderate in males that received 5,000 ppm, while severity was minimal in females that received 5,000 ppm and mild in females that received 10,000 ppm. Pigmentation severity was graded using the criteria described for the 13-week studies.

### 15-Month Interim Evaluations

Statistically significant changes in absolute or relative organ weights were considered to be secondary to body weight decreases (Table F6). No biologically significant changes in hematology or clinical chemistry values occurred (Table G4).

Golden yellow to golden brown granular pigmentation was observed within follicular epithelial cells and within the colloid of the thyroid gland of all dosed male and female mice. Severity of the pigmentation increased with dose and was more severe in males than in females. The severity was mild in low-dose males, moderate in high-dose males, minimal in low-dose females, and mild in high-dose females. Pigmentation was more severe in the follicular epithelium than in the colloid. Pigmentation severity was graded using criteria described for the 13-week studies. In addition to the pigmentation, minimal follicular cell hyperplasia was seen in 5 of 10 high-dose male mice. The hyperplasia was characterized by scattered follicles lined by columnar cells which were often crowded together and sometimes protruded into the follicular lumen.

A few neoplasms were observed in control and dosed mice at 15 months (Table 15). Neoplasms in dosed mice were not attributed to chemical administration.

### Table 15

Incidences of Neoplasms in Mice at the 15-Month Interim Evaluations in the 2-Year Feed Studies of HC Yellow 4<sup>a</sup>

	0 ppm	5,000 ppm <sup>b</sup>	10,CCI ppm	
Male				
Liver				
Hepatocellular adenoma	2/10	3/10	0/10	
Hepatocellular carcinoma	0/10	0/10	1/10	
Lung	•	·	·	
Alveolar/bronchiolar adenoma	1/10	0/10	0/10	
Female				
Lung				
Alveolar/bronchiolar adenoma	0/10	1/10	0/10	
Lymphoma, undifferentiated	0/10	1/10	0/10	
Pituitary gland, pars distalis				
Adenoma	1/8	0/10	0/8	

<sup>a</sup> Incidences given as number of lesions/number of tissues examined

<sup>o</sup> Only gross lesions were examined microscopically. The denominator is the number of tissues examined grossly.

# Body Weights, Feed Consumption, and Clinical Findings

Mean body weights of all dosed groups were generally lower than those of the controls throughout the studies (Tables 16 and 17 and Figure 3). The mean body weights of low-dose males and females were more than 10% lower than those of the controls after week 53. The mean body weights of high-dose mice were more than 10% lower than those of the controls after week 17 for males and week 14 for females. Feed consumption values for dosed groups were higher than those of the controls throughout the studies (Tables I3 and I4). The apparent increase in feed consumption by dosed animals was due to the scattering of feed by animals searching for unadulterated feed. No clinical findings were attributed to the administration of HC Yellow 4.

### TABLE 16

Mear	i Body	<sup>,</sup> Weights	and	Survival	of	Male	Mice i	in tl	he 2-	Year	Feed	Study	y of	'HC	Yellow	-4
------	--------	----------------------	-----	----------	----	------	--------	-------	-------	------	------	-------	------	-----	--------	----

Weeks	0	ppm		5,000 ppr	0		10,000 ppm	
on	Av. Wt.	Number of	Av. Wt.	Wt. (% of	Number of	Av. Wt.	Wt. (% of	Number of
Study	(g)	Survivors	(g)	controls)	Survivors	(g)	controls)	Survivors
		50	22.0	101	50		101	50
1	22.0	50	23.0	101	50	23.1	101	50
2	23.9	50	23.9	100	50	23.7	99	50
3	24.0	50	24.7	103	50	24.2	101	50
4	20.7	50	27.1	102	-50	23.7	90	50
3	28.3		28.3	101	50	27.3	97	50
0	29.2	50	29.2	100	50	28.3	97	50
1	30.2	50	30.2	100	50	29.3	97	50
8	30.5	50	30.2	99 00	50	28.3	93	50
9	31.7	49	31.4	99	50	. 30.4	90	50
10	32.6	48	32.3	99	50	31.1	95	50
11	33.3	48	32.9	99	50	31.3	94	50
12	33.7	48	33.5	99	49	31.0	94	50
13	34.1	48	. 34.0	100	49	31.0	93	50
14	35.0	48	34.3	98	49	32.4	93	50
17	36.5	46	35.7	98	47	32.7	90	50
21	38.1	46	37.3	98	47	33.5	88	50
25	38.4	45	38.0	99	45	33.8	88	50
29	39.4	45	38.7	98	45	34.2	8/	50
33	39.3	44	39.1	. 100	45	32.0	81	49
37	41.0	. 43	39.7	97	45	34.1	83	49
41	41.3	43	39.4	95	43	33.5	81	49
45	41.8	43	38.7	93	42	33.9	81	47
49	42.5	42	38.6	91	41	34.6	81	47
53	42.7	42	38.3	90	41	33.3	78	47
57	42.0	· 41	· 37.3	89	39	33.3	79	47
61	43.6	38	38.1	87	37	34.6	79	45
65	43.7	38	38.0	87	37	34.3	79	44
69	43.5	37	37.9	87	37	33.8	78	44
73	42.6	37	37.8	89	37	34.0	80	43
77	42.2	35	37.3	88	36	33.2	79	43
81	42.8	35	37.2	87	36	33.0	77	43
85	40.0	35	35.2	88	35	31.0	<b>78</b> ·	42
88	40.4	34	35.4	88	33	31.1	77	41
93	37.6	34	34.7	92	32	31.1	83	40
97	38.3	. 34 .	35.0	91	31	31.1	81	38
101	38.2	32	35.0	92	29	30.2	79	36
104	37.3	31	35.0	94	29	30.5	82	35
Terminal sacr	ifice	28			29			35
Mean for wee	ks							
1-13	29.3		29.3	100		28.1	96	
14-52	39.3		38.0	97		33.5	85	
53-104	41.1		36.6	89		32.5	79	

TABLE 17

Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of HC Yellow 4

Weeks		מתפופו		5,000 ppm			10,000 ppm	
om	Av. Wt.	Number of	Av. Wt.	Wt. (% of	Number of	Av. Wt.	Wt. (% of	Number of
Study	(g)	Survivors	(g)	controls)	Survivors	(g)	controls)	Survivors
1	17.1	50	16.9	<del>99</del>	50	17.1	100	50
2	18.3	50	18.0	98	50	17.8	97	50
3	19.3	50	18.9	98	50	18.3	95	50
4	19.3	50	19.4	101	50	18.9	98	50
5	20.9	50	20.1	96	50	19.8	95	50
6	21.1	50	20.7	98	50	20.2	96	50
7	22.1	50	21.6	98	50	21.2	96	50
Ŗ	22.2	50	22.0	99	50	21.1	95	50
ŏ	23.2	50	22.6	97	50	21 7	94	50
10	23.2	50	22.0	07	50	21.0	92	50
10	25.7	50	23.1	05	50	22.5	<u>en</u>	50
11	24.0	50	24.0	95	50	22.0	07 07	50
14	24.9	50	43.9	90	50	22.7	<i>74</i> 00	50
14	20.7	50	25.1	94	50	23.9	90	50
17	28.9	50	21.2	94	50	24.0	83	50
21	31.5	50	29.3	93	50	26.5	84	50
25	32.7	50	30.3	93	50	27.0	83 91	50 J
29	34.4	50	32.4	94	49	27.9	80	50
33	35.5	50	33.1	94	49	28.1	70	50
41	377	49	34.5	92	49	29.6	79	50
45	38.4	49	35.4	92	49	29.6	77	50
49	39.8	49	35.9	90	49	29.9	75	50
53	40.2	49	36.0	90	49	29.9	74	50
57	39.7	49	35.5	89	49	29.1	73	50
61	41.1	49	37.1	90	49	29.8	73	50
65	41.5	49	35.5	86	49	29.3	71	50
69	42.2	47	36.1	86	49	30.4	72	50
73	41.6	47	36.3	87	49	30.2	73	50
11	42.0	46	37.7	90	48	31.4	75	50
81	42.2	45	37.2	88	48	30.1	71	48
85	42.3	45	30.3	80	48	29.3	67	41
89 02	427	43	33.0 35.0	04 25	41	28.0	68	45
93	42.2	43	35.9	8J 81	45	28.5	65	45
101	43.0	43	35.3	85	42	27.8	67	44
104	42.0	43	35.4	84	39	27.7	66	44
Terminal sacr	ifice	43			38			43
Mean for we	ła							
1-13	21.5		20.9	97		20.3	94	
14-52	34.1		31.6	93		27.6	81	
53-104	41.7		36.1	87		29.3	70	



FIGURE 3 Growth Curves for Mice Administered HC Yellow 4 in Feed for 2 Years

### Survival

Survival in dosed male and female mice was similar to that of the controls (Table 18 and Figure 4).

Pathology and Statistical Analyses of Results This section describes the biologically noteworthy changes in the incidences of nonneoplastic lesions of the thyroid glands of mice. No neoplasms were attributed to the administration of HC Yellow 4. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group are presented in Appendixes C for male mice and D for female mice.

### TABLE 18

Survival of Mice in the 2-Year Feed Studies of HC Yellow 4

	0 юрит	5,010 ppm	10,020 ppm	
Male		<u></u>		
Animals initially in study	70	70	70	
6-month interim evaluation <sup>a</sup>	10	10	10	
15-month interim evaluation <sup>a</sup>	10	10	10	
Natural deaths	14	10	5	
Moribund kills	8	10	9	
Accidental deaths <sup>a</sup>	0	0	1	
Missing <sup>a</sup>	0	1	0	
Animals surviving to study termination	28	29	35	
Percent survival at end of study <sup>b</sup>	60	63	73	
Mean survival (days) <sup>c</sup>	516	512	568	
Survival analyses <sup>d</sup>	P=0.119N	P=0.937N	P=0.133N	
Female				
Animals initially in study	70	70	70	
6-month interim evaluation <sup>a</sup>	10	10	10	
15-month interim evaluation <sup>a</sup>	10	10	10	
Natural deaths	4	2	2	
Moribund kills	3	10	5	
Animals surviving to study termination	43	38	43	
Percent survival at end of study <sup>b</sup>	86	76	86	
Mean survival (days) <sup>c</sup>	589	594	600	
Survival analyses <sup>d</sup>	P=1.000N	P=0.375	P=1.000N	

<sup>a</sup> Censored from survival analyses

<sup>b</sup> Kaplan-Meier determinations. Survival rates adjusted for interim evaluations.

<sup>c</sup> Mean of all deaths (uncensored, censored, terminal sacrifice)

<sup>a</sup> 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 4 Kaplan-Meier Survival Curves for Mice Administered HC Yellow 4 in Feed for 2 Years

Thyroid Gland: The incidences of pigmentation and follicular cell hyperplasia were greatly increased in all dosed groups (Table 19). The pigment was gold-yellow to gold-brown and varied from fine granules to large aggregates. Pigment was present in the follicular cell cytoplasm (follicular cell, pigmentation), in the follicular lumens (follicle, pigmentation), and within macrophages in the interstitium between follicles (interstitium, pigmentation). Severity of pigmentation increased slightly with increasing dose and generally ranged from minimal to mild in the low-dose and mild to moderate in the high-dose groups (Plates 1 and 2). The severity was graded using the criteria described earlier in this report. The increase in hyperplasia was not accompanied by an increase in follicular cell neoplasms. Hyperplasia was of minimal to mild severity in all dosed groups. It involved multiple follicles lined by increased numbers of closely packed cells; as severity increased the follicular cells formed clusters that projected into the lumen. Chronic inflammation of minimal severity occurred in dosed males (Table 19). Inflammation, which consisted of scattered aggregates of small numbers of lymphocytes in the glandular interstitium, is not an uncommon finding in thyroid glands of older mice containing some degree of follicular cell hyperplasia.

Table 19

Incidences of Selected Thyroid Gland Lesions in Mice in the 2-Year Feed Studies of HC Yellow 4ª

	0 ppm	5,000 ppm	10,000 ppm
Male			
Follicular cell adenoma <sup>b</sup>	1/47 (2%)	0/48 (0%)	2/49 (4%)
Follicular cell hyperplasia	0/47 (0%)	27/48 (56%)**	41/49 (84%)°°
Follicular cell pigmentation	0/47 (0%)	44/48 (92%)**	49/49 (100%)°°
Follicular pigmentation	0/47 (0%)	44/48 (92%)**	48/49 (98%)°°
Interstitial pigmentation	0/47 (0%)	42/48 (88%)**	49/49 (100%)°°
Chronic inflammation	0/47 (0%)	7/48 (15%)**	29/49 (59%)°°
Female			
Follicular cell hyperplasia	0/48 (0%)	3/49 (6%)	13/50 (26%)°°
Follicular cell pigmentation	0/48 (0%)	49/49 (100%)°°	50/50 (100%)°°
Follicular pigmentation	0/48 (0%)	48/49 (98%)°°	50/50 (100%)°°
Interstitial pigmentation	0/48 (0%)	46/49 (94%)°°	50/50 (100%)°°

°° Significantly different (P≤0.01) from the control group by the logistic regression test

a Incidences given as number of lesion-bearing animals/number of animals examined at site

Historical incidence for 2-year NTP feed studies of untreated control groups (mean ± standard deviation): 14/856 (1.6% ± 1.7%), range 0%-4%

### **GENETIC TOXICOLOGY**

HC Yellow 4 (3 to 10,000  $\mu$ g/plate) was tested for induction of gene mutations in four strains of *Salmonella typhimurium* in a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9; results were positive for strains TA100, TA1537, and TA98 with and without S9 (Table E1; Mortelmans *et al.*, 1986). An equivocal response was noted in strain TA1535 in the absence of S9 activation; results were negative with S9.

HC Yellow 4 induced sister chromatid exchanges in Chinese hamster ovary cells in the absence but not the presence of S9 activation (Table E2). In the two trials without S9, a significant increase in sister chromatid exchanges was observed only at the highest dose tested (167 or 200  $\mu$ g/mL); the highest dose induced cell cycle delay and required an extended harvest to accumulate sufficient cells for analysis. With Aroclor 1254-induced male Sprague-Dawley rat liver S9, no significant increase was observed with concentrations up to 1,700  $\mu$ g/mL HC Yellow 4; cell cycle delay was not noted with S9. When tested for induction of chromosomal aberrations in Chinese hamster ovary cells, HC Yellow 4 was negative with and without S9 (Table E3). In the one trial conducted without S9, a dose-related increase in aberrations was noted, but this increase was not statistically significant either by trend analysis (P=0.027) or peak response (P>0.05); a delayed harvest protocol was necessary to offset cell cycle delay caused by chemical administration. With S9, no cell cycle delay was observed in either trial and the weakly positive response observed at the highest nonlethal dose tested in the first trial (3,000  $\mu$ g/mL) was not repeated in the second trial. A precipitate formed at the 2,500  $\mu$ g/mL concentration in Trial 2 and no viable cells were present in the 3,000  $\mu$ g/mL cultures.

HC Yellow 4 induced sex-linked recessive lethal mutations in germ cells of adult male *Drosophila melanogaster* when administered by injection at a dose of 10,000 ppm; results of the initial feeding test were negative (Table E4; Woodruff *et al.*, 1985). Following the positive result in the sex-linked recessive lethal assay, HC Yellow 4 (10,000 ppm by injection) was tested for induction of reciprocal translocations in germ cells of male *D. melanogaster*; results of this assay were negative (Table E5; Woodruff *et al.*, 1985).



### Plate 1

Normal thyroid gland of a control male B6C3F1 mouse in the 2-year feed study of HC Yellow 4. H&E, 300X



### Plate 2

Increased cellularity of the follicular epithelium in the thyroid gland of a male  $B6C3F_1$  mouse receiving 10,000 ppm HC Yellow 4 in the 2-year feed study. Note the dark staining due to the presence of pigment. Compare with Plate 1. H&E, 300X

- #\$

### DISCUSSION AND CONCLUSIONS

Toxicity and carcinogenicity studies were conducted by administering HC Yellow 4 in feed to F344/N rats and B6C3F<sub>1</sub> mice. Although human exposure to HC Yellow 4 occurs primarily via the dermal route, the dosed feed route of administration was selected to ensure systemic exposure. In the 14-day rat feed studies, doses of 5,000 to 80,000 ppm (equivalent to 450 to 13,000 mg/kg body weight) caused decreases in body weight and feed intake. In the 14-day mouse feed studies, doses of 1,250 to 20,000 ppm (equivalent to 150 to 3,200 mg/kg) caused no toxic effects.

In the 13-week studies, doses of 2,500, 5,000, 10,000, 20,000, or 40,000 ppm were given to rats and doses of 5,000, 10,000, 20,000, 40,000, or 80,000 ppm were given to mice. All rats survived to the end of the studies. Final mean body weights of male rats that received doses of 10,000 ppm or greater and females that received doses of 20,000 ppm or greater were significantly lower than those of the controls. Histopathologic examination of the thyroid gland of rats revealed pigmentation in the follicular cells of 8 of 10 males and 2 of 10 females at the highest dose level. Slight mineralization of tubules in the renal papilla occurred in male rats that received 40,000 ppm. Uterine atrophy was seen in all female rats in the 20,000 and 40,000 ppm dose groups and may be related to the reduced body weights observed in these dose groups. Decreased body weight gain, when severe, is associated with uterine atrophy. Chemical-related deaths occurred in male mice that received 40,000 or 80,000 ppm and female mice that received 80,000 ppm. Final mean body weights were decreased in male and female mice that received doses above 5,000 ppm. Histopathologic examination of the thyroid gland revealed the presence of golden brown pigment in the follicular cells. Thyroid pigmentation was noted previously in the 13-week feed studies with the structurally related dyes HC Blue No. 1 (NTP, 1985a) and HC Blue No. 2 (NTP, 1985b). Lymphoid depletion and atrophy of the spleen and thymus were observed in mice in the 40,000 and 80,000 ppm dose groups and may have been associated with the decreases in mean body weight observed in these dose groups.

The doses selected for the 2-year studies were 0, 2,500, or 5,000 ppm for male rats and 0, 5,000, or 10,000 ppm for female rats and for male and female mice. The dose selection was based on mortality and decreased body weight.

In the 2-year studies, HC Yellow 4 caused a significant decrease in the mean body weight of high-dose female rats and all dosed mice. Mean body weights of dosed male and low-dose female rats were similar to those of the controls. The survival of dosed rats and mice was similar to that of the controls. Because HC Yellow 4 had no effect on body weight or survival of dosed male rats, it is possible that male rats could have tolerated higher doses, but probably not a doubling of the dose. In the 13-week studies, male rats were more sensitive to body weight depression than females. At doses of 10,000 ppm and above, males showed consistently higher percentages of body weight depression than females. Females receiving 10,000 ppm had no body weight depression at 13 weeks and 7% at the end of 2 years, as compared to 8% body weight depression at the end of 13 weeks in males receiving the same dose. Therefore, it is likely that if 10,000 ppm had been used for male rats in the 2-year study, they would have shown a considerable weight loss at the end of the study.

No chemical-related histopathologic lesions were observed in male or female rats evaluated at 15 months. In the 2-year studies, however, an increased incidence of pituitary gland adenomas of the pars distalis occurred in male rats (0 ppm, 17/45; 2,500 ppm, 20/49; 5,000 ppm, 28/49). The historical incidence for this tumor in untreated control rats is 230/785 (29.3%) with a range of 12% to 60%.

The only significant chemical-related effect observed in mice was a dose-related increased incidence in thyroid gland pigmentation and follicular cell hyperplasia. No chemical-related increase in the incidence of neoplastic lesions was observed in mice.

As in the 14-day and 13-week studies, the thyroid gland of mice was the organ primarily affected by

HC Yellow 4 in the 2-year studies. Dose-related increased incidences in follicular cell pigmentation and hyperplasia were observed in both sexes. The nature of the pigment was undetermined. Results of special histologic stains demonstrated that the pigment was not hemosiderin or ceroid, but were otherwise inconclusive. While it is possible to speculate that the pigment may represent HC Yellow or a metabolite, there is no definite proof of this. It is unclear if there was a relationship between the presence of pigment and follicular cell hyperplasia in these studies. In two other NTP studies of semipermanent hair dyes, C.I. Disperse Blue 1 (NTP, 1986a) and HC Red No. 3 (NTP, 1986b) caused increased thyroid gland pigmentation without a concomitant increase in hyperplasia. The presence of N-(2-hydroxyethyl)-2hydroxy-4-nitroaniline as an impurity in HC Yellow 4 may have contributed to the increased incidence of thyroid follicular cell hyperplasia. Several aromatic amines, including aniline derivatives tested by NCI/NTP such as 4,4'-oxydianiline. 4,4'-methylenedianiline, and 4,4'-methylenebis (N,N-dimethyl)-benzamine, were found to increase the incidences of thyroid follicular cell adenoma and hyperplasia (Hayden et al., 1978; Weisburger et al., 1984; Hill et al., 1989).

HC Yellow 4 bears a close structural resemblance to three of the five semipermanent hair dyes tested by the NTP: HC Blue No. 1, HC Blue No. 2, and HC Red No. 3 (Table 20). Of these structurally related dyes, the strongest evidence of carcinogenicity was obtained with HC Blue No. 1. This dye produced hepatocellular neoplasms in mice and, to a lesser degree, male rats. Dosed female rats had increased incidences of lung neoplasms. HC Red No. 3 caused a marginal increase in the incidence of liver tumors in male mice. No liver tumors were caused by HC Blue No. 2 or HC Yellow 4 in rats or mice. All of these dyes were mutagenic in Salmonella typhimurium. The S. typhimurium gene mutation assay has a high positive predictivity for carcinogenicity (89% of chemicals mutagenic in S. typhimurium are carcinogenic in rodents) (Tennant

et al., 1987). In the case of HC Yellow 4 and these two other noncarcinogenic dyes, positive results in the in vitro S. typhimurium gene mutation test are not reflected in vivo. The difference in the carcinogenic potential of these dyes may be due to differences in the metabolism or excretion of these dyes. The hydroxyethyl groups on the nitrogen in position 1 in HC Yellow 4 and positions 1 and 4 in HC Blue No. 2, as well as the hydroxyl group in position 2 in HC Yellow 4, may favor conjugation and excretion. The methyl group on the nitrogen in position 4 in HC Blue No. 1 may favor dealkylation and formation of an N-hydroxyl group. In HC Red No. 3, the primary amine may undergo N-acetylation or N-hydroxylation.

Although C.I. Acid Orange 3 (NTP, 1988) and C.I. Disperse Blue 1 do not bear a close structural resemblance to the other dyes, they too are mutagenic and have the potential to be metabolized to aromatic amines which are then *N*-hydroxylated to produce the final carcinogenic metabolite. Both dyes have been found to be carcinogenic; C.I. Acid Orange 3 induced kidney tumors in female rats, and C.I. Disperse Blue 1 induced urinary bladder neoplasms in male and female rats and marginally increased incidences of liver and lung neoplasms in male mice (Table 20).

Conclusions: Under the conditions of these 2-year feed studies, there was equivocal evidence of carcinogenic activity\* of HC Yellow 4 in male F344/N rats based on the increased incidence of pituitary gland adenomas and hyperplasia. The male rats may have been able to tolerate a slightly higher dose of the chemical. There was no evidence of carcinogenic activity of HC Yellow 4 in female F344/N rats given 5,000 or 10,000 ppm. There was no evidence of carcinogenic activity of HC Yellow 4 in male or female B6C3F<sub>1</sub> mice given 5,000 or 10,000 ppm.

There was a chemical-related increase in the incidence of thyroid gland pigmentation and follicular cell hyperplasia in mice.

<sup>•</sup> Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 10.

### Table 20

### Comparison of Results of NTP Studies of Semipermanent Hair Dyes

Chemical (route)/ Structure	Species/ Sex	Dose (mg/kg)	Level of Evidence <sup>a</sup>	Organ/Tumor
HC Blue No. 1				
(feed)	Rat			
	male	66 or 129		Liver: neoplastic nodules,
			EE	carcinoma
HOCH2-CH2	female	74 or 154		Lung: alveolar/bronchiolar
>n			SE	neoplasms
HOCH2 - CH2 CH3	Mouse		<b>O</b> E	* ·
	male	309 or 650	CE	Liver: carcinoma; thyroid
	famala	779 1 634	CE	giand: adenoma
	Iemale	//8 of 1,034	CE	Liver: carcinoma
HC Blue No. 2				
(feed)	Rat			
	male	194 or 390	NE	None
	female	464 or 999	NE	None
HOCH2-CH2 N				
HOCH2-CH2 (CH2)20H	Mouse			
NO <sub>2</sub>	male	1,319 or 2,239	NE	None
	female	2,331 or 5,603	NE	None
LIC Ded No. 2				
HC Red No. 3	Dat			
(gavage)	male	250 or 500	NE	None
	female	250 or 500	NE	None
NHC <sub>2</sub> H <sub>4</sub> OH	Temate		1.2	
	Mouse			
NH2 NO2	male	125 or 250	EE	Liver: adenoma, carcinoma
	female	125 or 250	I	
HC Yellow 4 (current studies)	Pat			
(leeu)	Rat	140	FF	Bituitary gland; edenoma
OCH2CH2OH	female	260 or 500	NE	None
	remarc	200 01 500	ne.	Trone
NH-CH2CH2OH	Mouse			
	male	1.380 or 2.500	NE	None
0-N	female	1,080 or 2,800	NE	None
52		_,		
(avage)	Rat			
(Barage)	male	375 or 750	NE	None
	female	375 or 750	CE	Kidney: transitional cell
_NO2SO3 NOT	temaie	515 51 150	02	carcinoma
	Mouse			
	male	125 or 250	NE	None
	female	250 or 500	NE	None
	female	250 or 500	NE	None

 $- p_{a,b}$  :

### TABLE 20

Comparison of Results of NTP Studies of Semipermanent Hair Dyes (continued)

Chemical (route)/ Structure	Species/ Sex	Dose (mg/kg)	Level of Evidence	Organ/Tumor
C.I. Disperse Blue 1		<u> </u>		
(feed)	Rat			
	male	<b>45, 95, or 21</b> 7	CE	Urinary bladder (males and
NH <sub>2</sub> O NH <sub>2</sub>	female	56, 111, or 240	CE	temales): transitional cell papilloma and carcinoma, leiomyoma and leiomysarcoma, squamous cell papilloma and carcinoma
	Mouse	110 000 540	<b>P</b> P	T
$^{\rm H}_{\rm NH_2}$ $^{\rm H}_{\rm NH_2}$	male	112, 239, or 540	EE	Liver: adenoma and carcinoma; lung: alveolar/bronchiolar adenoma and carcinoma
	female	108, 235, or 520	NE	None

<sup>a</sup> Levels of evidence of carcinogenic activity: CE = clear evidence; SE = some evidence; EE = equivocal evidence; NE = no evidence; I = inadequate study

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## APPENDIX A SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR FEED STUDY OF HIC YELLOW 4

Table A1	Summary of the Incidence of Neoplasms in Male Rats	
	in the 2-Year Feed Study of HC Yellow 4	54
Table A2	Individual Animal Tumor Pathology of Male Rats	
	in the 2-Year Feed Study of HC Yellow 4	58
Table A3	Statistical Analysis of Primary Neoplasms in Male Rats	
	in the 2-Year Feed Study of HC Yellow 4	76
Table A4	Historical Incidence of Pituitary Gland Neoplasms	
	in Untreated Male F344/N Rats	81
Table A5	Summary of the Incidence of Nonneoplastic Lesions in Male Rats	
	in the 2-Year Feed Study of HC Yellow 4	82

### Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of HC Yellow 4<sup>a</sup>

	0	ppm	2,500	) ppm	5,00	) ppm
Disposition Summary						
Animals initially in study	70		70		70	
6-month interim evaluation	10		10		10	
5-month interim evaluation	9		10		10	
Early deaths						
Natural deaths	6		4		3	
Moribund kills	24		17		18	
Survivors						
Terminal sacrifice	21		29		28	
Aissexed					1	
Animals examined microscopically	50 <sup>b</sup>		50		49	
limentary System						
Esophagus	(48)		(48)		(49)	
ntestine large, cecum	(47)		(48)		(46)	
ntestine large, colon	(48)		(44)	(8.02)	(45)	
Polyp adenomatous			1	(2%)		
ntestine small, duodenum	(47)		(48)		(47)	
ntestine small, ileum	(45)		(48)		(46)	
ntestine small, jejunum	(46)		(47)		(46)	
Sarcoma					1	(2%)
Liver	(50)		(50)		(49)	
Adenocarcinoma, metastatic, lung					1	(2%)
Fibrosarcoma, metastatic, skin	1	(2%)				
Hepatocellular adenoma	1	(2%)				
Acsentery	(3)		(5)		(1)	
ancreas	(50)		(48)		(48)	
Acinus, adenoma	1	(2%)	3	(6%)	2	(4%)
Acinus, adenoma, multiple	1	(2%)	1	(2%)		
harynx	(1)					
Palate, papilloma squamous	1	(100%)				
alivary glands	(49)		(50)		(48)	
Sarcoma			1	(2%)		
Stomach, forestomach	(50)		(48)		(49)	
Papilloma squamous	1	(2%)	1	(2%)		
Stomach, glandular	(49)		(48)		(48)	
l'ongue					(3)	
Papilloma squamous	۰.				2	(67%)
Cardiovascular System						
Jeart	(50)		(50)		(49)	
		· · · · · · · · · · · · · · · · · · ·				
Endocrine System	(50)		(50)		(48)	
Caroinomo	(50)	(2%)	(50)		(-0)	
Carcinolita Adronal aland madulla	۱ (۳۵۱)	(270)	(40)		(49)	
Bhaabaanaantama malianant	(50)	(1%)	·(+7) 1	(2%)	(-0)	
r neochromocytoma mangnant	12	(470)	11	(27%)	14	(20%)
Pilotemi, photoshume reterno horier	13	(120%)	11 ∠	(12%)	14	(10%)
Bilaterai, pneochromocytoma benign	0	(1270)	0	(1270)	2	(470)

### Table A1

Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of HC Yellow 4 (continued)

Embedderine System (continued) lates, parcreatic         (48) Adenoma         (47) (40)         (48) (47)         (44) (43)         (48) (47)           Paraltynoid gland         (47)         (44)         (37)         (49)         (49)           Paraltynoid gland         (45)         (49)         (49)         (49)         (49)           Para distalis, adenoma, multiple         17         (38%)         18         (37%)         (2         (43%)           Tyroid gland         (49)         (49)         (49)         (48)         (48)         (48)           C-cell, adenoma, multiple         1         (28)         5         (19%)         6         (13%)           C-cell, adenoma         (49)         (50)         (49)         (49)         (49)         (49)           C-cell, adenoma         (49)         (50)         (49)         (49)         (49)         (49)           C-cell, adenoma         1         (27%)         13         (26%)         (49)         (49)           Carcinoma         1         (27%)         13         (49)         (49)         (49)           Generatal Body System         1         (27%)         13         (26%)         14         (27%)           <		0 թ	und<	2,50	0 lebuu	5,00	0 ppm
Lates, pancreatic       (48)       (47)       (43)       (47)         Adenoma       1       (278)       4       (99)       3       (67)         Paraltyroid gland       (47)       (44)       (27)       (44)       (27)         Para distalis, adenoma       17       (38%)       18       (37%)       26       (53%)         Para distalis, adenoma, multiple       17       (38%)       (49)       (49)       (49)       (48)         Thyroid gland       (49)       (49)       (49)       (48)       (50)       (49)         C-cell, adenoma, multiple       1       (27%)       5       (10%)       6       (13%)         C-cell, adenoma       (49)       (50)       (49)       (49)       (49)       (49)         C-cell, adenoma       1       (27%)       13       (26%)       7       (14%)         Carcinoma       1       (27%)       13       (26%)       7       (14%)         Carcinoma       1       (27%)       1       (27%)       1       (27%)         Prostatal setona       1       (27%)       1       (27%)       1       (27%)         Seminal vesite       (48)       (50) <th>Endocrime System (continued)</th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th>	Endocrime System (continued)						
Adecoma       1       (2%)       4       (9%)       3       (6%)         Parathycoid gland       (47)       (44)       (27)       (25%)       (49)       (49)       (20)       (25%)       (25%)       (49)       (49)       (49)       (20)       (48)       (48)       (48)       (48)       (48)       (48)       (48)       (48)       (49)       (40)       (49)       (40)       (40)       (49)       (40)       (40)       (49)       (40) </th <th>Islets, pancreatic</th> <th>(48)</th> <th></th> <th>(47)</th> <th></th> <th>(48)</th> <th></th>	Islets, pancreatic	(48)		(47)		(48)	
Parathypoid gland $(47)$ $(44)$ $(37)$ Adenoma $(45)$ $(49)$ $(26)$ Para distalis, adenoma, multiple       17 $(38\%)$ $18$ $(37\%)$ $26$ $(53\%)$ Para distalis, adenoma, multiple       1 $(28\%)$ $5$ $(10\%)$ $6$ $(13\%)$ C-cell, adenoma, multiple       1 $(27\%)$ $5$ $(10\%)$ $6$ $(13\%)$ C-cell, adenoma, multiple       1 $(27\%)$ $5$ $(10\%)$ $6$ $(13\%)$ C-cell, adenoma $6$ $(12\%)$ $5$ $(10\%)$ $6$ $(13\%)$ C-cell, adenoma $(49)$ $(50)$ $(49)$ $(49)$ $(49)$ $(49)$ $(49)$ $(49)$ $(49)$ $(49)$ $(2\%)$ $(2\%)$ $(2\%)$ $(2\%)$ $(49)$ $(49)$ $(50)$ $(49)$ $(49)$ $(46)$ $(49)$ $(50)$ $(48)$ $(50)$ $(48)$ $(50)$ $(48)$ $(50)$ $(48)$ $(50)$ $(48)$ $(50)$ $(48)$ $(50)$ $(49)$ $(50)$ $(50)$ $(46)$	Adenoma	1	(2%)	4	(9%)	3	(6%)
Adenoma       2       (5%)         Pars distalis, adenoma, multiple       17       (38%)       18       (37%)       26       (33%)         C-sell, adenoma, multiple       1       (2%)       5       (10%)       6       (13%)         C-cell, adenoma, multiple       1       (2%)       5       (10%)       6       (13%)         C-cell, adenoma, multiple       1       (2%)       5       (10%)       6       (13%)         C-cell, adenoma       1       (2%)       5       (10%)       6       (13%)         C-cell, adenoma       1       (2%)       1       (2%)       1       (2%)         Gemeral Body System	Parathyroid gland	(47)		(44)		(37)	
Pituliary gland (45) (49) (49) (49) Pars distalis, adenoma 117 (38%) 18 (37%) 26 (53%) Pars distalis, adenoma, multiple 2 (4%) 2 (4%) Thyroid gland (49) (49) C-cell, adenoma, multiple 1 (2%) 5 (10%) 6 (13%) C-cell, adenoma 1 (2%) 1 (2%) General Body System None General Body System Protial gland (48) (50) (49) Preputal gland (48) (50) (49) Preputal gland (48) (50) (49) Preputal gland (48) (50) (49) Protate (48) (50) (49) Protate (48) (50) (49) Protate (48) (50) (46) Seminal vesicle (48) (50) (46) Seminal vesicle (48) (50) (48) Ester (50) (49) Bilateral, interstitial cell, adenoma 37 (74%) 40 (80%) 36 (73%) Interstitial cell, adenoma 10 (20%) 3 (6%) 5 (10%) Hematopoletic System Bone marrow (49) (50) (48) Tymph node (50) (50) (48) Lymph node (50) (50) (48) Lymph node (50) (50) (48) Lymph node (49) (50) (44) Sarcona 1 (2%) Thymus (41) (2%) Thymus (41) (2%) Thymos benign 1 (2%) Mammary gland (28) (18) (26) Mammary gland (28) (17) 1 (6%) (17) Subcutaneous tissue, fibroma 2 (4%) (2%) (10%)	Adenoma					2	(5%)
Pars distalis, adenoma, multiple       17 (39%)       18 (37%)       26 (33%)         Thyroid gland       (49)       (49)       (49)       (48)         C-cell, adenoma, multiple       1 (2%)       3 (10%)       6 (13%)       C (33%)         Follicular cell, adenoma       1 (2%)       3 (10%)       6 (13%)       C (33%)         General Body System       1 (2%)       1 (2%)       1 (2%)         General Body System       (49)       (50)       (49)         Fputial gland       (48)       (50)       (49)         Adenoma       1 (2%)       1 (2%)       1 (2%)         Bilateral, adenoma       1 (2%)       1 (2%)       1 (2%)         Proviate       (48)       (50)       (49)       (46)         Seminal vesicle       (48)       (50)       (49)       (46)         Seminal vesicle       (48)       (50)       (49)       (46)         Seminal vesicle       (48)       (50)       (49)       (46)         Bilateral, interstitial cell, adenoma       37 (74%)       40 (80%)       36 (73%)         Interstitial cell, adenoma       10 (20%)       3 (6%)       5 (10%)         Lymph node, mandibular       (46)       (46)       (46)	Pituitary gland	(45)		(49)		(49)	
Fram Sustais, accoma, multiple $2$ (*%) <th< td=""><td>Pars distalis, adenoma</td><td>17</td><td>(38%)</td><td>18</td><td>(37%)</td><td>26</td><td>(53%)</td></th<>	Pars distalis, adenoma	17	(38%)	18	(37%)	26	(53%)
Inyron gana       (**) <td>Pars distalis, adenoma, multiple</td> <td>(40)</td> <td></td> <td>2</td> <td>(4%)</td> <td>2</td> <td>(4%)</td>	Pars distalis, adenoma, multiple	(40)		2	(4%)	2	(4%)
C-cell, adenoma, multiple       1 (2%)       5 (10%)       5 (15%)         Follicular cell, adenoma       1 (2%)       1 (2%)       1 (2%)         General Body System       6       1 (2%)       1 (2%)         General Body System       6       (49)       (50)       (49)         Adenoma       8 (17%)       13 (26%)       7 (14%)         Carcinona       1 (2%)       1 (2%)       1 (2%)         Bilateral, adenoma       1 (2%)       1 (2%)       1 (2%)         Prostate       (48)       (50)       (49)       (40)         Seminal vesicle       (48)       (50)       (49)       (40)         Testes       (50)       (49)       (50)       (49)         Jumph node, manibular       (49)       (50)       (49)         Lymph node, mescateric       (49)       (50)       (41)         Lymph node, mescateric       (49)       (43)       (47)         Thymos       1 (2%)       (18)       (26)         Stor       (48)       (50)       (47)         Stor       1 (2%)       1 (2%)       (43)         Thymos       1 (2%)       1 (2%)       (43)         Starcona       1 (2%)	C soli adonomo	(49)	(1004)	(49)	(100%)	(48)	(120%)
Controlling, nutriple       1 (2%)         General Rody System       1 (2%)         General Rody System       (49)         None       (50)       (49)         Genital System       (49)       (50)       (49)         Epiditymis       (49)       (50)       (49)         Adenoma       8 (17%)       13 (26%)       7 (14%)         Carcinoma       1 (2%)       1 (2%)       1 (2%)         Bilateral, adenoma       1 (2%)       1 (2%)       (49)         Seminal vesicle       (48)       (50)       (49)         Seminal vesicle       (48)       (50)       (49)         Bilateral, interstitial cell, adenoma       10 (20%)       3 (6%)       5 (10%)         Hemastopoletic System       Bone marrow       (49)       (50)       (49)         Lymph node, mandibular       (46)       (46)       (46)       (46)         Lymph node, madibular       (46)       (46)       (47)       Thymoma benign       1 (2%)         Integumentary System       Maammary gland       (28)       (18)       (26)       (48)         Stin       (41)       (43)       (47)       Thymoma benign       1 (2%)       1 (2%)         Integume	C-cell adenoma multiple	0	(1270)	5	(10%)	0	(15%)
General Body System None           Genital System         (49)         (50)         (49)           Epidifymis         (49)         (50)         (49)           Preputial gland         (48)         (50)         (49)           Adenoma         8         (17%)         13         (26%)         7         (14%)           Carcinoma         1         (2%)         1         (2%)         1         (2%)           Bilateral, adenoma         1         (2%)         1         (2%)         1         (2%)           Prostate         (48)         (50)         (48)         (49)         (46)         (48)           Seminal vesicle         (48)         (50)         (48)         (50)         (49)           Bilateral, interstitial cell, adenoma         37         (74%)         40         (80%)         36         (73%)           Interstitial cell, adenoma         10         (20%)         3         (6%)         5         (10%)           Lymph node, mandibular         (46)         (46)         (46)         (46)         (47)         (47)           Spleen         (50)         (50)         (47)         (47)         (50)         (47)	Follicular cell, adenoma	1	(270)			1	(2%)
Genital System           Genital System         (49)         (50)         (49)           Preputial gland         (48)         (50)         (49)           Adenoma         8         (17%)         13         (25%)         7           Bilateral, adenoma         1         (2%)         1         (2%)         1           Prostate         (48)         (50)         (48)         (50)         (48)           Seminal vesicle         (48)         (50)         (48)         (50)         (48)           Testes         (50)         (50)         (48)         (50)         (48)           Bilateral, interstitial cell, adenoma         37         (74%)         40         (80%)         36         (73%)           Bone marrow         (49)         (50)         (49)         (50)         (49)         (46)           Lymph node, madibular         (46)         (46)         (46)         (46)         (46)         (46)         (46)         (46)         (46)         (46)         (46)         (46)         (46)         (46)         (46)         (46)         (46)         (46)         (47)         (47)         (47)         (47)         (47)         (47)	General Body System None						
Epididymis       (49)       (50)       (49)         Preputial gland       (48)       (50)       (49)         Adecoma       8       (17%)       13       (26%)       7       (14%)         Carcinoma       1       (2%)       1       (2%)       7       (14%)         Bilateral, adenoma       1       (2%)       1       (2%)       7       (14%)         Seminal vesicle       (48)       (50)       (48)       (50)       (48)         Testes       (50)       (50)       (48)       (50)       (48)         Bilateral, interstitial cell, adenoma       37       (74%)       40       (80%)       36       (73%)         Bone marrow       (49)       (50)       (48)       (50)       (48)         Lymph node       (50)       (50)       (47)       (46)       (46)       (46)       (46)       (46)       (46)       (46)       (46)       (46)       (46)       (47)       (48)       (50)       (47)       (48)       (50)       (47)       (47)       (48)       (50)       (47)       (48)       (50)       (47)       (48)       (50)       (47)       (48)       (50)       (47)       (46)	Genital System						
Preputial gland       (48)       (50)       (49)         Adenoma       8 (17%)       13 (26%)       7 (14%)         Carcinoma       1 (2%)       1 (2%)         Bilateral, adenoma       1 (2%)       1 (2%)         Prostate       (48)       (49)       (46)         Seminal vesicle       (48)       (50)       (48)         Testes       (50)       (50)       (49)         Bilateral, interstitial cell, adenoma       37 (74%)       40 (80%)       36 (73%)         Interstitial cell, adenoma       10 (20%)       3 (6%)       5 (10%)         Hematopoletic System       50       (50)       (48)         Lymph node, mesenteric       (49)       (50)       (49)         Lymph node, mesenteric       (49)       (50)       (48)         Sarcoma       1 (2%)       (43)       (47)         Thymos       (41)       (43)       (47)         Thymos       1 (2%)       1 (4%)       (47)         Salarcoma       1 (2%)       1 (4%)       (47)         Salarcoma       1 (4%)       1 (4%)       (47)         Spleen       (50)       (50)       (47)         Saland cell carcinoma       1 (4%) </td <td>Epididymis</td> <td>(49)</td> <td></td> <td>(50)</td> <td></td> <td>(49)</td> <td></td>	Epididymis	(49)		(50)		(49)	
Aderoma       8       (17%)       13       (26%)       7       (14%)         Garcinoma       1       (2%)       1       (2%)       1       (2%)         Bilateral, adenoma       1       (2%)       1       (2%)       1       (2%)         Prostate       (48)       (50)       (49)       (46)       (48)       (50)       (49)         Bilateral, interstitial cell, adenoma       37       (74%)       40       (80%)       36       (73%)         Interstitial cell, adenoma       10       (20%)       3       (6%)       5       (10%)         Bone marrow       (49)       (50)       (48)       (10%)       (46)       (47)       (10%)       (11%)       (11%)       (11%)       (11%)       (11%)       (11%)       (11%)       (11%)       (11%)       (11%)       (11%)       (11%)       (11%)       (11%)       (11%)       (11%)       (11%)       (11%)       (11%	Preputial gland	(48)		(50)		(49)	
Carcinoma       1 $(2\%)$ 1 $(2\%)$ Bilateral, adenoma       1 $(2\%)$	Adenoma	8	(17%)	13	(26%)	7	(14%)
Bilateral, adenoma       1 $(2\%)$ 1 $(2\%)$ Prostate       (48)       (49)       (46)         Seminal vesicle       (48)       (50)       (48)         Testes       (50)       (50)       (49)         Bilateral, interstitial cell, adenoma       37       (74%)       40       (80%)       36       (73%)         Interstitial cell, adenoma       10       (20%)       3       (6%)       5       (10%)         Hemastopoletic System       Bone marrow       (49)       (50)       (48)       (49)       (50)       (49)         Lymph node, mandibular       (46)       (46)       (46)       (46)       (46)       (47)       Spleen       (50)       (48)       (50)       (48)       Sarcoma       1       (2%)       Thymus       (11)       (43)       (47)       Thymus       (41)       (43)       (47)       Thymoma benign       1       (4%)       1       (4%)       1       (4%)       1       (4%)       1       (4%)       1       (4%)       1       (4%)       1       (4%)       1       (4%)       1       (4%)       1       (4%)       1       (4%)       1       (50)       (4%) <td>Carcinoma</td> <td>1</td> <td>(2%)</td> <td></td> <td></td> <td></td> <td></td>	Carcinoma	1	(2%)				
Prostate       (48)       (49)       (46)         Seminal vesicle       (48)       (50)       (48)         Testes       (50)       (50)       (49)         Bilateral, interstitial cell, adenoma       37       (74%)       40       (80%)       36       (73%)         Interstitial cell, adenoma       10       (20%)       3       (6%)       5       (10%)         Hematopoletic System       Bone marrow       (49)       (50)       (48)         Lymph node, machibular       (46)       (46)       (46)         Lymph node, mesenteric       (49)       (50)       (47)         Spleen       (50)       (50)       (48)         Sarcoma       1       (2%)       (47)         Thymos       (41)       (43)       (47)         Thymoma benign       1       (2%)       1       (4%)         Adenoma       1       (4%)       (50)       (47)         Basal cell carcinoma       3       (11%)       1       (6%)         Skin       (48)       (50)       (47)       (4%)       (4%)         Subcutaneous tissue, fibroma       3       (11%)       1       (2%)       1       (2%)	Bilateral, adenoma	1	(2%)			1	(2%)
Seminal vesicle       (48)       (50)       (48)         Testes       (50)       (50)       (49)         Bilateral, interstitial cell, adenoma       37       (74%)       40       (80%)       36       (73%)         Interstitial cell, adenoma       10       (20%)       3       (6%)       5       (10%)         Hemastopoletic System       Bone marrow       (49)       (50)       (48)       (49)       (20%)       (49)         Lymph node, madibular       (46)       (46)       (46)       (46)       (49)       (2%)       (47)         Spleen       (50)       (50)       (47)       (47)       (43)       (47)         Thymus       (41)       (43)       (47)       (4%)       (47)         Thymoma benign       1       (2%)       1       (4%)         Fibroadenoma       3       (11%)       1       (47)         Skin       (48)       (50)       (47)       (47)         Basal cell carcinoma       3       (11%)       1       (4%)         Keratoacanthoma       1       (2%)       1       (2%)         Subcutaneous cill carcinoma       1       (2%)       1       (2%)	Prostate	(48)		(49)		(46)	
Testes       (50)       (50)       (49)         Bilateral, interstitial cell, adenoma       37       (74%)       40       (80%)       36       (73%)         Interstitial cell, adenoma       10       (20%)       3       (6%)       36       (73%)         Hematopoietic System       9       (50)       (40)       (40)       (40)       (40)         Lymph node, mantibular       (46)       (46)       (46)       (46)       (46)       (46)         Lymph node, mesenteric       (49)       (50)       (50)       (47)       (49)       (50)       (48)         Sarcoma       1       (2%)       1       (2%)       (47)       (41)       (43)       (47)         Thymus       (41)       (43)       (47)       (43)       (47)       (47)         Integumentary System       1       (2%)       1       (4%)       1       (4%) <td< td=""><td>Seminal vesicle</td><td>(48)</td><td></td><td>(50)</td><td></td><td>(48)</td><td></td></td<>	Seminal vesicle	(48)		(50)		(48)	
Bilateral, interstitial cell, adenoma $37$ ( $14\%$ ) $40$ ( $80\%$ ) $36$ ( $13\%$ )         Interstitial cell, adenoma       10 ( $20\%$ )       3 ( $6\%$ )       5 ( $10\%$ )         Hematopoletic System       Bone marrow       ( $49$ )       ( $50$ )       ( $48$ )         Lymph node       ( $50$ )       ( $50$ )       ( $49$ )         Lymph node, mesenteric       ( $49$ )       ( $50$ )       ( $47$ )         Spleen       ( $50$ )       ( $50$ )       ( $48$ )         Sarcoma       1       ( $2\%$ )       ( $48$ )         Thymus       ( $41$ )       ( $43$ )       ( $47$ )         Thymoma benign       1       ( $2\%$ )       ( $47$ )         Integumentary System       Mammary gland       ( $28$ )       ( $18$ )       ( $26$ )         Adenoma       1       ( $4\%$ )       1       ( $4\%$ )       1         Fibroadenoma       3       ( $11\%$ )       1       ( $6\%$ )       3         Skin       ( $48$ )       ( $50$ )       ( $47$ )       1       ( $2\%$ )         Skin       ( $48$ )       ( $50$ )       ( $47$ )       1       ( $2\%$ )       1       ( $2\%$ )         Skin       ( $48$ )       ( $50$ )       ( $47$ )       1       ( $2\%$ )       1       ( $2\%$ )	Testes	(50)	(2.407)	(50)	(000)	(49)	(200)
Hematopoletic System       (49)       (50)       (48)         Lymph node       (50)       (50)       (49)         Lymph node, madibular       (46)       (46)       (46)         Lymph node, madibular       (46)       (46)       (47)         Spleen       (50)       (50)       (47)         Spleen       (50)       (50)       (47)         Spleen       (50)       (50)       (48)         Sarcoma       1       (2%)       (43)         Thymus       (41)       (43)       (47)         Thymoma benign       1       (2%)       (47)         Mammary gland       (28)       (18)       (26)         Adenoma       1       (4%)       1       (4%)         Fibroadenoma       3       (11%)       1       (6%)         Skin       (48)       (50)       (47)         Basal cell carcinoma       1       (2%)       1       (2%)         Keratoacanthoma       1       (2%)       1       (2%)         Squamous cell carcinoma       1       (2%)       1       (2%)         Subcutaneous tissue, fibroma       5       (10%)       1       (2%)	Interstitial cell, adenoma	37 10	(74%) (20%)	40	(80%) (6%)	30 5	(13%) (10%)
Bone marrow       (49)       (50)       (48)         Lymph node       (50)       (50)       (49)         Lymph node, mandibular       (46)       (46)       (46)         Lymph node, mesenteric       (49)       (50)       (47)         Spleen       (50)       (50)       (48)         Sarcoma       1       (2%)       (47)         Thymus       (41)       (43)       (47)         Thymoma benign       1       (2%)       (47)         Integumentary System         Mammary gland       (28)       (18)       (26)         Adenoma       1       (4%)       1       (4%)         Fibroadenoma       3       (11%)       1       (6%)       (47)         Skin       (48)       (50)       (47)       (4%)       (4%)       (4%)         Skin       (48)       (50)       (47)       (50)       (47)       (4%)	Hematoroietic System						
Lymph node       (50)       (50)       (49)         Lymph node, mandibular       (46)       (46)       (46)         Lymph node, mesenteric       (49)       (50)       (47)         Spleen       (50)       (50)       (48)         Sarcoma       1       (2%)       (47)         Thymus       (41)       (43)       (47)         Thymoma benign       1       (2%)       (47)         Integrumentary System         Mammary gland       (28)       (18)       (26)         Adenoma       1       (4%)       1       (4%)         Fibroadenoma       3       (11%)       1       (6%)       (47)         Basal cell carcinoma       1       (2%)       (47)       1       (2%)         Keratoacanthoma       1       (2%)       1       (2%)       1       (2%)         Squamous cell carcinoma       1       (2%)       1       (2%)       1       (2%)         Subcutaneous tissue, fibroma       5       (10%)       1       (2%)       1       (2%)         Subcutaneous tissue, lipoma       2       4(%)       1       (2%)       1       (2%)	Bone marrow	(49)		(50)		(48)	
Lymph node, mandibular       (46)       (46)       (46)         Lymph node, mesenteric       (49)       (50)       (47)         Spleen       (50)       (50)       (48)         Sarcoma       1       (2%)       (47)         Thymus       (41)       (43)       (47)         Thymoma benign       1       (2%)       (47)         Integumentary System         Mammary gland       (28)       (18)       (26)         Adenoma       1       (4%)       1       (4%)         Fibroadenoma       3       (11%)       1       (6%)         Skin       (48)       (50)       (47)         Basal cell carcinoma       1       (2%)       1       (2%)         Keratoacanthoma       1       (2%)       1       (2%)         Squamous cell carcinoma       1       (2%)       1       (2%)         Subcutaneous tissue, fibroma       5       (10%)       1       (2%)         Subcutaneous tissue, fibrosarcoma       2       4(%)       1       (2%)	Lymph node	(50)		(50)		(49)	
Lymph node, mesenteric $(49)$ $(50)$ $(47)$ Spleen $(50)$ $(50)$ $(48)$ Sarcoma       1 $(2\%)$ $(41)$ $(43)$ $(47)$ Thymus $(41)$ $(43)$ $(47)$ $(47)$ Thymoma benign       1 $(2\%)$ $(47)$ Integummentary System $(41)$ $(43)$ $(47)$ Mammary gland $(28)$ $(18)$ $(26)$ Adenoma       1 $(4\%)$ 1 $(4\%)$ Fibroadenoma       3 $(11\%)$ 1 $(6\%)$ $(47)$ Basal cell carcinoma $(48)$ $(50)$ $(47)$ $(4\%)$ $(2\%)$	Lymph node, mandibular	(46)		(46)		(46)	
Spleen       (50)       (50)       (48)         Sarcoma       1       (2%)       (47)         Thymus       (41)       (43)       (47)         Thymoma benign       1       (2%)       (47)         Integumentary System       (48)       (47)         Mammary gland       (28)       (18)       (26)         Adenoma       1       (4%)       1         Fibroadenoma       3       (11%)       1       (6%)         Skin       (48)       (50)       (47)         Basal cell carcinoma       1       (2%)       1       (2%)         Keratoacanthoma       1       (2%)       1       (2%)         Squamous cell carcinoma       1       (2%)       1       (2%)         Subcutaneous tissue, fibroma       5       (10%)       1       (2%)         Subcutaneous tissue, fibrosarcoma       2       4%)       1       (2%)	Lymph node, mesenteric	(49)		(50)		(47)	
Sarcoma1 $(2\%)$ Thymus(41)(43)(47)Thymoma benign1 $(2\%)$ (47)Integumentary System(28)(18)(26)Mammary gland(28)(18)1Adenoma1(4%)1Fibroadenoma3(11%)1Skin(48)(50)(47)Basal cell carcinoma1(2%)Keratoacanthoma1(2%)Squamous cell carcinoma1(2%)Subcutaneous tissue, fibrosarcoma2(4%)Subcutaneous tissue, fibrosarcoma2(4%)Subcutaneous tissue, lipoma1(2%)	Spleen	(50)		(50)		(48)	
Thymus Thymoma benign $(41)$ 1 $(2\%)$ $(43)$ $(47)$ Integumentary SystemMammary gland Adenoma $(28)$ 1 $(4\%)$ $(18)$ 1 $(6\%)$ Fibroadenoma1 3 $(11\%)$ $(18)$ 1 $(6\%)$ Skin $(48)$ 1 $(2\%)$ $(50)$ 1 $(2\%)$ Basal cell carcinoma Keratoacanthoma1 1 $(2\%)$ Papilloma squamous Subcutaneous tissue, fibroma Subcutaneous tissue, fibrosarcoma1 2 $(2\%)$ Subcutaneous tissue, fibrosarcoma Subcutaneous tissue, lipoma2 $(4\%)$ 1 $(2\%)$	Sarcoma			1	(2%)	4	
Integumentary SystemMammary gland(28)(18)(26)Adenoma1(4%)1Fibroadenoma3(11%)1(6%)Skin(48)(50)(47)Basal cell carcinoma1(2%)1(2%)Keratoacanthoma1(2%)1(2%)Squamous cell carcinoma1(2%)1(2%)Subcutaneous tissue, fibrona5(10%)1(2%)Subcutaneous tissue, fibrosarcoma2(4%)1(2%)Subcutaneous tissue, fibrosarcoma2(4%)1(2%)	Thymus Thymoma benign	(41) 1	(2%)	(43)		(47)	
Mammary gland(28)(18)(26)Adenoma1(4%)1(4%)Fibroadenoma3(11%)1(6%)Skin(48)(50)(47)Basal cell carcinoma1(2%)1Keratoacanthoma1(2%)1Papilloma squamous1(2%)1Subcutaneous tissue, fibroma2(4%)1Subcutaneous tissue, fibrosarcoma2(4%)1Subcutaneous tissue, fibrosarcoma2(4%)1Subcutaneous tissue, fibrosarcoma2(4%)1Subcutaneous tissue, fibrosarcoma2(4%)1Subcutaneous tissue, fibrosarcoma2(4%)1Subcutaneous tissue, fibrosarcoma1(2%)Subcutaneous tissue, fibrosarcoma2(4%)1Subcutaneous tissue, fibrosarcoma2(4%)1Subcutaneous tissue, fibrosarcoma2(4%)1Subcutaneous tissue, fibrosarcoma2(4%)1Subcutaneous tissue, fibrosarcoma31(2%)	Infeanmentary System		<u> </u>	<u> </u>			·
Adenoma1 $(4\%)$ 1 $(4\%)$ Fibroadenoma3 $(11\%)$ 1 $(6\%)$ Skin(48)(50)(47)Basal cell carcinoma1 $(2\%)$ Keratoacanthoma1 $(2\%)$ Papilloma squamous1 $(2\%)$ Squamous cell carcinoma1 $(2\%)$ Subcutaneous tissue, fibrosarcoma2 $(4\%)$ Subcutaneous tissue, fibrosarcoma2 $(4\%)$ Subcutaneous tissue, lipoma1 $(2\%)$	Mammary gland	(28)		(18)		(26)	
Fibroadenoma3 (11%)1 (6%)Skin(48)(50)(47)Basal cell carcinoma1 (2%)1 (2%)Keratoacanthoma1 (2%)1 (2%)Squamous cell carcinoma1 (2%)1 (2%)Subcutaneous tissue, fibroma5 (10%)1 (2%)Subcutaneous tissue, fibrosarcoma2 (4%)1 (2%)Subcutaneous tissue, fibrosarcoma1 (2%)	Adenoma	1	(4%)	(10)		1	(4%)
Skin(48)(50)(47)Basal cell carcinoma1(2%)Keratoacanthoma1(2%)Papilloma squamous1(2%)Squamous cell carcinoma1(2%)Subcutaneous tissue, fibroma5(10%)Subcutaneous tissue, fibrosarcoma2(4%)Subcutaneous tissue, lipoma1(2%)	Fibroadenoma	3	(11%)	1	(6%)	-	<b>`</b>
Basal cell carcinoma1(2%)Keratoacanthoma1(2%)Papilloma squamous1(2%)Squamous cell carcinoma1(2%)Subcutaneous tissue, fibroma5(10%)Subcutaneous tissue, fibrosarcoma2(4%)1Subcutaneous tissue, lipoma1(2%)	Skin	(48)		(50)		(47)	
Keratoacanthoma1(2%)1(2%)Papilloma squamous1(2%)1(2%)Squamous cell carcinoma51(2%)Subcutaneous tissue, fibroma5(10%)1(2%)Subcutaneous tissue, fibrosarcoma2(4%)1(2%)Subcutaneous tissue, lipoma1(2%)1(2%)	Basal cell carcinoma	ì	(2%)	. ,			
Papilloma squamous1(2%)Squamous cell carcinoma1(2%)Subcutaneous tissue, fibroma5(10%)Subcutaneous tissue, fibrosarcoma2(4%)1Subcutaneous tissue, lipoma1(2%)	Keratoacanthoma			1	(2%)	1	(2%)
Squamous cell carcinoma1 (2%)Subcutaneous tissue, fibrona5 (10%)Subcutaneous tissue, fibrosarcoma2 (4%)Subcutaneous tissue, lipoma1 (2%)	Papilloma squamous			1	(2%)		
Subcutaneous tissue, fibroma5 (10%)Subcutaneous tissue, fibrosarcoma2 (4%)1 (2%)Subcutaneous tissue, lipoma1 (2%)	Squamous cell carcinoma			-	(10.00)	1	(2%)
Subcutaneous tissue, lipoma2 (4%)1 (2%)Subcutaneous tissue, lipoma1 (2%)	Subcutaneous tissue, fibroma	-	(10)	5	(10%)	-	(09)
Succutaneous itssue, lipoma 1 (2%)	Subcutaneous tissue, fibrosarcoma	2	(4%)		(20%)	1	(2%)
	Subcutancous fissue, npoma			1	(270)		

,

Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of HC Yellow 4 (continued)

	0	ppm	2,5	00 ppm	5,00	0 ppm
Musculoskeletal System						
Bone	(50)		(50)		(49)	
Osteosarcoma			1	(2%)		
Skeletal muscle	(1)		(2)			
Nervous System				·····		
Brain	(50)		(50)		(49)	
Astrocytoma malignant					1	(2%)
Respiratory System						
ung	(50)		(50)		(49)	
Adenocarcinoma					ĺ	(2%)
Alveolar/bronchiolar adenoma	2	(4%)	1	(2%)	3	(6%)
Carcinoma, metastatic, adrenal gland	1	(2%)				
Carcinoma, metastatic, preputial gland	1	(2%)				
Osteosarcoma, metastatic, bone			1	(2%)		
Osteosarcoma, metastatic, uncertain primary site	1	(2%)				
Pheochromocytoma malignant, metastatic,			-	(8.04)		
adrenal gland			1	(2%)	, -	
Mediastinum, adenocarcinoma, metastatic, lung				(20)	1	(2%)
mediastinum, sarcoma, metastatic, salivary glands	1 4 77		1	(2%)	/10>	
Papilloma squamous	(4/)	(206)	(50)		(49)	
	1	(2%)				
Special Senses System	- 4					
<u>iar</u>	(6)		(4)		(2)	
Papilloma squamous	1	(17%)		(050)		
Squamous cell carcinoma	/41		1	(25%)	10	
aruerian giand	(1)		(1)	(1000)	(6)	
Adenoma			1	(100%)		
Jrinary System						
Sidney	(50)		(50)		(49)	
Adenocarcinoma, metastatic, lung					1	(2%)
Renal tubule, adenoma	1	(2%)				
Jrinary bladder	. (48)		(48)		(47)	
Systemic Lesions						
Aultiple organs <sup>c</sup>	(50)		(50)		(49)	
Leukemia mononuclear	19	(38%)	21	(42%)	16	(33%)
Lymphoma malignant undifferentiated cell	• 2	(2010)	2	(4%)	1	(2%)
Mesothelioma malignant	2	(4%)	- 1	(2%)	-	(-/-)
	2			(2.12)		

### Lesions in Male Rats

### Table A1

0 ppm 2,500 ppm 5,000 ppm Tumor Summary Total animals with primary neoplasms<sup>d</sup> 49 50 48 Total primary neoplasms 143 148 137 Total animals with benign neoplasms 49 49 48 Total benign neoplasms 115 119 115 Total animals with malignant neoplasms 27 27 19 Total malignant neoplasms 28 29 22 Total animals with secondary neoplasms<sup>e</sup> 4 3 1 Total secondary neoplasms 4 3 3 Total animals with malignant neoplasms of uncertain primary site 1

Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of HC Yellow 4 (continued)

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

<sup>b</sup> Does not include one early death that occurred prior to the 15-month interim evaluation

c Number of animals with any tissue examined microscopically

<sup>d</sup> Primary tumors: all tumors except metastatic tumors

e Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

Individual Animal Tumor Pathology	of Ma	le ]	Ra	ts i	in	the	2	-Ye	ear	Fe	eed	S	tud	ly (	of I	HC	Y	ell	ow	4:	0	P	pm					
Number of Days on Study	2 8 8	4 8 5	5 0 8	5 8 7	5 9 8	6 0 5	6 1 0	6 1 9	6 2 5	6 3 7	6 3 7	6 3 9	6 5 1	6 5 5	6 5 8	6 6 2	6 6 5	6 6 6	6 7 3	6 8 9	6 9 4	7 0 7	7 1 0	7 1 0	7 1 3			
Carcass ID Number	0 7 5	1 1 5	1 4 5	0 5 1	0 2 5	1 2 4	0 6 4	0 9 5	0 7 4	0 2 4	0 7 3	1 4 4	0 9 3	0 3 5	0 7 1	0 5 4	0 3 3	1 1 4	0 2 3	0 5 3	1 2 3	0 2 2	0 5 2	0 9 2	1 0 1			
Alimentary System									-	•			-															
Fsonhagus	+	м	+	м	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine large		+	` <b>_</b>	Δ		, +	÷	÷	÷	÷	÷	÷	÷	÷	÷	÷	<u>ہ</u>	÷	÷	-	+		1					
Intestine large	т 1		т 1		т 1	т 1	T	т 1		т 1	т 1	т 1	- T - 1	т 1	T	- <b>T</b>			т 1	т 1		- T	т 1	- T				
Intestine large, cecum		- 7			. <u>.</u>	. <u>.</u>	Ţ		. <u>.</u>				. <u> </u>		. <u> </u>	Ţ		. <u> </u>	. <u>.</u>			<b>.</b>	-	+	A			
Intestine large, colon	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	· †	+	+	+			
Intestine large, rectum	+	+	+	A	+	+	+	+	+	.+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A			
intestine small	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A			
Intestine small, duodenum	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	Α			
Intestine small, ileum	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	М	+	Α	+	+	+	+	+	+	+	Α			
Intestine small, jejunum	+	+	+	Α	+	+	+	+	· +	+	+	+	+	+	Μ	+	Α	+	+	+	+	+	+	+	Α			
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Fibrosarcoma, metastatic, skin																												
Hepatocellular adenoma																												
Mesentery													+					+	+									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+			
Acinus, adenoma																												
Acinus, adenoma, multiple																												
Pharvnx									+																			
Palate, papilloma squamous									х																			
Salivary glands	+	+	+	+	+	+	+	м	[ + ]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Stomach, forestomach	+	+		+	+	+	+	+	÷ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- ÷			
Papilloma squamous	•	·				·	x	•	·	•	•	·	·	•	•	•	•	•	•		•	-	•					
Stomach glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+			
Tooth	•		•		•	+		•	•	•	•		'	•	•	•		'		'	•		•		•			
Cardiovascular System Heart	+	+	+	+	+	+	+	, +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		 	
																									-		 	
Endocrine System																										,		
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Carcinoma																									Х			
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Pheochromocytoma malignant											Х																	
Pheochromocytoma benign											х	x	x	х					х				х	x	x			
Rilateral pheochromocytoma benign																						x						
Islets, nancreatic	+	.+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Adenoma	•		•		•		•	•	•	•	•		•	•	•		•	'		•	•	•	•	,	•			
Parathyroid gland	т	ъ	ъ	1	Ŧ	Ŧ	ᆂ	Ŧ	Ŧ	Ŧ	м	-	Ŧ	+	м	-	+	+	Ŧ	+	Ŧ	+	+	ъ	+			
Pituitany dand	т 	M	т м	τ 1	т 	т 	т 	т Т	- -	т -	1VI	т Т	т -	т -	۲ <b>۵</b> ۲	. т -	- -	- -	т Т	т. Т	т Т	т —	- -	- -	- <del>-</del>			
Pars distalis adename		141	141	. т <sup>.</sup>	v	T	v	T	Ŧ	v	171	v	Ŧ	T	T'	т	v	Ŧ	т	т.	т	т	$\mathbf{v}$	v	т <sup>и</sup>			
Thursid aland								. 1		<u>_</u>	.1		.1	L.	д	д.	~	L	ь	д	ь	д		<u>л</u>	Т			
C coll adapama	+	+	Ŧ	+	+	+	+	+	+	+	Ť	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	А	Ŧ	Ŧ	т	T	т	Ŧ	Ŧ	T			
C cell adenome multiple											л																	
C-ten, adenoma, muniple																												

+: 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	i Mal	le I	Rat	ts i	m (	the	2-	Ye	ær	Fe	eed	Si	tud	ly o	of I	IC	¥	ello	DW	4:	۵	) (PI	pım	1 <b>(c</b>	ont	inued)
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7		7	7	
Number of Dame on Study	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
Number of Days on Study	1	2	4	5	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	
	0	1	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	1	1	1	1	Total
Carcass ID Number	8 5	4 3	3 2	6 2	1 1	1 2	3 1	4 3	4 4	6 1	8 1	1 1	1 2	2 1	3 1	3 2	3 3	1 3	2 1	8 2	8 3	1 3	2 2	3 4	3 5	Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	М	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin Hepatocellular adenoma															х						x					1 1
Mesentery																										3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma		Х																								1
Acinus, adenoma, multiple																			Х							1
Pharynx																										1
Palate, papilloma squamous																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	50
Papilloma squamous																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																										. 1
Cardiovascular System																										50
	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	50
																		÷								1
Aurenai giand, medulia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheechromocytoma malignant										X			••			<b>N</b> 7			<b>.</b>							2
Pilotomi about a benign						<b>.</b> ,			.,	Х			Х			х			х			х				13
Bilaterai, pneocnromocytoma benign			X			X			X							r -	X	X								6
isiets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	• +	• +	48
Adenoma Bomthymid cloud								X			<b>P</b> -															1
rarainyroid giand Dituitory aland	+	+	+	+	+	+	+	+	+	+	M	. +	+	+	+	+	+	+	+	+	+	+	+	• +	• +	47
rituliary giand	+	M	. +	+	+	+	+	+	+	+	+	M	( +	+	+	+	+	+	+	+	+	+	+	· +	. +	45
rars distails, adenoma						X	X	X		X	X		X	X	X			X						X	•	17
Inyrold gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	; +	+	49
C-cell, adenoma C-cell, adenoma, multiple									х					X	X	х					х		Х	-		6 1

.

TABLE A2

Individual Animal Tumor Pathology	of Ma	le :	Ra	ts i	in 1	the	2-	·Ye	ar	Fe	ed	S	tud	ly (	o <b>f</b> :	HC	Y	ell	ow	4:	0	) p	рш	I (C	onti	nued)	)	
Number of Days on Study	2 8 8	4 8 5	5 0 8	5 8 7	5 9 8	6 0 5	6 1 0	6 1 9	6 2 5	6 3 7	6 3 7	6 3 9	6 5 1	6 5 5	6 5 8	6 6 2	6 6 5	6 6 6	6 7 3	6 8 9	6 9 4	7 0 7	7 1 0	7 1 0	7 1 3			
Carcass ID Number	0 7 5	1 1 5	1 4 5	0 5 1	0 2 5	1 2 4	0 6 4	0 9 5	0 7 4	0 2 4	0 7 3	1 4 4	0 9 3	0 3 5	0 7 1	0 5 4	0 3 3	1 1 4	0 2 3	0 5 3	1 2 3	0 2 2	0 5 2	0 9 2	1 0 1			
General Body System None																												
Genital System Epididymis Preputial gland Adenoma Carcinoma Bilateral, adenoma Prostate Seminal vericle	+++++++++++++++++++++++++++++++++++++++	+++++++++++++++++++++++++++++++++++++++	+ + + X +	+++++++++++++++++++++++++++++++++++++++	+++++	+++++++++++++++++++++++++++++++++++++++	+++++	++++++	+ + M	++++++	+ + + + +	+ + X + +	+++++++++++++++++++++++++++++++++++++++	+++++++++++++++++++++++++++++++++++++++	++++++	++++++	M M M	+++++++++++++++++++++++++++++++++++++++	+++++	++++++	+++++++++++++++++++++++++++++++++++++++	+++++++++++++++++++++++++++++++++++++++	+++++++++++++++++++++++++++++++++++++++	+++++++++++++++++++++++++++++++++++++++	+++++++++++++++++++++++++++++++++++++++			
Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	+	+	+ X	+ X	+ ×	+ X	+ X	+ ×	+ X	+ X	+ X	+	+ ×	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X	+ X			
Hematopoietic System Blood Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen Thymus Thymoma benign	+ + + + +	+ + + + + M	+++++++	A + + + + +	++++++	+ + + + +	+ + + + + +	+ + M + + +	+ + + + + M	+ + + + + +	+ + + + + M	+ + M + + + + + + + + + + + + + + + + +	+ + + + + +	+ + + + +	+ + + M + M	+ + + + + + + + + + + + + + + + + + + +	+ + M + + +	+++++++++++++++++++++++++++++++++++++++	+ + + + + + + + + + + + + + + + + + + +	+ + + + +	+ + + + + +	+ + + + +	+ + • M • + • +	+++++++++++++++++++++++++++++++++++++++	+++++		<i>.</i>	
Integumentary System Mammary gland Adenoma Fibroadenoma Skin Basal cell carcinoma Subcutaneous tissue, fibrosarcoma	+	+	M	ГМ [+	м +	+	+	м + х	++	+	+	м +	+ 1	+	м +	÷ +	+	+	+	м +	+	₩ +	( + X	•	м			
Musculoskeletal System Bone Skeletal muscle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ +	+	+	÷	+	+	+	+			
Nervous System Brain	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Ŧ	ł	+	• +	• •	+			

ataM slaM mi amoiss.I

TABLE A2 Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of HC Yellow 4: 0 ppm (continued)

Nervous System Brain	+	+ •	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		05
Mussenlosken System Bone Skeletal muscle	+	+ ·	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		т 05
Integumentary System Mammary gland Fibroadenoma Skin Basal cell carcinoma Skin Busal cell carcinoma	+	+ ·	₩ *	+ x +	M +	+	+	+	+ +	+	+ x +	+	M +	M +	x + +	₩	+ x +	M +	+	+ *	₩ +	M +	M +	₩	+ +	;	5 1 8 <del>1</del> 3 1 87 87
Шешяйороіеціс System Blood Lymph node, mandibular Lymph node, mesenteric Spleen Thymus Thymus	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + +	+ + + + + +	++++++	+ + + + +	+ + + + +	+ + + + +	+ + + + +	+ + + + + +	+++++	+ + + + +	M + + + + +	+ + + + +	+ + + + +	+ + + + + +	W + + + + +	++++++	+ + + + +	+ + + + + +	+ + + + +	M+++++	W+++++	W+++++	X + + + + + +		I 14 05 64 94 05 64 1
Gemital System Epididymis Preputial gland Adenoma Carcinoma Bilateral, adenoma Frostate Seminal vesicle Testes Testes Interstitial cell, adenoma Interstitial cell, adenoma	X ++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++ ++	X + + + + W +	x + + + + + + + + + + + + + + + + + + +	X + + + + + + + +	X + + + + + + + + + + + + + + + + + + +	X + + + + + + + +	X + + + + + +	X + + + + + + + + + + + + + + + + + + +	X + + + X + +	X + + + + + + + + + + + + + + + + + + +	X + + + X + +	X + + + + + + + + + + + + + + + + + + +	X + + + + + + + +	X + + + + + + + + + + + + + + + + + + +	X + + + + + + + + + + + + + + + + + + +	X + + + + + + + + + + + + + + + + + + +	X + + + + + + + + + + + + + + + + + + +	X + + + + X + + +	X + + + + + + + + + + + + + + + + + + +	X + + + + X + + +	X + + + + + + + + + + + + + + + + + + +	X + + + + + + + + + + + + + + + + + + +	X + + + + X + +	X + + + + + + + + + + + + + + + + + + +	X + + + + + + +	,	01 28 05 8t 8t 1 1 1 8 8 81 61
None General Body System															•												<u>.</u>
Carcass ID Number	S 8 0	3 4 1	2 8 0	2 9 0		2 1 0	1 8 0	3 7 0	4 4 0	Т 9 0	1 8 0	I I I	2 1 1	1 2 1	1 8 1	2 3 1	8 8 1	Е Т 0	1 2 0	2 8 0	E 8 0	8 1 1	z z 1	† 5 1	5 E I	L L L	lato \esuesi etomu
Number of Ways on Study	T Z L	z z L	₽ 2 L	5 7 2		τ ε 	1 E L	1 8 1	1 8 1	ו 1 1 1	ו 1 2 1	1 E L	1 E L	1 E L	1 E L	1 E L	ז 2 2	2 E L	2 E L	7 E L	2 8 1	2 E L	z E L	2 8 1	2 8 1		<del></del>

19

Individual Animal Tumor Pathology	of Mal	e	Ra	its	in	ı ti	he	2-	Ye	ar	F	eed	S	tud	ly (	o <b>f</b> :	HC	Y	ell	ow	4:	0	) pi	pm	(a	onti	nued)	)	
Number of Days on Study	2 8 8	4 8 5	5 0 8		5 : 3 : 7 :	5 9 8	6 0 5	6 1 0	6 1 9	6 2 5	6 3 7	6 3 7	6 3 9	6 5 1	6 5 5	6 5 8	6 6 2	6 6 5	6 6 6	6 7 3	6 8 9	6 9 4	7 0 7	7 1 0	7 1 0	7 1 3			
Carcass ID Number	0 7 5	1 1 5	1 4 5	( 5 1	) ( 5 2 1 2	0 2 5	1 2 4	0 6 4	0 9 5	0 7 4	0 2 4	0 7 3	1 4 4	0 9 3	0 3 5	0 7 1	0 5 4	0 3 3	1 1 4	0 2 3	0 5 3	1 2 3	0 2 2	0 5 2	0 9 2	1 0 1			
Respiratory System Lung Alveolar/bronchiolar adenoma Carcinoma, metastatic, adrenal gland Carcinoma, metastatic, preputial gland Osteosarcoma, metastatic, uncertain	+	+	+ بر	+ - K	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	+	+ x			
primary site Nose Papilloma squamous Trachea	+ +	+	- N - H	⁄I - ⊦ -	+ · + ·	x + +	+	+ +	+ +	+ +	+ +	М +	+ +	+ +	+	+ +	+	+	+	+ +	+	+ +	+ +	+ +	+	+ +			
Special Senses System Ear Papilloma squamous Eye Harderian gland		+	-								+			+ + +									+		+				
Urinary System Kidney Renal tubule, adenoma Urinary bladder	+ +	+ X N	- + : 1 +	+ -	+ ·	+	+ +	+	+ +	+	++	+	+ +	+ +	+ +	+	+	+ M	+	+	+	+	++	++	+	+ +			
Systemic Lesions Multiple organs Leukemia mononuclear Mesothelioma malignant	+	+ X	- + C		+ - X :	+ X	+ X	+ x	+	+	+ x	+	+	+ X	+ X	+	+ X	+	+ X	+ X	+ X	+ X	+ X	+	+ X	+			

Table A2 Imdividual Amir

Individual Animal Tumor Pathology	of N	visio.	e I	R81	ts i	im	the	2	-Y(	C91	F	eed	S	tud	ly (	oľ i	HC	Y	ell	₽₩	4:	0	P	pm	(0	ont	inued)	
Number of Days on Study		7 2 1	7 2 2	7 2 4	7 2 5	7 3 1	7 3 2																					
Carcass ID Number		0 8 5	1 4 3	0 3 2	0 6 2	0 1 1	0 1 2	0 3 1	0 4 3	0 4 4	0 6 1	0 8 1	1 1 1	1 1 2	1 2 1	1 3 1	1 3 2	1 3 3	0 1 3	0 2 1	0 8 2	0 8 3	1 1 3	1 2 2	1 3 4	1 3 5		Total Tissues/ Tumors
Respiratory System Lung Alveolar/bronchiolar adenoma Carcinoma, metastatic, adrenal gland Carcinoma, metastatic, preputial gland		+	+	+	+	+	+	+	• +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+ x	+	+		50 2 1 1
Osteosarcoma, metastatic, uncertain primary site Nose Papilloma squamous Trachea		+ +	+ +	+ +	+ +	+	+ +	+ +	· + · +	- + - +	+	+ +	M +	+ ]	+ +	+ +	+	+ X +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +		1 47 1 50
Special Senses System Ear Papilloma squamous Eye Harderian gland			+											+								_	+ x					6 1 6 1
Urinary System Kidney Renal tubule, adenoma Urinary bladder		+	+ +	+ +	++	+	+	+ +	· +	- + - +	• + • +	+	+	+	+	+	+	+ +	+ +	+ +	+ +	+	+ +	+	+	+ +		50 1 48
Systemic Lesions Multiple organs Leukemia mononuclear Mesothelioma malignant		+ x	+ X	+	+ X	÷	+ X	+	· 4	- +	+ X	+	+	+	+	+	÷	+ X	+	+	+	+	+	+	+	+	-	50 19 2

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Individual Animal Tumor Pathology	of Mal	e ]	Ra	ts i	in 1	the	2	-Ye	ar	Fe	eed	S	tud	ly (	of ]	HC	Y	ell	<b>0</b> ₩	4:	2	2,50	0	pp	m		
	3	3	4	4	5	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7		
Number of Days on Study	6	9	6	8	8	1	2	2	2	2	4	5	5	6	7	7	1	2	2	2	2	3	3	3	3		
	7	6	7	1	8	9	0	3	6	6	6	3	8	8	2	3	8	3	3	8	8	0	0	0	0		
		1	2	1	1	1	1	1	1	1	1	2	1	2	1	2	1	2	2	1	2	1	1	1	1		
Carcass ID Number	8	7	2	8	8	5	5	9	7	8	9	1	9	õ	6	8	6	4	6	8	õ	5	6	7	7.		
	5	5	4	5	4	5	4	5	3	3	4	4	3	5	5	2	2	5	4	ĩ	4	3	1	1	2		
Alimentary System																											-
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	1+	+		
Intestine large	+	+	Α	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+		
Intestine large, cecum	+	+	Α	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+		
Intestine large, colon	+	+	Α	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	Μ	i	
Polyp adenomatous																											
Intestine large, rectum	+	+	Α	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+		
Intestine small	+	+	Α	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	.+	+	+	+	+	+	• +	+		
Intestine small, duodenum	+	+	Α	÷	+	+	+	. <b>A</b>	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+		
Intestine small, ileum	+	+	Α	+	+	+	+	Α	+	+	+	+	+	+	+	+	<b>+</b>	+	+	+	+	+	4	• +	+		
Intestine small, jejunum	+	+	Α	+	+	+	+	Α	+	+	+	+	+	´+	+	+	.+	+	+	+	+	+	÷	• +	+		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+		
Mesentery			+	+	+				+					+													
Pancreas	+	+	+	+	+	+	+	A	+	+	+	+	• +	Μ	+	+	.+	+	+	+	+	+	+	• +	+		
Acinus, adenoma																						X					
Acinus, adenoma, multiple																											
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	+	+	+	. +	+	+	+	• +	+	- +	+		
Sarcoma																						X					
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	- +	+		
Stomach, forestomach	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	+		
Papilloma squamous	X							-														÷					
Stomach, glandular	• +	+	A	+	+		+	+	+	+	+	+	• +	+	+	+	+	+	+	+	+	• +	+	. +	+	,	
Cardiovascular System						_																					
Heart	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	+	+	+	+	+	+	+	• +	-	- +	+		
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	- +	+		
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+		
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	Μ	[ +	+	· +	+	+	+	+	+	+	+	+	• +	+	- +	+		
Pheochromocytoma malignant																											
Pheochromocytoma benign													Х				Х		Х								
Bilateral, pheochromocytoma benign																				Х		Х		Х			
Islets, pancreatic	+	+	+	+	+	+	+	Α	+	+	+	+	+	Μ	[ +	+	+	+	+	+	+	· +	4	- +	+		
Adenoma																		X						Х	X		
Parathyroid gland	+	+	+	М	+	+	+	Μ	(+	Μ	[ +	M	1+	+	+	+	+	+	+	+	+	+	N	1 +	+		
Pituitary gland	М	+	+	+	+	+	+	+	+	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	- +	·, +		
Pars distalis, adenoma									х			Х	X	X	Х	Х	X		Х	:		Х	X	х			
Pars distalis, adenoma, multiple																											
Thyroid gland	+	+	Α	+	+	+	+	+	+	+	+	+	• +	+	+	+	+	+	+	+	+	• +	.1	- +	· +		
C-cell, adenoma					Х										X					•		Х					
			_																								

# General Body System Tissue NOS

### Lesions in Male Rats

Table A2

										_		-						_		_			_			
		7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3.	3	3	3	3	3	3	3	3	3	3	
	0	U	0	U	U	U	U	0	U	0	0	U	0	U	0	U	0	0	1	1	1	1	1	1	1	
	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	Total
Carcass ID Number	8	9	0	0	1	1	2	2	3	3	4	4	4	5	5	5	6	6	6	7	7	7	8	8	8	Tissues
	2	2	1	2	1	3	1	3	2	5	2	3	4	1	2	3	2	3	1	2	3	4	1	3	4	Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Μ	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	М	+	+	+	+	+	+	+	+	+	+	+	М	+	М	+	+	+	+	+	+	+	+	+	+	44
Polyp adenomatous														х												1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																										5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Acinus, adenoma										Х		Х														3
Acinus, adenoma, multiple							X																			1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	М	48
Papilloma squamous																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																					-		_			
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant																							Х			1
Pheochromocytoma benign			Х				Х	Х	Х				х					х	Х						Х	11
Bilateral, pheochromocytoma benign		Х								Х														Х		6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Μ	+	47
Adenoma																х										4
Parathyroid gland	+	+	+	+	+	+	+	Μ	[ <b>+</b>	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma					Х								х	х				х	х	х		Х				18
Pars distalis, adenoma, multiple							Х										Х									2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-ceil, adenoma															х									х		5

65

		_				_															_						
Number of Days on Study	3 6 7	3 9 6	4 6 7	4 8 1	5 8 8	6 1 9	6 2 0	6 2 3	6 2 6	6 2 6	6 4 6	6 5 3	6 5 8	6 6 8	6 7 2	6 7 3	7 1 8	7 2 3	7 2 3	7 2 8	7 2 8	7 3 0	7 3 0	7 3 0	7 3 0		
Carcass ID Number	2 8 5	1 7 5	2 2 4	1 8 5	1 8 4	1 5 5	1 5 4	1 9 5	1 7 3	1 8 3	1 9 4	2 1 4	1 9 3	2 0 5	1 6 5	2 8 2	1 6 2	2 4 5	2 6 4	1 8 1	2 0 4	1 5 3	1 6 1	1 7 1	1 7 2		
Genital System							_						_		_												
Epididumis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +	+		
Proputial cland		÷	Ĺ		÷	÷	Ĺ.	÷	÷	÷	÷	÷	÷	÷	<u>.</u>	÷	÷	÷	÷	÷		÷		. <u> </u>	÷		
Adapoma			•	ż		•	'	•		ÿ	•	•	ż	ÿ		•		•	,	ÿ		•	Ý	. '	÷		
Prostate	Т	-	-		1	+	Т	Т	Т	Î	Ŧ	т	Â	<u>,</u>	ъ	Т	Т	<u>т</u>	т		Т	т	1		$\hat{\mathbf{w}}$		
Flosiale Seminal traciale	т - т	Ţ	Ť	. т 	Ť		Ť	т 	T	Ť	Ţ	т т	T	т 	T	- T	T	т 	T J		т 	- -	T	· т	141		
Tester			- T	· T	Ţ	Ť	<b>.</b>	T	Ţ	T	T	T	T	T	T	T	Ţ	Ţ	T	Ŧ	<b>T</b>	т -		· T	Ŧ		
Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	Ŧ	т	x	т	т	x	x	x	x	x	x	• •	x	т	x	×	x	X	x	т	x	x	x	x	x		
Hematopoietic System				_	_								·														
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+		
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	. +	+		
Lymph node, mesenteric	+		+		+	÷	+	+.	. <b>.</b>	+	+	÷	÷.	+	÷	÷	+	+	+	+	4	+	-+	. +	+		
Spleen		÷				÷		÷		÷	÷	÷	÷.	÷	÷	÷.	÷	÷.	+	÷.	÷	÷	÷	. <u>.</u>	÷		
Sarcoma	•	•	'	•	'			•	'	•	•	•	•	•	•	•	•	•	•		•	'	•	•	•		
Thymus	М	+	+	+	+	ţ	+	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	M	1 M	[ +	1	·
Integumentary System																											
Mammary gland	М	: +	+	+	+	Μ	+	+	+	Μ	Μ	Μ	М	Μ	Μ	Μ	Μ	+	Μ	+	+	+	M	1 M	[ M		.`
Fibroadenoma																											
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+		
Keratoacanthoma																											
Papilloma squamous																					Х						
Subcutaneous tissue, fibroma															Х						Х						
Subcutaneous tissue, lipoma							х																				
Musculoskeletal System								_		_																	
Bone	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	+		
Osteosarcoma	-		-			х																					
Skeletal muscle								+		+																	
Nervous System						_		_								_		_									•
Brain	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+		

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Individual Animal Tumor Pathology	of Ma	le	Rø	nts	im	ťh	e 2	2-¥0	281	F	eed	l St	tund	ly o	of I	HC	Y	ell	0W	4:	2	,50	1	pp	m	1 <b>(</b> α	ontinued)	
Number of Days on Study	7 3 0	7 3 0	7 3 0	7	7 3 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1		7 3 1		
Carcass ID Number	1 8 2	1 9 2	200	200	2 0 1 2 1	2 1 3	2 2 1	2 2 3	2 3 2	2 3 5	2 4 2	2 4 3	2 4 4	2 5 1	2 5 2	2 5 3	2 6 2	2 6 3	2 6 1	2 7 2	2 7 3	2 7 4	2 8 1	2 8 3	2	2 8 4	Total Tissu Tumo	es/ prs
Genital System Epididymis Preputial gland Adenoma Prostate Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	+ + + + X		+	+ - + + - + + - + + - + + - + + + + + +	+ + + + + + + +	+ + { + + + + + + { >	+ + + + + + + +	+ + + X + + + +	+ + + + + + + +	+ + + + + + X	+ + + + + + X	+ + X + + + X	+ + + + + + X	+ + + + + +	+ + + + X	+ + X + + + X	+ + + + + + X	+ + + + + + X	+ + + + + X	+ + + + + + X	+ + X + + + + X	+ + + + + X	+ + + + + X	+ + + + X		+ + + + X	50 50 13 49 50 50 40 3	
Hematopoletic System Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen Sarcoma Thymus	+++++++++++++++++++++++++++++++++++++++	- +	+ - + - + -		+ + + + + + + +				- + - + - M - + - +	· + · + 1 + · + · +	· + · + · +	* + + + +	+ + + + + X +	+ + + + + + + + + + + + + + + + + + +	+++++++++++++++++++++++++++++++++++++++	+++++++++++++++++++++++++++++++++++++++	+ + + + + + +	+ + + + + +	+ + M + + +	+ + + + + + M	++ ++ +	+ + + + +	++++++	+ + + + +	•	+ + + + +	50 50 46 50 50 1 43	
Integumentary System Mammary gland Fibroadenoma Skin Keratoacanthoma Papilloma squamous Subcutaneous tissue, fibroma Subcutaneous tissue, lipoma	N +	A P 		 + · K	 + -+	₩ ₽	√I > + -	 { F -	- N	1 № - +	1 M	I M	I M	1 M	ім +	ім +	ім + х	+	м +	: M +	( M +	( + + X	+	· +	-	+ +	18 1 50 1 1 5 1	
Musculoskeletal System Bone Osteosarcoma Skeletal muscle	+		+ •	+ ·	+ -	+ -	+ -	+ 4	- - +	- +	- +	• +	· +	• +	• +	+	+	+	+	+	+	+	+	- +	_	+	50 1 2	
Nervous System Brain	H		+ ·	+	+ -	+ -	+ -	+ +	⊦ +	- 4	- +	• +	• +	- +	+	• +	+	+	• +	+	+	• +	· +	- +	-	+	50	

67

Individual Animal Tumor Pathology	of Mal	<b>e</b> ]	Ra	ts	in	the	2	-Ye	ear	Fe	eed	S	tud	ly e	of I	HC	Y	ell	ow	4:	2	2,50	Ņ	pp	<b>m</b> (	conti	nued	)
Number of Days on Study	3 6 7	3 9 6	4 6 7	4 8 1	5 8 8	6 1 9	6 2 0	6 2 3	6 2 6	6 2 6	6 4 6	6 5 3	6 5 8	6 6 8	6 7 2	6 7 3	7 1 8	7 2 3	7 2 3	7 2 8	7 2 8	7 3 0	7 3 0	7 3 0	7 3 0			
Carcass ID Number	2 8 5	1 7 5	2 2 4	1 8 5	1 8 4	1 5 5	1 5 4	1 9 5	1 7 3	1 8 3	1 9 4	2 1 4	1 9 3	2 0 5	1 6 5	2 8 2	1 6 2	2 4 5	2 6 4	1 8 1	2 0 4	1 5 3	1 6 1	1 7 1	1 7 2			
Respiratory System Lung Alveolar/bronchiolar adenoma Osteosarcoma, metastatic, bone Pheochromocytoma malignant, metastatic, adrenal gland Mediastinum, sarcoma, metastatic, salivary glands Nose Trachea	++++	++++	++++	++++	+++++	+ x +	++++	++++	++++	+ + +	++++	++++	+ ++	++++	++++	+++	++++	++++	++++	++++	++++	+ X + +	+	+	++++			-
Special Senses System Ear Squamous cell carcinoma Eye Harderian gland Adenoma		+ x					+			-					-													
Urinary System Kidney Urinary bladder	+++	+++	++	+ +	++	+ +	+++	+ A	+++	+++	+++	+++	+ +	+++	+++	+++	+++	÷ +	+++	+++	++	++	++	++	+ M			<u>.</u>
Systemic Lesions Multiple organs Leukemia mononuclear Lymphoma malignant undifferentiated cell type Mesothelioma malignant	+ x	+	+ x	+	+ x	+	+ X	+ X	+ x x	+ x	* x	+ x	+	+	+	+	+ x	+ x	+ X	+	+ X	+	+	+	+			

Individual Animal Tumor Pathology	of Mal	e ]	Ra	ts i	ĺm	the	2	-Y¢	ear	F	eed	S	tund	ly (	Dĺ	HC	Y	ell	033	4:	2	,50	<u>م</u>	pp	da.	(continued)
Number of Days on Study	7 3 0	7 3 1																								
Carcass IID Number	1 8 2	1 9 2	2 0 1	2 0 2	2 1 1	2 1 3	2 2 1	2 2 3	2 3 2	2 3 5	2 4 2	2 4 3	2 4 4	2 5 1	2 5 2	2 5 3	2 6 2	2 6 3	2 6 1	2 7 2	2 7 3	2 7 4	2 8 1	2 8 3	2 8 4	Total Tissues/ Tumors
Respiratory System Lung Alveolar/bronchiolar adenoma Osteosarcoma, metastatic, bone Pheochromocatoma malignant	+	÷	+	• +	+	+	+	+	• +	· +	• +	+	+	+	÷	+	+	+	+	÷	+	+	+	+ X	+	- 50 1 1
metastatic, adrenal gland Mediastinum, sarcoma, metastatic, salivary glands													1	1									x			1
Trachea	+	+	+	+	+	+	+	• +	• +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- 50
Special Senses System Ear Squamous cell carcinoma Eye Harderian gland Adenoma				+					+ + X								+	+				+				4 1 6 1
Urinary System Kidney	+	+		• +	 · +	· +		. +	 	- 	. +	 · +	· +				+	+			—– - +	+				- 50
Urinary bladder	+	+	+	• +	+	+	+	• +	- +	- +	• +	• +	• +	· +	+	+	+	+	+	+	+	+	+	+	• +	- 48
Systemic Lesions Multiple organs Leukemia mononuclear Lymphoma malignant undifferentiated cell type Mesothelioma malignant	+ X	+	+ + X	- + :	· + X	• <b>+</b>	+	- + X	- + C	- + X	- + X X	+	· + X	+	• +	+ X	+	+	• +	+	• +	• +	+	+ x	- + : >	- 50 C 21 2 1

Individual Animal Tumor Pathology	of Mal	le ]	Ra	ts i	n 1	the	2-	Ye	ar	Fe	æd	S	tud	ly e	of 1	HC	Y	ell	ow	4:	5	,00	0	ppm	1		
	3	4	4	5	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7			
Number of Days on Study	6	3	3	5	5	7	8	0	5	5	6	7	8	9	9	9	9	Ó	0	1	1	2	2	2			
· · · · · · · · · · · · · · · · · · ·	7	0	6	3	7	0	8	5	4	8	8	6	Ō	4	4	4	6	2	4	4	5	9	9	9			
	3	3	3	3	4	4	3	4	3	3	3	3	4	3	3	3	4	3	3	3	3	2	2	2		 	
Carcass ID Number	- 8 5	9 5	9 4	9 2	1 4	1 3	6 5	0 4	1 4	8 4	0 5	3 4	2 5	1 3	4 3	8 3	1 2	8 2	2 4	4 1	6 4	9 1	9 3	9 4			
Alimentary System							_		,																		-
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine large	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine large, cecum	+	+	+	+	Α	+	+	+	Α	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine large, colon	+	+	+	+	Α	+	+	+	М	+	+	+	+	Μ	+	+	+	+	+	+	+	+	+	+			
Intestine large, rectum	+	+	+	+	+	+	+	+	Α	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+.			
Intestine small	· +	+	+	+	A	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine small, duodenum	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine small, ileum Intestine small, jejunum Sarcoma	+	+	+	+	A A	+ +	+ +	+	A A	+	A A	+	+	+	+	+	+	+	+	+	+	+	+	+ +			
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Adenocarcinoma, metastatic, lung									х																		
Mesentery		Μ			+										Μ						•						
Pancreas	+	+	+	+	+	+	+	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Acinus, adenoma										Х																	
Salivary glands	+	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+			
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		•	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Stomach, glandular	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Papilloma squamous			+																		x	x					
Cardiovascular System											_	_															
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Endocrine System																											
Adrenal gland	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Adrenal gland, cortex	+	Μ	:+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Ŧ	+			
Adrenal gland, medulla	+	Μ	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+			
Pheochromocytoma benign						x					x	X			Х					X			X				
Bilateral, pheochromocytoma benign														X											•		
Islets, pancreatic	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Adenoma Barathuraid aland	+	м	· _	-	м	<b>^</b>			-	Т		т	т	-	т	м	-	т		м	<u> </u>	<u>ــ</u>	м	· _			
	+	M		Ŧ	141	Ŧ	Ŧ	Τ.	Ŧ	т	Ŧ	т	т	т	т	141	Ŧ	т	Ŧ	141	· •	т	IVI	T			
Pituitary gland	<b>ب</b>	Ŧ	+	+	Ŧ	+	Ŧ	Ŧ	+	Ŧ	+	+	+	Ŧ	+	+	+	+	+	+	+	+	÷	+			
Pars distalis, adenoma	x	Ŧ	1.	x	×	x	x	•			•	x	x	x	•	x	•	x	x		x	x	x	x			
Pars distalis, adenoma, multiple																	х										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+			
C-cell, adenoma Follicular cell, adenoma																						x					
General Rody System	. <u> </u>									<u>.</u>																 	_

None

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Table A2

Individual Animal Tumor Pathology	of Mal	e I	Rai	ts i	im 1	the	2-	Ye	8r	Fe	eed	S	tud	ly o	of I	HC	Y	ello	) W	4:	5	,¢1	1	ppi	m	(continued)	
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	,	
Number of Days on Study	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	i	
	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	0	0	0	0	0	1	
	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	3	3	4	4	4	Tota	
Carcass ID Number	- 9	0	Ő	1	1	2	2	3	3	5	5	5	5	6	7	7	7	7	7	0	8	9	0	1	2	Tiss	ues/
	5	1	3	1	2	2	3	1	2	2	3	4	5	3	1	2	3	4	5	3	1	1	1	1	1	Tum	iors
Alimentary System						· · ·																					
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	+	+	+	+	+	+	+	+	+	+	• -	⊢ 49	
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		⊢ 48	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• -4	⊦ 46	
Intestine large, colon	+	+	+	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	. 4	⊦ 45	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• -	⊦ 47	
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	· +		+ 47	
Intestine small duodenum	. +	+	+	÷	+	+	+	+	÷	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	• +		+ 47	
Intestine small, ileum		÷	÷	÷	÷	_	+	÷	+	+	+	+	+	+	+	+	÷	+	+	+	+	. <b>.</b>				⊢ 46	
Intestine small, jejunum					÷	÷	÷	÷	÷			+	+	, +	+	+	+	÷	+	÷	+	. +				⊢ 46	
Sarcoma	. Y	'	•	•		'	'	•	•	•	•	•		•	•	•	•		•	•	•					1	
Liver	<u>л</u>		<u>ــ</u>	т	<u>т</u>	ъ	Ъ	Т	Ŧ	Ŧ		ъ	Т	<b>–</b>	ъ	1	ъ	ъ	Ŧ	Ŧ	+	<b>+</b>		<b>.</b>		⊥ <u>40</u>	
Adapagarajagana matastatia lung	т	т	т	т	т	т	т	т	т	т	т	т	т	т	т	т	т	т	т	т	т	т	т	. т		r 49 1	
Adenocarcinoma, metastatic, lung																										1	
Mesentery																										, 10	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +		r 48	
Acinus, adenoma													X													2	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +		⊢ 48	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	• +		⊢ 49	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +		⊦ 49	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	• •	⊦ 48	
Tongue																										3	
Papilloma squamous																										2	
Cardiovascular System																											<u> </u>
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	- +	• •	⊦ 49	
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	- +	- +		+ 48	
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	· +	+	+	+	+	+	+	+	+	+	+	• +	- +	- +		+ 48	
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	· +	+	+	+	+	+	+	+	+	+	+	• +	+	- +		+ 48	
Pheochromocytoma benign				Х	X	X				Х			Х	X				Х						Х	C	14	
Bilateral, pheochromocytoma benign									Х																	2	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	• +	+	• +	+	+	+	+	+	+	+	+	• +	· 4	- +		+ 48	
Adenoma																			х							3	
Parathyroid gland	+	+	+	+	+	+	+	М	(+	+	• +	M	1+	+	M	i M	+	+	+	М	. +	• +		N	4.	+ 38	
Adenoma		X		,	,					-	,		,								X					2	
Pituitary gland	+	• +	+	• +	+	+	+	+	+	+	• +	+	• +	+	+	+	+	+	+	+	+	• +	- <b>-</b> +	- +		+ 49	
Pars distalis, adenoma		x	x	Ś	x	x	x		x	x	Ś		,	x				X	x				-		3	X 26	
Pars distalis, adenoma, multiple																							У	C		2	
Thyroid gland	+	· +	. +	• +	+	+	+	+	+	+	• +	+	• +	+	+	+	+	+	+	+	+	- +		- +		+ 48	
C-cell, adenoma	•		•		x		·	·	•	•	•	•	•	•	x	x		•	•	•	×	· `	>	ς.		6	
Follicular cell_adenoma								x															-			1	
romenar och, adenoma								л																		1	

General Body System

None
TABLE A2 Individual Animal Tumor Pathology	of Ma	le	R	ats	in	th	e 2	2-Y	ear	F	eed	S	tud	ly d	of I	HC	Y	elle	DW	4:	5	5,0(	0	pp	m (	(con	itinu	ied)
Number of Days on Study	3 6 7	43	4 4 3 3 ) (	4 :	5 5 5 5 3 7	5 5 5 7 7 0	5 7 8 8	6 0 5	6 5 4	6 5 8	6 6 8	6 7 6	6 8 0	6 9 4	6 9 4	6 9 4	6 9 6	7 0 2	7 0 4	7 1 4	7 1 5	7 2 9	7 2 9	7 2 9				
Carcass ID Number	3 8 5	3	3 3 9 9 5 4	3 3 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9	3 4 9 1 2 4	4	365	4 0 4	3 1 4	3 8 4	3 0 5	3 3 4	4 2 5	3 1 3	3 4 3	3 8 3	4 1 2	3 8 2	3 2 4	3 4 1	3 6 4	2 9 1	2 9 3	2 9 4				
Genital System Epididymis Preputial gland Adenoma Bilotanl adapare	+++		+ •	+ +	+ + + + X	+ +	+ + + + X	· + · +	+++++++++++++++++++++++++++++++++++++++	+ +	+ +	+++	+++	+++	+ +	+ +	+ + X	+++	+++	+++	++	+	+ +	+++				
Prostate Seminal vesicle Testes Bilateral, interstitial cell, adenoma Interstitial cell, adenoma	+ + +	· -	+ + + + + + + + + + + + + + + + + + + +	+ · + · * ·	+ + + + + +	+ + + + + +	+ + + + + +	+ + X	+ + + X	M M + X	+ + X	+ + + X	+ + X	M + +	+ + X	+ + X	+ + +	+ + +	+ + +	+ + + X	+ + X	+ + + X	+ + X	+ + X				
<b>Jematopoietic System</b> Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen	+++++++++++++++++++++++++++++++++++++++	· · · · · · · · · · · · · · · · · · ·		+ + + + + + + + + + + + + + + + + + + +	+ + + + M + + +	 		· + · + · +	+ + + + +	+ + + + + +	A + M + + +	+++++++	+++++++	+ + + + + +	+ + + + +	++++++	+++++	+ + + + + +	+ + + + +	+ + + + + +	+ + M + + +	+ + + M +	+ + + + + + + + + + + + + + + + + + + +	+++++++++++++++++++++++++++++++++++++++				
Thymus ntegumentary System Mammary gland Adenoma	+	• •	⊦ ·	+ ·	+ +	+ N	и + и м	· +	+ ( M	+	+ M	+	+	+	+ M	+	+	+	+	+ м	+ 	+	+	+				
Skin Keratoacanthoma Squamous cell carcinoma Subcutaneous tissue, fibrosarcoma	+	· -	2	+ · K	+ +	⊦ 4	+ +	• +	+	+	+	+ x	+	+	+	+	+	+	+	М	+	+	+	+				
Ausculoskeletal System Bone	+	• •	+ -	+ ·	+ +	+ 4	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Vervous System Brain Astrocytoma malignant Spinal cord	+	• •		+ ·	+ +	+ +	+ +	. +	+	+ +	+	+	+	÷	+ x	+	+	+	+	+	+	+	+					
Respiratory System Lung Adenocarcinoma Alveolar/bronchiolar adenoma Mediastinum, adenocarcinoma,	+	• •	+ -	+ ·	+ +	+ 4	+ +	.+	+ x	+	+	+	+	+	+	+	+	+	+	+	+	+	+ x	+				
metastatic, lung Nose Trachea	+ +	• •	⊦ - ⊦ -	+ · + ·	+ + + +	⊦ + ⊦ +	+ + + +	· + · +	x + +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+				

Individual Animal Tumor Patholog	y of Mal	e	Ra	ts i	in	the	2.	-Ye	8r	Fe	ed	S	tud	y (	of I	HC	¥	e114	DW	4:	5	,¢1	\$D	pp	) IRI	1 (0	ontinued)
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Carcass IID Number	2 9 5	3 0 1	3 0 3	3 1 1	3 1 2	3 2 2	3 2 3	3 3 1	3 3 2	3 5 2	3 5 3	3 5 4	3 5 5	3 6 3	3 7 1	3 7 2	3 7 3	3 7 4	3 7 5	4 0 3	3 8 1	3 9 1	4 0 1	4 1 1	• • • •	4 2 1	Total Tissues, Tumors
Gemital System Epididymis Preputial gland Adenoma Bilateral, adenoma Prostate Seminal vesicle Testes Bilateral, interstitial cell, adenoma 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 + + + X	· · · · · · · · · · · · · · · · · · ·		+ + + X	49 49 7 1 46 48 49 36 5
Hematopoietic System Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen Thymus	+ + M +	+ + + + +	· + · + · +	- + - + - + - +	· + · + · + · +	· + · + · + · +	+ + + + +	+ + + + + +	+ + + + + + +	+ + + + + + +	+ + + + + +	+ + + + + +	+ + + + + +	+ + + + + M	+++++++++++++++++++++++++++++++++++++++	++++++	++++++	+++++++	+ + + + + +	+++++++++++++++++++++++++++++++++++++++	+++++++	+ + + + + +	+++++++++++++++++++++++++++++++++++++++	  	 + + +	++++++	48 49 46 47 48 47
Integumentary System Mammary gland Adenoma Skin Keratoacanthoma Squamous cell carcinoma Subcutaneous tissue, fibrosarcoma	M +	+ ] +	- N - + X	4 № - + K	fi + • +	- +	+++	м +	ім +	: M +	+	м +	ім +	: M +	+	м +	+ +	+ +	м +	: м +	+	. м +	[ ]∿ +	4 P 		+ X M	26 1 47 1 1 1
Musculoskeletal System Bone	+	-+	- 4	- +	• 4	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+ -	+	+	49
Nervous System Brain Astrocytoma malignant Spinal cord	+	-+	- 4	+ 4	- +	- +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	. +		+	+	49 1 1
Respiratory System Lung Adenocarcinoma Alveolar/bronchiolar adenoma Mediastinum, adenocarcinoma, metastatic, lung	+	+	- 4	 	- +	+ +	• +	+	+ x	+	+	+	• +	+	+ x	+	+	+	+	+	+	• +	+	+ -	+	+	49 1 3 1
Nose Trachea	+ +	· -  · -	⊦ + ⊦ -1	⊦ + ⊦ +	- +	⊦ + ⊦ +	• +	• +	+	+	+	+	· + · +	+ +	++	+ +	+ +	+ +	+	+	+	• +	· +	⊦ · ⊦ ·	+ +	+ +	49 49

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	3	4	4	5	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	
Number of Days on Study	6 7	3	3	5	5	7	8	05	5 ∡	5 8	6 8	7	8 0	9 ∡	9 ∡	9 ∡	9	02	0 4	1	1	2	2	2	
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	3	3	3	3	4	4	3	4	3	3	3	3	4	3	3	3	4	3	3	3	3	2	2	2	
Carcass ID Number	8	9	9	9	1	1	6	0	1	8	0	3	2	1	4	8	1	8	2	4	6	9	9	9	
	5	5	4	2	4	3	5	4	4	4	5	4	3	3	3	3	2	2	4	1	4	1	3	4	
Special Senses System																									
Ear																		+	+						
Eye	+							+									+		+	+					
Harderian giand																	+		+						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	
Adenocarcinoma, metastatic, lung									X																
Urinary bladder	+	+	+	+	A	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	.+	+	+	• +	
Leukemia mononuclear						Х	X	Х			х		х	х	Х	х		х			Х	X			
Lymphoma malignant undifferentiated							v																		
cen type							•																		

TABLE A2 Individual Animal Tumor Pathology of	6 ₽	lalo	e 1	Rat	ts i	im	the	e 2	;-¥0	<b>C</b> 81	·F	eed	IS	tud	ly d	oľ I	HC	: Y	ello	DW	4:	5	<b>,</b> C1	<b>MD</b> (	ppi	m	(coi	ntinued)
Number of Days on Study		7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	, ; )																				
Carcass IID Number		2 9 5	3 0 1	3 0 3	3 1 1	3 1 2	3 2 2	3 2 3	3 3 1	3 3 2	3 5 2	3 5 3	3 5 4	3 5 5	3 6 3	3 7 1	3 7 2	3 7 3	3 7 4	3 7 5	4 0 3	3 8 1	3 9 1	4 0 1	4 1 1	4 2 1		Total Tissues/ Tumors
Special Semses System Ear Eye Harderian gland				+		+		+	-					++									++		+	+	<b>⊢</b> ⊦	2 12 6
Urinary System Kidney Adenocarcinoma, metastatic, lung Urinary bladder		+ +	++	++	+	+	· +	+	- + - R	- + ⁄I +	- +	· +	• +	· +	+	+	+	+ +	+	+ +	++	++	+	+	+	+	+	49 1 47
Systemic Lesions Multiple organs Leukemia mononuclear Lymphoma malignant undifferentiated cell type		+ X	+	+	+	+	+ X	+	- + X	- + x x	- + X	• +	• +	• +	+	+	+	+	+	+ X	+	+	+	+	+	+	F	49 16 1

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# TABLE A3

# Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of HC Yellow 4

	0 ррт	2,500 ppm	5,000 ppm
Adrenal Medulla: Benign Pheochromos			
Overall rates <sup>a</sup>	19/50 (38%)	17/49 (35%)	16/48 (33%)
Adjusted rates <sup>b</sup>	58.9%	51.1%	45.6%
Terminal rates <sup>c</sup>	9/21 (43%)	13/29 (45%)	10/28 (36%)
First incidence (days)	637	658	570
Life table tests <sup>d</sup>	P=0.108N	P=0.132N	P=0.143N
Logistic regression tests <sup>d</sup>	P=0.253N	P=0.321N	P=0.317N
Cochran-Armitage test <sup>d</sup>	P=0.352N		
Fisher exact test <sup>d</sup>		P=0.447N	P=0.393N
Adrenal Medulla: Benign or Malignant	t Pheochromocytoma	·	
Overall rates	19/50 (38%)	18/49 (37%)	16/48 (33%)
Adjusted rates	58.9%	54.1%	45.6%
Terminal rates	9/21 (43%)	14/29 (48%)	10/28 (36%)
First incidence (days)	637	658	570 ` ´
Life table tests	P=0.105N	P=0.171N	P=0.143N
Logistic regression tests	P=0.251N	P=0.398N	P=0.317N
Cochran-Armitage test	P=0.354N		
Fisher exact test		P=0.531N	P=0.393N
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	2/50 (4%)	1/50 (2%)	3/49 (6%)
Adjusted rates	7.6%	3.4%	10.7%
Terminal rates	1/21 (5%)	1/29 (3%)	3/28 (11%)
First incidence (days)	666	729 (T)	729 (Ť)
Life table tests	P=0.501	P=0.412N	P=0.619
Logistic regression tests	P=0.429	P=0.481N	P=0.535
Cochran-Armitage test	P=0.391		
Fisher exact test		P=0.500N	P=0.490
Lung: Alveolar/bronchiolar Adenoma o	r Adenocarcinoma		
Overall rates	2/50 (4%)	1/50 (2%)	4/49 (8%)
Adjusted rates	7.6%	3.4%	12.9%
Terminal rates	1/21 (5%)	1/29 (3%)	3/28 (11%)
First incidence (days)	666	729 (T)	654
Life table tests	P=0.321	P=0.412N	P=0.451
Logistic regression tests	P=0.246	P=0.481N	P=0.347
Cochran-Armitage test	P=0.231		
Fisher exact test		P=0.500N	P=0.329
Mammary Gland: Fibroadenoma			
Overall rates	3/50 (6%)	1/50 (2%)	0/49 (0%)
Adjusted rates	13.6%	3.4%	0.0%
Terminal rates	2/21 (10%)	1/29 (3%)	0/28 (0%)
First incidence (days)	725	729 (Ť)	_e ` ´
Life table tests	P=0.034N	P=0.198N	P=0.079N
Logistic regression tests	P=0.039N	P=0.207N	P=0.090N
Cochran-Armitage test	P=0.062N		
		B 0 0001	D 0 106N

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# Table A3

Statistical Amalysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of HC Yellow 4 (continued)

	a bbu	2,500 ppm	5,010 ppm
Mammary Gland: Adenoma or Fibroadenoma			
Overall rates	4/50 (8%)	1/50 (2%)	1/49 (2%)
Adjusted rates	16.7%	3.4%	3.6%
Terminal rates	2/21 (10%)	1/29 (3%)	1/28 (4%)
First incidence (days)	710	729 (T)	729 (T)
Life table tests	P=0.060N	P=0.104N	P=0.119N
Logistic regression tests	P=0.073N	P=0.124N	P=0.137N
Cochran-Armitage test	P=0.104N		
Fisher exact test		P=0.181N	P=0.187N
Pancreas: Adenoma			
Overall rates	2/50 (4%)	4/48 (8%)	2/48 (4%)
Adjusted rates	8.7%	13.8%	6.0%
Terminal rates	1/21 (5%)	4/29 (14%)	1/28 (4%)
First incidence (days)	722	729 (T)	658
Life table tests	P=0.478N	P=0.493	P=0.616N
Logistic regression tests	P=0.556N	P=0.464	P=0.689N
Cochran-Armitage test	P=0.569		
Fisher exact test		P=0.319	P=0.676
Pancreatic Islets: Adenoma			
Overall rates	1/48 (2%)	4/47 (9%)	3/48 (6%)
Adjusted rates	5.0%	13.4%	8.8%
Terminal rates	1/20 (5%)	3/28 (11%)	1/28 (4%)
First incidence (days)	729 (T)	723	570
Life table tests	P=0.339	P=0.295	P=0.368
Logistic regression tests	P=0.264	P=0.266	P=0.305
Cochran-Armitage test	P=0.253		
Fisher exact test		P=0.174	P=0.308
Parathyroid Gland: Adenoma			
Overall rates	0/47 (0%)	0/44 (0%)	2/37 (5%)
Adjusted rates	0.0%	0.0%	10.0%
Terminal rates	0/20 (0%)	0/27 (0%)	2/20 (10%)
First incidence (days)		_	729 (T)
Life table tests	P=0.083	-	P=0.237
Logistic regression tests	P=0.083	-	P=0.237
Cochran-Armitage test	P = 0.072		
Fisher exact test		-	P=0.191
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	17/45 (38%)	20/49 (41%)	28/49 (57%)
Adjusted rates	59.1%	53.0%	67.4%
Terminal rates	10/20 (50%)	12/29 (41%)	15/28 (54%)
First incidence (days)	598	626	367
Life table tests	P=0.140	P=0.434N	P=0.176
Logistic regression tests	P=0.034	P=0.489	P=0.047
Cochran-Armitage test	P=0.036		
Fisher exact test		P=0.464	P=0.047

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# TABLE A3

Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of HC Yellow 4 (continued)

	0 ppm	2,500 ppm	5,000 ppm
Prenutial Gland: Adenoma			
Overall rates	9/48 (19%)	13/50 (26%)	8/49 (16%)
Adjusted rates	37 9%	36.6%	23.9%
Terminal rates	7/21 (33%)	8/29 (28%)	5/28 (18%)
First incidence (days)	639	481	553
ife table tests	P = 0.261 N	P=0.485	P = 0.310N
ogistic regression tests	P = 0.2011V	P = 0.295	P = 0.51010
Cochran-Armitage test	P=0.430N	1 0.275	1 - 0.15111
Fisher exact test		P=0.269	P=0.481N
Preputial Gland: Adenoma or Carcinom	8		
Overall rates	10/48 (21%)	13/50 (26%)	8/49 (16%)
Adjusted rates	39.2%	36.6%	23.9%
Ferminal rates	7/21 (33%)	8/29 (28%)	5/28 (18%)
First incidence (days)	508	481	553
Life table tests	P=0.192N	P=0.576	P=0.232N
ogistic regression tests	P=0.325N	P=0.373	P=0.367N
Cochran-Armitage test	P=0.335N		
Fisher exact test		P=0.358	P=0.379N
Skin (Subcutaneous Tissue): Fibroma			
Overall rates	0/50 (0%)	5/50 (10%)	0/49 (0%)
Adjusted rates	0.0%	15.6%	0.0%
Cerminal rates	0/21 (0%)	3/29 (10%)	0/28 (0%)
First incidence (days)	-	672	-
Life table tests	P=0.520N	P=0.067	-
ogistic regression tests	P=0.585N	P=0.041	-
Cochran-Armitage test	P=0.603		•
Fisher exact test		P=0.028	
Skin (Subcutaneous Tissue): Fibroma o	r Fibrosarcoma		
Overall rates	2/50 (4%)	5/50 (10%)	1/49 (2%)
Adjusted rates	7.0%	15.6%	2.6%
Ferminal rates	1/21 (5%)	3/29 (10%)	0/28 (0%)
First incidence (days)	619	672	676
Life table tests	P=0.318N	P=0.336	P = 0.449N
Logistic regression tests	P=0.408N	P=0.232	P = 0.508N
Cochran-Armitage test	P=0.421N		
Fisher exact test		P=0.218	P=0.508N
l'estes: Adenoma			
Overall rates	47/50 (94%)	43/50 (86%)	41/49 (84%)
Adjusted rates	100.0%	100.0%	97.5%
Terminal rates	21/21 (100%)	29/29 (100%)	27/28 (96%)
First incidence (days)	508	467	436
Life table tests	P = 0.011N	P=0.018N	P=0.018N
Logistic regression tests	P = 0.056N	P=0.140N	P=0.075N
Cochran-Armitage test	P = 0.077N		<b>n</b>
Fisher exact test		P=0.159N	P=0.094N

#### Lesions in Male Rats

# TABLE A3

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Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of HC Yellow 4 (continued)

	0 ppm	2,500 ppm	5,000 ppm
Thyroid Gland (C-cell): Adenoma			
Overall rates	7/49 (14%)	5/49 (10%)	6/48 (13%)
Adjusted rates	30.3%	14.7%	21.4%
Terminal rates	6/21 (29%)	3/29 (10%)	6/28 (21%)
First incidence (days)	637	588	729 (T)
Life table tests	P=0.272N	P = 0.220N	P=0.294N
Logistic regression tests	P=0.407N	P=0.344N	P=0.410N
Cochran-Armitage test	P=0.454N		
Fisher exact test		P=0.380N	P=0.516N
All Organs: Mononuclear Cell Leukemia			
Overall rates	19/50 (38%)	21/50 (42%)	16/49 (33%)
Adjusted rates	46.1%	51.1% <sup>`</sup>	40.5%
Terminal rates	2/21 (10%)	10/29 (34%)	6/28 (21%)
First incidence (days)	485	467 <sup>`</sup>	570 ` ´
Life table tests	P=0.192N	P=0.466N	P=0.238N
Logistic regression tests	P=0.332N	P=0.414	P=0.371N
Cochran-Armitage test	P=0.330N		
Fisher exact test		P=0.419	P=0.365N
All Organs: Benign Tumors			
Overall rates	49/50 (98%)	49/50 (98%)	48/49 (98%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	21/21 (100%)	29/29 (100%)	28/28 (100%)
First incidence (days)	485	367	367
Life table tests	P=0.085N	P=0.084N	P=0.104N
Logistic regression tests	P=0.694N	P=0.962	P=0.887N
Cochran-Armitage test	P=0.634N		•
Fisher exact test		P=0.753N	P=0.747N
All Organs: Malignant Tumors			
Overall rates	27/50 (54%)	27/50 (54%)	19/49 (39%)
Adjusted rates	59.9%	59.8%	44.7%
Terminal rates	4/21 (19%)	12/29 (41%)	6/28 (21%)
First incidence (days)	485	367	436
Life table tests	P=0.054N	P=0.307N	P=0.070N
Logistic regression tests	P=0.085N	P=0.541	P=0.100N
Cochran-Armitage test	P=0.079N		
Fisher exact test		P=0.579N	P=0.094N
All Organs: Benign or Malignant Tumors			
Overall rates	49/50 (98%)	50/50 (100%)	48/49 (98%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	21/21 (100%)	29/29 (100%)	28/28 (100%)
First incidence (days)	485	367	367
Life table tests	P = 0.087 N	P=0.111N	P = 0.104 N
	P = 0.608N	_f	P = 0.887N
LOGISTIC REPRESSION TESTS			
Logistic regression tests Cochran-Armitage test	P = 0.665N		

#### TABLE A3

Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of HC Yellow 4 (continued)

(T)Terminal sacrifice

<sup>b</sup> Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality

<sup>c</sup> Observed incidence at terminal kill

<sup>d</sup> 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.

<sup>e</sup> Not applicable; no tumors in animal group f Value of statistic connect be computed

Value of statistic cannot be computed

<sup>&</sup>lt;sup>a</sup> 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.

# Table A4

Historical Incidence of Pituitary Gland Neoplasms in Untreated Male F344/N Rats<sup>a</sup>

Study		Incidence in Contr	rols
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G	Mason Research Institute		
4-Hydroxyacetanilide	16/48	1/48	17/48
HC Yellow 4	17/45	0/45	17/45
Pentaerythritol tetranitrate	13/49	0/49	13/49
Quercetin	14/46	0/46	14/46
Total	60/188 (31.9%)	1/188 (0.5%)	6/188 (32.4%)
Standard deviation	4.7%	1.0%	4.9%
Range	27%-38%	0%-2%	27%-38%
Overall Historical Incidence			
Total	230/785 (29,3%)	3/785 (0.4%)	233/785 (29.7%)
Standard deviation	11.5%	0.8%	11.5%
Range	12%-60%	0%-2%	12%-60%

<sup>a</sup> Data as of 3 April 1991 for pars distalis or unspecified site

# TABLE A5

Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of HC Yellow  $4^a$ 

0	ppm	2,50	) ppm	5,0	00 ppm
					<u> </u>
70		70		70	
10		10		10	
9		10		10	
6		4		3	
24		17		18	
21		29		28	
				1	
50 <sup>b</sup>		50		49	
(47)		(49)		(46)	
(4/)	(2%)	(40)		(40)	
1 (40)	(270)	(44)		(45)	
(48)	(20)	(44)		(43)	
I	(270)			-	(11%)
4	(8%)	(17)		2 (47)	(11%)
(47)	(201)	(4/)		(47)	(10%)
1	(2%)			2	(4%)
1	(2%)	(50)		(10)	
(50)	(0.01)	(50)	(0.07)	(49)	(00)
4	(8%)	1	(2%)	4	(8%)
1	(2%)			1	(2%)
17	(34%)	21	(42%)	16	(33%)
6	(12%)	5	(10%)	10	(20%)
1	(2%)				
2	(4%)	3	(6%)	4	(8%)
. 5	(10%)	2	(4%)	6	(12%)
3	(6%)			1	(2%)
9	(18%)	8	(16%)	3	(6%)
7	(14%)	4	(8%)	5	(10%)
		1	(2%)	1	(2%)
1	(2%)	3	(6%)	1	(2%)
1	(2%)	3	(6%)	3	(6%)
3	(6%)	1	(2%)		
34	(68%)	36	(72%)	41	(84%)
(3)		(5)		(1)	
		-		1	(100%)
2	(67%)			1	(100%)
(50)		(48)		(48)	
22	(44%)	21	(44%)	23	(48%)
5	(10%)	1	(2%)	3	(6%)
1	(2%)	3	(6%)	5	(10%)
_				4	(8%)
				2	(4%)
1	(2%)				
(50)		(48)		(49)	
2	(4%)	2	(4%)	. ,	
1	(2%)	1	(2%)	1	(2%)
*	<u> </u>	3	(6%)	1	(2%)
(49)		(48)		(48)	
()		1	(2%)		
2	(6%)	•	()	1	(2%)
2	(4%)	1	(2%)	-	()
	$\begin{array}{c} 0\\ \hline \\ 70\\ 10\\ 9\\ 6\\ 24\\ 21\\ 50^{b}\\ \hline \\ (47)\\ 1\\ (48)\\ 1\\ 4\\ (47)\\ 1\\ (48)\\ 1\\ 4\\ (47)\\ 1\\ 1\\ (50)\\ 4\\ 1\\ 1\\ (50)\\ 2\\ 5\\ 5\\ 3\\ 3\\ 9\\ 7\\ 7\\ 1\\ 1\\ 1\\ 3\\ 34\\ (3)\\ 2\\ (50)\\ 22\\ 5\\ 1\\ 1\\ (50)\\ 22\\ 5\\ 1\\ 1\\ (49)\\ 3\\ 2 \end{array}$	0 ppm 70 10 9 6 24 21 50 <sup>b</sup> (47) 1 (2%) (48) 1 (2%) 4 (8%) (47) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 1 (2%) 2 (4%) 5 (10%) 3 (6%) 3 (6%) 3 (6%) 4 (8%) 1 (2%) 1 (2%) 1 (2%) 3 (6%) 3 (6%) 4 (8%) 3 (6%) 3 (6%) 4 (8%) 3 (6%) 3 (6%) 4 (8%) 5 (10%) 5 (10%) 1 (2%) 1 (2%	0 ppm         2,504           70         70           10         10           9         10           6         4           24         17           21         29 $50^b$ 50           (47)         (48)           1         (2%)           (48)         (44)           1         (2%)           4         (8%)           (47)         (47)           1         (2%)           4         (8%)           1         (2%)           1         (2%)           1         (2%)           1         (2%)           1         (2%)           1         (2%)           2         (4%)           1         (2%)           2         (4%)           3         (6%)           3         (6%)           3         (6%)           1         (2%)           3         (6%)           3         (6%)           3         (6%)           3         (6%)           2         1 <td>0 ppm         2,500 ppm           70         70           10         10           9         10           6         4           24         17           21         29           50<sup>b</sup>         50           (47)         (48)           1         (2%)           4         (8%)           (47)         (47)           1         (2%)           4         (8%)           (47)         (47)           1         (2%)           1         (2%)           1         (2%)           1         (2%)           1         (2%)           1         (2%)           1         (2%)           1         (2%)           1         (2%)           2         (4%)           3         (6%)           1         (2%)           2         (4%)           3         (6%)           1         (2%)           3         (6%)           1         (2%)           3         (6%)           1         (2%)</td> <td><math display="block">\begin{array}{c ccccccccccccccccccccccccccccccccccc</math></td>	0 ppm         2,500 ppm           70         70           10         10           9         10           6         4           24         17           21         29           50 <sup>b</sup> 50           (47)         (48)           1         (2%)           4         (8%)           (47)         (47)           1         (2%)           4         (8%)           (47)         (47)           1         (2%)           1         (2%)           1         (2%)           1         (2%)           1         (2%)           1         (2%)           1         (2%)           1         (2%)           1         (2%)           2         (4%)           3         (6%)           1         (2%)           2         (4%)           3         (6%)           1         (2%)           3         (6%)           1         (2%)           3         (6%)           1         (2%)	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

#### Table AS

Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of HC Yellow 4 (continued)

	Ø	bbuu	2,50	0 ppm	5,60	0 ppm
Cardiovascular System					- · ·	
Heart	(50)		(50)		(49)	
Cardiomyopathy	33	(66%)	42	(84%)	34	(69%)
Thrombus			2	(4%)	2	(4%)
Endocrine System						
Adrenal gland, cortex	(50)		(50)		(48)	
Hyperplasia					3	(6%)
Adrenal gland, medulla	(50)		(49)		(48)	. ,
Hyperplasia	12	(24%)	16	(33%)	14	(29%)
Islets, pancreatic	(48)		(47)		(48)	
Hyperplasia			3	(6%)		
Parathyroid gland	(47)		(44)		(38)	
Hyperplasia	2	(4%)	1	(2%)	1	(3%)
Pituitary gland	(45)	(100)	(49)	(000)	(49)	(20.21)
Pars distalis, anglectasis	8	(18%)	11	(22%)	10	(20%)
Pars distalis, cyst Pars distalia, hyperplacia	1	(2%)	1	(2%)	3	(0%)
Pare intermedia cret	0	(18%)	15	(21%)	18	(31%)
Thyroid gland	(40)		(40)		(49)	(2%)
C-cell hyperplasia	(45)	(8%)	(45)	(18%)	(40)	(13%)
Follicle, cyst	1	(2%)	,	(1070)	v	(15%)
Follicular cell, hyperplasia	-	(=/*)	1	(2%)	1	(2%)
None						
Genital System						
Epididymis	(49)		(50)		(49)	
Granuloma sperm					1	(2%)
Preputial gland	(48)		(50)		(49)	
Inflammation, chronic active	11	(23%)	6	(12%)	5	(10%)
Prostate	(48)	(0 <b>~</b> )	(49)	(0.07)	(46)	(1~)
Epithelium, hyperplasia	4	(8%)	1	(2%)	2	(4%)
Interneticial call humanulasia	(50)	(100)	(50)	15 401	(49)	(500)
Seminiferous tubule, atrophy	20 34	(40%) (68%)	31	(54%) (62%)	29 21	(39%) (43%)
Wamatazaiatia Sustam						
I vmnh node	(50)		(50)		(40)	
Mediastinal fibrosis	(50)		(50)		(45)	(2%)
Renal, nigmentation	1	(2%)	1	(2%)	1	(270)
Lymph node, mesenteric	(49)	(2/0)	(50)	(2/0)	(47)	
Fibrosis	1	(2%)	()		()	
Infiltration cellular, histiocyte	10	(20%)	3	(6%)	7	(15%)
Spleen	(50)		(50)		(48)	. /
Cyst			í	(2%)		
Fibrosis	4	(8%)	2	(4%)	5	(10%)
Hematopoietic cell proliferation	20	(40%)	12	(24%)	25	(52%)
Thymus	(41)		(43)		(47)	
Cyst		(2.21)			1	(2%)
Epithelial cell, hyperplasia	1	(2%)				

#### TABLE A5

Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of HC Yellow 4 (continued)

	0	ppm	2,50	0 ppm	5,00	) ppm
Integumentary System	,					
Mammary gland	(28)		(18)		(26)	
Galactocele	2	(7%)	2	(11%)	2	(8%)
Acinus, hyperplasia	7	(25%)	6	(33%)	5	(19%)
Skin	(48)	()	(50)	()	(47)	()
Acanthosis	1	(2%)	()		1	(2%)
Cyst enithelial inclusion	2	(4%)			3	(6%)
Hyperkeratosis	2	(4%)	2	(4%)	4	(9%)
Musculoskeletal System None		,				
Nervous System						
Brain	(50)		(50)		(49)	
Hemorrhage	(30)	(4%)	2	(4%)	1	(2%)
		()		()	-	()
Respiratory System	, ,				•	, -
Lung	(50)		(50)		(49)	
Fibrosis	2	(4%)			2	(4%)
Infiltration cellular, histiocyte	6	(12%)	6	(12%)	5	(10%)
Inflammation, acute	2	(4%)			ì	(2%)
Metaplasia, osseous		. ,	1	(2%)	1	(2%)
Alveolar epithelium, hyperplasia			4	(8%)	2	(4%)
Nose	(47)		(50)		(49)	
Fungus	2	(4%)	1	(2%)	1	(2%)
Inflammation, acute	4	(9%)	4	(8%)	2	(4%)
				····	····	
Far	(6)		(4)		(2)	
Inflammation acute	1	(17%)	()		(-)	
Fve	(6)	(1770)	(6)		(12)	
Hemorrhage	. (9)	(17%)	(9)		()	
I ens cataract	4	(67%)	4	(67%)	6	(50%)
Retina, atrophy	2	(33%)		()	. 3	(25%)
		······································		· · · · · · · · · · · · · · · · · · ·	<u> </u>	
Urinary System	(60)		(50)		(40)	
Nuncy	(50)	(604)	(50)	(10/)	(49)	(90%)
Cyst	3	(0%)	2	(4%)	. 4	(0%)
Hydronephrosis	**	(000)	10	(000)	2	(4%)
rephropathy	49	(98%)	49	(98%)	4/	(90%)
Urinary bladder	(48)		(48)		(47)	(20%)
Calculus gross observation	2	(10)			1	(270)
Calculus micro observation only	2	(4%)			1	(2%)

a Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site. Does not include one early death that occurred prior to the 15-month interim evaluation b

# APPENDIX B

# SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR FEED STUDY OF HC YELLOW 4

Table B1	Summary of the Incidence of Neoplasms in Female Rats	
	in the 2-Year Feed Study of HC Yellow 4	<b>9</b> 7
Table B2	Individual Animal Tumor Pathology of Female Rats	07
	in the 2-Year Feed Study of HC Yellow 4	ወ⁄ስ
Table B3	Statistical Analysis of Primary Neoplasms in Female Rats	20
	in the 2-Year Feed Study of HC Yellow 4	1.00.0
Table B4a	Historical Incidence of Uterine Neoplasms in Untreated Female F344/N Rots	112
Table B4b	Historical Incidence of Mammary Gland Neoplasms	113
	in Untreated Female F344/N Rats	117
Table B5	Summary of the Incidence of Nonneoplastic Lesions in Female Rats	110
	in the 2-Year Feed Study of HC Yellow 4	114

# Table B1

Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of HC Yellow 4ª

Disposition Summary         Animali initially in study         70         70         70           Animali initially in study         70         70         70         70           Somoth interine evaluation         10         10         10         10           Early deaths         2         4         1         1           Moribund         21         15         15           Survivon         26         30         34           Moribund         1         1         1           Animals examined microscopically         50         50         50           Alimentary System         (49)         (49)         (49)         (49)           Intestine large, occum         (49)         (40)         (49)         (40)           Intestine large, occum         (49)         (40)         (40)         (40)           Intestine large, occum         (49)         (40)         (40)         (40)           Intestine large, occum         (50)         (50)         (50)         (50)           Liver         (50)         (50)         (50)         (50)         (50)           Intestine large, occum         1         (2%)         (50)         (50) <t< th=""><th></th><th>0</th><th><b>bb</b>m</th><th>5,00</th><th>D ppm</th><th>10,03</th><th>0 ppm</th></t<>		0	<b>bb</b> m	5,00	D ppm	10,03	0 ppm
Animals initially in study       70       70       70         Smonth interim evaluation       10       10       10         15-month interim evaluation       10       10       10         Smonth interim evaluation       10       10       10         Smonth interim evaluation       10       10       10         Staturd deaths       2       4       1         Marine deaths       21       15       15         Moribund       1       1       1         Animals examined microscopically       50       50       50         Alimentary System       (45)       (47)       (47)         Intestine large, colon       (48)       (46)       (49)         Intestine large, colon       (48)       (47)       (50)         Liver       (50)       (50)       (50)       (50)         Liver       (50)       (50)       (50)       (50)         Liver       (27)       (49)       (50)       (50)         Liver       (23)       (49)       (50)       (50)         Liver       (23)       (49)       (50)       (50)         Salvary glads       (50)       (50)       (50)	Disposition Summary						
Samoth interin evaluation         10         10         10         10           Samoth interin evaluation         10         10         10         10           Carly deaths         2         4         1           Morbund Kills         21         15         15           Survices         26         30         34           Morbund Kills         21         15         15           Survices         26         30         34           Minals scaffice         26         30         50           Animal scaffice         26         30         50           Animals scaffice         26         30         50           Minestine large, cecum         (48)         (47)         (47)           Intestine large, colon         (48)         (49)         (49)           Intestine large, colon         (48)         (49)         (40)           Intestine smail, iteum         (49)         (47)         (50)           Liver         (50)         (50)         (50)         (50)           Carcinoma, metastatic, ovary         1         (27%)         1         (27%)           Fancreas         (49)         (40)         (40)	Animals initially in study	70		70		70	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	5-month interim evaluation	10		10		10	
Early deaths in the set of the s	5-month interim evaluation	10		10		10	
Natural desitis         2         4         1           Moribund kills         21         15         15           Invivors         30         34           Moribund         1         1           Animals examined microscopically         50         50         50           Alimentary System         1         1         1           Intestine large, cocum         (48)         (49)         (47)           Intestine large, cocum         (48)         (47)         (47)           Intestine large, cocum         (48)         (47)         (50)           Liver         (50)         (50)         (50)         (50)           Carcinoma, metastatic, ovary         1         (278)         1         (50)           Hepatocellular actenoma         1         (278)         1         (6)         1           Stomach, forestomach         (50)         (50)         (50)         (50)         (50)         (50)           Stomach, glandular         (50)         (50)         (50)         (50)         (50)         (50)           Stomach, gland, medulla         (49)         (45)         (47)         (27)         1         (27)           Adtrenal gland,	Farly deaths			••			
Monthand kills         21         15         15           Survivors         26         30         34           Monthund         1         1         1           Animals examined microscopically         50         50         50           Alimentary System         (49)         (49)         (49)           Intestine large, cecum         (48)         (47)         (47)           Intestine large, cecum         (48)         (47)         (47)           Intestine large, cecum         (48)         (47)         (47)           Intestine small, duodenum         (49)         (47)         (50)           Liver         (50)         (50)         (50)         (50)           Carcinona, metastatic, ovary         1         (27%)         1         (27%)           Hepatocellular actenoma         1         (27%)         (49)         (40)         (40)           Acinus, adenoma         2         (47%)         2         (47%)         2         (47%)         2         (47%)         2         (47%)         2         (47%)         2         (47%)         2         (47%)         2         (47%)         2         (47%)         2         (47%)         2	Natural deaths	2		4		1	
Survivors     In     10     10       Terminal sacrifice     26     30     34       Animals examined microscopically     50     50     50       Alimentary System intestine large, cocum     (48)     (47)     (47)       Intestine large, cocum     (48)     (47)     (47)       Intestine large, cocum     (48)     (47)     (47)       Intestine small, duodenum     (49)     (46)     (49)       Intestine small, duodenum     (49)     (47)     (50)       Carcinoma, metastatic, ovary     1     (2%)     (50)       Hepatocellular actenoma     1     (2%)     (47)     (50)       Mesentery     (3)     (4)     (48)     (49)       Actions, actastatic, ovary     1     (25%)     (6)       Panceas     (49)     (50)     (50)     (50)       Stomach, forestomach     (50)     (50)     (50)     (50)       Stomach, forestomach     (50)     (50)     (50)     (50)       Cardiovascular System     1     (2%)     3     (7%)     2       Adtrenal gland, doutlar     (50)     (50)     (48)     (49)       Stomach, forestomach     (50)     (50)     (50)     (50)       Adtrenal gland, doutl	Moribund kills	21		15		15	
Description         Particular ascrifice         26         30         34           Moribund         1         1         1         1           Animals examined microscopically         50         50         50           Alimentary System         Intestine large, cocum         (48)         (49)         (49)           Intestine large, cocum         (48)         (46)         (49)         (47)         (47)           Intestine large, cocum         (49)         (47)         (50)         (50)         (50)           Liver         (50)         (50)         (50)         (50)         (50)         (50)           Carcinoma, metastatic, ovary         1         (2%)         (49)         (45)         (49)           Hepatocellular aschoma         1         (2%)         (50)         (50)         (50)           Carcinoma, metastatic, ovary         1         (2%)         (50)         (50)         (50)           Stowards, forestomach         (50)         (50)         (50)         (50)         (50)         (50)           Stomach, glandular         (50)         (50)         (50)         (50)         (50)         (50)           Carcinona squamous         1         (2%)		21		15		15	
Initial actinic         D         J         J           Animals examined microscopically         50         50         50           Alimentary System         (49)         (49)         (49)           Intestine large, coun         (48)         (47)         (47)           Intestine large, colon         (48)         (47)         (47)           Intestine large, colon         (48)         (47)         (50)           Intestine small, iduadenum         (49)         (48)         (49)           Intestine small, iduadenum         (49)         (47)         (50)           Carcinona, metastatic, ovary         1         (2%)         1           Hepatocellular actronona         1         (2%)         (49)           Acinus, adenoma         2         (4%)         2         (4%)           Slovary glands         (50)         (50)         (50)           Stomach, glandular         (50)         (50)         (50)           Cardiovascular System         1         (2%)         2           Adtrenal gland, cortex         (50)         (50)         (50)           Zonach, glandular         1         (2%)         3         (7%)         2           Adternal glan	Terminal sacrifice	26		30		34	
Animals examined microscopically       50       50         Animals examined microscopically       50       50         Animals examined microscopically       50       50         Alimentary System       (48)       (49)       (47)         intestine large, coum       (48)       (47)       (47)         intestine large, cound       (48)       (47)       (47)         intestine smail, duodenum       (49)       (47)       (50)         intestine smail, duodenum       (49)       (47)       (50)         Carcinona, metastatic, ovary       1       (27%)       (50)         Hepatocellular carcinoma       1       (27%)       (49)       (50)         Carcinona, metastatic, ovary       1       (25%)       (49)       (50)         Pancreas       (49)       (50)       (50)       (50)         Stomach, forestomach       (50)       (50)       (50)         Papilloma squamous       1       (27%)       1       (27%)         Adrenal gland, cortex       (50)       (50)       (50)       (50)         Endocrine System       1       (27%)       3       (7%)       2       (4%)         Adrenal gland, cortex       (50) <t< td=""><td>Moribund</td><td>1</td><td></td><td>1</td><td></td><td>54</td><td></td></t<>	Moribund	1		1		54	
Animals examined microscopically         50         50         50           Mimentary System Intestine large, coum         (48)         (47)         (47)           Intestine large, coum         (48)         (47)         (47)           Intestine large, coum         (48)         (47)         (47)           Intestine small, duodenum         (49)         (48)         (49)           intestine small, ileum         (49)         (47)         (50)           intestine small, ileum         (49)         (47)         (50)           iver         (50)         (50)         (50)         (50)           Carcinoma, metastatic, ovary         1         (27%)         (47)         (50)           Animus, adenoma         2         (4%)         2         (4%)         (50)           Actinus, adenoma         (50)         (50)         (50)         (50)         (50)           Stomach, (andular         (50)         (50)         (50)         (50)         (50)           Cardiovascular System         1         (27%)         1         (27%)           Aderona         1         (27%)         1         (27%)           Aderona         1         (27%)         3         (77%) <td>Worldung</td> <td>1</td> <td></td> <td>1</td> <td></td> <td></td> <td></td>	Worldung	1		1			
Alimentary System         (48)         (49)         (49)           intestine large, cecum         (48)         (47)         (47)           intestine large, cecum         (48)         (44)         (47)           intestine small, duodenum         (49)         (48)         (49)           intestine small, duodenum         (49)         (47)         (50)           Liver         (50)         (50)         (50)         (50)           Carcinoma, metastatic, ovary         1         (2%)         Hepatocellular actionoma         1         (2%)           Hepatocellular actionoma         1         (2%)         (49)         (49)         (49)           Actinus, adenoma         2         (4%)         2         (4%)         (50)           Vescentery         (3)         (48)         (50)         (50)         (50)           Stomach, forestomach         (50)         (50)         (50)         (50)         (50)           Papilloma squamous         (50)         (50)         (50)         (50)         (50)           Adrenal gland, cortex         (50)         (50)         (50)         (48)         (49)           Pheochromocytoma malignant         1         (2%)         3	Animals examined microscopically	50		50		50	
intestine large, cecum       (48)       (49)       (49)         ntestine large, colon       (48)       (47)       (47)         intestine small, duodenum       (49)       (48)       (49)         intestine small, duodenum       (49)       (48)       (49)         intestine small, duodenum       (49)       (47)       (50)         jver       (50)       (50)       (50)         Carcinoma, metastatic, ovary       1       (2%)       1         Hepatocellular aeronoma       1       (2%)       1         Vescntery       (3)       (4)       (6)         Carcinoma, metastatic, ovary       1       (25%)       2         Acinus, adenoma       2       (4%)       2       (4%)         Acinus, adenoma       2       (4%)       (50)       (50)         Salivary glands       (50)       (50)       (50)       (50)         Acinus, adenoma       (50)       (50)       (50)       (50)         Pastopatiloma squamous       1       (2%)       1       (2%)         Adrenal gland, cortex       (50)       (50)       (50)       (50)         Adrenal gland, medulla       (9)       (46)       (47) <td< td=""><td>Alimentary System</td><td></td><td></td><td></td><td></td><td></td><td></td></td<>	Alimentary System						
ntestine large, colon (48) (47) (47) ntestine large, rectum (48) (46) (49) ntestine small, lucuenum (49) (47) (50) intestine small, lucum (49) (47) (50) intestine small, lucum (49) (47) (50) Carcinoma, metastatic, ovary 1 (2%) Hepatocellular adenoma 1 (2%) Mesentery (3) (4) (6) Carcinoma, metastatic, ovary 1 (25%) Pancreas (49) (50) (49) Acinus, adenoma 2 (4%) 2 (4%) Stomach, forestomach (50) (50) (50) Stomach, forestomach (50) (50) (50) Stomach, glandular (50) (50) (50) Cardiovascular System Heart (50) (50) (50) (50) Endocrine System Adrenal gland, cortex (50) (49) (50) Adrenal gland, cortex (50) (50) (50) Endocrine System Adrenal gland, cortex (50) (49) (46) (49) Pheochromocytoma malignant 1 (2%) 3 (7%) 2 (4%) Stomach, and 1 (2%) (50) (48) Adrenal gland, medula (49) (46) (49) Pheochromocytoma benign 1 (2%) 3 (7%) 2 (4%) Stets, pancreatic (50) (50) (50) (50) Adrenoma 1 (2%) 3 (7%) 2 (4%) Stets, pancreatic (50) (50) (50) (48) Adrenoma 1 (2%) 3 (7%) 2 (4%) Stets, pancreatic (50) (50) (50) (48) Adrenoma 1 (2%) 3 (7%) 2 (4%) Stets, pancreatic (50) (50) (50) (50) Adrenoma 1 (2%) 3 (7%) 2 (4%) Stets, pancreatic (50) (50) (50) (50) Adrenoma 1 (2%) 1 (3%) Predictiones (50) (50) (50) (50) Adrenoma 1 (2%) 1 (2%) Adrenoma 1 (2%) 1 (2%) Adrenoma 1 (2%) 7 (14%) 7 (14%) Provid gland (50) (50) (50) Biliateral, C-cell, adenoma (50) (50) Biliateral, C-cell, adenoma (50) (50) Biliateral, C-cell, adenoma (50) C-cell, adenoma (50) (50) Biliateral, C-cell, adenoma (50) C-cell, adenoma (50) C-cell, adenoma (50) C-cell, adenoma (50) C-cell, adenoma (50) Biliateral, C-cell, adenoma (50) Biliateral, C-cell, adenoma (50) Biliateral, C-cell, adenoma (50) Biliateral, C-cell, adenoma (50) C-cell, adenoma (50) C-cell, adenoma (50) Biliateral, C-cell, adenoma (50) Biliateral, C-cell, adenoma (50) Biliateral, C-	ntestine large, cecum	(48)		(49)		(49)	
intestine large, rectum $(46)$ $(46)$ $(49)$ intestine small, duedenum $(49)$ $(48)$ $(49)$ intestine small, ileum $(49)$ $(47)$ $(50)$ jver $(50)$ $(50)$ $(50)$ Carcinoma, metastatic, ovary       1 $(2\%)$ Hepatocellular adenoma       1 $(2\%)$ Hepatocellular adenoma       1 $(2\%)$ Mesentery $(3)$ $(4)$ $(6)$ Carcinoma, metastatic, ovary       1 $(2\%)$ 2         Panceas $(49)$ $(50)$ $(49)$ Salivary glands $(50)$ $(50)$ $(50)$ Somach, forestomach $(50)$ $(50)$ $(50)$ Papiltoma squamous       1 $(2\%)$ 1         Cardiovascular System	ntestine large, colon	(48)		(47)		(47)	
intestine small, duodenum       (49)       (48)       (49)         intestine small, lieum       (49)       (47)       (50)         Carcinoma, metastatic, ovary       1       (2%)       1         Hepatocellular carcinoma       1       (2%)       1         Hepatocellular carcinoma       1       (2%)       1         Mesontery       (3)       (4)       (6)         Carcinoma, metastatic, ovary       1       (25%)       7         Pancreas       (49)       (50)       (49)         Acinus, adenoma       2       (4%)       (50)         Stomach, forestomach       (50)       (50)       (50)         Papiloma squamous       1       (2%)       1         Stomach, glandular       (50)       (50)       (50)         Cardiovascular System       1       (2%)       1         Adrenal gland, cortex       (50)       (49)       (46)         Adrenal gland, medulla       (49)       (46)       (49)         Pheochromocytoma malignant       1       (2%)       3       (7%)         Adrenal gland, medulla       (49)       (46)       (49)       (45)         Pheochromocytoma benign       1	Intestine large, rectum	(48)		(46)		(49)	
intestine small, ileum $(49')$ $(47')$ $(50)$ Liver $(50)$ $(50)$ $(50)$ Carcinoma, metastatic, ovary       1 $(2\%)$ Hepatocellular adenoma       1 $(2\%)$ Hepatocellular adenoma       1 $(2\%)$ Mesentery $(3)$ $(4)$ $(6)$ Carcinoma, metastatic, ovary       1 $(25\%)$ Pancreas $(49)$ $(50)$ $(49)$ Stomach, forestomach $(50)$ $(50)$ $(50)$ Papilloma squamous $(50)$ $(48)$ $(50)$ Stomach, grandular $(50)$ $(50)$ $(50)$ Cardiovascular System       1 $(2\%)$ $(2\%)$ Heart $(50)$ $(50)$ $(50)$ Cardiovascular System       1 $(2\%)$ $(2\%)$ Heart $(50)$ $(49)$ $(40)$ Pheochromocytoma malignant       1 $(2\%)$ $(2\%)$ Aderona       1 $(2\%)$ $(2\%)$ $(43)$ Adenoma       1 $(2\%)$ $(45)$ Aderona	Intestine small, duodenum	(49)		(48)		(49)	
Liver (50) (50) (50) (50) Carcinoma, metastatic, ovary 1 (2%) Hepatocellular carcinoma 1 (2%) Hepatocellular adenoma 1 (2%) Mesentery (3) (4) (6) Carcinoma, metastatic, ovary 1 (25%) Pancreas (49) (50) (49) Acinus, adenoma 2 (4%) 2 (4%) Stivarach, forestomach (50) (48) (50) Papilloma squamous (50) (48) (50) Stomach, forestomach (50) (50) (50) Stomach, glandular (50) (50) (50) Cardiovascular System Heart (50) (50) (50) (50) Endocrine System Heart (50) (50) (50) (50) Cardiovascular System (1 (2%) (50) (50) Pheochromocytoma malignant 1 (2%) (50) (48) Aderona 1 (2%) (50) (48) (49) Pheochromocytoma benign 1 (2%) (50) (48) Aderona 1 (2%) (50) (48) Aderona 1 (2%) (50) (48) Aderona 1 (2%) (50) (50) Parathyroid gland (40) (40) (48) (49) Paratistis, adenoma 31 (63%) 31 (65%) (29) Paratistis, adenoma 1 (2%) (50) (50) Paratistis, adenoma 31 (63%) 31 (65%) (29) Paratistis, adenoma 1 (2%) (50) (50) Paratistis, adenoma 31 (63%) (50) (50) Para distalis, adenoma 1 (2%) (50) (50) Para distalis, adenoma 31 (63%) (50) (50) Para distalis, adenoma 1 (2%) (50) (50) Para distalis, adenoma 1 (2%) (50) (50) Para distalis, adenoma (50) (50) (50) Bilateral, C-cell, adenoma (1 (2%)) C-cell, adenoma (1 (2%)) (1 (2%)) C-cell, adenoma (1 (2	Intestine small, ileum	(49)		(47)		(50)	
Carcinoma, metastatic, ovary         1 $(2\%)$ $(10\%)$ Hepatocellular carcinoma         1 $(2\%)$ 1 $(2\%)$ Hepatocellular adenoma         1 $(2\%)$ 1 $(2\%)$ Mescentery         (3)         (4)         (6)         7           Parcreas         (49)         (50)         (49)         2           Solivary glands         (50)         (50)         (50)         (50)           Solivary glands         (50)         (50)         (50)         (50)           Stomach, forestomach         (50)         (50)         (50)         (50)           Stomach, glandular         (50)         (50)         (50)         (50)           Eadocrine System         (50)         (50)         (50)         (50)           Adrenal gland, medulla         (49)         (46)         (49)           Pheochromocytoma malignant         1         (2%)         1         (2%)           Adenoma         1         (2%)         1         (2%)         1           Pheochromocytoma benign         1         (2%)         1         (2%)         1         (2%)           Adenoma         1	Liver	(50)		(50)		(50)	
Hepatocellular carcinoma       1 (2%)         Hepatocellular adenoma       1 (2%)         Mesentery       (3)       (4)         Carcinoma, metastatic, ovary       1 (25%)         'ancreas       (49)       (50)         Acinus, adenoma       2 (4%)       2 (4%)         Salivary glands       (50)       (50)         Silvary glands       (50)       (50)         Stomach, forestomach       (50)       (50)         Papiloma squamous       1 (2%)         Stomach, glandular       (50)       (50)         Cardiovascular System       1 (2%)         Heat (50)       (50)       (50)         Zadrenal gland, cortex       (50)       (49)         Aderona gland, cortex       (50)       (49)         Aderona gland, cortex       (50)       (49)         Aderona gland, cortex       (50)       (46)         Aderona       1 (2%)       1 (2%)         Pheochromocytoma malignant       1 (2%)       1 (2%)         Parathyroid gland       (46)       (39)       (45)         Adenoma       1 (2%)       1 (2%)       1 (2%)         Parathyroid gland       (46)       (39)       (45) <td< td=""><td>Carcinoma, metastatic, ovary</td><td>(50)</td><td></td><td>1</td><td>(2%)</td><td>(00)</td><td></td></td<>	Carcinoma, metastatic, ovary	(50)		1	(2%)	(00)	
Hepatocellular adenoma       1 (2%)         Hepatocellular adenoma       1 (2%)         Vascneray       (3)       (4)       (6)         Carcinoma, metastatic, ovary       (49)       (50)       (49)         vancreas       (49)       (50)       (49)         Salivary glands       (50)       (50)       (50)         Sitomach, forestomach       (50)       (48)       (50)         Papilloma squamous       1       (2%)       1       (2%)         Cardiovascular System       (50)       (50)       (50)       (50)         Cardiovascular System       (50)       (49)       (50)       (50)         Adrenal gland, cortex       (50)       (49)       (50)       (50)         Adrenal gland, medulla       (49)       (46)       (49)         Pheochromocytoma bengn       1 (2%)       1 (2%)       1 (2%)         Pheochromocytoma bengn       1 (2%)       1 (2%)       1 (2%)         Parathyroid gland       (46)       (39)       (45)         Adenoma       1 (2%)       1 (2%)       1 (2%)         Parathyroid gland       (49)       (48)       (49)         Parathyroid gland       (49)       (48)       (	Henatocellular carcinoma	1	(2%)	-	(=/0)		
Tripatocontain abelindia       1 $(2\pi)$ <	Henstocellular adenoma	1	(270)	1	(2%)		
Carcinoma, metastatic, ovary       (1)       (2)       (1)         2ancreas       (49)       (50)       (49)         Acinus, adenoma       2       (4%)       2       (4%)         Salvary glands       (50)       (50)       (50)       (50)         Stomach, forestomach       (50)       (48)       (50)       (50)         Papilloma squamous       1       (2%)       1       (2%)         Stomach, glandular       (50)       (50)       (50)       (50)         Carcinovascular System       (50)       (50)       (50)       (50)         Adrenal gland, cortex       (50)       (49)       (46)       (49)         Pheochromocytoma benign       1       (2%)       1       (2%)         Adenoma       1       (2%)       1       (2%)         Adenoma       1       (2%)       1       (2%)         Adenoma       1       (2%)       1       (2%) <td>Asparochular aucholia Mesenterv</td> <td>(2)</td> <td></td> <td></td> <td>(200)</td> <td>(6)</td> <td></td>	Asparochular aucholia Mesenterv	(2)			(200)	(6)	
Carcitational, inclusion, orally       1       (207)         Parcreas       (49)       (50)       (49)         Acinus, adenoma       2       (4%)       2       (4%)         Shomach, forestomach       (50)       (50)       (50)       (50)         Papilloma squamous       1       (2%)       1       (2%)         Stomach, glandular       (50)       (50)       (50)       (50)         Cardiovascular System       (50)       (50)       (50)       (50)         Cardenoma       1       (2%)       1       (2%)         Aderenal gland, cortex       (50)       (49)       (46)       (49)         Pheochromocytoma malignant       1       (2%)       3       (7%)       2       (4%)         Adenoma       1       (2%)       3       (7%)       2       (4%)         Adenoma       1       (2%)       1       (3%)       448       (49)       (48)       (49) <td>Corcinoma metostatia ovoru</td> <td>(3)</td> <td></td> <td>(4)</td> <td>(25%)</td> <td>(0)</td> <td></td>	Corcinoma metostatia ovoru	(3)		(4)	(25%)	(0)	
rancess       (49)       (50)       (49)         Acinus, adenoma       2       (4%)       2       (4%)         Salivary glands       (50)       (50)       (50)       (50)         Papilloma squamous       1       (2%)       1       (2%)         Stomach, forestomach       (50)       (50)       (50)       (50)       (50)         Cardiovascular System       1       (2%)       (50)       (50)       (50)         Cardiovascular System	Carcinolita, inclastatic, ovary	(40)		(50)	(2570)	(40)	
Addrenal gland, sources $2 (4\%)$ $2 (4\%)$ $(50)$ Stomach, forestomach       (50)       (50)       (50)         Papilloma squamous       1       (2%)         Stomach, glandular       (50)       (50)       (50)         Cardiovascular System       (50)       (50)       (50)         Cardiovascular System       (50)       (50)       (50)         Endocrine System       (50)       (50)       (50)         Adrenal gland, cortex       (50)       (49)       (50)         Adrenal gland, cortex       (50)       (49)       (46)         Pheochromocytoma benign       1       (2%)       3       (7%)       2       (4%)         Adrenal gland, medulla       (49)       (50)       (48)       (49)       (46)       (49)       (48)       (48)       (48)       (48)       (48)       (49)       (48)       (49)       (48)       (49)       (45)       (45)       (46)       (39)       (45)       (46)       (49)       (50)       (50)       (50)       (50)       (50)       (50)       (50)       (50)       (50)       (50)       (50)       (50)       (50)       (50)       (50)       (50)       (50) </td <td></td> <td>(49)</td> <td>(10)</td> <td>(30)</td> <td>(10)</td> <td>(49)</td> <td></td>		(49)	(10)	(30)	(10)	(49)	
Salvary gands       (50)       (50)       (50)       (50)         Stomach, forestomach       (50)       (48)       (50)         Papilloma squamous       1       (2%)         Stomach, glandular       (50)       (50)       (50)         Cardilovascular System       (50)       (50)       (50)         Heart       (50)       (50)       (50)         Endocrine System       (50)       (49)       (50)         Adrenal gland, cortex       (50)       (49)       (50)         Adrenal gland, cortex       (50)       (49)       (46)         Pheochromocytoma malignant       1       (2%)       1       (2%)         Pheochromocytoma benign       1       (2%)       (48)       (49)         Parathyroid gland       (46)       (39)       (45)       (48)         Adenoma       1       (2%)       1       (3%)         Parathyroid gland       (40)       (48)       (49)       (49)         Para distalis, adenoma       1       (2%)       1       (2%)         Para distalis, adenoma       1       (2%)       1       (2%)         Para distalis, adenoma       1       (2%)       1       (2%)	Acinus, adenoma	4	(4%)	4	(4%)	(50)	
Notmach, torestomach       (50)       (44)       (50)         Papilloma squamous       1       (2%)         Stomach, glandular       (50)       (50)       (50)         Cardiovascular System       (50)       (50)       (50)         Heart       (50)       (50)       (50)         Endocrine System       (50)       (49)       (50)         Adrenal gland, cortex       (50)       (49)       (50)         Adrenal gland, medulla       (49)       (46)       (49)         Pheochromocytoma malignant       1       (2%)       3       (7%)       2       (4%)         Adrenna       1       (2%)       3       (7%)       2       (4%)         Pheochromocytoma benign       1       (2%)       3       (7%)       2       (4%)         Adenoma       1       (2%)       3       (7%)       2       (4%)         Parathyroid gland       (40)       (39)       (45)       (46)       (39)       (45)         Adenoma       1       (2%)       1       (3%)       1       (2%)         Parathyroid gland       (49)       (48)       (49)       (49)       Para distalis, adenoma       1	banvary gianos	(30)		(30)		(50)	
Fraphloma squamous       1 (2%)         Stomach, glandular       (50)       (50)       (50)         Cardiovascular System       (50)       (50)       (50)         Endocrine System       (50)       (50)       (50)         Adrenal gland, cortex       (50)       (49)       (50)         Adrenal gland, medulla       (49)       (46)       (49)         Pheochromocytoma malignant       1 (2%)       3 (7%)       2 (4%)         Adenoma       1 (2%)       3 (7%)       2 (4%)         Adenoma       1 (2%)       3 (7%)       2 (4%)         Pheochromocytoma benign       1 (2%)       1 (2%)       1 (2%)         Adenoma       1 (2%)       3 (7%)       2 (4%)         Adenoma       1 (2%)       1 (2%)       1 (2%)         Parathyroid gland       (46)       (39)       (45)         Adenoma       1 (2%)       1 (3%)       29 (59%)         Pars distalis, adenoma       31 (63%)       31 (65%)       29 (59%)         Pars distalis, adenoma       1 (2%)       1 (2%)       1 (2%)         Pars distalis, carcinoma       1 (2%)       1 (2%)       1 (2%)         Pars distalis, carcinoma       1 (2%)       1 (2%)       1	nomacn, ioresiomacn	(50)		(48)		(30)	(00)
Cardiovascular       (50)       (50)       (50)         Cardiovascular System       (50)       (50)       (50)         Adrenal gland, cortex       (50)       (49)       (50)         Adrenal gland, medulla       (49)       (46)       (49)         Adrenal gland, medulla       (49)       (46)       (49)         Pheochromocytoma benign       1       (2%)       3       (7%)       2       (4%)         Adenoma       1       (2%)       3       (7%)       2       (4%)         Pheochromocytoma benign       1       (2%)       3       (7%)       2       (4%)         Adenoma       1       (2%)       3       (7%)       2       (4%)         Adenoma       1       (2%)       1       (3%)       4         Parathyroid gland       (46)       (39)       (45)       4         Adenoma       1       (2%)       1       (3%)       4         Pituitary gland       (49)       (48)       (49)       9         Pars distalis, adenoma, multiple       2       (4%)       4       (8%)       1       (2%)         Pars distalis, carcinoma       1       (2%)       1       (2	rapilloma squamous	(50)		(50)		1	(2%)
Cardiovascular System       (50)       (50)       (50)         Endocrine System $Adrenal gland, cortex$ (50)       (49)       (50)         Adrenal gland, cortex       (50)       (49)       (50) $Adrenal gland, cortex$ 1 (2%)         Adrenal gland, medulla       (49)       (46)       (49)       1 (2%)         Pheochromocytoma malignant       1 (2%)       3 (7%)       2 (4%)         Islets, pancreatic       (50)       (50)       (48)         Adenoma       1 (2%)       3 (7%)       2 (4%)         Parathyroid gland       (46)       (39)       (45)         Adenoma       1 (2%)       1 (3%)       1 (2%)         Pituitary gland       (49)       (48)       (49)         Pars distalis, adenoma       31 (63%)       31 (65%)       29 (59%)         Pars distalis, adenoma, multiple       2 (4%)       4 (8%)       1 (2%)         Pars distalis, carcinoma       1 (2%)       1 (2%)       1 (2%)         Thyroid gland       (50)       (50)       (50)       (50)         Bilateral, C-cell, adenoma       9 (18%)       7 (14%)       7 (14%)         C-cell, adenoma       9 (18%)       7 (14%)       7 (14%)	Stomach, glandular	(50)		(50)		(50)	
Heart       (50)       (50)       (50)         Endocrine System       Adrenal gland, cortex       (50)       (49)       (50)         Adrenal gland, cortex       1       (2%)       1       (2%)         Adrenal gland, medulla       (49)       (46)       (49)         Pheochromocytoma malignant       1       (2%)       3       (7%)       2       (4%)         Slets, pancreatic       (50)       (50)       (48)       (49)       (48)       (49)       (48)         Adenoma       1       (2%)       3       (7%)       2       (4%)         Adenoma       1       (2%)       3       (7%)       2       (4%)         Adenoma       1       (2%)       3       (7%)       2       (4%)         Adenoma       1       (2%)       1       (3%)       1       (2%)         Parathyroid gland       (46)       (39)       (45)       4       (49)       Pars distalis, adenoma       1       (2%)       1       (2%)       1       (2%)       1       (2%)       1       (2%)       1       (2%)       1       (2%)       1       (2%)       1       (2%)       1       (2%)       1 <td>Cardiovascular System</td> <td></td> <td></td> <td>(=0)</td> <td></td> <td>(50)</td> <td></td>	Cardiovascular System			(=0)		(50)	
Endocrine SystemAdrenal gland, cortex $(50)$ $(49)$ $(50)$ Adenoma1 $(2\%)$ 1 $(2\%)$ Adrenal gland, medulla $(49)$ $(46)$ $(49)$ Pheochromocytoma malignant1 $(2\%)$ 3 $(7\%)$ 2Pheochromocytoma benign1 $(2\%)$ 3 $(7\%)$ 2Slets, pancreatic $(50)$ $(50)$ $(48)$ Adenoma1 $(2\%)$ 1 $(2\%)$ Parathyroid gland $(46)$ $(39)$ $(45)$ Adenoma1 $(2\%)$ 1 $(3\%)$ Pituitary gland $(49)$ $(48)$ $(49)$ Pars distalis, adenoma31 $(63\%)$ 31 $(65\%)$ 29Pars distalis, adenoma1 $(2\%)$ 1 $(2\%)$ Pars distalis, carcinoma1 $(2\%)$ $(50)$ $(50)$ $(50)$ Bilateral, C-cell, adenoma9 $(18\%)$ 7 $(14\%)$ 7C-cell, carcinoma1 $(2\%)$ $(2\%)$ $(2\%)$ Follicular cell. adenoma1 $(2\%)$ $(2\%)$ $(2\%)$	-leart	(50)		(50)		(50)	
Adrenal gland, cortex $(50)$ $(49)$ $(50)$ Adenoma1 $(2\%)$ 1 $(2\%)$ Adrenal gland, medulla $(49)$ $(46)$ $(49)$ Pheochromocytoma malignant1 $(2\%)$ 3 $(7\%)$ 2Pheochromocytoma benign1 $(2\%)$ 3 $(7\%)$ 2Islets, pancreatic $(50)$ $(50)$ $(48)$ Adenoma1 $(2\%)$ 1 $(2\%)$ Parathyroid gland $(46)$ $(39)$ $(45)$ Adenoma1 $(2\%)$ 1 $(3\%)$ Pituitary gland $(49)$ $(48)$ $(49)$ Pars distalis, adenoma31 $(63\%)$ 31 $(65\%)$ 29Pars distalis, adenoma, multiple2 $(4\%)$ 4 $(8\%)$ 1 $(2\%)$ Pars distalis, carcinoma1 $(2\%)$ 1 $(2\%)$ 1 $(2\%)$ Thyroid gland $(50)$ $(50)$ $(50)$ $(50)$ $(50)$ Bilateral, C-cell, adenoma $(2\%)$ $(18\%)$ 7 $(14\%)$ 7C-cell, adenoma $(2\%)$ $(2\%)$ $(2\%)$ $(2\%)$ Follicular cell, adenoma $(2\%)$ $(2\%)$ $(2\%)$ $(2\%)$ Follicular cell, adenoma $(2\%)$ $(2\%)$ $(2\%)$ Follicular cell, adenoma $(2\%)$ $(2\%)$ $(2\%)$	Endocrine System			(		(20)	
Adenoma       1 $(2\%)$ 1 $(2\%)$ Adrenal gland, medulla $(49)$ $(46)$ $(49)$ Pheochromocytoma malignant       1 $(2\%)$ 3 $(7\%)$ 2 $(4\%)$ Pheochromocytoma benign       1 $(2\%)$ 3 $(7\%)$ 2 $(4\%)$ Islets, pancreatic       (50)       (50)       (48)       1 $(2\%)$ Adenoma       1 $(2\%)$ 1 $(2\%)$ 1 $(2\%)$ Parathyroid gland       (46)       (39)       (45)       1 $(2\%)$ Parathyroid gland       (49)       (48)       (49)       1 $(2\%)$ Pars distalis, adenoma       31 $(63\%)$ 31 $(65\%)$ 29 $(59\%)$ Pars distalis, adenoma, multiple       2 $(4\%)$ 4 $(8\%)$ 1 $(2\%)$ Phyroid gland       (50)       (50)       (50)       1 $(2\%)$ 1 $(2\%)$ Phyroid gland       (50)       (50)       (50)       (50)       1 $(2\%)$ 1 $(2\%)$ Bilateral, C-cell, adenoma       9	Adrenal gland, cortex	(50)	(00)	(49)		(50)	(00)
Adrenal gland, medulla $(49)$ $(46)$ $(49)$ Pheochromocytoma malignant1 $(2\%)$ 3 $(7\%)$ 2 $(4\%)$ Pheochromocytoma benign1 $(2\%)$ 3 $(7\%)$ 2 $(4\%)$ Silets, pancreatic $(50)$ $(50)$ $(48)$ 1 $(2\%)$ Adenoma1 $(2\%)$ 1 $(2\%)$ 1 $(2\%)$ Parathyroid gland $(46)$ $(39)$ $(45)$ 1Adenoma1 $(2\%)$ 1 $(3\%)$ 1Parathyroid gland $(49)$ $(48)$ $(49)$ 1Adenoma1 $(2\%)$ 1 $(3\%)$ 29Pars distalis, adenoma31 $(63\%)$ 31 $(65\%)$ 29Pars distalis, adenoma, multiple2 $(4\%)$ 4 $(8\%)$ 1Pars distalis, carcinoma1 $(2\%)$ 1 $(2\%)$ Chycid gland $(50)$ $(50)$ $(50)$ $(50)$ Bilateral, C-cell, adenoma9 $(18\%)$ 7 $(14\%)$ 7C-cell, carcinoma1 $(2\%)$ 1 $(2\%)$ Follicular cell, adenoma1 $(2\%)$ 1 $(2\%)$	Adenoma	1	(2%)	<b></b>		1	(2%)
Pheochromocytoma malignant       1 $(2\%)$ Pheochromocytoma benign       1 $(2\%)$ 3 $(7\%)$ 2 $(4\%)$ Islets, pancreatic $(50)$ $(50)$ $(50)$ $(48)$ Adenoma       1 $(2\%)$ 1 $(2\%)$ Parathyroid gland $(46)$ $(39)$ $(45)$ Adenoma       1 $(2\%)$ 1 $(3\%)$ Parathyroid gland $(49)$ $(48)$ $(49)$ Adenoma       1 $(2\%)$ 1 $(3\%)$ Parathyroid gland $(49)$ $(48)$ $(49)$ Pars distalis, adenoma       31 $(63\%)$ 31 $(65\%)$ 29 $(59\%)$ Pars distalis, adenoma, multiple       2 $(4\%)$ 4 $(8\%)$ 1 $(2\%)$ Pars distalis, carcinoma       1 $(2\%)$ 1 $(2\%)$ 1 $(2\%)$ Thyroid gland $(50)$ $(50)$ $(50)$ $(50)$ 1 $(2\%)$ C-cell, adenoma       9 $(18\%)$ 7 $(14\%)$ 7 $(14\%)$ <td< td=""><td>Adrenal gland, medulla</td><td>(49)</td><td></td><td>(46)</td><td></td><td>(49)</td><td></td></td<>	Adrenal gland, medulla	(49)		(46)		(49)	
Pheochromocytoma benign       1 $(2\%)$ 3 $(7\%)$ 2 $(4\%)$ islets, pancreatic $(50)$ $(50)$ $(50)$ $(48)$ Adenoma       1 $(2\%)$ 1 $(2\%)$ Parathyroid gland $(46)$ $(39)$ $(45)$ Adenoma       1 $(2\%)$ 1 $(3\%)$ Parathyroid gland $(49)$ $(48)$ $(49)$ Adenoma       1 $(2\%)$ 1 $(3\%)$ Pituitary gland $(49)$ $(48)$ $(49)$ Pars distalis, adenoma       31 $(63\%)$ 31 $(65\%)$ 29 $(59\%)$ Pars distalis, adenoma, multiple       2 $(4\%)$ 4 $(8\%)$ 1 $(2\%)$ Pars distalis, carcinoma       1 $(2\%)$ 1 $(2\%)$ 1 $(2\%)$ Thyroid gland $(50)$ $(50)$ $(50)$ $(50)$ 1 $(2\%)$ Bilateral, C-cell, adenoma       9 $(18\%)$ 7 $(14\%)$ 7 $(14\%)$ C-cell, carcinoma       1 $(2\%)$ 1	Pheochromocytoma malignant	1	(2%)	_		-	
istets, pancreatic       (50)       (50)       (48)         Adenoma       1       (2%)       1       (2%)         Parathyroid gland       (46)       (39)       (45)         Adenoma       1       (2%)       1       (3%)         Parathyroid gland       (49)       (48)       (49)         Adenoma       1       (2%)       1       (3%)         Pituitary gland       (49)       (48)       (49)         Pars distalis, adenoma, multiple       2       (4%)       4       (8%)       1       (2%)         Pars distalis, carcinoma       1       (2%)       1       (2%)       1       (2%)         Thyroid gland       (50)       (50)       (50)       (50)       1       (2%)         Bilateral, C-cell, adenoma       (50)       (50)       (14%)       7       (14%)         C-cell, adenoma       9       (18%)       7       (14%)       7       (14%)         Follicular cell, adenoma       1       (2%)       1       (2%)       1       (2%)	Pheochromocytoma benign	1	(2%)	3	(7%)	2	(4%)
Adenoma       1 $(2\%)$ 1 $(2\%)$ Parathyroid gland $(46)$ $(39)$ $(45)$ Adenoma       1 $(2\%)$ 1 $(3\%)$ Pituitary gland $(49)$ $(48)$ $(49)$ Pars distalis, adenoma       31 $(63\%)$ 31 $(65\%)$ 29 $(59\%)$ Pars distalis, adenoma, multiple       2 $(4\%)$ 4 $(8\%)$ 1 $(2\%)$ Pars distalis, carcinoma       1 $(2\%)$ 1 $(2\%)$ 1 $(2\%)$ Phyroid gland $(50)$ $(50)$ $(50)$ $(50)$ $(2\%)$ Bilateral, C-cell, adenoma       9 $(18\%)$ 7 $(14\%)$ 7 $(14\%)$ C-cell, carcinoma       1 $(2\%)$ $(2\%)$ $(2\%)$ $(2\%)$ $(2\%)$ $(2\%)$	slets, pancreatic	(50)		(50)		(48)	
Parathyroid gland $(46)$ $(39)$ $(45)$ Adenoma       1 $(2\%)$ 1 $(3\%)$ Pituitary gland $(49)$ $(48)$ $(49)$ Pars distalis, adenoma       31 $(63\%)$ 31 $(65\%)$ 29 $(59\%)$ Pars distalis, adenoma, multiple       2 $(4\%)$ 4 $(8\%)$ 1 $(2\%)$ Pars distalis, carcinoma       1 $(2\%)$ 1 $(2\%)$ 1 $(2\%)$ Phyroid gland $(50)$ $(50)$ $(50)$ $(50)$ $(50)$ $(50)$ Bilateral, C-cell, adenoma       9 $(18\%)$ 7 $(14\%)$ 7 $(14\%)$ C-cell, carcinoma       1 $(2\%)$ 1 $(2\%)$ $(2\%)$ $(2\%)$	Adenoma	1	(2%)			1	(2%)
Adenoma       1 $(2\%)$ 1 $(3\%)$ Pituitary gland $(49)$ $(48)$ $(49)$ Pars distalis, adenoma       31 $(63\%)$ 31 $(65\%)$ 29 $(59\%)$ Pars distalis, adenoma, multiple       2 $(4\%)$ 4 $(8\%)$ 1 $(2\%)$ Pars distalis, adenoma, multiple       2 $(4\%)$ 4 $(8\%)$ 1 $(2\%)$ Pars distalis, carcinoma       1 $(2\%)$ 500 $(50)$ $(50)$ $(50)$ $(50)$ $(50)$ $(2\%)$ Bilateral, C-cell, adenoma       9 $(18\%)$ 7 $(14\%)$ 7 $(14\%)$ C-cell, carcinoma       1 $(2\%)$ $(2\%)$ $(2\%)$ $(2\%)$ $(2\%)$ Follicular cell, adenoma       1 $(2\%)$ $(2\%)$ $(2\%)$ $(2\%)$	arathyroid gland	(46)		(39)		(45)	
Pars distalis, adenoma $(49)$ $(48)$ $(49)$ Pars distalis, adenoma, multiple31 $(63\%)$ 31 $(65\%)$ 29 $(59\%)$ Pars distalis, adenoma, multiple2 $(4\%)$ 4 $(8\%)$ 1 $(2\%)$ Pars distalis, carcinoma1 $(2\%)$ 1 $(2\%)$ Phyroid gland $(50)$ $(50)$ $(50)$ 1 $(2\%)$ Bilateral, C-cell, adenoma9 $(18\%)$ 7 $(14\%)$ 7 $(14\%)$ C-cell, carcinoma1 $(2\%)$ 1 $(2\%)$ 1 $(2\%)$ Follicular cell, adenoma1 $(2\%)$ 1 $(2\%)$	Adenoma	1	(2%)	1	(3%)		
Pars distalis, adenoma       31 (63%)       31 (65%)       29 (59%)         Pars distalis, adenoma, multiple       2 (4%)       4 (8%)       1 (2%)         Pars distalis, carcinoma       1 (2%)       1 (2%)         Thyroid gland       (50)       (50)       (50)         Bilateral, C-cell, adenoma       1 (2%)       1 (2%)       1 (2%)         C-cell, adenoma       9 (18%)       7 (14%)       7 (14%)         Follicular cell, adenoma       1 (2%)       1 (2%)       1 (2%)	Pituitary gland	(49)		(48)		(49)	
Pars distalis, adenoma, multiple       2 (4%)       4 (8%)       1 (2%)         Pars distalis, carcinoma       1 (2%)       1 (2%)         Thyroid gland       (50)       (50)       (50)         Bilateral, C-cell, adenoma       1 (2%)       1 (2%)       1 (2%)         C-cell, adenoma       9 (18%)       7 (14%)       7 (14%)         C-cell, carcinoma       1 (2%)       1 (2%)       1 (2%)	Pars distalis, adenoma	31	(63%)	31	(65%)	29	(59%)
Pars distalis, carcinoma       1 (2%)         Thyroid gland       (50)       (50)         Bilateral, C-cell, adenoma       1 (2%)         C-cell, adenoma       9 (18%)       7 (14%)         C-cell, carcinoma       1 (2%)         Follicular cell, adenoma       1 (2%)	Pars distalis, adenoma, multiple	2	(4%)	4	(8%)	1	(2%)
Introd gland     (50)     (50)     (50)       Bilateral, C-cell, adenoma     1     (2%)       C-cell, adenoma     9     (18%)     7     (14%)       C-cell, carcinoma     1     (2%)     1     (2%)       Follicular cell, adenoma     1     (2%)     1     (2%)	Pars distalis, carcinoma	1	(2%)				
Bilateral, C-cell, adenoma       1 (2%)         C-cell, adenoma       9 (18%)       7 (14%)       7 (14%)         C-cell, carcinoma       1 (2%)       1 (2%)       1 (2%)         Follicular cell, adenoma       1 (2%)       1 (2%)       1 (2%)	Thyroid gland	(50)		(50)		(50)	
C-cell, adenoma     9 (18%)     7 (14%)     7 (14%)       C-cell, carcinoma     1 (2%)     1 (2%)     1 (2%)	Bilateral, C-cell, adenoma	. /		. ,		ì	(2%)
C-cell, carcinoma 1 (2%) Follicular cell, adenoma 1 (2%) 1 (2%)	C-cell, adenoma	9	(18%)	7	(14%)	7	(14%)
Follicular cell adenoma 1 (2%) 1 (2%)	C-cell, carcinoma	1	(2%)		. /		
	Follicular cell, adenoma	-		1	(2%)	1	(2%)

Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of HC Yellow 4 (continued)

General Body System           None         Genital System           Genital System         (47)         (47)         (44)           Adenona         6         (13%)         5         (11%)         2         (5%)           Bilateral, adenoma         1         (2%)         (50)         (47)         (44)         (50)           Granuloa cell tumor benign         1         (2%)         (50)         (42)         (43)         (50)         (42)         (43)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50) <th></th> <th>0</th> <th>ррт</th> <th>5,00</th> <th>0 ppm</th> <th>10,00</th> <th>0 ppm</th>		0	ррт	5,00	0 ppm	10,00	0 ppm
None         Genital System         (47)         (47)         (44)           Adecoma         6 (13%)         5 (11%)         2 (5%)           Bilateral, adenoma         1 (2%)         2 (5%)           Orany         (50)         (49)         (50)           Carcinoma         1 (2%)         (50)         (10%)         2 (5%)           Orany         (50)         (49)         (50)         (50)           Carcinoma         1 (2%)         (50)         (50)         (50)           Charmados cell tumor benign         1 (2%)         12 (24%)         Storomal, multiple         1 (2%)           Sarcoma stromal         1 (2%)         12 (24%)         Storoma stromal         1 (2%)         Storoma stromal         1 (2%)         Storoma stroma         1 (2%)         Storoma stroma         1 (2%)         Storoma stroma         Storoma stroma         Storoma stroma         1 (2%)         Storoma stroma         Sto	General Body System						
Genital System         (47)         (47)         (44)           Adecoma         6 (13%)         5 (11%)         2 (5%)           Bilateral, adenoma         1 (2%)         2 (5%)           Orary         (50)         (49)         (50)           Carcinoma         1 (2%)         (50)         (11%)         2 (5%)           Carcinoma         1 (2%)         (50)         (11%)         1 (2%)           Carcinoma         (48)         (50)         (50)         (50)           Charmas ecel tumor benign         1 (2%)         1 (2%)         12 (24%)           Pohy stromal, multiple         3 (5%)         1 (2%)         12 (24%)           Sarcoma stromal         1 (2%)         1 (2%)         12 (24%)           Mediastinal, carcinoma, metastatic, tworoid gland         1 (2%)         1 (2%)         148)           Lymph node, mandibular         (49)         (50)         (49)         (50)           Lymph node, mesenteric         (49)         (50)         (49)         (50)           Spicen         1 (2%)         (45)         (47)         44           Mammary gland         1 (2%)         (45)         (47)           Adeconarcinoma         1 (2%)         3 (6%)	None						. •
Clitoral gland (47) (47) (47) (44) Adenoma 6 (13%) 5 (11%) 2 (5%) Carcinoma 1 (2%) (50) Carcinoma 1 (2%) (50) Carcinoma 1 (2%) (50) Carcinoma (48) (50) (49) (50) Carcinoma (48) (50) (50) (50) Folyp stromal (48) (50) (49) (49) Events (48) (50) (49) (49) Events (48) (50) (49) (49) Events (48) (50) (49) (49) Events (48) (50) (50) (50) Mediastinal, carcinoma, metastatic, ovary 1 (2%) Mediastinal, carcinoma, metastatic, ovary 1 (2%) Mediastinal, carcinoma, metastatic, ovary 1 (2%) Mediastinal, carcinoma, metastatic, thyroid gland 1 (2%) Events (49) (45) (49) (49) Events (48) (47) (47) (48) Adenocarcinoma, metastatic, mammary gland 1 (2%) (50) (49) Spicen (50) (49) (50) (49) (50) Fibroadenoma 1 (2%) (47) (47) Adenocarcinoma (48) (37) (47) Adenocarcinoma (48) (2%) (37) (47) Adenocarcinoma (48) (2%) (30) (49) Fibroadenoma (12%) (50) (49) Skin (48) (2%) (50) (49) Basal cell carcinoma (12%) (2%) Subcutaneous tissue, fibroma (2%) (2%) Subcutaneous tissue, fibroma (2%) (2%) (50) (49) Brain (48) (2%) (50) (49) Brain (50) (50) (50) (50) Musculoskeletal System Steletal muscle (1) (1) (1) (1) Nervous System Brain (50) (50) (50) (50) Carcinoma matignant (2%) Sina (50) (50) (50) Carcinoma matignant (2%) Subcutaneous tissue, fibroma (50) (50) (50) Carcinoma metastatic, pituitary gland (12%) (50) (50) Carcinoma metastatic, pituitary gland (12%) (50) (50) Carcinoma metastatic, pituitary gland (12%) (50) (50) Carcinoma matignant (2%) (50) (50) Carcinoma metastatic, pituitary gland (2%) (50) Carcinoma metastatic, pituitary gland (2%) Carcinoma metastatic, pituitary	Genital System						
Adenoma       6       (13%)       5       (11%)       2       (5%)         Bilateral, adenoma       1       (2%)       (50)       (49)       (50)         Orary       (50)       (49)       (50)       (50)       (50)         Granulosa cell tumor benign       1       (2%)       (50)       (50)       (50)         Potp stromal, multiple       1       (2%)       (2%)       (24%)         Sarcoma stromal       1       (2%)       (2%)       (24%)         Hematopoietic System       600       (49)       (49)       (49)         Lymph node       (12%)       (48)       (47)       (48)         Jymph node, mandibular       (49)       (45)       (48)       (47)         Adenocarcinoma, metastatic, ovary       (49)       (50)       (49)       (50)         Jymph node, masibular       (49)       (50)       (49)       (50)       (49)         Spleen       (50)       (49)       (50)       (49)       (50)       (43)         Thymus       (47)       (42)       (43)       (47)       (42)       (43)         Thymus       (1       (2%)       (2%)       (4%)       (50)       (4%)<	Clitoral gland	(47)		(47)		(44)	
Carcinoma       2 (5%)         Bilateral, adenoma       1 (2%)         Ovary       (50)       (49)       (50)         Carcinoma       1 (2%)       (50)       (50)         Granulosa cell tumor benign       1 (2%)       (50)       (50)         Otras       (48)       (50)       (50)       (50)         Polyp stromal       4 (8%)       7 (14%)       12 (2%)         Sarcoma stromal       1 (2%)       1 (2%)       (2%)         Hematopoietic System       1 (2%)       (49)       (49)         Bone marrow       (50)       (50)       (49)       (49)         Lymph node, mandibular       (49)       (45)       (48)         Adenocarcinoma, metastatic, thyroid gland       1 (2%)       (49)       (50)         Lymph node, maenteric       (49)       (45)       (49)       (50)         Spleen       (47)       (42)       (43)       (47)         Integumentary System       Mammary gland       (45)       (37)       (47)         Adenocarcinoma       1 (2%)       3 (8%)       2 (4%)         Fibroadenoma       1 (2%)       3 (8%)       2 (4%)         Skin       (48)       (2%)       (50) <td>Adenoma</td> <td>6</td> <td>(13%)</td> <td>5</td> <td>(11%)</td> <td>2</td> <td>(5%)</td>	Adenoma	6	(13%)	5	(11%)	2	(5%)
Bilateral, adenoma       1       (2%)       (49)       (50)         Carcinoma       1       (2%)       (50)       (49)       (50)         Carcinoma       1       (2%)       (50)       (50)       (50)         Uterus       (48)       (50)       (50)       (50)       (24%)         Potyp stromal, multiple       1       (2%)       1       (2%)         Sarcoma stromal       1       (2%)       (49)       (50)       (49)         Mediastinal, carcinoma, metastatic, ovary       1       (2%)       (48)       (48)       (48)         Jymph node, mesenteric       (49)       (45)       (48)       (49)       (50)       (49)         Spleen       (50)       (49)       (50)       (49)       (50)       (49)         Integumentary System       (48)       (37)       (47)       (42)       (43)         Integumentary System       (48)       (50)       (49)       (50)       (49)         Shin       (48)       (50)       (49)       (50)       (47)       (46)         Adenocarcinoma       1       (2%)       16       (3%)       16       (3%)         Skin       (48)	Carcinoma					2	(5%)
Chargy         (50)         (49)         (50)           Carcinoma         1         (2%)         1         (2%)         (50)         (40)         (50)         (40)         (50)         (40)         (50)         (40)         (50)         (40)         (50)         (40)         (50)         (40)         (50)         (40)         (50)         (40)         (50)         (40)         (50)         (40)         (50)         (40)         (50)         (40)         (50)         (40)         (50)         (40)         (50)         (40)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (	Bilateral, adenoma	1	(2%)				
Carcinoma (Tanulosa cell tumor benign)       1 (2%)         Uterus       (48)       (50)         Pohy stromal       4 (8%)       7 (14%)       12 (24%)         Pohy stromal, multiple       1 (2%)       1 (2%)       12 (24%)         Sarcoma stromal       1 (2%)       1 (2%)       12 (24%)         Hematopoietic System       1 (2%)       1 (2%)       12 (24%)         Hematopoietic System       1 (2%)       1 (2%)       1 (2%)         Mediastinal, carcinoma, metastatic, ovary       1 (2%)       1 (2%)       1 (2%)         Mediastinal, carcinoma, metastatic, ovary       1 (2%)       (45)       (48)         Adenocarcinoma, metastatic, mammary gland       1 (2%)       (49)       (50)         Jymph node, mesenteric       (49)       (50)       (49)       (50)         Spleen       (50)       (49)       (50)       (49)         Integumentary System       (48)       (37)       (47)         Mamary gland       1 (2%)       2 (4%)       (48)         Adenocarcinoma       1 (2%)       2 (4%)       (43)         Fibroadenoma       1 (2%)       1 (2%)       2 (4%)         Skin       (48)       (50)       (49)       (49)	Ovary	· (50)		(49)		(50)	
Granulosa cell tumor benign       1       (2%)         Ulterus       (48)       (50)       (50)         Potyp stromal, multiple       1       (2%)       12       (24%)         Potyp stromal, multiple       1       (2%)       12       (24%)         Sarcoma stromal       1       (2%)       12       (24%)         Hematopoletic System       1       (2%)       (49)       (49)       (50)       (50)         Mediastinal, carcinoma, metastatic, ovary       1       (2%)       1       (2%)       (48)         Jymph node, mandibular       (49)       (45)       (48)       (46)       (47)       (42)       (43)         Lymph node, mesenteric       (50)       (49)       (50)       (49)       (50)       (49)         Spleen       (50)       (47)       (42)       (43)       (47)       (42)       (43)         Integumentary System       1       (2%)       2       (4%)       16       (4%)       16       (4%)         Fibroadenoma       19       (40%)       16       (43%)       16       (4%)       16       (4%)       16       (4%)       16       (4%)       16       (4%)       16       (4%)	Carcinoma			1	(2%)		
Uterus       (48)       (50)       (50)         Potyp stromal, multiple       4       (3%)       7       (14%)       12       (24%)         Potyp stromal, multiple       1       (2%)       1       (2%)       12       (24%)         Hematopoletic System       1       (2%)       1       (2%)       (49)       (49)         Hematopoletic System       1       (2%)       1       (2%)       (48)         Mediastinal, carcinoma, metastatic, ovary       1       (2%)       (48)       (48)         Jumph node, mandibular       (49)       (50)       (49)       (50)         Lymph node, mandibular       (49)       (50)       (49)       (50)         Thymus       (47)       (42)       (43)       (50)       (49)       (50)         Mammary gland       (48)       (37)       (47)       (42)       (43)       (45)       (50)       (49)       (50)       (49)       (50)       (49)       (50)	Granulosa cell tumor benign			1	(2%)		
Potyp stromal, multiple       4 (3%)       7 (14%)       12 (24%)         Potyp stromal, multiple       1 (2%)       1 (2%)         Sarcoma stromal       1 (2%)       1 (2%)         Hematopoietic System       500 (50) (49) (49)       (49)         Bone marrow       (50) (50) (50) (50)       (50)         Mediastinal, carcinoma, metastatic, ovary       1 (2%)       1 (2%)         Jymph node, mandibular       (49) (49) (49) (50)       (49)         Jymph node, mesenteric       (49) (50) (49) (50)       (49) (50)         Spleen       (59) (49) (50)       (43)         Integumentary System       (47)       (42) (43)         Mammary gland       (48) (37) (47)       (47)         Adenocarinoma       1 (2%)       2 (4%)         Fibroadenoma       19 (40%) 16 (43%) 16 (43%) 16 (43%)       16 (34%)         Fibroadenoma, multiple       9 (19%) 3 (8%) 2 (4%)       2 (4%)         Skin       (48)       (2%)       1 (2%)         Subcutaneous tissue, fibroma       1 (2%)       1 (2%)         Subcutaneous tissue, lipoma       1 (2%)       3 (6%) 1 (2%)         Subcutaneous tissue, pipma       1 (2%)       3 (6%) 1 (2%)         Subcutaneous tissue, pipma       1 (2%)       500 (50)	Uterus	(48)		(50)		(50)	
Polyp stromal, multiple       1       (2%)         Sarcoma stromal       1       (2%)         Hematopoletic System       50       (49)       (49)         Lymph node       (50)       (50)       (49)       (49)         Lymph node, mandibular       (49)       (45)       (48)         Adenocarcinoma, metastatic, thyroid gland       1       (2%)       (45)       (48)         Adenocarcinoma, metastatic, mammary gland       1       (2%)       (49)       (50)       (49)         Lymph node, mesenteric       (49)       (50)       (49)       (50)       (49)       (50)         Thregumentary System       Mammary gland       (48)       (37)       (47)         Adenoma       1       (2%)       2       (43)         Integumentary System       Mammary gland       (48)       (37)       (47)         Adenoma       1       (2%)       3       (8%)       2       (4%)         Fibroadenoma       19       (40%)       16       (43%)       16       (34%)         Fibroadenoma       1       (2%)       3       (6%)       1       (2%)         Skin       (48)       (50)       (49)       1 <td< td=""><td>Polyp stromal</td><td>4</td><td>(8%)</td><td>7</td><td>(14%)</td><td>12</td><td>(24%)</td></td<>	Polyp stromal	4	(8%)	7	(14%)	12	(24%)
Sarcoma stromat       1 (2%)         Hematopoletic System       Bone marrow       (50)       (49)       (49)         Lymph node       (50)       (50)       (50)       (50)       (50)         Mediastinal, carcinoma, metastatic, ovary       1 (2%)       1 (2%)       (48)         Lymph node, manituduar       (49)       (45)       (48)         Lymph node, mastatic, mammary gland       1 (2%)       (43)       (50)         Lymph node, mesenteric       (49)       (50)       (49)       (50)         Lymph node, mesenteric       (49)       (50)       (49)       (50)         Thromas       (50)       (47)       (42)       (43)         Integumentary System       Mamary gland       (48)       (37)       (47)         Adenocarcinoma       19 (40%)       16 (43%)       16 (34%)         Fibroadenoma       19 (40%)       16 (43%)       16 (34%)         Skin       (48)       (50)       (49)         Skin       (48)       (50)       (49)         Carcinoma adenosquamous       1 (2%)       1 (2%)         Keratoacanthoma       1 (2%)       1 (2%)       1 (2%)         Subcutaneous tissue, fibroma       1 (2%)       1 (2%)	Polyp stromal, multiple			1	(2%)		
Hematopoletic System Bone marrow         (50)         (49)         (49)           Lymph node         (50)         (50)         (50)         (50)           Mediastinal, carcinoma, metastatic, ovary         1         (2%)         (48)           Lymph node, mandibular         (49)         (45)         (48)           Lymph node, mandibular         (49)         (50)         (49)           Lymph node, mesenteric         (49)         (50)         (49)           Lymph node, mesenteric         (49)         (50)         (49)           Spleen         (50)         (49)         (50)         (49)           Thymus         (47)         (42)         (43)         (43)           Integumentary System         (47)         (42)         (43)           Madenoma         1         (2%)         2         (4%)           Fibroadenoma         19         (49%)         16         (3%)         2         (4%)           Skin         (48)         (50)         (49)         2         (4%)         16         (3%)         2         (4%)           Skin         (12%)         3         (50)         (49)         16         (3%)         16         (3%)         12	Sarcoma stromal			1	(2%)		
Bone marrow       (50)       (49)       (49)         Lymph node       (50)       (50)       (50)       (50)         Mediastinal, carcinoma, metastatic, ovary       1       (2%)       1       (2%)         Lymph node, mandibular       (49)       (45)       (48)         Adenocarcinoma, metastatic, mammary gland       1       (2%)       1       (49)         Lymph node, mesenteric       (49)       (50)       (49)       (50)       (49)         Spleen       (50)       (49)       (50)       (49)       (50)       (49)         Spleen       (50)       (49)       (42)       (43)       (43)         Integumentary System         Mammary gland       (48)       (37)       (47)         Adenocarcinoma       1       (2%)       2       (4%)         Fibroadenoma       19       (40%)       16       (34%)       16       (34%)         Fibroadenoma multiple       9       (19%)       3       (8%)       2       (4%)         Skin       (48)       (50)       (49)       (49)       (49)       (49)       (49)       (49)       (49)       (49)       (49)       (49)       (48) <t< td=""><td>Hematopoietic System</td><td></td><td></td><td></td><td></td><td></td><td></td></t<>	Hematopoietic System						
Lymph node         (50)         (50)         (50)           Mediastinal, carcinoma, metastatic, ovary         1         (2%)           Mediastinal, carcinoma, metastatic, thyroid gland         1         (2%)           Lymph node, manibular         (49)         (45)         (48)           Adenocarcinoma, metastatic, mammary gland         1         (2%)         (49)           Spleen         (50)         (49)         (50)         (49)           Spleen         (50)         (49)         (50)         (49)           Mammary gland         (48)         (37)         (47)           Adenocarcinoma         1         (2%)         (43)           Integumentary System         Mammary gland         (48)         (37)         (47)           Adenora         3         (6%)         2         (4%)           Fibroadenoma         1         (2%)         3         (8%)         2         (4%)           Skin         (48)         (50)         (49)         (49)         (49)         (48)         (50)         (49)         (4%)         (4%)         (4%)         (50)         (4%)         (4%)         (4%)         (4%)         (4%)         (50)         (50)         (4%)	Bone marrow	(50)		(49)		(49)	
Mediastinal, carcinoma, metastatic, ovary       1 (2%)         Mediastinal, carcinoma, metastatic, thyroid gland       1 (2%)         Lymph node, madibular       (49)         Adenocarcinoma, metastatic, mammary gland       1 (2%)         Lymph node, mesenteric       (49)         Spleen       (50)         Thymus       (47)         Integumentary System       (47)         Mammary gland       (48)         Adenocarcinoma       1 (2%)         Adenoma       3 (6%)         Fibroadenoma       19 (40%)         Fibroadenoma, multiple       9 (19%)         Skin       (48)         Carcinoma adenosquamous       1 (2%)         Keratoacanthoma       1 (2%)         Subcutaneous tissue, fibroma       1 (2%)         Musculoskeletal System       1 (2%)         Skeletal muscle       (1)       (1)         Marcinoma, metastatic, pituitary gland       1 (2%)         Officiend adenosquamous       500       (50)         Keratoacanthoma       1 (2%)         Skeletal muscle       (1)       (1)         Oligodendroglioma malignant       1 (2%)         Spina cord       (1)       (2)	Lymph node	(50)		(50)		(50)	
Mediastinal, carcinoma, metastatic, thyroid gland       1       (2%)         Lymph node, masibular       (49)       (45)       (48)         Adenocarcinoma, metastatic, mammary gland       1       (2%)       (49)       (50)         Lymph node, mesenteric       (49)       (50)       (49)       (50)         Spleen       (50)       (47)       (42)       (43)         Integumentary System       Mammary gland       (48)       (37)       (47)         Adenocarcinoma       1       (2%)       2       (4%)         Adenocarcinoma       1       (2%)       2       (4%)         Adenoma       3       (6%)       2       (4%)         Fibroadenoma       19       (40%)       16       (13%)       16       (24%)         Skin       (48)       (50)       (49)       3       (8%)       2       (4%)         Skin       (48)       (50)       (49)       3       (4%)       16       (2%)         Subcutaneous tissue, fibroma       1       (2%)       1       (2%)       3       (6%)       1       (2%)         Musculoskeletal System       1       (2%)       (50)       (50)       (50)       (50)	Mediastinal, carcinoma, metastatic, ovary	• •		1	(2%)	• •	
Lymph node, manibular (49) (45) (48) Adenocarcinoma, metastatic, mammary gland 1 (2%) Spleen (50) (49) (50) Thymus (47) (42) (43) Integumentary System Mammary gland (48) (37) (47) Adenocarcinoma 1 (2%) Adenocarcinoma 3 (6%) 2 (4%) Fibroadenoma 19 (40%) 16 (43%) 16 (34%) Fibroadenoma 19 (40%) 16 (43%) 16 (34%) Skin (48) (50) (49) Basal cell carcinoma 1 (2%) Carcinoma adenosquamous 1 (2%) Keratoacanthoma 1 (2%) 3 (6%) 1 (2%) Subcutaneous tissue, fibroma 1 (2%) Subcutaneous tissue, fibroma 1 (2%) Subcutaneous tissue, fibroma 1 (2%) Subcutaneous tissue, fibroma 1 (2%) Sketetal muscle (1) (1) (1) (1) Musculoskeletal System Sketetal muscle (1) (2%) System 1 (2%) Station (50) (50) (50) Carcinoma, metastatic, pituitary gland 1 (2%) Spinal cord (1) (2)	Mediastinal, carcinoma, metastatic, thyroid gland	1	(2%)				
Adenocarcinoma, metastatic, mammary gland       1       (2%)         Lymph node, mesenteric       (49)       (50)       (49)         Spleen       (50)       (49)       (50)         Thymus       (47)       (42)       (43)         Integumentary System       (47)       (42)       (43)         Mammary gland       (48)       (37)       (47)         Adenocarcinoma       1       (2%)       (43)         Adenoma       3       (6%)       2       (4%)         Adenoma       1       (2%)       (43)       16       (34%)         Fibroadenoma       19       (40%)       16       (43%)       16       (34%)         Fibroadenoma, multiple       9       (19%)       3       (8%)       2       (4%)         Skin       (48)       (50)       (49)       16       (34%)       16       (34%)         Skin       (12%)       1       (2%)       3       (6%)       1       (2%)         Subcutaneous tissue, fibroma       1       (2%)       3       (6%)       1       (2%)         Musculoskeletal System       1       (2%)       (50)       (50)       (50)       (50)	Lymph node, mandibular	(49)		(45)		(48)	
Lymph node, mesenteric $(49)$ $(50)$ $(49)$ Spleen $(50)$ $(49)$ $(50)$ Thymus $(47)$ $(42)$ $(43)$ Integumentary System         Mammary gland $(48)$ $(37)$ $(47)$ Adenoma       1 $(2\%)$ $(43\%)$ 16         Adenoma       3 $(6\%)$ 2 $(4\%)$ Fibroadenoma       19 $(40\%)$ 16 $(43\%)$ 16 $(34\%)$ Fibroadenoma       19 $(40\%)$ 16 $(43\%)$ 16 $(34\%)$ Skin       (48) $(50)$ (49)       16 $(43\%)$ 16 $(43\%)$ Basal cell carcinoma       1 $(2\%)$ 1 $(2\%)$ 3 $(6\%)$ 1 $(2\%)$ Subcutaneous tissue, fibroma       1 $(2\%)$ 3 $(6\%)$ 1 $(2\%)$ Musculoskeletal System       1 $(2\%)$ $(50)$ $(50)$ $(50)$ $(50)$ Carcinoma, metastatic, pituitary gland       1 $(2\%)$ $(2\%)$ $(2)$ $(2)$	Adenocarcinoma, metastatic, mammary gland	1	(2%)		•		
Spleen       (50)       (49)       (50)         Thymus       (47)       (42)       (43)         Integumentary System         Mammary gland       (48)       (37)       (47)         Adenocacricioma       1       (2%)       (43)       (47)         Adenocacricioma       1       (2%)       (43)       (47)         Adenoma       1       (2%)       (43%)       16       (34%)         Fibroadenoma       19       (40%)       16       (43%)       16       (34%)         Fibroadenoma       19       (40%)       3       (8%)       2       (4%)         Skin       (48)       (50)       (49)       (49)       (49)       (49)       (49)         Basal cell carcinoma       1       (2%)       1       (2%)       (49)	Lymph node, mesenteric	(49)		(50)		(49)	
Thymus       (47)       (42)       (43)         Integumentary System       Mammary gland       (48)       (37)       (47)         Adenocarcinoma       1       (2%)       (47)       (47)         Adenoma       3       (6%)       2       (4%)         Fibroadenoma       1       (2%)       3       (8%)       2       (4%)         Fibroadenoma, multiple       9       (19%)       3       (8%)       2       (4%)         Skin       (48)       (50)       (49)       (49)       (48)       (50)       (49)         Basal cell carcinoma       1       (2%)       2       (4%)       (4%)       (50)       (49)         Basal cell carcinoma adenosquamous       1       (2%)       1       (2%)       3       (6%)       1       (2%)         Subcutaneous tissue, fibroma       1       (2%)       3       (6%)       1       (2%)         Musculoskeletal System       1       (2%)       3       (50)       (50)       (50)         Carcinoma, metastatic, pituitary gland       1       (2%)       (50)       (50)       (50)         Carcinoma, metastatic, pituitary gland       1       (2%)       500	Spieen	(50)		(49)		(50)	
Integumentary System           Mammary gland         (48)         (37)         (47)           Adenocarcinoma         1         (2%)         2         (4%)           Adenoma         3         (6%)         2         (4%)           Fibroadenoma         19         (40%)         16         (43%)         16         (34%)           Fibroadenoma         19         (40%)         16         (43%)         2         (4%)           Skin         (48)         (50)         (49)         3         (8%)         2         (4%)           Carcinoma adenosquamous         1         (2%)         1         (2%)         3         (6%)         1         (2%)           Subcutaneous tissue, fibroma         1         (2%)         3         (6%)         1         (2%)           Musculoskeletal System         1         (2%)         3         (6%)         1         (2%)           Nervous System         Brain         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50)         (50	Thymus	(47)	:	(42)		(43)	· .
Mammary gland       (48)       (37)       (47)         Adenocarcinoma       1       (2%)       2       (4%)         Adenoma       3       (6%)       2       (4%)         Fibroadenoma       19       (40%)       16       (43%)       16       (34%)         Fibroadenoma, multiple       9       (19%)       3       (8%)       2       (4%)         Skin       (48)       (50)       (49)       3       (8%)       2       (4%)         Basal cell carcinoma       1       (2%)       3       (50)       (49)       3       (48)       (50)       (49)         Basal cell carcinoma adenosquamous       1       (2%)       3       (6%)       1       (2%)         Subcutaneous tissue, fibroma       1       (2%)       3       (6%)       1       (2%)         Musculoskeletal System       1       (2%)       3       (6%)       1       (2%)         Nervous System       1       (2%)       (50)       (50)       (50)       (50)         Carcinoma, metastatic, pituitary gland       1       (2%)       (2)       (2)         Spinal cord       (1)       (1)       (2)       (2)       <	Integumentary System			<u> </u>			
Adenocarcinoma       1       (2%)         Adenoma       3       (6%)       2       (4%)         Fibroadenoma       19       (40%)       16       (43%)       16       (34%)         Fibroadenoma, multiple       9       (19%)       3       (8%)       2       (4%)         Skin       (48)       (50)       (49)       (49)       (49)       (49)       (49)         Basal cell carcinoma       1       (2%)       1       (2%)       (4%)       (49)       (4%)       (49)       (4%)         Basal cell carcinoma       1       (2%)       1       (2%)       (4%)       (1%)       (2%)       (4%)       (4%)       (4%)       (4%)       (4%)       (4%)       (4%)       (4%)       (4%)       (1)       (1)       (1)       (1)       (1)       (1)       (1)       (1)       (2)       (2)	Mammary gland	(48)		(37)		(47)	
Adenoma       3 (6%)       2 (4%)         Fibroadenoma       19 (40%)       16 (43%)       16 (34%)         Fibroadenoma, multiple       9 (19%)       3 (8%)       2 (4%)         Skin       (48)       (50)       (49)         Basal cell carcinoma       1 (2%)       2 (4%)         Carcinoma adenosquamous       1 (2%)       3 (6%)       1 (2%)         Keratoacanthoma       1 (2%)       3 (6%)       1 (2%)         Subcutaneous tissue, fibroma       1 (2%)       3 (6%)       1 (2%)         Musculoskeletal System       1 (2%)       3 (6%)       1 (2%)         Musculoskeletal System       1 (2%)       50)       (50)       (50)         Brain       (50)       (50)       (50)       (50)       (50)         Carcinoma, metastatic, pituitary gland       1 (2%)       (50)       (50)       (50)         Carcinoma, metastatic, pituitary gland       1 (2%)       (50)       (50)       (50)         Spinal cord       (1)       (2)       (2)       (2)	Adenocarcinoma	ì	(2%)		•		
Fibroadenoma       19       (40%)       16       (34%)       16       (34%)         Fibroadenoma, multiple       9       (19%)       3       (8%)       2       (4%)         Skin       (48)       (50)       (49)       1       (2%)       (49)       1         Basal cell carcinoma       1       (2%)       1       (2%)       (49)       1       (2%)         Carcinoma adenosquamous       1       (2%)       1       (2%)       1       (2%)         Subcutaneous tissue, fibroma       1       (2%)       3       (6%)       1       (2%)         Musculoskeletal System       1       (2%)       3       (6%)       1       (2%)         Nervous System       1       (2%)       (1)       (1)       (1)       (1)         Steletal muscle       (1)       (1)       (1)       (1)       (1)       (1)         Steletal muscle       (50)       (50)       (50)       (50)       (50)         Carcinoma, metastatic, pituitary gland       1       (2%)       (2)       (2)         Spinal cord       (1)       (2)       (2)       (2)	Adenoma	3	(6%)			2	(4%)
Fibroadenoma, multiple       9 (19%)       3 (8%)       2 (4%)         Skin       (48)       (50)       (49)         Basal cell carcinoma       1 (2%)       1 (2%)         Carcinoma adenosquamous       1 (2%)       1 (2%)         Keratoacanthoma       1 (2%)       3 (6%)       1 (2%)         Subcutaneous tissue, fibroma       1 (2%)       3 (6%)       1 (2%)         Musculoskeletal System       1 (2%)       3 (6%)       1 (2%)         Musculoskeletal System       1 (2%)       1 (1)       (1)         Nervous System       1 (2%)       50)       (50)       (50)         Carcinoma, metastatic, pituitary gland       1 (2%)       (50)       (50)       (50)         Spinal cord       1 (2%)       (1)       (2)       (2)	Fibroadenoma	19	(40%)	16	(43%)	16	(34%)
Skin       (48)       (50)       (49)         Basal cell carcinoma       1 (2%)       1 (2%)         Carcinoma adenosquamous       1 (2%)       1 (2%)         Keratoacanthoma       1 (2%)       3 (6%)       1 (2%)         Subcutaneous tissue, fibroma       1 (2%)       3 (6%)       1 (2%)         Musculoskeletal System       1 (2%)       1 (1)       (1)       (1)         Nervous System       1       (50)       (50)       (50)         Brain       (50)       (50)       (50)       (50)         Carcinoma, metastatic, pituitary gland       1 (2%)       (2)       (2)	Fibroadenoma, multiple	9	(19%)	3	(8%)	2	(4%)
Basal cell carcinoma       1 (2%)         Carcinoma adenosquamous       1 (2%)         Keratoacanthoma       1 (2%)         Subcutaneous tissue, fibroma       1 (2%)         Subcutaneous tissue, lipoma       1 (2%)         Musculoskeletal System         Skeletal muscle       (1)         Nervous System         Brain       (50)         Carcinoma, metastatic, pituitary gland       1 (2%)         Oligodendroglioma malignant       1 (2%)         Spinal cord       (1)       (2)	Skin	(48)		(50)		(49)	
Carcinoma adenosquamous       1       (2%)         Keratoacanthoma       1       (2%)         Subcutaneous tissue, fibroma       1       (2%)         Subcutaneous tissue, lipoma       1       (2%)         Musculoskeletai System       1       (2%)         Skeletal muscle       (1)       (1)       (1)         Nervous System       1       (50)       (50)         Carcinoma, metastatic, pituitary gland       1       (2%)         Oligodendroglioma malignant       1       (2%)         Spinal cord       (1)       (2)	Basal cell carcinoma	· 1	(2%)				
Keratoacanthoma       1       (2%)         Subcutaneous tissue, fibroma       1       (2%)         Subcutaneous tissue, lipoma       1       (2%)         Musculoskeletai System       (1)       (1)         Skeletal muscle       (1)       (1)         Nervous System       (50)       (50)         Brain       (50)       (50)         Carcinoma, metastatic, pituitary gland       1       (2%)         Oligodendroglioma malignant       1       (2%)	Carcinoma adenosquamous			1	(2%)		
Subcutaneous tissue, fibroma       1 (2%)       3 (6%)       1 (2%)         Subcutaneous tissue, lipoma       1 (2%)       1 (2%)         Musculoskeletai System       (1)       (1)       (1)         Nervous System       (1)       (1)       (1)         Nervous System       (50)       (50)       (50)         Carcinoma, metastatic, pituitary gland       1 (2%)       (50)       (50)         Oligodendroglioma malignant       1 (2%)       (2)	Keratoacanthoma			1	(2%)		
Musculoskeletal System         Skeletal muscle       (1)       (1)         Nervous System         Brain       (50)       (50)         Carcinoma, metastatic, pituitary gland       1       (2)         Oligodendroglioma malignant       (1)       (2)	Subcutaneous tissue, fibroma Subcutaneous tissue, lipoma	1 1	(2%) (2%)	3	(6%)	1	(2%)
Nervous SystemBrain(50)(50)Carcinoma, metastatic, pituitary gland1(2%)Oligodendroglioma malignant1(2%)Spinal cord(1)(2)	Musculoskeletal System Skeletal muscle	(1)		(1)		(1)	
Brain(50)(50)(50)Carcinoma, metastatic, pituitary gland1(2%)Oligodendroglioma malignant1(2%)Spinal cord(1)(2)	Namious Suptom					·	
Drain(30)(30)(30)Carcinoma, metastatic, pituitary gland1(2%)Oligodendroglioma malignant1(2%)Spinal cord(1)(2)	Incrvous System	150		. (50)		(60)	
Oligodendroglioma malignant     1     (2%)       Spinal cord     (1)     (2)	Dialiti Caroinoma metastatia nituitare aland	(50)	(2%)	(50)		(50)	
Spinal cord (1) (2)	Oligodendrogliona malignant	1	(2%)				
	Sninal cond	1 (1)	(270)			(2)	
	Neonlasm NOS	(1)	(100%)			(2)	

#### Table B1

Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of HC Yellow 4 (continued)

	0	<b>b</b> buu	5,00	0 ppm	10,03	9 ppm
Respiratory System Lung Adenocarcinoma, metastatic, mammary gland Alveolar/bronchiolar adenoma Alveolar/bronchiolar adenoma, multiple Carcinoma adenosquamous, metastatic, skin Squamous cell carcinoma, metastatic, nose Nose Squamous cell carcinoma Trachea	(50) 1 1 1 (50) 1 (50)	(2%) (2%) (2%) (2%) (2%)	(50) 1 1 (49) (50)	(2%) (2%)	(50) 2 (48) (50)	(4%)
Special Senses System Ear Fibroma Papilloma squamous Harderian gland Adenoma Zymbal's gland Carcinoma	(2) 1 (9) 1	(50%) (11%)	(3) (4)		(3) 1 (15) 1 (1) 1	(33%) (7%) (100%)
Urinary System Kidney Urinary bladder	(49) (48)		(50) (48)		(50) (50)	
Systemic Lesions Multiple organs <sup>b</sup> Leukemia mononuclear	(50) 14	(28%)	(50) 15	(30%)	(50) 10	(20%)
Tumor Summary Total animals with primary neoplasms <sup>c</sup> Total primary neoplasms Total animals with benign neoplasms Total animals with benign neoplasms Total animals with malignant neoplasms Total animals with metal secondary neoplasms Total animals with secondary neoplasms Total secondary neoplasms Total animals with neoplasms uncertain- benign or malignant Total uncertain neoplasms	49 119 43 96 19 22 4 5 1		49 106 48 88 18 18 2 4		48 96 43 83 13 13	

<sup>a</sup> Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.

<sup>b</sup> Number of animals with any tissue examined microscopically

<sup>c</sup> Primary tumors: all tumors except metastatic tumors

<sup>d</sup> Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

	у ог геп	12110			5 11	11 L		4-	16	аг	ге	eu	30	uu	y U	1 1							PI	/III			
Number of Days on Study	4 0 9	4 2 2	4 4 7	5 3 1	5 8 2	6 0 0	6 1 2	6 2 5	6 4 5	6 4 7	6 5 0	6 5 8	6 5 8	6 5 8	6 9 2	6 9 9	7 0 0	7 0 1	7 0 2	7 1 0	7 1 0	7 2 3	7 2 8	7 3 1	7 3 5		
Carcass ID Number	5 5 5	4 9 5	4 8 5	4 7 5	5 3 5	5 4 5	5 0 5	4. 7 4	4 7 2	4 4 4	5 3 4	4 9 3	5 4 4	5 6 4	5 1 5	4 8 4	5 1 4	4 3 5	5 3 3	4 5 4	5 0 4	5 0 3	4 5 3	4 6 4	4 3 1		
												<u></u>														 	
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, cecum	+	Α	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, colon	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+		
Intestine small	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+		
Intestine small, duodenum	+	+	+	+	+	Α	+	+	+	·+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small, ileum	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small, jejunum	+	Α	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	[ +		
Liver	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Hepatocellular carcinoma																								Х			
Mesentery			+																	+							
Pancreas	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+		
Acinus, adenoma																							Х				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Stomach	+	+	+	+	+	+	+	+	+	+	+	` <b>+</b>	+	+	+	+	+	+	+	+	+	+	+	+	+		
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Cardiovascular System Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	 	
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adrenal gland, cortex Adenoma	+	+	+	+	+	+	+	+	+	+	+	+	+	·+	+	+	+	+	+	+	+	+	+	+	+		
Adrenal gland, medulla Pheochromocytoma malignant Pheochromocytoma benign	+	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	. +		
Islets, pancreatic Adenoma	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Μ	[ +	+	+	M	[+		
Adenoma																							х	Ś			
Pituitary gland	· +	+	+	+	+	Α	+	+	+	· +	+	· +	+	+	+	+	+	+	+	+	+	+	+	+	+		
Pars distalis, adenoma	·		X	X	X		x		X	X	x	x	X	X			x	x			x	X	X	x	x		
Pars distalis, adenoma, multiple														-									-				
Pars distalis, carcinoma																				х							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
C-cell, adenoma									х			х	х								x				X		
C call completeres						x						-															

None

+: Tissue examined microscopically A: Autolysis precludes examination

M: Missing tissue I: Insufficient tissue

X: Lesion present Blank: Not examined

Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of HC Yellow 4: 0 ppm (continued)

				_	-															_					_	
Number of Days on Study	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6																			
Carcass ID Number	4 3 2	4 4 3	4 5 1	4 6 2	4 7 1	4 8 1	4 9 1	5 0 1	5 1 1	5 1 2	5 2 2	5 2 3	5 3 1	5 3 2	5 4 1	5 5 1	5 5 4	5 6 2	5 6 3	4 3 3	4 3 4	4 8 3	5 0 2	5 2 5	5 4 3	Total Tissues/ Tumors
Alimentary System																										
Econhague	т	1	<u>т</u>		Ŧ	т	т	<u>т</u> ,	· _	т	Ŧ	т	т	н.	т	.4.										50
Esophagus Intesting James		Ţ	-	-	Ţ	Ţ	Ţ	Τ.	Ţ	Ţ	Ţ	Ť	Ţ	-	Ţ	<b>T</b>	-	Ţ	÷.	+	+	+	+	-	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
intestine large, rectum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	М	. +	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	<b>,</b> +	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Mesentery																		+								3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinus, adenoma																					Х					2
Salivary glands	+	+	+	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endoarino Suctor																									<u> </u>	
Adronal aland															,											<b>E ^</b>
Adrenal gland south	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenema	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
		Ă																								1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
r neocnromocytoma malignant																		х					-			1
Pheochromocytoma benign																							X			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			Х																							1
Parathyroid gland	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	М	+	+	+	+	+	+	+	+	+	46
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	Х				Х	Х	Х			Х	Х		Х	х	х			х	Х	Х	Х				31
Pars distalis, adenoma, multiple			Х	Х																						2
Pars distalis, carcinoma																										1
r are provided, cur entre inte													-		+	+	-	-	1	ж.	+	.1.		1	-	50
Thyroid gland	+	+	+	+	+	+	+	+	+	Ŧ	+	+	т	T	T	т	T	Ŧ		T	T	<b>—</b>	т	т	T	50
Thyroid gland C-cell, adenoma	+	+	x	+	+	+	+	+	x	Ŧ	+	+	т	т	т	т	т	т	1	т	x	т	Ŧ	т	x	9

General Body System None

Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of HC Yellow 4: 0 ppm (continued)

									_	****																
Number of Days on Study	4 0 9	4 2 2	4 4 7	5 3 1	5 8 2	6 0 0	6 1 2	6 2 5	6 4 5	6 4 7	6 5 0	6 5 8	6 5 8	6 5 8	6 9 2	6 9 9	7 0 0	7 0 1	7 0 2	7 1 0	7 1 0	7 2 3	7 2 8	7 3 1	7 3 5	
Carcass ID Number	5 5 5	4 9 5	4 8 5	4 7 5	5 3 5	5 4 5	5 0 5	4 7 4	4 7 2	4 4 4	5 3 4	4 9 3	5 4 4	5 6 4	5 1 5	4 8 4	5 1 4	4 3 5	5 3 3	4 5 4	5 0 4	5 0 3	4 5 3	4 6 4	4 3 1	
Genital System										<u> </u>																
Clitoral gland	۰	Ŧ	+	+	<u> </u>	÷.	м	+	+	+	+	+	+	+	+	+	т.	+	-	<u>н</u>	Ŧ	Ł	ᆂ	-	ъ	
Adenoma	•	•		•	•	•	141	$\dot{\mathbf{x}}$	ÿ	'	•	×	•	•	'	•	•	•	•	•				'	•	
Bilateral adenoma		,						~	~			Δ					Y									
		Ŧ	<u>т</u>	-	<b>–</b>	т	Т	Т	т	т	т	ᆂ	Т	т	Т	Ŧ	Ĩ	-	Т	Т	` <b>⊥</b>	Т	<u>т</u>	ъ	Т	
Uterus	т 	- T - L		- -	т. 	Ā	- T	+ +	т -	т 		т 	т 	т 	T L	т 	т 	т 	Ť	т 	т 	т 	т 	- T - L		
Polyp stromal	т	т	т	т	т	л	т	x	т	Ŧ	Ŧ	т	т	x	т	T	т	Ŧ	т	т	т	x	x	т	т	
Namatonoiatia Susta-																										•
																•										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mediastinal, carcinoma, metastatic,						•••																				
thyroid gland						X																				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	м	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma, metastatic, mammary																										
giand	X																					•			-	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Spieen Thymus	+	++	+	+	+	+ M	+	+	+	+	+	+	++	+	+	++	+	+	+	+	+	+	+ M	+	+	
Integumentary System Mammary gland	+	м	M	[+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	 : +	+	
Adenocarcinoma	x																									
Adenoma														•			х									
Fibroadenoma					Х		Х	Х							Х	•		х				Х		Х		
Fibroadenoma, multiple										Х			Х	X		х										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+	
Basal cell carcinoma																										
Subcutaneous tissue, fibroma																					Х					
Subcutaneous tissue, lipoma															х		•									
Musculoskeletal System										-																· · · ·
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skeletal muscle				•																						
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Carcinoma, metastatic, pituitary gland	•	•	•	•		·	·	·		•	•	•	•	•	•	•	•	•	,	x	•	•	•	•	•	
Oligodendroglioma malignant		х																								
Spinal cord									+																	
Neoplasm NOS									X																	
-																										

92

Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of HC Yellow 4: 0 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 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 6	7 3 6	7 3 6	7 3 6	7 3 6		7 3 6	
Carcass ID Number	4 3 2	4 4 3	4	<b>i</b> i	4 6 2	4 7 1	4 8 1	4 9 1	5 0 1	5 1 1	5 1 2	5 2 2	5 2 3	5 3 1	5 3 2	5 4 1	5 5 1	5 5 4	5 6 2	5 6 3	4 3 3	4 3 4	4 8 3	5 0 2	5 2 5		5 4 3	Total Tissues/ Tumors
Conital Suctor													_															
Clitoral gland Adenoma	+	• -	- 1	M	+	+	M	+	+ X	+	+	+	+	+	+	+	+	+ X	+	+ X	+	+	+	+	+	-	+	47 6
Bilateral, adenoma Ovary Uterus Polyp stromal	+ +	• 4	⊦ - ⊦ -	+	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ M	+	+ +	-	+ +	1 50 48 4
Hematopoietic System			-																									
Bone marrow Lymph node Mediastinal, carcinoma, metastatic,	+ +	• +	⊦ - ⊦ -	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+++	+ +	+ +	+ +	+ +	+ +	+ +	+ +	. + +	+ +	+ +	+ +	-	+ +	50 50
thyroid gland Lymph node, mandibular Adenocarcinoma, metastatic, mammary	+	• 4	+ -	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	1 49
gland Lymph node, mesenteric Spleen	+		F -	+	+	+	+	+	+	+	+	M +	[+]	• +	+	+	+	+	+	+	+	+	+	+	+	-	+	1 49 50
Thymus	4	- P	A -	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+.	47
Integumentary System Mammary gland Adenocarcinoma Adenoma Fibroadenoma Fibroadenoma, multiple Skin Basal cell carcinoma	+ X +		 	+	+ x +	+ x +	+ x +	+ X X +	+ X +	+ X +	+	+	 +	+ X +	+ X X +	+ x +	+ X +	+ x +	+ X M	+	+	+ X +	+ X +	+	+ +	+	+ x +	48 1 3 19 9 48 1
Subcutaneous tissue, fibroma Subcutaneous tissue, lipoma																												1 1
Musculoskeletal System Bone Skeletal muscle	-		+ -	ł	+	+	+	+	+	+	+	+	+	• +	+	+	+	+	++	+	+	÷	+	+	+	F	+	50 1
Nervous System Brain Carcinoma, metastatic, pituitary gland Oligodendroglioma malignant Spinal cord Neoplasm NOS	4		₽ .	+	+	+	+	+	+	+	+	+	+	• +	· +	+	+	+	+	+	+	÷	· +	+	· -4	+	+	50 1 1 1 1

. -

Number of Days on Study	4 0 9	4 2 2	4 '4 7	5 3 1	5 8 2	6 0 0	6 1 2	6 2 5	6 4 5	6 4 7	6 5 0	6 5 8	6 5 8	6 5 8	6 9 2	6 9 9	7 0 0	7 0 1	7 0 2	7 1 0	7 1 0	7 2 3	7 2 8	7 3 1	7 3 5		
Carcass ID Number	5 5 5	4 9 5	4 8 5	4 7 5	5 3 5	5 4 5	5 0 5	4 7 4	4 7 2	4 4 4	5 3 4	4 9 3	5 4 4	5 6 4	5 1 5	4 8 4	5 1 4	4 3 5	5 3 3	4 5 4	5 0 4	5 0 3	4 5 3	4 6 4	4 3 1		
Respiratory System Lung	+	· +	• +	• +	+	+	. +	+	+	+	+	+	<b>.</b> +	+	+	+	+	+	+	+	+	+	• +	+	+		
Adenocarcinoma, metastatic, mammary gland Alveolar/bronchiolar adenoma Alveolar/bronchiolar adenoma, multiple Squamous cell carrinoma metastatic	х											x				x											
Nose Squamous cell carcinoma Trachea	+	• •	· +	• +	+	+ +	+	+ +	+ +	+	x + x +	+	+	+	+	· +	• +	· +									
Special Senses System																										 	 
Fibroma Eye Harderian gland Adenoma							+			+ +		+ +	+			+ +		+			+ + X						
Urinary System Kidney Urinary bladder	+ +	- + - A	- +	- +	+	A A	++	+++	+++	++	+++	+++	+++	+++	+ +	+++	++	++	++	++	+	· +	• 4	- +	· +		
Systemic Lesions Multiple organs Leukemia mononuclear	+	• +	+ + X	+ x	+	+	+	+	+	+	+ x	+	+	+ x	+ x	+ x	+ x	+	+ x	+	+	• +	• +	- + X	+		

#### Table B2

(continued) 777 77 7 7 7 7 7 77777 7777 7777 77 Number of Days on Study Total Carcass ID Number 3 4 5 6 7 8 9 0 1 1 2 2 3 3 4 5 5 6 6 3 3 8 0 2 4 Tissues/ 2 3 1 2 1 1 1 1 1 2 2 3 1 2 1 1 4 2 3 3 4 3 2 5 3 Tumors **Respiratory System** Lung 50 + + + + Adenocarcinoma, metastatic, mammary gland 1 Alveolar/bronchiolar adenoma 1 Alveolar/bronchiolar adenoma, multiple 1 Squamous cell carcinoma, metastatic, nose 1 Nose 50 + Squamous cell carcinoma 1 Trachea 50 + Special Senses System 2 Ear + х Fibroma 1 Eye + 12 Harderian gland + 9 1 Adenoma Urinary System Kidney 49 + Urinary bladder 48 + Systemic Lesions Multiple organs + + + + X 50 + + + + + + + + + х Leukemia mononuclear хх х 14

Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of HC Yellow 4: 0 ppm

95

······································			_		_		_				_																_	
Number of Days on Study	4 7 8	5 4 4	5 4 5	6 1 1	6 1 2	6 1 9	6 2 8	6 6 4	6 6 6	6 6 8	6 7 2	6 8 5	6 8 6	7 1 0	7 1 0	7 1 0	7 1 0	7 1 3	7 1 3	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	; ; ;		
Carcass ID Number	6 6 5	5 7 5	6 5 5	5 9 5	6 9 5	6 7 5	6 0 4	6 4 5	6 9 4	5 8 4	6 3 5	6 5 4	6 0 3	6 1 4	6 1 5	6 2 5	6 8 4	5 7 4	6 9 2	6 7 4	5 7 1	5 7 2	5 7 3	5 8 2	5 8 3			
Alimentary System										·													<u> </u>					
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +		ł		
Intestine large	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	Å	+	+	+	+	+	+	+	+	+		+		
Intestine large, cecum	, +	+	+	+	+	+	+	+	+	+	+	+	+	+	A	÷	+	+	+	+	+	+	+			÷		
Intestine large, colon		÷	+	+	÷	+	+	+	÷	+	+	+	+	й	Δ	+	+		+	+	+	- <b>+</b>	4			, <b>L</b>		
Intestine large, colon	т 	т 	т Т	т -	т -	т 	Ļ	Ţ	т -	т 	- 1 - 1	_	т Т		Δ	<u>_</u>		т -	т 	- -	м	т 1 —	г Ц	т : 		Г L		
Intestine large, rectum	т 1		т Т	Ť	Ť	Ţ	т 	Ţ	Ť	- -	т 	т 	T	Ť	A A	Ť	т -	Ŧ	- -	т _	141			· •		г 1		
Intestine small duodenum	+	· +	+	+	+	Ť	+	+	+	· †	<b>T</b>	+	+	+	A	+	+	+	+	+	+	+	+			г. ,		
Intestine small, duodenum	+	+	Ť	+	+ V	1	+	+	Ţ	+	+	+	Ť	+	A	Ţ	-	+	+	+	+	+	+	· •		r		
Intestine small, neum	+	+	+	+	M	. +	÷.	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	• +		+		
intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	- +		+		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +		t-		
Carcinoma, metastatic, ovary									Х																			
Hepatocellular adenoma																							X					
Mesentery	+								+																			
Carcinoma, metastatic, ovary									Х																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +		F		
Acinus, adenoma																												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +		F		
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +		F		
Stomach, forestomach	M	[ +	+	+	+	+	+	+	+	+	+	Μ	+	+	+	+	+	+	+	+	+	+	+	- +		F		
Stomach, glandular	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +		F		
Cardiovascular System																										<u> </u>		
неап	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· · · +		F		
Endocrine System																												
Adrenal gland	+	+	+	+	+	+	+	+	+	+	·+	+	+	+	+	+	+	+	+	+	+	+	+	- +		+		
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	• +		+		
Adrenal gland, medulla	+	+	I	Μ	M	: +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +		+		
Pheochromocytoma benign																							X	2				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	·+	+	+	+	+	+	+	+	+	+	+	+		+		
Parathyroid gland	+	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	i N	14		÷		
Adenoma												х																
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- 4	+ +	+		
Pars distalis, adenoma	x			•	•	•	x	•	•		x	x		x	•	•	•	•	x	x	x		×	Ċ	c	-		
Pars distalis, adenoma multinle		x				x		x	x		-								4 1						-			
Thyroid gland	ب	- A1	_ ــــــــــــــــــــــــــــــــــــ	Ŧ	Ŧ	1	Ŧ	+	+	Ŧ	Ŧ	+	Ŧ	+	+	+	+	Ŧ	Ŧ	+	+	. <b>.</b>	<b>د</b> .			+		
C-cell adenome	т	т	· •	- Y	x	Ŷ			1.	1-					'	•	1.		•		4.		ſ	1		•		
Follicular cell, adenoma				Л	л	л						,																

# Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of HC Yellow 4: 5,000 ppm

**General Body System** 

None

96

7 77 Number of Days on Study 3 5 5 5 5 5 5 5 5 5 5 5 55 4 ₫ A A 4 A Δ 6 6 6 7 7 7 6 6 6 6 6 6 6 6 6 6 666 Total 566666 Carcass ID Number 9012778890001123344555666 Tissues/ 2 2 3 4 1 3 1 2 1 1 2 4 1 2 1 1 4 1 4 1 2 3 1 2 3 Tumors Alimentary System Esophagus 49 Intestine large 49 Intestine large, cecum 49 Intestine large, colon 47 + + M Intestine large, rectum + + + 46 M + + M Intestine small + + + + + 49 Intestine small, duodenum + M 48 + Intestine small, ileum + 47 М + + + + + + + + + + + + + + + + + Intestine small, jejunum + + ++ + + + ++ + М + Μ + + + + + + + + + + + 46 Liver 50 + + + Carcinoma, metastatic, ovary 1 Hepatocellular adenoma 1 Mesentery + + 4 Carcinoma, metastatic, ovary 1 Pancreas 50 + + + + Acinus, adenoma 2 х Salivary glands 50 + 4 Stomach 50 + + + + + + + + + + + + ++ + + + + + + + + + + + Stomach, forestomach + 48 + + + + + + + + + + + + + + + + ++ + + Stomach, glandular 50 4 + + + + + 4 + + + **Cardiovascular** System Heart 50 **Endocrine** System Adrenal gland 49 Adrenal gland, cortex 49 + + + Μ + + + + + + + + + Adrenal gland, medulla + М + + + + + + 46 + + + + + + Pheochromocytoma benign х Х 3 Islets, pancreatic + + + 50 + Parathyroid gland + + М + + + M + + + + + + + + + М + MM +39 Adenoma 1 Pituitary gland + + +48 + M + + + + + + + Pars distalis, adenoma х х \* \* \* \* \* \* \* \* \* \* \* \* \* \* \* \* \* \* 31 хх ХХ Pars distalis, adenoma, multiple 4 Thyroid gland 50 + + + + + + + + + + + + + + + + + + х C-cell, adenoma Х х х 7 Follicular cell, adenoma х 1

Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of HC Yellow 4: 5,000 ppm (continued)

General Body System

None

Number of Days on Study	 4 7 8	5 4 4	5 4 5	6 1 1	6 1 2	6 1 9	6 2 8	6 6 4	6 6 6	6 6 8	6 7 2	6 8 5	6 8 6	7 1 0	7 1 0	7 1 0	7 1 0	7 1 3	7 1 3	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	4	7 3 4		_	
Carcass ID Number	6 6 5	5 7 5	6 5 5	5 9 5	6 9 5	6 7 5	6 0 4	6 4 5	6 9 4	5 8 4	6 3 5	6 5 4	6 0 3	6 1 4	6 1 5	6 2 5	6 8 4	5 7 4	6 9 2	6 7 4	5 7 1	5 7 2	5 7 3	5 8 2	8	5 8 3		-	
Genital System Clitoral gland Adenoma Ovary Carcinoma	 ++	++	+	+ +	+	+	+	+	+ + x	++	+ +	+ +	м +	+	+ +	+ X +	+ X +	+ +	++	+ +	+	+				+ +			
Granulosa cell tumor benign Uterus Polyp stromal Polyp stromal, multiple Sarcoma stromal	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+ X	+	+	+	+	+	+	+	4	- + >	⊦ . {	+			
Hematopoietic System Bone marrow Lymph node Mediastinal, carcinoma, metastatic, ovary	++	+++	+ +	+ +	++++++	+++	+ +	++	+ + x	++	+++	+++	+++	++	A +	++	+++	++	+++	+ +	+	++	4	- 4		 +, +		- - -	
Lymph node, mandibular Lymph node, mesenteric Spleen Thymus	+ + +	+ + +	+ + + +	+ '+ +	+ + + M	+ + + M	+ + + +	+ + + +	+ + +	+ + + M	+ + + +	M + + +	+ + + +	+++++	+ + A +	+++++	M + + +	+ + + +	++++	+ + +	+ + + +	+++++++++++++++++++++++++++++++++++++++	  	⊢ -    	► · ⊢ ·	+ + +	i 		
Integumentary System Mammary gland Fibroadenoma Fibroadenoma, multiple Skin Carcinoma adenosquamous Keratoacanthoma Subcutaneous tissue, fibroma	+	+ + X	+ + X	+	+ x +	+ x +	+	м +	+ x +	+ + x	+ x +	+ + x	+ x +	+	+	м +	+ x +	+ x +	+ X +	м + х	1 M +	( + X		- 4		+		· .	
Musculoskeletal System Bone Skeletal muscle	 +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		 · -		 -	+			
Nervous System Brain	 +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		• -1	+ 4	 ⊦	+			

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Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of HC Yellow 4: 5,000 ppm (continued)

										_			_			_	_											
Number of Days on Study	7 3 4		7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5		7 3 5	-							
Carcass ID Number	5 9 2		6 0 2	6 1 3	6 2 4	6 7 1	6 7 3	6 8 1	6 8 2	6 9 1	7 0 1	7 0 2	7 0 4	6 1 1	6 1 2	6 2 1	6 3 1	6 3 4	6 4 1	6 4 4	6 5 1	6 5 2	6 5 3	6 6 1	6 6 2		6 6 3	Total Tissues/ Tumors
Genital System Clitoral gland Adenoma Ovary Carcinoma Granulosa cell tumor benign Uterus Polyp stromal Polyp stromal, multiple Sarcoma stromal	+ X + X +		+ +	+++	+ X +	+++	+ + + X	+ + +	+++	- M - M +	( + ( + X	+ + X	+++	+ + X	++++	+++	++++	+++	+++	M + +	+ +	+ + +	++++	++++	+++		+ + + +	47 5 49 1 1 50 7 1 1
Hematopoletic System Bone marrow Lymph node Mediastinal, carcinoma, metastatic, ovary Lymph node, mandibular Lymph node, mesenteric Spleen Thymus	- - - - - - -		- ++ ++++	+ + + + + + M	+ + + + + + M	+ + M + + + +	+++++++++++++++++++++++++++++++++++++++	++++++	+++++++++++++++++++++++++++++++++++++++	+ + + + + +	+ + + +	+++++++	+++++++	+++++++	++++++	++ ++++	++++++++	++++++	++++++++	+++++++	+ + + + + + + + +	+++++++	+ + M + + + +	+ + ! N + N	+++++++++++++++++++++++++++++++++++++++		+++++++++++++++++++++++++++++++++++++++	49 50 1 45 50 49 42
Integumentary System Mammary gland Fibroadenoma Fibroadenoma, multiple Skin Carcinoma adenosquamous Keratoacanthoma Subcutaneous tissue, fibroma	4	- ]	M +	м +	+	+ X +	+	+ X +	+ X +	+ X +	+ X +	M +	т м +	( + +	+	м +	+ X +	м +	+ X +	+ x +	M +	• M	+ X +	+ X +	+	- ]	м +	37 16 3 50 1 1 3
Musculoskeletal System Bone Skeletal muscle	+	-	+	+	+	+	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+ +	+	+	+	• +	-	+	50 1
Nervous System Brain		-	+	+	+	+	+	+	+	• +	+	+	+	+	+	Ŧ	+	+	+	+	+	+	+	+	+	_	+	50

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Number of Days on Study	4 7 8	5 4 4	5 4 5	6 1 1	6 1 2	6 1 9	6 2 8	6 6 4	6 6 6	6 6 8	6 7 2	6 8 5	6 8 6	7 1 0	7 1 0	7 1 0	7 1 0	7 1 3	7 1 3	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4		
Carcass ID Number	6 6 5	5 7 5	6 5 5	5 9 5	6 9 5	6 7 5	6 0 4	6 4 5	6 9 4	5 8 4	6 3 5	6 5 4	6 0 3	6 1 4	6 1 5	6 2 5	6 8 4	5 7 4	6 9 2	6 7 4	5 7 1	5 7 2	5 7 3	5 8 2	5 8 3	<u> </u>	 
Respiratory System Lung Alveolar/bronchiolar adenoma Carcinoma adenosouamous, metastatic	· +	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	 +	+	+	+	+	+	+	+		 
skin Nose Trachea	+ +	+ +	X + +	+	+ +	+ +	++	++	+ +	+ +	++	+ +															
Special Senses System Ear Eye Harderian gland	+	-		ļ	+	+		· .	۰,				+ +					.+ +		• .		+ +		+ +	+ +	4	× .
U <b>rinary System</b> Kidney Urinary bladder	+ M	+	+	++	- + M	+	++	+	++	+ +	++	+++	+ + +	`+ +	+ +	+	+ +	+ +	. + +	+ +	+ +	++	+ +	+ +	+ +		
Systemic Lesions Multiple organs Leukemia mononuclear	÷	+ x	+	+ X	+ X	+	+ 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 HC Yellow 4: 5,000 ppm (continued)

Number of Days on Study	7 3 4	7 3 5																									
Carcass IID Number	5 9 2	6 0 2	6 1 3	6 2 4	6 7 1	6 7 3	6 8 1	6 8 2	6 9 1	7 0 1	7 0 2	7 0 4	6 1 1	6 1 2	6 2 1	6 3 1	6 3 4	6 4 1	6 4 4	6 5 1	6 5 2	6 5 3	6 6 1	6 6 2	6 6 3		Total Tissues/ Tumors
Respiratory System Lung Alveolar/bronchiolar adenoma	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	ł	+	50 1
Carcinoma adenosquamous, metastatic, skin Nose Trachea	+ +	+	+	• +	+	++	+ +	+ +	+ +	M +	++	+ +	-  -	F F	1 49 50												
Special Senses System Ear Eye Harderian gland																	_			+						+	3 8 4
Urinary System Kidney Urinary bladder	+ +	• +	• +	• +	+	· + · +	+ +	+	+ +	+ +	+	+ +	+ +	++	+ +	+ +	+ +	+ +	+ +	++	++	+ +	+	+		+	50 48
Systemic Lesions Multiple organs Leukemia mononuclear	+	• +	• +	• +	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ x	-	+ {	50 15

101

102

TABLE B2

Number of Days on Study	4 9 7	5 3 1	5 4 5	5 5 7	6 3 2	6 3 2	6 4 3	6 5 0	6 5 1	6 7 2	6 8 6	6 9 2	7 1 0	7 1 5	7 1 6	7 2 2	7 2 9										
Carcass ID Number	8 2 5	7 2 4	7 1 4	7 5 5	7 6 5	8 2 4	7 4 5	7 2 3	8 4 4	7 1 3	7 7 5	7 8 5	7 9 5	8 0 5	7 1 2	7 7 2	7 9 2	7 9 4	8 0 2	8 0 4	8 1 2	8 1 3	8 1 4	8 1 5	8 2 1		
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		· .
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, cecum	+	+	+	÷	+	+	+	+	+	÷	+	+	+	+	Å	+	+	4	+	+	+	+	+	+	+		
Intestine large, colon	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, rectum	+	+	+	+	+	+	+	+	÷	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small	+	+	+	+	+	+	÷	+	+		+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+		
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	À	+	+	+	+	+	+	+	+	+	+		
Intestine small, ileum	+	+	+	+	+	+	+	+	+	4	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	À	+	+	+	+	+	+	+	+	+	+		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Mesenterv		·	+		+																+				+		
Pancreas	+	+	+	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Papilloma squamous														х													
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+		
Cardiovascular System			_																							 	<u>,</u>
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• !	
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adenoma		•			x																						
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	М	+	+	+	+	+	+	+	+	+		
Pheochromocytoma benign																											
Islets, pancreatic	+	+	М	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adenoma											х																
Parathyroid gland	+	+	Μ	Μ	+	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+	+	Μ	+	+	+	+		
Pituitary gland	+	+	+	+	+	+	+	+	+	+	.+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Pars distalis, adenoma				х		х	х	х	х		х	х	х	х	х				х			х		Х	Х		
Pars distalis, adenoma, multiple																											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	.+	+	+	+		
Bilateral, C-cell, adenoma																											
C-cell, adenoma		Х								х	х										х						
Follicular cell, adenoma																											

Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of HC Yellow 4: 10,000 ppm

None

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#### Lesions in Female Rats

### Table B2

Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of HC Yellow 4: 10,000 ppm (continued)

					_													_						_	_	
Number of Days on Study	7 2 9	7 2 9	7 2 9	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 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
	8	8	8	7	8	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	Total
Carcass ID Number	2 3	3 1	3 5	9 1	0 1	1 1	4 1	4 2	4 4	5 3	6 1	6 2	6 3	6 4	7 1	8 1	8 2	8 3	8 4	2 1	2 2	3 1	3 2	3 3	3 5	Tissues/ Tumors
Alimentary System										,																
Fsonhagus	+	+	+		+	+	+	Ŧ	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intertine large	+ +		1		т 	+ +	+ +	+ +		т 	+ +	т 	т _		т -	т _			т Т	+ +	т 	т 	+ +		- -	50
Intestine large cecum			1	. <b>+</b>	т -	- T	- -			- -	+ +	+ +		т -	т т	- -		+ +			- -	· -	- -		- -	40
Intestine large, cecum	- T	-	-		T M	т Г 1	- -	т -		-	Ţ	- -	- -	- -	Ť	Ť		- -	- -	<b>T</b>		Ţ	- -	T M	- <b>T</b>	47
Intestine large, colon		<b>T</b>	-	. <u> </u>	141	ι <del>τ</del>	<b>T</b>	Ţ	- -	T	Ť	Ť	Ţ	т -	Ť	Ť	Ŧ	Ţ	Ŧ	<b>T</b>		Ť		11/1	. <del>.</del>	47
Intestine large, rectum	+	+	+	· +	+	+	+	+	+	+	+	+	+	Ť	+	+	+	+	+	+	+	+	M	+	+	49
Intestine small due denue	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ducaenum	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																+					+					6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																										1
Stomach, glandular	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal gland, medulla	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	.+	+	+	49
Pheochromocytoma benign																		х	х							2
Islets, pancreatic	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Parathyroid gland	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	м	(+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	[+]	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	x	x		X	X		x		x		x		x		x	x	x	x	-	x	,	-	x	x		29
Pars distalis, adenoma, multiple																-	-					x				1
Thyroid gland	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell. adenoma		•		•			x	•	•	•	•	•	•		•	•	•	•	•		•		•	•	,	1
C-cell, adenoma																	x	x					x			7
Follicular cell, adenoma	x																									1
	~																									•

General Body System

None

				_			_			_			_		_	_							_	_	_	_	_		 
Number of Days on Study	4 9 7	5 3 1	5 4 5	5 5 7	6 3 2	6 3 2	6 4 3	6 5 0	6 5 1	6 7 2	6 8 6	6 9 2	7 1 0	7 1 5	7 1 6	7 2 2	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	1 2 9			
Carcass ID Number	8 2 5	7 2 4	7 1 4	7 5 5	7 6 5	8 2 4	7 4 5	7 2 3	8 4 4	7 1 3	7 7 5	7 8 5	7 9 5	8 0 5	7 1 2	7 7 2	7 9 2	7 9 4	8 0 2	8 0 4	8 1 2	8 1 3	8 1 4	8 1 5	8 2 1	3 2 L	-		
Genital System Clitoral gland Adenoma Carcinoma Ovary Uterus Polyp stromal	+	· +	+ + +		+ + X	+ + X	+ + X	M + +	+ + +	+ + +	++++	+ + +	++++	м + +	+ + +	+ + +	++++	++++	+ + X	++++	+ + X	++++	+ +	· + X · +	 	 + +		•	
Hematopoietic System Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen Thymus	+++++++	+ + M + + +	+ + + + +		+++++++++++++++++++++++++++++++++++++++	+ + M + M	M + + + + + +	+ + + + + M	+ + + + + +	+ + + + + + + +	+ + + + + + +	+ + + + + + +	+ + + + + +	+ + + + + +	++++++	+ + + + +	+ + + + +	+ + + + + M	+++++++++++++++++++++++++++++++++++++++	+ + + + + + + +	+ + + + M	+++++++	+ + + + + + + + + + + + + + + + + + + +	· + · + · + · +		 + + + + + + +			
Integumentary System Mammary gland Adenoma Fibroadenoma Fibroadenoma, multiple Skin Subcutaneous tissue, fibroma	+	· +	+	- +	м + Х	 +	_+ +	+ x +	++	+ X +	++	++	++	+ +	+	+	м +	+ x +	+ x +	+ x +	+	+	· +	- N	4 - 2 4 -	 * +			
Musculoskeletal System Bone Skeletal muscle	+	• +	+ +	- +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	Ŧ		• 4	- +		+			 
Nervous System Brain Spinal cord	+	+ +	+	• +	+	+	+	,+	+	+	+	+	+ +	÷	+	+	+	+	+	+	÷	+	+	- +		+			
Respiratory System Lung Alveolar/bronchiolar adenoma Nose Trachea	+ + +	· +	+ +	 - + - +	· + · +	++++++	++++	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ X + + +	, + + +	+++++	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	· + · +	- + - +	 	 + +			

7 7 7 Number of Days on Study 9 9 9 0 0 1 1 1 1 1 1 1 1 1 1 1 1 1 1 4 4 4 4 4 4 7777 Total Carcass ID Number 5666678888 22 Tissues/ 2339 0 14 4 4 3 3 3 3 3 1 5 2 4 3 2 3 4 1 1 2 3 4 1 2 1 2 3 5 Tumors 1 1 1 1 1 Genital System Clitoral gland + M + 44 M + M + + + M + + + + X Adenoma х 2 2 Carcinoma х 50 Ovary + + + + + + Uterus + + + +++ ++ + + +50 + + + Polyp stromal х х х х 12 х хх Hematopoietic System Bone marrow 49 4 + + Lymph node 50 + + + + + + +4 + + + + + + + + + Lymph node, mandibular 48 + + + + + + + + + + + + + + + + + М + + + + + + + Lymph node, mesenteric 49 + Spleen + + + + + + + + + + + + + 50 + + ++ + + + + + + + Thymus Μ + м M + + 43 Integumentary System Mammary gland 47 + + + + + + + + Adenoma Х 2 х х хх хх Fibroadenoma Х ХХ х хх 16 Fibroadenoma, multiple х 2 Skin + + + + + + + + + + 49 Subcutaneous tissue, fibroma 1 **Musculoskeletal** System Bone 50 Skeletal muscle 1 Nervous System Brain 50 Spinal cord 2 **Respiratory** System 50 Lung Alveolar/bronchiolar adenoma х 2 Nose + 48 + + Μ Trachea 50 + + + + + + + +

77 7 7 77 Number of Days on Study 8777787 7 8 7 7 7 7 8 777788888888 7 8 9 0 1 7 9 9 **Carcass ID Number** 2 2 1 5 6 24 1 0 0 1 1 1 1 2 2 4 5 5 5 3 4 3 5 5 5 5 2 2 2 4 4 2 3 4 5 1 4 4 5 4 2 Special Senses System Ear + + Papilloma squamous I Eye + + + + + + + + Harderian gland + + + + + + + + Adenoma Zymbal's gland + X Carcinoma **Urinary System** Kidney + Urinary bladder + + + + + + + + + + + Systemic Lesions Multiple organs + + + + ++ + + + + + + + + + + + + + +x ххх х х X. Leukemia mononuclear

#### Table B2

Number of Days on Study Total Carcass ID Number 2 3 3 9 0 1 4 4 4 5 6 6 6 6 7 8 8 8 8 2 2 3 3 3 3 Tissues/ 3 1 5 1 1 1 1 2 4 3 1 2 3 4 1 1 2 3 4 1 2 1 2 3 5 Tumors Special Senses System Ear 3 + х Papilloma squamous 1 Eye + + 17 + + + X + Harderian gland + 15 + + Adenoma 1 Zymbal's gland 1 Carcinoma 1 Urinary System Kidney 50 + + + + + + + + + + + + + + Urinary bladder + + 50 + + + + + + + + + + + + + + + + + + + Systemic Lesions Multiple organs + + x x 50 + + + + X + + Leukemia mononuclear 10

# Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of HC Yellow 4

	0 ppm	5,000 ppm	10,000 ррт
Adrenal Medulla: Benign Pheochromocyt	oma		
Overall rates <sup>a</sup>	1/49 (2%)	3/46 (7%)	2/49 (4%)
Adjusted rates <sup>b</sup>	3.7%	10.0%	5.9%
Terminal rates <sup>c</sup>	1/27 (4%)	3/30 (10%)	2/34 (6%)
First incidence (days)	729 (T)	729 (T)	729 (T)
Life table tests <sup>d</sup>	P = 0.492	P=0.342	P = 0.581
Logistic regression tests <sup>d</sup>	P = 0.492	P = 0.342	P=0.581
Cochran-Armitage test <sup>d</sup>	P = 0.400		
Fisher exact test <sup>d</sup>		P=0.285	P=0.500
Adrenal Medulla: Benign or Malignant I	Pheochromocytoma		
Overall rates	2/49 (4%)	3/46 (7%)	2/49 (4%)
Adjusted rates	7.4%	10.0%	5.9%
Terminal rates	2/27 (7%)	3/30 (10%)	2/34 (6%)
First incidence (days)	729 (T)	729 (T)	729 (Ť) ĺ
Life table tests	P=0.493N	P=0.549	P=0.610N
Logistic regression tests	P=0.493N	P=0.549	P=0.610N
Cochran-Armitage test	P=0.593		
Fisher exact test		P=0.470	P=0.691N
Clitoral Gland: Adenoma			,
Overall rates	7/47 (15%)	5/47 (11%)	2/44 (5%)
Adjusted rates	20.6%	15.2%	6.7%
Terminal rates	3/25 (12%)	3/29 (10%)	2/30 (7%)
First incidence (days)	625	710	729 (T)
Life table tests	P=0.039N	P = 0.303N	P=0.059N
Logistic regression tests	P=0.063N	P=0.357N	P=0.091N
Cochran-Armitage test	P=0.073N		
Fisher exact test		P=0.379N	P=0.095N
Clitoral Gland: Carcinoma			,
Overall rates	0/47 (0%)	0/47 (0%)	2/44 (5%)
Adjusted rates	0.0%	0.0%	6.7%
Terminal rates	0/25 (0%)	0/29 (0%)	2/30 (7%)
First incidence (days)	_e	-	729 (T)
Life table tests	P=0.112	-	P=0.279
Logistic regression tests	P=0.112	-	P=0.279
Cochran-Armitage test	P = 0.088		
Fisher exact test		-	P=0.231
Clitoral Gland: Adenoma or Carcinoma			
Overall rates	7/47 (15%)	5/47 (11%)	4/44 (9%)
Adjusted rates	20.6%	15.2%	13.3%
Terminal rates	3/25 (12%)	3/29 (10%)	4/30 (13%)
First incidence (days)	625	710	729 (T)
Life table tests	P=0.144N	P=0.303N	P=0.193N
Logistic regression tests	P=0.212N	P=0.357N	P=0.277N
Cochran-Armitage test	P=0.240N		
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#### TABLE B3

Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of HC Yellow 4 (continued)

	0 ppm		10 <b>,01</b> 0 ppm	
Mammary Gland: Adenoma				
Overall rates	3/50 (6%)	0/50 (0%)	2/50 (4%)	
Adjusted rates	10.1%	0.0%	5.9%	
Terminal rates	2/27 (7%)	0/31 (0%)	2/34 (6%)	
First incidence (days)	700	_	729 CT	
Life table tests	P=0.319N	P=0.102N	P=0.407N	
Logistic regression tests	P=0.345N	P=0.107N	P=0.442N	
Cochran-Armitage test	P=0.390N			
Fisher exact test		P=0.121N	P=0.500N	
Mammary Gland: Fibroadenoma				
Overall rates	28/50 (56%)	19/50 (38%)	18/50 (36%)	
Adjusted rates	74.5%	47.7%`́	49.6%	
Terminal rates	18/27 (67%)	11/31 (35%)	16/34 (47%)	
First incidence (days)	582	612	650	
Life table tests	P=0.005N	P=0.030N	P=0.005N	
Logistic regression tests	P=0.013N	P=0.034N	P=0.015N	
Cochran-Armitage test	P = 0.028N			
Fisher exact test		P=0.054N	P=0.035N	
Mammary Gland: Adenoma or Fibroadenom	18			
Overall rates	29/50 (58%)	19/50 (38%)	20/50 (40%)	
Adjusted rates	75.3%	47.7%	55.2%	
Terminal rates	18/27 (67%)	11/31 (35%)	18/34 (53%)	
First incidence (days)	582	612	650	
Life table tests	P=0.009N	P=0.021N	P=0.008N	
Logistic regression tests	P=0.022N	P=0.021N	P=0.023N	
Cochran-Armitage test	P=0.044N			
Fisher exact test		P=0.036N	P=0.055N	
Mammary Gland: Adenoma, Fibroadenoma,	or Adenocarcinoma	•		
Overall rates	30/50 (60%)	19/50 (38%)	20/50 (40%)	
Adjusted rates	75.8%	47.7%	55.2%	
Terminal rates	18/27 (67%)	11/31 (35%)	18/34 (53%)	
First incidence (days)	409	612	650	
Life table tests	P=0.006N	P=0.015N	P = 0.005N	
Logistic regression tests	P=0.016N	P=0.016N	P=0.019N	
Cochran-Armitage test	P = 0.028N			
Fisher exact test		P=0.022N	P=0.036N	
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	33/49 (67%)	35/48 (73%)	30/49 (61%)	
Adjusted rates	77.8%	89.2%	69.2%	
Terminal rates	18/27 (67%)	25/29 (86%)	20/33 (61%)	
First incidence (days)	447	478	557	
Life table tests	P=0.091N	P=0.526N	P=0.131N	
Logistic regression tests	P=0.248N	P=0.390	P=0.295N	
Cochran-Armitage test	P=0.295N			
Eisbor graat tost		D 0.252	D 0 000D	

#### TABLE B3

Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of HC Yellow 4 (continued)

	0 ppm	5,000 ppm	10,000 ppm
Pituitary Gland (Pars Distalis): Adeno	ma or Carcinoma	· · ·	
Overall rates	34/49 (69%)	35/48 (73%)	30/49 (61%)
Adjusted rates	78.5%	89.2%	69.2%
Terminal rates	18/27 (67%)	25/29 (86%)	20/33 (61%)
First incidence (days)	447	478	557
Life table tests	P = 0.067N	P=0.453N	P=0.100N
ogistic regression tests	P = 0.182N	P = 0.479	P = 0.222N
Cochran-Armitage test	P = 0.225N		- ••====•
Fisher exact test		P=0.437	P=0.262N
Skin (Subcutaneous Tissue): Fibroma			
Overall rates	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rates	3.2%	6.9%	2.2.%
Terminal rates	0/27 (0%)	0/31 (0%)	0/34 (0%)
First incidence (days)	710	544	632
Life table tests	P=0.568N	P=0.349	P=0.727N
agistic regression tests	P=0.533	P = 0.250	P = 0.749
Cochran-Armitage test	P = 0.610	1 0.250	1 0.775
Fisher exact test		P=0.309	P=0.753N
Thyroid Gland (C-cell): Adenoma			
Overall rates	9/50 (18%)	7/50 (14%)	8/50 (16%)
Adjusted rates	27.0%	18.5%	20.5%
Ferminal rates	5/27 (19%)	4/31 (13%)	5/34 (15%)
First incidence (days)	645	611	531
ife table tests	P=0.317N	P = 0.310N	P = 0.356N
agistic regression tests	P=0.454N	P = 0.390N	P = 0.485N
Cochran-Armitage test	P = 0.446N	1 0.5701	
Fisher exact test	1	P=0.393N	P=0.500N
Thyroid Gland (C-cell): Adenoma or C	ercinome		
Queroll rates	10/50 (20%)	7/50 (14%)	8/50 (16%)
Adjusted rates	78.6%	18.5%	20.5%
Terminal rates	5/27 (19%)	4/31 (13%)	5/34 (15%)
First incidence (daw)	600	611	531
ife table tests	P = 0.234N	P = 0.230N	P = 0.271 N
Life table tests	P = 0.363N	P = 0.308N	P = 0.399N
Coshran Armitage test	P-0 344N	1-0.5001	1 - 0.55711
Fisher exact test	1-0.54414	P=0.298N	P=0.398N
litemen Stremel Belum			
Overall rates	4/50 (8%)	8/50 (16%)	12/50 (24%)
Adjusted mater	4/30 (670)	22.6%	31 30%
nujusicu rates		43.070 6/21 (100/-)	51.370 004 /0401
ierminai raies	0/2/ (0%)	0/31 (19%)	5/34 (20%)
First incidence (days)	025 D 0 051	080	0 <i>32</i>
Life table tests	P=0.056	P=0.246	r=0.0/1
Logistic regression tests	r=0.025	r=0.201	r=0.031
Cocnran-Armitage test	P=0.020	D 0.170	D 0 000
Fisher exact test		P=0.178	P=0.027

#### Table B3

Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of HC Yellow 4 (continued)

	ന്നപ്പർ വ	5,000 ppm	10,000 ppm
Uterus: Stromal Polyp or Stromal Sarcoma			
Overall rates	4/50 (8%)	9/50 (18%)	12/50 (24%)
Adjusted rates	11.4%	26.7%	31.3%
Terminal rates	0/27 (0%)	7/31 (23%)	9/34 (26%)
First incidence (days)	625	686	632
Life table tests	P=0.061	P=0.176	P=0.071
Logistic regression tests	P = 0.028	P=0.137	P = 0.031
Cochran-Armitage test	P = 0.022		
Fisher exact test		P=0.117	P=0.027
All Organs: Mononuclear Cell Leukemia			
Overall rates	14/50 (28%)	15/50 (30%)	10/50 (20%)
Adjusted rates	37.1%	34.6%	23.2%
Terminal rates	6/27 (22%)	5/31 (16%)	4/34 (12%)
First incidence (days)	447	544	497
Life table tests	P=0.135N	P=0.534N	P=0.159N
Logistic regression tests	P = 0.292N	P=0.443	P = 0.321 N
Cochran-Armitage test	P = 0.212N		
Fisher exact test		P=0.500	P=0.241N
All Organs: Benign Tumors			
Overall rates	43/50 (86%)	48/50 (96%)	43/50 (86%)
Adjusted rates	95.4%	96.0%	91.4%
Terminal rates	25/27 (93%)	29/31 (94%)	30/34 (88%)
First incidence (days)	447	478	531
Life table tests	P = 0.106N	P=0.540N	P = 0.131N
Logistic regression tests	P = 0.441 N	P=0.122	P=0.470N
Cochran-Armitage test	P=0.564N		
Fisher exact test		P=0.080	P=0.613N
All Organs: Malignant Tumors			
Overall rates	19/50 (38%)	18/50 (36%)	13/50 (26%)
Adjusted rates	44.6%	39.9%	30.2%
Terminal rates	6/27 (22%)	6/31 (19%)	6/34 (18%)
First incidence (days)	409	544	497
Life table tests	P=0.078N	P=0.373N	P = 0.093N
Logistic regression tests	P=0.205N	P=0.533	P = 0.233N
Cochran-Armitage test	P = 0.122N		
Fisher exact test		P=0.500N	P=0.142N
All Organs: Benign or Malignant Tumors			
Overall rates	49/50 (98%)	49/50 (98%)	48/50 (96%)
Adjusted rates	98.0%	98.0%	96.0%
Terminal rates	26/27 (96%)	30/31 (97%)	32/34 (94%)
First incidence (days)	409	478	497
Life table tests	P=0.074N	P=0.238N	P=0.095N
Logistic regression tests	P=0.451N	P=0.731	P=0.581N
Cochran-Armitage test	P=0.378N	/04	
Fisher exact test		P=0.753N	P=0.500N

#### TABLE B3

Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of HC Yellow 4 (continued)

(T)Terminal sacrifice

<sup>b</sup> Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality

<sup>c</sup> Observed incidence at terminal kill

<sup>e</sup> Not applicable; no tumors in animal group

<sup>&</sup>lt;sup>1</sup> 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.

<sup>&</sup>lt;sup>d</sup> 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.

#### Table B4a

Historical Incidence of Uterine Neoplasms in Untreated Female F344/N Rats<sup>a</sup>

Study		<b>Incidence</b> in Controls	5
-	Stromal Polyps	Stromal Sarcoma	Stromal Polyp or Stromal Sarcoma
Historical Incidence at EG&G	Mason Research Institute		
4-Hydroxyacetanilide	15/50	0/50	15/50
HC Yellow 4	4/50	0/50	4/50
Pentaerythritol tetranitrate	8/50	0/50	8/50
Quercetin	7/50	0/50	7/50
Total	34/200 (17.0%)		34/200 (17.0%)
Standard deviation	9.3%		9.3%
Range	8%-30%		8%-30%
Overall Historical Incidence			
Total	142/800 (17.8%)	8/800 (1.0%)	149/800 (18.6%)
Standard deviation	5.1%	1.8%	5.4%
Range	8%-30%	0%-6%	8%-30%

<sup>a</sup> Data as of 3 April 1991

#### Table B4b

Historical Incidence of Mammary Gland Neoplasms in Untreated Female F344/N Rats<sup>a</sup>

Study		Incidence in Controls					
	Fibroma	Fibroadenoma	Fibroma, Fibroadenoma, or Adenoma				
Historical Incidence at EG&G N	lason Research Institute						
4-Hydroxyacetanilide HC Yellow 4 Pentaerythritol tetranitrate Quercetin Total	0/50 0/50 0/50 0/50	19/50 28/50 27/50 29/50 103/200 (51.5%)	19/50 29/50 27/50 29/50 104/200 (52.0%)				
Standard deviation Range		9.2% 38%-58%	9.5% 38%-58%				
Total Standard deviation Range	0/800	314/800 (39.3%) 15.1% 8%-58%	322/800 (40.3%) 15.2% 8%–58%				

<sup>a</sup> Data as of 3 April 1991

# TABLE B5

Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of HC Yellow 4<sup>a</sup>

	0	ррт	5,00	0 ppm	10,00	Ю ррт
Disposition Summary	······································					
Animals initially in study	70		70		70	
6-month interim evaluation	10		10		10	
15-month interim evaluation	10		10		10	
Early deaths						
Natural deaths	2		4		1	
Moribund kills	21		15		15	
Survivors		`				
Terminal sacrifice	26		30		34	
Moribund	1		1			
Animals examined microscopically	50		50		50	÷
Nimentary System						
ntentine lorge coour	(40)	· .	140			
Parasite	(48)	(201)	(49)		(49)	
ratasile	1	(2%)	(47)		(17)	
Parasite	(48)	(20%)	(4/)	(20%)	(4/)	
ralashic	1 (49)	(2%)	1	(2%)	(40)	
Bamaita	(48)	(101)	(40)	(201)	(49)	
	(50)	(4%)	(50)	(2%)	(50)	
Perophilia fogue	(50)	(740%)	(30)	16 401 >	(30)	(0.007)
Clear cell focus	3/	(1470)	34	(04%)	41	(0270)
Eccinophilic focus	1	(2%)	5	(0%)	2	(4%)
Eosinophilic locus Fatty abanga diffusa	7	(1 407)	1 7	(2%)	2	(4%)
Fatty change, diffuse	7	(14%)	/	(14%)	4	(8%)
Henotodianhmamatia nodulo	1	(14%)	2	(4%)	3	(0%)
Hepatodiapinaginatic nodule	4	(8%)	3	(0%)	. 9	(18%)
Inflammation granulomatous	1 20	(2%)	22	(	27	(E A07.)
Mixed cell focus		(00%)	22	(44%)	27	(34%)
Necrosis	U	(12%)	2	(10%)	/	(14%)
Thrombus			3	(0%)	1	(2011)
Bile duet hyperplacie	26	(5001)	1	(2%)	1	(2%)
blie duct, hyperpiasia	20	(52%)	24 (50)	(48%)	34	(04%)
Acinus atrophy	(49)	(20%)	(50)		(49)	
Duot humerolasia	1	(270)	1	(20%)		
tomach forestomach	(60)		1 (40)	(270)	(50)	
Aconthosis	(30)	(2%)	(48)	(15%)	(50)	(80%)
Hunerkerstosis	1	(4%)	1	(1370)	4	(0%)
Mineralization	2	(-1,0)	4	(070)	2	(4%)
Necrosis	1	(2%)				
I lleer	1	(270)	2	(1%)	1	(201)
tomach glandular	(50)		(50)	(+/0)	(50)	(270)
Hyperplasia	(30)		1	(2%)	(50)	
						-
leart	(50)		(50)		(50)	
Cardiomyopathy	23	(46%)	28	(56%)	23	(46%)
	20	()		(2000)		(13,0)

#### Lesions in Female Rats

#### Table B5

Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of HC Yellow 4 (continued)

	0 ppm		5,000 ppm		10,030 ppm	
Endocrine System						
Adrenal gland, cortex	(50)		(49)		(50)	
Hyperplasia	ì	(2%)	2	(4%)	2	(4%)
Adrenal gland, medulla	(49)		(46)		(49)	
Hyperplasia	6	(12%)	3	(7%)	4	(8%)
Pituitary gland	(49)		(48)		(49)	
Hyperplasia					1	(2%)
Pars distalis, angiectasis	29	(59%)	28	(58%)	22	(45%)
Pars distalis, cyst	5	(10%)	5	(10%)	9	(18%)
Pars distalis, hyperplasia	11	(22%)	14	(29%)	11	(22%)
Pars intermedia, anglectasis	1	(2%)			1	(201)
Pars intermedia, cyst	(50)		(50)		(50)	(2%)
	(50)		(50)	(20%)	(50)	
C.cell hyperplasia	10	(20%)	14	(28%)	11	(22%)
С-сен, пуретризва	10	(20%)	14	(28%)		(2270)
General Body System None						
Genital System						
Clitoral gland	(47)		(47)		(44)	
Necrosis	1	(2%)	4	(9%)		
Ovary	(50)		(49)		(50)	
Cyst	2	(4%)	5	(10%)	3	(6%)
Uterus	(48)		(50)		(50)	
Endometrium, hyperplasia			1	(2%)	1	(2%)
Hematopoietic System						
Lymph node	(50)		(50)		(50)	
Mediastinal, infiltration cellular, histiocyte	1	(2%)			2	(4%)
Lymph node, mesenteric	(49)		(50)		(49)	
Degeneration, cystic			1	(2%)	1	(2%)
Infiltration cellular, histiocyte	2	(4%)	1	(2%)	1	(2%)
Spleen	(50)		(49)		(50)	
Fibrosis	1	(2%)	2	(4%)		
Hematopoietic cell proliferation	30	(60%)	23	(47%)	31	(62%)
Intiltration cellular, histiocyte	3	(6%)	1	(2%)	1	(2%)
Pigmentation	28	(56%)	15	(31%)	31	(62%)
Thrombus			1	(2%)		
I nymus	(47)	(201)	(42)		(43)	
срипенан сен, пурегрназна	1	(2%)				
Integumentary System						
Mammary gland	(48)		(37)		(47)	
Galactocele	14	(29%)	7	(19%)	9	(19%)
Acinus, hyperplasia	3	(6%)	6	(16%)	5	(11%)

#### TABLE B5

Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of HC Yellow 4 (continued)

	0 ррт		5,000 ppm		10,000 ppm	
Musculoskeletal System						
Bone	(50)		(50)		(50)	
Hyperostosis					1	(2%)
Nervous System						
Brain	(50)		(50)		(50)	
Hemorrhage	2	(4%)	1	(2%)	2	(4%)
Spinal cord	(1)				(2)	
Hemorrhage					. 1	(50%)
Respiratory System				• • • • • • • •	_	
Lung	(50)		(50)		(50)	
Infiltration cellular, histiocyte	ý	(18%)	<b>ì</b> 16	(32%)	) á	(16%)
Alveolar epithelium, hyperplasia				. ,	3	(6%)
Nose	(50)		(49)		(48)	
Fungus			ì	(2%)		
Inflammation, acute	2	(4%)	2	(4%)	4	(8%)
Special Senses System	· · · · · ·	۰.				
Eve	(12)		(8)		(17)	
Hemorrhage	í	(8%)			ì	(6%)
Inflammation, acute	2	(17%)	2	(25%)		
Lens, cataract	5	(42%)	7	(88%)	8	(47%)
Retina, atrophy	1	(8%)	1	(13%)		
Urinary System	· · ·		a.			
Kidney	(49)		(50)		(50)	
Cvst	1	(2%)	()		<b>N</b> - <b>1</b>	
Nephropathy	37	(76%)	44	(88%)	41	(82%)
Urinary bladder	(48)	. /	(48)		(50)	
Inflammation, chronic active				· ·	1	(2%)
Transitional epithelium, hyperplasia					1	(2%)

<sup>a</sup> Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.

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# APPENDIX C SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR FEED STUDY OF HIC YELLOW 4

Table C1	Summary of the Incidence of Neoplasms in Male Mice	
	in the 2-Year Feed Study of HC Yellow 4	119
Table C2	Individual Animal Tumor Pathology of Male Mice	
	in the 2-Year Feed Study of HC Yellow 4	122
Table C3	Statistical Analysis of Primary Neoplasms in Male Mice	
	in the 2-Year Feed Study of HC Yellow 4	140
Table C4	Historical Incidence of Thyroid Gland Follicular Cell Neoplasms	
	in Untreated Male B6C3F, Mice	143
Table CS	Summary of the Incidence of Nonneoplastic Lesions in Male Mice	
	in the 2-Year Feed Study of HC Yellow 4	144

### Table C1

Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of HC Yellow 4ª

	0	<b>bb</b> m	5,0	CO ppm	10,0	20 ppm
Disposition Summary		··			<u> </u>	
Animals initially in study	70		70		70	
6-month interim evaluation	10		10		10	
15-month interim evaluation	10		10		10	
Early deaths						
Natural deaths	14		10		5	
Moribund kills	8		10		9	
Accidental death					1	
Terminal coefficient	20		20		25	
Missing	28		29 1			
Animals examined microscopically	50		49		50	
Alimentory System				<u></u>		
Gallbladder	(30)		(0)		(46)	
Intestine large, colon	(39)		(14)		(40) (47)	
Intestine large, rectum	(40)		(14)		(49)	
Adenocarcinoma	()		()		1	(2%)
Intestine small, ileum	(41)		(14)		(45)	
Intestine small, jejunum	(42)		(14)		(45)	
Liver	(49)		(22)		(48)	
Hemangioma	1	(2%)				
Hemangiosarcoma	1	(2%)				
Hemangiosarcoma, multiple	1	(2%)	_	(		
Hepatocellular carcinoma	4	(8%)	5	(23%)	8	(17%)
Hepatocellular adenoma	1	(2%)	2	(9%)	1	(2%)
Linoma	0	(10%)	,	(32%)	4	(8%)
Mesenterv	m	(270)			(1)	
Sarcoma	(-)				(1)	(100%)
Pancreas	(45)		(16)		(49)	()
Salivary glands	(50)		(17)		(49)	-
Stomach, forestomach	(46)		(19)		(48)	
Papilloma squamous	3	(7%)	2	(11%)	ì	(2%)
Stomach, glandular	(46)		(16)		(47)	
Cardiovascular System	·····					
Heart	(50)		(17)		(49)	
Sarcoma, metastatic, skeletal muscle			ì	(6%)		
Radocrine System						
Adrenal gland cortex	(50)		(17)		(40)	
Adenoma	(30)	(2%)	(17)		(40)	
Adenoma, multiple	1	(2%)				
Thyroid gland	(47)	()	(48)		(49)	
Follicular cell, adenoma	1	(2%)			2	(4%)
General Body System None						

Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of HC Yellow 4 (continued)

		ррт	5,000 ppm		10,000 ppm	
Genital System						
Epididymis	(50)		(47)		(49)	
Preputial gland	(9)		(11)		(6)	
Fibrosarcoma	ì	(11%)	• •			
Prostate	(47)		(15)		(45)	
Testes	(50)		(17)		(49)	
Sertoli cell tumor benign	1	(2%)				
Hematopoietic System						
Bone marrow	(49)		(16)		(47)	
yraph node	(46)		(28)		(47)	
Mediastinal, pancreatic, sarcoma, metastatic,			~ ~ ~			
skeletal muscle			1	(4%)		
Lymph node, mandibular	(42)		(9)		(40)	
ymph node, mesenteric	(38)		(24)		(45)	
Spleen	(49)		(21)		(48)	
Hemangiosarcoma	ì	(2%)				
Thymus	(28)		(9)		(29)	
integumentary System		···				
Skin	(49)		(32)		(48)	
Squamous cell carcinoma			, • •		1	(2%)
Subcutaneous tissue, fibroma			1	(3%)		
Subcutaneous tissue, fibrosarcoma	5	(10%)	2	(6%)	3	(6%)
Subcutaneous tissue, fibrosarcoma, multiple	• 1	(2%)				
Musculoskeletal System						
Skeletal muscle			(1)			
Sarcoma			1	(100%)		
Nervous System	· .					
Brain	(50)		(18)		(49)	
Meningioma benign			1	(6%)		
Respiratory System				· · · · · · · · · · · · · · · · · · ·		
Lung	(50)		(29)		(49)	
Alveolar/bronchiolar adenoma	ÌΎ	(14%)	` <b>ś</b>	(28%)	5	(10%)
Alveolar/bronchiolar adenoma, multiple					1	(2%)
Alveolar/bronchiolar carcinoma	2	(4%)	1	(3%)	1	(2%)
Hepatocellular carcinoma, metastatic, liver			1	(3%)	2	(4%)
Sarcoma, metastatic, skeletal muscle			1	(3%)		•
Special Senses System						
Harderian gland	(2)				(3)	
Adamama	ì	(5007)			`ź	(100%)

#### Lesions in Male Mice

#### TABLE C1

Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of HC Yellow 4 (continued)

	யில் ம	5,CLO ppm	10,000 ppm
Urimary System Kidney Adenocarcinoma Sarcoma, metastatic, skeletal muscle Urinary bladder	(49) (44)	(22) 1 (5%) (17)	(49) 1 (2%) (50)
Systemic Lesions Multiple organs <sup>b</sup> Lymphoma malignant mixed Lymphoma malignant undifferentiated cell	(50) 1 (2%) 1 (2%)	(49) 1 (2%)	(50) 1 (2%)
Tumor Summary			
Total animals with primary neoplasms <sup>c</sup>	28	23	23
Total primary neoplasms	44	31	34
Total animals with benign neoplasms	19	17	13
Total benign neoplasms	25	19	16
Total animals with malignant neoplasms	16	12	16
Total malignant neoplasms	19	12	18
Total animals with secondary neoplasms <sup>d</sup>		2	2
Total secondary neoplasms		5	2

<sup>a</sup> Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.

<sup>b</sup> Number of animals with any tissue examined microscopically

<sup>c</sup> Primary tumors: all tumors except metastatic tumors <sup>d</sup> Secondary tumors: metastatic tumors or tumors invasi

<sup>d</sup> Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

muividua Annua 10mor Pathology 0		C	1411		111	un		-10	- 1 IS	r		5		iy i		<u> </u>	· I			4:		• P	P	<u></u>			 	
Number of Days on Study	0 5 1	0 6 2	0 9 3	1 0 4	1 4 6	2 2 4	2 4 8	3 2 2	3 7 1	3 9 8	4 0 9	4 2 0	4 4 9	5 0 8	5 1 9	6 1 6	6 9 2	6 9 4	7 2 1	7 2 3	7 2 3	7 2 3	7 3 4	7 ' 3 : 4 ·	7 3 4	7 3 4		
Carcass ID Number	1 0 5	1 3 5	0 1 5	1 1 5	1 2 5	1 2 3	1 3 4	0 3 5	0 5 4	0 2 4	0 3 4	0 3 3	0 6 5	0 5 1	0 4 1	1 3 3	0 8 4	1 2 1	0 7 2	0 6 4	0 8 1	0 9 5	0 1 1	) ( L : L :	0 1 2	0 1 3		
Alimontom Suntam									·		_														•			
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	М	+	+	+	• +		+	+	+		
				. <u>А</u>	. 171	L 🕂	Ţ	+	<u> </u>	M	A.	IVI.	. <b>T</b>	IVI.		T	IVI.	Ţ	- <b>T</b>	Ţ				<b>r</b> '	Ţ.,	Ŧ		
Intestine large	+	+	A	. + 	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	• +		+ ·	+	+		
Intestine large, cecum	+	· +	· M	1 1	l +	+	+	+	A	+	M	+	+	+	+	A	A	+	+	+	+	• +		+	+	+		
Intestine large, colon	+	+	A	. +	+	+	· +	+	+	+	+	+	+	+	+	A	A	+	+	+	+	• +		+ '	+	+		
Intestine large, rectum	+	+	M	1 +	+	+	M	+	A	+	+	M	. +	+	+	A	A	+	+	+	+	• •		+ ·	+	+		
Intestine small	+	. +	M		. +	+	A	+	A	A	+	+	+	+	+	A	A	+	+	+	+	• +		+ ·	+	+		
Intestine small, duodenum	+	+	M		. +	+	A	+	A	A	+	+	+	+	A	A	A	+	+	+	+	• +		+ ·	+	+		
Intestine small, ileum	+	+	M		. +	+	A	+	A	A	M	A	+	+	+	A	A	+	+	+	+	• +		+ ·	+	+		
Intestine small, jejunum	+	+	· M	1 A	. +	+	<u>.</u> А	+	A	A	+	+	+	+	A	A	A	+	+	+	+	• •		+	+	+		
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	• +		t	+	+		
Hemangioma															v													
Hemangiosarcoma															л				v									
Hepatocellular carcinoma, multiple Hepatocellular carcinoma, multiple Hepatocellular adenoma																		x	л	x								
Lipoma																												
Mesentery									Α		М		+															
Pancreas	+	+	A	A	. +	+	Μ	+	+	Μ	+	+	+	+	+	+	Μ	+	+	+	+	• +		+	+	+		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +		+	+	+		
Stomach	+	+	· A	. +	+	+	Α	+	A	+	+	+	+	+	+	+	Α	+	+	+	+	• +		+	+	+		
Stomach, forestomach	+	+	A	4	+	+	Á	+	Μ	+	+	+	+	+	+	+	Α	+	+	+	+	• +	, .	+	+	+		
Papilloma squamous																												
Stomach, glandular	+	+	· A	. +	+	+	Α	+	Α	+	+	+	+	+	+	+	·A	+	+	+	+	• +		+	+	+		
Tooth																	+											
Cardiovascular System					-																						 	
Heart	+	- +	• +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-+	• +	÷ ۰	+	+	+		
Lymphoma malignant undifferentiated cell type, minimal													x															
Endocrine System		_							_																		 	
Adrenal gland	+	• +	• +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	⊦ ·	+	+	+		
Adrenal gland, cortex Adenoma	+	- +	• +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-1	- +	+ -	+	+	+		
Adenoma, multiple																												
Adrenal gland, medulla	+	+	• +	• +	+	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	+			- ۳	+	+	+		
Islets, pancreatic	+	+	· A	. +	+	• +	М	+	+	Μ	+	+	Μ	+	+	+	Μ	+	+	+	-	1	. ح	+	+	+		
Parathyroid gland	N	1 N	1+	• +	M	1+	М	M	+	+	М	+	+	+	Μ	+	Μ	Ι	Μ	[ +		- N	۸·	+	+	Μ		
Pituitary gland	N	1 +	- I	+	• +	+	+	Μ	+ 1	+	М	+	+	+	Μ	+	+	+	Μ	( +			+ •	+	+	+		
Thyroid gland	+	+	• +	• +	+	• +	+	Μ	: +	+	+	+	+	+	+	+	+	+	+	+	-	+	. ۲	+	+	+		
Follicular cell, adenoma														х														
														_					_								 	

Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of HC Vellow 4. 0 nnm

+: Tissue examined microscopically A: Autolysis precludes examination

M: Missing tissue I: Insufficient tissue

X: Lesion present Blank: Not examined

#### Lesions in Male Mice

TABLE C2 Individual Animal Tumor Pathology of	í Mal	e I	Mie	ce i	im '	the	e 2.	-Ye	ear	F	eed	S	tud	ly (	oľ l	HC	Y	'ell	ow	4:	: (	Dp	þı	m (	(co	ontin	ued)
Number of Days on Study	7 3 4	733	7 3	7 3 4																							
Carcass ID Number	0 1 4	0 2 1	0 2 2	0 2 3	0 3 1	0 4 3	0 4 4	0 6 1	0 6 2	0 6 3	0 8 3	0 9 1	0 9 2	0 9 3	0 9 4	1 0 2	1 0 3	1 1 1	1 1 2	1 1 3	1 1 4	1 3 2	1 4 1	1	 	1 4 3	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+ +	+	+	48
Gallbladder	+	+	+	М	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	μ.,	÷	+	39
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4	+ +	ł	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	4		÷	+	44
Intestine large, colon	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +			+	+	47
Intestine large rectum		+	÷	÷	÷	M	+	Ň	÷.	+	+	Ň	· +	+	+	+	÷	÷	M	+	÷	. +	-		+	+	40
Intestine small		÷		÷.	÷		÷	+		+	- -	1	_		÷	+	÷.	+	4	÷					1	Ļ.	40
Intestine small duodenum	÷	÷	÷		÷	Ļ		÷	÷		÷	_	÷	Ļ		÷			_	÷	-				Ļ	÷	42
Intestine small, ileum	т 1	- -				т 	т. Т			, ,	т Т		- -	T L	- -	, ,	- -		г -	4		T L	1	r Lu	Ļ	т 	42
Intestine small, iciunum	- T	Ţ	- <u>-</u>	Ţ	Ţ	- <u>-</u>	Ţ	т 	Ţ	Ţ	T	T	T	Ţ	Ţ	T	Ţ	Ţ	Ţ	Ţ	Ţ	· •			T L	Τ.	41
Liver		Ţ	+	- <u>-</u>	Ţ			Ţ	T	Ţ	- <b>T</b>	Ţ	Ţ	Ţ.	Ţ	Ţ	T					· T		г -	T.	T	42
	+	+	+	Ŧ	Ŧ	+	Ŧ	Ŧ	+	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	т	Ŧ	Ŧ	+	Ŧ	- T	. +		r -	T	Ŧ	49
Hemangioma																					А	•					1
Hemangiosarcoma																											1
Hemangiosarcoma, multiple								•••																			1
Hepatocellular carcinoma	X			X				Х																			4
Hepatocellular carcinoma, multiple																											1
Hepatocellular adenoma			X								Х						X				X	. X	. 2	< 2	X	Х	8
Lipoma																	Х										1
Mesentery																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	⊦ -	+	+	45
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	-	⊦ -	ł	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	-	+ -	+	+	46
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +		+ -	ł	+	46
Papilloma squamous								Х							Х		Х										3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +		+ -	÷	+	46
Tooth										+	+					+		+	+				-	+ -	+	+	9
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• -	+ -	ŧ	+	50
Lymphoma malignant undifferentiated cell type, minimal																											1
Endocrine System													-				_				-	_					
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +		+ •	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• •	+ •	+	+	50
Adenoma														Х													1
Adenoma, multiple																						Х					1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +		+ •	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	• •	+ •	+	+	45
Parathyroid gland	+	I	Μ	[ +	Μ	: +	+	+	+	Μ	[ +	+	+	+	+	Μ	: +	Μ	M	M	[₽	<b>í</b> №	1 -	+ -	+	М	27
Pituitary gland	M	[ +	+	Μ	+	Μ	: +	+	+	М	[ +	+	+	+	+	+	+	+	+	+	+	• +		+ I	М	М	38
Thyroid gland	+	+	+	+	Μ	( +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	R	1+		+ -	ŧ	+	47
Follicular cell, adenoma																											1

<u>a</u> <u>----</u>

Individual Animal Tumor Pathology	of Mal	<b>e</b> ]	Mi	ce	in	the	: 2-	-Ye	ar	Fe	eed	S	tud	y (	of l	HC	Y	ell	OW	4:	0	P	pm	(0	ontir	nued)
		^		1	1	~	2	2	2	2	٨	<u>^</u>	A	۲	<	6	6	6	7	7		7	7	7	7	
Number of Days on Study	٦ ج	6	Q	0	Å	ĩ	<u>,</u>	2	7	0	0	7	4	0	1	1	ŏ	0	2	2	2	2	2	2	, 2	
	1	2	3	4	6	<b>4</b>	8	2	1	8	9	õ	9	8	9	6	2	4	1	3	ĩ	3	4	4	4	
		_		•			_	_		-	-	ź	-	-		-			_	-	_	-			-	
	1	1	0	1	1	1	1	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	
arcass ID Number	0	3	1	1	2	2	3	3	5	2	3	3	6	5	4	3	8	2	7	6	8	9	-1	1	1	
	5	5	5	5	5	3	4	5	4	4	4	3	5	1	1	3	4	1	2	4	1	5	1	2	3	
eneral Body System None																										
								ببنكنك															—			·····
enital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Penís			Μ		+	+		+		+		+														
Preputial gland						+					+									+						
Fibrosarcoma	-												<b>.</b> -							X						
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	
Sertoli cell tumor benign	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
ematanaietic System																-										
Rone marrow		34	<b>т</b> .	т	<u>т</u>	۲	J.		.L	. ر	<u>ـ</u> ـــــــــــــــــــــــــــــــــــ		L.		.ر			J.			a.		.1		L.	
I ymph node	т с	1 1	. т . т	τ 	т 	т Д	т -	т л	M	т -	Ŧ	т _	- -	т Д	т Д	M	A	т М	т 	т 	т	т 	т ,		т Д	
Lymph node, mandibular	+	+	T M	. т . м	T L	- <b>T</b>	+ -	т "	141	+ -	+ 	T	т 	+ _	т 	1VI 1VI	M	141	т 	т 	+	+ +	+	+	+ _	
Lymph node, manufoular Lymph node mesentoric	+	M .	L IVI A	. MI	- <b>T</b>	T M	Ň	T M	- <b>J</b> N L	+ -	Ť	141	+ _	+ -	т "	IAI IAI	V IVI	141	+ -	т 	+ .1	+ -	+	+	+	
Lympu nowe, mescateric Spleen	+	+ 	A .	т ,	Ť	 1¥1	т. 1АЛ	141	141	- -	<u>л</u>	+ _	+ -	т 	+ _	۲A1	л Л	1A1	+ -	<b>T</b>	+	т 	+	+	т 1	
Uemangiosarcoma	+	Ŧ	A	т	т	Ŧ	т	Ŧ	т	Τ.	Ŧ	Ŧ	Ŧ	т	v	T	Ŧ	Ŧ	т	т	Ŧ	Ŧ	Ŧ	Ŧ	т	
Thomas	L	۲	۸	۸	L	м	м	м	-	м	۸	<b>н</b> .	Ŧ	<b></b>	M	м	т	м		L.	M	M	L	M	Ŧ	
	т т	т		A			141	IVI		IVI		т	т —	т 		IVI	1	IVI	т	т 		191		141		
ntegumentary System																										
Mammary gland	М	Μ	M	M	Μ	Μ	Μ	Μ	Μ	Μ	Μ	Μ	М	М	Μ	М	М	Μ	Μ	Μ	Μ	Μ	Μ	Μ	Μ	
Skin	+	+	+	+	+	+	+	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	
Subcutaneous tissue, fibrosarcoma														$\mathbf{X}$							Х	Х				
Subcutaneous tissue, fibrosarcoma,																										
multiple																				х						
lusculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
lervous System															_											
Brain	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	.+	+	+	+	+	+	+	
espiratory System																	<u></u>									
Lung	+	+	+	+	+	+	+	+	+	+	+	4	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma Alveolar/bronchiolar carcinoma	•	•	•	•	•	•	•	•	•		•		•		•			•	x	x	•	•	X	•	•	
														-	т.	т.	+	+	+	+	+	+	+	+	+	
Nose	+	-+	-+	- +	- +	- +	+	-	- +	-	-	+	-	т	- T.				•	•			•			

Individual Animal Tumor Patha	ology of Male	e I	Mi	ce i	im 1	úlhe	2	-¥@	30 I 1	F	eed	S	tud	ly	oľ	HC	2 7	ell	low	4	; (	DF	pn	n (c	01	ntinued)	
<u></u>	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7		7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3		3	
reador of Days of Stady	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4		4	
			0		0	0	0	0	 0		0	0	0	0	0	1	1	1	1	1	1	1				1	 Total
Corcoss ID Number	0 1	2	2	2	ž	4	4	6	6	6	Ř	ğ	ŏ	ğ	ğ	Ô	Ô	1	1	1	1	3	Ā	4		4	Tissnes/
	4	1	2	3	1	3	4	1	2	3	3	1	2	3	4	2	3	1	2	3	4	2	1	2		3	Tumors
General Body System None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		• +	• +	-	+	50
Penis																											5
Preputial gland		+			+		+					+	+				+										9
Florosarcoma	,							,										<b>b</b> /				L					1
riosiale Seminal vesicle	+	т 	. <u>+</u>	- -	- -			Ŧ	- -	- -	- <del>-</del>	+		- T - T	- <del>-</del>	- -	- -	141	ι <del>τ</del>		т ц					τ ∔	47 40
Testes	+	+	. <b>.</b>	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	. <b>.</b>	+	4				r F	+	50
Sertoli cell tumor benign		•	x	•	•	•	•	•	•	•	•			•	•	•		•	•	•	•						1
Hematopoietic System		-	_				_		-					-					_								· · · · · · · · · · · · · · · · · · ·
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	1		⊢ <b>-</b>	F	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			- +	F	+	46
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	1		r +	F	+	42
Lymph node, mesenteric	+	Ι	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	M	[ +	+			- +	ŀ	+	38
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			- +	F	+	49
Hemangiosarcoma																											1
1 hymus	+	+	• IVi			. +	+	1	+	M	+	+	+	+	+	+			ι + 	M.	. +			- +		+	28
Integumentary System															-							_					
Mammary gland	M	M	I M	[ M	M	+	M	M	M	Μ	M	M	I M	[ <b>M</b>	I M	M	M	[ M	I M	I M	f R	4 A	A N	A N	А	M	1
Skin	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-			- +	F	+	49
Subcutaneous tissue, fibrosarcom	na																		Х	•			2	Ĺ			5
multiple	14,																										1
Musculoskeletal System							·																				50
	+	+	· +	+	+	+	+	+	+	+	+	+	+	+	· +	+	+	+	· +	+				/ 1 	۲ 	+	JU
Nervous System								.1						,		,		,	. ,	,		L					50
	+	+	· +	+	+	+	+	+	+	+	+	+	+	+	· +	+	+	+	· +	· +	-				+	+	JU
Respiratory System																					-						60
Lung Absolon/bronchiston a terror	+	+	• +	+	+	+	+	+	+	+	+	+	· +	+	+	+	+	+	• +	+	: H	с н		r 1	۲	+	50
Auveolar/bronchiolar agenoma												X	X	X V						X	•						2
Nose	<b>ـ</b>	+		+	L.	+	ъ	+	Ŧ	+	+	L	<b>.</b>	<u>م</u> بر			L			له .	A.	А.	<b>.</b> -	<b>-</b> -	L	<b>-</b>	2 49
Trachea	+	+	- + - +	+	M	· +	+	+	+	+	+	+		+	- +	+	- +	- <del>-</del>		+ ·	л г	ы т Н -	- 4	 + -	,- ⊨	+	48
	•	•	•				•	•	•	•	•	,	•		•	•	•		'	'					•	•	

Individual Animal Tumor Patho	logy of	Mal	le I	Mi	ce	in	the	e 2	-Ye	ear	F	eed	S	tud	ly (	of :	HC	Y	ell	ow	4:	0	) p	рш	i (c	onti	nued	)	• .
		0	0	0	1	1	2	2	3	3	3	4	4	4	5	5	6	6	6	7	7	7	7	7	7	7			
Number of Days on Study		5 1	6 2	9 3	0 4	4 6	2 4	4 8	2 2	7 1	9 8	0 9	2 0	4 9	0 8	1 9	1 6	9 2	9 4	2 1	2 3	2 3	2 3	3 4	3 4	3 4			
Carcass ID Number		1 0 5	1 3 5	0 1 5	1 1 5	1 2 5	1 2 3	1 3 4	0 3 5	0 5 4	0 2 4	0 3 4	0 3 3	0 6 5	0 5 1	0 4 1	1 3 3	0 8 4	1 2 1	0 7 2	0 6 4	0 8 1	0 9 5	0 1 1	0 1 2	0 1 3	-		
Special Senses System Harderian gland Adenoma																											•	ł	
Urinary System								_																			-		
Kidney Ureter		. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ +	A	+	+	+	+	+	+	+	+			
Urethra Urinary bladder		+	+ +	A	A	+	+	A	+	A	÷	A	÷	+	+	+	<b>+</b>	A	+	+	Ŧ	+	+	Ŧ	+	+			
Systemic Lesions																													
Multiple organs Lymphoma malignant mixed		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Lymphoma malignant undifferentia cell type	ated								_					x															

.

Individual Animal Tumor Pathology	of Mai	.e	MIİ	ce	Ĭm	îlho	e 2	-¥	C&I	N.	eed	15	tuc	1y	oí	НC	с м —	ell	0W	4):	: (	) [P	þш	1 (c	ont	inued)	
Number of Days on Study	7 3 4																										
Carcass IID Number	0 1 4	0 2 1	0 2 2	0 2 3	0 3 1	0 4 3	0 4 4	0 6 1	0 6 2	0 6 3	0 8 3	0 9 1	0 9 2	0 9 3	0 9 4	1 0 2	1 0 3	1 1 1	1 1 2	1 1 3	1 1 4	1 3 2	1 4 1	1 4 2	1 4 3	ר ז ז	fotal fissues/ fumors
Special Senses System Harderian gland Adenoma									+							+ X								•			2 1
Urinary System Kidney Ureter Urethra Urinary bladder	+	+	· +	· +	- +	• +	+	• +	+	+	+	+	+	+	· +	+	++	+	++	++	+	++	+	+	+		49 1 1 44
Systemic Lesions Multiple organs Lymphoma malignant mixed Lymphoma malignant undifferentiated cell type	+	+		· +	- +	- +	+	· +	+ X	+	+	+	+	+	• +	+	+	+	+	+	+	+	+	+	+		50 1 1

Individual Animal Tumor Pathology	of Ma	le ]	Mi	ce	in	the	e 2	-Ye	ear	F	eed	IS	tuo	ły	of	HC	C	(ell	0₩	4	: 4	5,00	00	ppn	n		
Number of Dave on Study	0	0	1	1	1	2	2	3	3	3	3	4	5	5	5	6	6	6	6	6	7	7	7	7			
Number of Days on Study	3	9 4	0	5 2	6 8	1	9 1	8	7	8 4	9 9	0 9	1 2	0 7	2	1	6	5 8	5	8 7	3 1	3 4	3 4	3 4			
Canaga ID Number	1	1	1	1	2	2	2	2	1	2	2	2	1	2	1	2	1	2	2	2	1	1	1	1			
	5	5	5	5 4	5	3	4 4	4	3	8 4	5	5 4	8 3	3 3	8 4	4	0 1	5 1	8 1	2	5 1	5 2	2	6 3			
Alimentary System							_											<u> </u>						_			
Esophagus	+	+	+	+	Α	+	+	· +	+	+	.+	+	+	+	М	+	+										
Gallbladder	M	M	+	Α	A	Α	I	+	+	.+	+	Μ	M	· +	+	+	+										
Intestine large	A	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+										
Intestine large, cecum	A	- <del>+</del> . - ±	+	M	A	M	+	+	+	+	+	+	+	+	+	+	+										
Intestine large rectum	A A	Ŧ		- T	M	M	Ŧ	+ +	Ŧ	+ +		Ŧ		- -		+	Ť									•	
Intestine small		- <del>-</del>	+	A	A	M	+	+	+	+	т +	- <del>-</del>	+	+	+	+	+										
Intestine small, duodenum	.+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+										
Intestine small, ileum	Å	+	+	A	Α	M	+	+	+	+	+	+	+	+	+	+	+										
Intestine small, jejunum	A	+	+	A	M	Μ	+	+	+	+	÷	+	+	+	+	+	+				•						
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+				+				
Hepatocellular carcinoma															Х	'X			Х				Х				
Hepatocellular carcinoma, multiple													Х	Х													
Hepatocellular adenoma													Х	Х			Х						Х				
Mesentery											М																
Pancreas	+	+	+	+	Μ	Μ	+	+	+	+	+	+	+	+	+	+	+										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Papilloma squamous																											
Tooth	+	+	Ŧ	Ŧ	А	А	Ŧ	. +	+	Ŧ	Ŧ	+	+	Ŧ	Ŧ	+	Ŧ										
Cardiovascular System										_																	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Sarcoma, metastatic, skeletal muscle																	х										
Endocrine System									_																		
Adrenal gland	+	+	+	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+										
Adrenal gland, cortex	+	+	+	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+										
Adrenal gland, medulla	+	+	+	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+										
Islets, pancreatic	+	+	+	+	Μ	M	+	+	+	+	+	+	+	M	+	+	+										
Parathyroid gland	M	M	(+)	+	+	M	+	M	M	+	+	+	M	M	M	. M	1+										
Thyroid gland	+	+	м +	+	м +	+	++	+ M	м +	+	++	+	+	м +	+	+	+	+	+	÷	.+	+	+	+			
General Body System None																											
Genital System																	,				_						
Epididymis	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	·+	+	+	+			
Penis				·+		+		+				+															
Preputial gland		+										+	+				+										
Prostate	+	+	+	+	Α	+	+	+	+	+	+	Μ	[+]	+	+	+	+										
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+								
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			_	_						

#### Lesions in Male Mice

Table C2

Individual Animal Tumor Pathology	of Ma	le l	Mi	CC	im	tlho	2	2-Y(	Pai	· F	880	IS	au	ď۶	oí	HIC	2 1	(ell	0	4):	5	5,M	rd	pp	m (	continued)	
Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 6																						
Carcass ID Number	1 7 1	1 8 1	1 9 4	1 8 2	1 9 1	1 9 2	1 9 3	2 0 1	2 1 1	2 1 2	2 1 3	2 2 1	2 2 2	2 2 3	2 3 1	2 3 4	2 4 1	2 4 2	2 5 2	2 6 1	2 6 2	2 6 5	2 7 1	2 8 2	2 8 3	Tota Tiss Tum	ues/ ues/
Alimentary System			_			_	_			_	_	_			_	_						_					
Esophagus																										15	
Gallbladder																										9	
Intestine large																										14	
Intestine large, cecum																										13	
Intestine large, rectum																										14	
Intestine small																					+					15	
Intestine small, duodenum																					+					15	
Intestine small, ileum																					+					14	
Liver							+	-									+				т			+		22	
Hepatocellular carcinoma							x	۲.									•									5	
Hepatocellular carcinoma, multiple																										2	
Hepatocellular adenoma							X	C .									Х							Х		7	
Mesentery Pancress																					+					16	
Salivary glands																					'					10	
Stomach			+	-														+		+						20	
Stomach, forestomach			+	-														+								19	
Papilloma squamous			Х															X								2	
Tooth																				т						10	
Cardiovascular System																_						_				17	
Sarcoma, metastatic, skeletal muscle																										1	
Endocrine System			_	_																_	_		_				
Adrenal gland										·							+									17	
Adrenal gland, cortex																	+									17	
Adrenal gland, medulla																										16	
Parathyroid gland																					+					15	
Pituitary gland																										13	
Thyroid gland	-	- +		+ +	- +	• +	-	+ +	• +	+	• +	• +	+	- 4	- +	• +	• +	+	+	+	+	+	• +	+	• +	48	
General Body System None				-																							
Genital System												_										_					
Epididymis	-	F	-	+ +	- +	- +	• •	+ +	- +	- +	- +	- +			- +	- +	• +	• +	• +	• +	• +	• +	• +	+	- +	47	
Prenutial aland				+	- +	-	-	+.																+	-	8	
Prostate	-	-	4	-				+	-	+	- +	-							+	-	+	•				11	
Seminal vesicle						+										+				+						21	
Testes																										17	

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TABLE C2

Individual Animal Tumor Pathology	of Ma	e	Mi	ce	in	the	2	-Ye	ear	F	eed	IS	tuc	ly	of	HC	C Y	el	low	4:	5	,00	)0	ppm	(continued)
Number of Days on Study	0 7 3	0 9 4	1 0 0	1 5 2	1 6 8	2 7 1	2 9 1	3 2 8	3 7 7	3 8 4	3 9 9	4 0 9	5 1 2	5 6 7	5 9 2	6 0 7	6 2 6	6 5 8	6 7 5	6 8 7	7 3 1	7 3. 4	7 3 4	7 3 4	
Carcass ID Number	1 6	1	1 7	1 5	2 5	2 7	2 4	2 4 2	1 7 2	2	2	2 5	1 8 2	23	1 8	2	1 6 1	2 5	2 8 1	2 7	1 5	1 5 2	1 6 2	1 6 2	
		<u> </u>		4	3	3	4	3	3 	4	3	4	3	3	4	4	1	1	1	2	1	2	2	3	
Hematopoietic System																									
Bone marrow	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+	+	+								
Lymph node	+	+	+	+	Μ	Α	+	+	Μ	+	+	+	+	+	+	+	+			+				+	
Mediastinal, pancreatic, sarcoma,																									
metastatic, skeletal muscle																	X								
Lymph node, mandioular	M	M	101 	I MI	M		Ť	+	M	+	M	+	+	+	+	T M	M +			м				Т	
Spleen	+	- MI	. +	. <b>-</b>	M		M -	Ť	- MI		+			- -	- -	1V1	- <del>+</del>	т	<b>т</b>	1.01				Ŧ	
Thymus	+	м		- <del>-</del>	+	A	м	+	м	+	м	+	+	M	́м	м	+	Ŧ	т	Ŧ					
		101			_		141			1				14,				_							
Integumentary System											,														
Mammary gland	Μ	Μ	M	۱ M	M	M	М	Μ	Μ	М	M	Μ	M	Μ	M	Μ	Μ								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma							х			х														•	
Musculoskeletal System												_								-					
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	+		+	
Skeletal muscle	-			-													+								
Sarcoma																	x								
Newous Sustem	4					_		-		_		-					_	· · · ·	_						
Brain	+	+	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+								
Meningioma benign				•	•		•	•	•	•	•														
Pagninatory System		_							_			_		_					_						
Lung	ــ	+			-	-	+	+	+	+	+	+	+	+	+	+	+			+					
Alveolar/hronchiolar adenoma	Ŧ	Ŧ	4	Ŧ	Ŧ	Ŧ	T	ť	Ŧ	T	Ŧ	T	т.	T.	4										
Alveolar/bronchiolar carcinoma																				x					
Hepatocellular carcinoma, metastatic,														x											•,
liver Sarcoma metastatia akalatal musela														л			x								,
Nose	<b>ب</b>	+	1		м	T	Ŧ	+	+	+	м	[ <b>+</b>	+	+	+	+	- +								
Trachea	+	+	+	· +	A	+	+	+	+	+	+	+	+	+	+	+	+								
s autitus		'		•		•	•	•	-	•			,	•		'									
Special Senses System None																					-				

Individual Animal Tumor Pathology	of Ma	le	Mi	ce i	im '	the	2.	Ye	81°	Fe	eed	S	turd	ly i	oľ	HC	2 ¥	ell	ØW	4:	5	5,M	ND	pp	m	(continued)
Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 5	7 3 6																					
Carcass ID Number	1 7 1	1 8 1	1 9 4	1 8 2	1 9 1	1 9 2	1 9 3	2 0 1	2 1 1	2 1 2	2 1 3	2 2 1	2 2 2	2 2 3	2 3 1	2 3 4	2 4 1	2 4 2	2 5 2	2 6 1	2 6 2	2 6 5	2 7 1	2 8 2	2 8 3	Total Tissues/ Tumors
Hematopoietic System Bone marrow Lymph node Mediastinal, pancreatic, sarcoma,	+	- 4	-			+		,		+		+		+	+				+	+	+	+			+	16 28
metastatic, skeletal muscle Lymph node, mandibular Lymph node, mesenteric Spleen Thymus	-	- 4 4	-			+				+		+		+	+			+	+	+	+ +	+			÷	1 9 24 21 9
Integumentary System Mammary gland Skin Subcutaneous tissue, fibroma Subcutaneous tissue, fibrosarcoma			+			+			+		+	+ x								+		+	+	·M	 ( +	32 1 2
Musculoskeletal System Bone Skeletal muscle Sarcoma				+	+	+		+	+			+	+	+	+				+	+	+		+	• +	+	39 1 1
Nervous System Brain Meningioma benign					+ X																					18 1
Respiratory System Lung Alveolar/bronchiolar adenoma Alveolar/bronchiolar carcinoma Hepatocellular carcinoma, metastatic, liver Sarcoma, metastatic, skeletal muscle Nose Trachea	2	+ {	+ X	+	+ x	+				+ X	+ X							+			+ X		+ X	-	+ X	29 8 1 1 1 14 16

None

Individual Animal Tumor Pathology of	Ma	le ]	Mi	ce i	in '	the	2	-Ye	ar	Fe	ed	Śt	ud	y (	<b>of</b> i	HC	Y	ell	Ø₩	4:	5	<b>,0</b> 0	)0	ppm	1 (œ	ontin	ued)	l i
Number of Days on Study	0 7 3	0 9 4	1 0 0	1 5 2	1 6 8	2 7 1	2 9 1	3 2 8	3 7 7	3 8 4	3 9 9	4 0 9	5 1 2	5 6 7	5 9 2	6 0 7	6 2 6	6 5 8	6 7 5	6 8 7	7 3 1	7 3 4	7 3 4	7 3 4				1
Carcass ID Number	1 6 5	1 5 5	1 7 5	1 5 4	2 5 5	2 7 3	2 4 4	2 4 3	1 7 3	2 8 4	2 1 5	2 5 4	1 8 3	2 3 3	1 8 4	2 6 4	1 6 1	2 5 1	2 8 1	2 7 2	1 5 1	1 5 2	1 6 2	1 6 3				
Urinary System Kidney Sarcoma, metastatic, skeletal muscle Urethra Urinary bladder	+	++	+	+	A M A	+ A	+	+++	+ A	+	+ M	+	+	+	+	+	+ x +			+		+	+	+				
Systemic Lesions Multiple organs Lymphoma malignant undifferentiated cell type	+	+	· +	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
						-			:											-	•						-	
· .																												
																				•	•							
	·																											

#### Lesions in Male Mice

#### Table C2

Individual Amimal Tumor Pathology	oľ i	Mal	@ ]	Mi	ce	îm	tlh	e :	2-7	Yes	8r	Fo	eed	1 \$	tuo	dy	oľ	HC	C Y	[e]]	0%	4:	E	3,¢	ró	pp	min	(continued)
Number of Days on Study	·	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 7 3 3 5 4	7 1 3 3 5 1	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6													
Carcass IID Number		1 7 1	1 8 1	1 9 4	1 8 2	1 9 1	1 9 2	1 9 3	L 2 9 ( 3 1	2 2 0 1 1 1	2 1 1	2 1 2	2 1 3	2 2 1	2 2 2	2 2 3	2 3 1	2 3 4	2 4 1	2 4 2	2 5 2	2 6 1	2 6 2	2 6 5	2 7 1	2 8 2	2 8 3	Total Tissues/ Tumors
Urimary System Kidney Sarcoma, metastatic, skeletal muscle Urethra Urinary bladder																		+		+				+			+	22 1 1 17
Systemic Lesions Multiple organs Lymphoma malignant undifferentiated cell type		+	+	• +	- +	- +	+ +		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ x	+	+	+	+	- 49 1

														<u> </u>														
Number of Days on Study	2 2 0	2 9 7	3 0 8	3 9 4	4 0 5	4 4 8	4 8 4	5 6 7	6 0 2	6 1 7	6 4 5	6 6 8	6 7 9	7 0 1	7 0 8	7 3 0	-											
Carcass ID Number	3 0 4	3 1 5	3 0 3	3 3 5	4 1 4	4 0 5	3 2 3	4 2 2	3 5 3	3 0 2	3 9 1	2 9 1	3 7 1	3 6 2	3 8 1	2 9 2	2 9 3	2 9 4	3 0 1	3 1 1	3 1 2	3 1 3	3 1 4	3 2 2	3 3 1			
Alimentary System																												
Esonhagus	+	м	+	+	+	+	+	м	+	м	+	+	+	+	+	+	+	+	+	+	+	+	+	Ŧ	+			
Gallbladder	. +	M	+	+	м	+	÷	+	+	+	+	+	+	+	Ň	+	÷	+	+	м	i +	+	+	÷	÷			
Intestine large	+	+	+	+	+	+	+	+	+	÷	+	+	÷	÷.	A	÷	+	+	+	+	+	+	+	+	+			
Intestine large, cecum	+	+	+	+	+	+	÷	+	+	+	+	÷	÷	+	A	+	+	+	+	+	+	+	+	+	+			
Intestine large, colon	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	A	+	+	+	M	· +	+	·+	+	+	+			
Intestine large, rectum	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	÷			
Adenocarcinoma	•		•	•	•				•	•	•	•	•		••	•		·		•	•	•	'	•	•			
Intestine small	+	+	A	+	+	+	+	+	+	+	+	·+	+	+	A	+	+	+	+	+	+	+	+	+	+			
Intestine small, duodenum	, +	+	A	÷	+	÷	÷	÷	+	+	+	+	+	÷	A	+	÷	+	÷	+	÷	+	+	+	+			
Intestine small, ileum	.+	м́	A	+	+	÷	+	+	÷	÷	พ่	+	+	+	A	÷	÷	÷	+	+	+	+	+	÷	м			
Intestine small jejunum	+	M	Δ		÷.		+	÷	÷	÷	+	÷.	÷	÷	Δ		, _	÷	м	· 1	+	+	+	+	+			
I iver	+	M	4	+	÷	÷	÷	+	+	÷	+	+	+	+	A	÷	+	+	+	+	+	+	+	+	÷			
Henatocellular carcinoma	•	141		•				•	•	'		T				x	x	•		×	×	'	,		•			
Hepatocellular carcinoma multiple										x							-			-	~							
Henstocellular adenoma																x						x						
Mesentery					м	+																						
Sarcoma					141	x																						
Pancreas	+	+	+	+	+	4	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+		·	
Saliyary glands	+	Ń	+	+	+	÷	÷	+	+	+	÷	+	+	+	+	+	+	+	+	÷	÷	÷.	+	÷	+			
Stomach		M	+	÷	+	+	+	+	+	+	+	+	+	+	Å	÷	+	÷	+	+	+	+	+	+	+			
Stomach forestomach	- -	M	÷	÷	+	+	÷	÷	+	÷	+	+	+	+	A	÷	÷	+	+	+	+	+	÷	÷	+			
Papilloma squamous	ſ	141	T	•	'	,	'		r	'	'		•	1	~ 1	•	T	•		•	'	×	'	'	'			
Stomach glandular	+	м	+	Ŧ	+	÷	Ŧ	+	+	+	+	Ŧ	+	+	A	+	Ŧ	+	+	+	+	4	+	+	+			
Tooth	•	141	•	•	•	•	÷	,	•	•	,	•	•			•	•	•	+			•	•	•	•			
Cardiovascular System									_				_	-				_										
Heart	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Endocrine System			_						_																_	_		
Adrenal gland	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+			
Adrenal gland, cortex	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+	А	+	+	+	+	+	+	+	+	+	+			
Adrenal gland, medulla	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Α	+	+	+	+	+	+	+	+	+	+			
Parathyroid gland	Μ	M	Μ	M	+	+	+	Μ	M	M	+	+	Μ	+	Α	Μ	+	Μ	Μ	+	Μ	M	M	i +	М			
Pituitary gland	М	M	+	+	М	М	+	+	+	+	М	+	+	Μ	Α	+	+	+	+	+	+	+	Μ	( +	+			
Thyroid gland Follicular cell, adenoma	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
General Body System None		<u> </u>																				<u> </u>	,					

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Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of HC Yellow 4: 10,000 ppm

#### Lesions in Male Mice

TABLE C2

Individual Animal Tumor Pathology	of Mal	e I	Mie	ce i	im	the	2.	-Ye	-201	F	eed	S	tud	ly 🛛	of 1	HC	Y	ell	0W	4:	1	10,0	MX	DI	p	<b>m</b> (c	ontinued)
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	. 7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	0	0	0	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	_ 1	1	
	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4	4	4	4	4	4	4	. 4	4	Total
Carcass ID Number	3	3	4	4	5	5	2	3	5	6	6	6	7	7	8	9	0	0	0	1	1	1	2	2	2	2	Tissues
	2	4	1	2	1	2	1	3	4	1	3	4	2	3	2	2	1	2	3	1	2	3	1	3	4	4	Tumors
Alimentary System																											<u> </u>
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	ન		+ ۰	+	47
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +			+ •	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			۰ ۲	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	₽	1+	ન	- +	۴ •	+	48
Intestine large, colon	+	+	+	+	+	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	- +	+ •	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- H		۲ -	+	49
Adenocarcinoma												Х															1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +		- +	۰ ۱	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	۲ -	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +		۴ -	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	· +	· -1		۰ ۱	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4		۰ ۱	+	48
Hepatocellular carcinoma		Х					Х		Х			Х															8
Hepatocellular carcinoma, multiple																											1
Hepatocellular adenoma														Х									X	C I			4
Mesentery																											1
Sarcoma																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	- 4		⊦۰	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +		- +	۰ ۱	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	· - I		+ •	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	- 4		+ ۱	+	48
Papilloma squamous																											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +		-	⊢÷ •	+	47
Tooth	+																			+			-	-		+	6
Cardiovascular System																		_									• <u> </u>
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• •		<b>⊦</b> ·	+	49
Endocrine System																										_	h <u></u>
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• - 4		+ •	+	48
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• •		+ •	+	48
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	· P	γ.	+ •	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• -	+ -	+ •	+	49
Parathyroid gland	+	M	11	+	М	( +	М	+	Μ	M	M	M	M	+	Μ	M	( +	1	+	Μ	[ +	• +	• -	⊢ B	ví ·	+	20
Pituitary gland	+	M	[ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Ι	+	• +	• +	+ -	+ •	+	40
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	• -		+ •	+	49
Follicular celt adenoma									x			Y															2

General Body System

None

TABLE C2

Individual Animal Tumor Pathology	of Mal	e	Mi	ce	in	the	2	-Ye	ar	Fe	eed	S	tud	ly (	of 1	HC	Y	ell	ow	4:	1	0,0	00	) þ	pn	a (con	tinued)	
Number of Days on Study	2 2 0	2 9 7	3 0 8	3 9 4	4 0 5	4 4 8	4 8 4	5 6 7	6 0 2	6 1 7	6 4 5	6 6 8	6 7 9	7 0 1	7 0 8	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	3 0 4	3 1 5	3 0 3	3 3 5	4 1 4	4 0 5	3 2 3	4 2 2	3 5 3	3 0 2	3 9 1	2 9 1	3 7 1	3 6 2	3 8 1	2 9 2	2 9 3	2 9 4	3 0 1	3 1 1	3 1 2	3 1 3	3 1 4	3 2 2	3 3 1			
Genital System Coagulating gland Epididymis Penis Preputial gland Prostate Seminal vesicle Testes	M + + + +	++++++	+ +	+ +++	++++++	+ ++++	+ +++	+ +++	+++++	+++++++	+ + + + +	+ +++	+ +++	+ +++	+ + + A A	+ +++	+ M + +	+++++	+ ++++	+ +++	+ M + +	+	+ + + + +	· •	+ + + + +			
Hematopoietic System Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen Thymus	+ + + + + A	M M M M M	1 + 1 + 1 + 1 + 1 + 1 N	+ + + + + + H	+ + + + + + M	+ + M + + + +	+ + + + + M	+ + M + + M M	+ + M + + M	+ + + + M + +	+ + M + + M	+ + + + + M	+ M M + M	M + + + + +	A A M M M	+ + + + + + M	+ + + + + + +	+ + + + + H	+ + + + + +	++++++	+ + + + + M	+++++++++++++++++++++++++++++++++++++++	+++++++++++++++++++++++++++++++++++++++		+ + + + + + + N	+ . + + /		
Integumentary System Mammary gland Skin Squamous cell carcinoma Subcutaneous tissue, fibrosarcoma	M +	- M +	1 N +	( M	1 M +	- M +	м + х	M + X	M +	M +	- M +	M +	M + X	м + Х	1 M +	M	м +	М +	1 M +	1 M +	( M +	1 M +	[ N +	4 N	4 N	M +		
Musculoskeletal System Bone	+	N	1 +	• +	+	+	+	+	+	+	+	+	+	м		+	+	+	+	+	+	+	+		+ +	+		
Nervous System Brain	+	N	1 +	- +	+	+	+	+	+	+	+	+	+	• +	+	+	+	+	+	+	+	+			+ +	+		
Respiratory System Lung Alveolar/bronchiolar adenoma Alveolar/bronchiolar adenoma, multiple Alveolar/bronchiolar carcinoma Hepatocellular carcinoma, metastatic,		M	4 +	+	+	+	+	+	+	+	+	+	+	+	+	+ x	+	+	+	+ x	+	· +	1	+ -	+ +	+		•
liver Nose Trachea	+ +	N N	1 + 1 -	- +	+	+ +	+. +	+	+ +	. + . +	+ +	+ +	++	М +	[ + A	+ +	X + +	+ +	+	+	X + +	• +	+ + + +	⊦ - ⊦ -	÷ - + -	+ +		

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TABLE C2

THORADOWSD AND MANDEL LEUCHOLOGY OF	1411901		TAT 0	ce	μm	¢κиα	2 2	- 11 (	eau	E.C	ceu		LUIO	19.0			<u>, л</u>			-0:	ر 			· [P]	Ът	ш (с	onunued)
Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	3 1	
Carcass ID Number	3 3 2	3 3 4	3 4 1	3 4 2	3 5 1	3 5 2	3 2 1	3 3 3	3 5 4	3 6 1	3 6 3	3 6 4	3 7 2	3 7 3	3 8 2	3 9 2	4 0 1	4 0 2	4 0 3	4 1 1	4 1 2	4 1 3	4 2 1	4 2 3	4 2 4	4 2 4	Total Tissues/ Tumors
Gemital System Coagulating gland Epididymis Penis Preputial gland Prostate Seminal vesicle	+	- - -	· +	+++++++++++++++++++++++++++++++++++++++	+ + +	++++	+ +	+++	+ I +	+++++	++++	+ M +	+	++++	++++	++++	+ M +	++++	++++	++++	++++	+++	++++	++++	. <u>-</u> 	+ +	1 49 4 6 45 49
Testes ——————————————————————————————————	+	-	- +			+	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	49 
Bone marrow Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen Thymus	+ + + + +		- + - + - + - + ( +	· + · + · +	· + · + · +	+ + + + + + + + + + + + + + + + + + +	· + · + · + · +	+ + + + +	+ + + + M	+ + + + + +	+ + + + + + M	+ + + + + + +	+ + + + + +	+ + M + + + +	+ + + + + + M	+ + + + + + M	+ + + + + +	+ + + + + +	+ + M + + + +	+ + + + + +	+ + + + +	+ + + + +	+ + + + + +	+ + + + +	 	+ + + M + +	47 40 45 48 29
Integumentary System Mammary gland Skin Squamous cell carcinoma Subcutaneous tissue, fibrosarcoma	₩ +	I R 	4 N - +	í № • +	1 M +	. ₩ +	4 M • +	: M +	I M +	: M +	( M +	- M +	м +	- M +	: M +	м +	М +	м +	М +	і м +	M	[ M	: M +	( M +	<b>1</b> ]	M +	48 1 3
Musculoskeletal System Bone	+	• •	- +	· +	• +	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	48
Nervous System Brain	+	• -	- 4	• +	- +	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	49
Respiratory System Lung Alveolar/bronchiolar adenoma Alveolar/bronchiolar adenoma, multiple Alveolar/bronchiolar carcinoma Hepatocellular carcinoma, metastatic,	+	• •	 X	 + -	- + x	+	- + X	+	• +	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+ X		+	49 5 1 1
liver Nose Trachea	+ +		+ +	· + - +	- +	+++	- +	+ +	• +	+ +	+	+ +	+ +	+ +	+ +	M +	+ +	+ +	+ +	+ +	+ +	+	+ +	+		+ +	2 47 48

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10.000

Individual Animal Tumor Pathology of	Male	: 1	Mic	e i	<b>n</b> (	the	2	-Ye	ar	Fe	eed	S	tud	ly	of	HC	Y	ella	w	4:	1	0,0	00	PI	pm	(continued)
Number of Days on Study	2 2 0	2 9 7	3 0 8	3 9 4	4 0 5	4 4 8	4 8 4	5 6 7	6 0 2	6 1 7	6 4 5	6 6 8	6 7 9	7 0 1	7 0 8	7 3 0										
Carcass ID Number	3 0 4	3 1 5	3 0 3	3 3 5	4 1 4	4 0 5	3 2 3	4 2 2	3 5 3	3 0 2	3 9 1	2 9 1	3 7 1	3 6 2	3 8 1	2 9 2	2 9 3	2 9 4	3 0 1	3 1 1	3 1 2	3 1 3	3 1 4	3 2 2	3 3 1	
Special Senses System Ear Eye Harderian gland Adenoma												+	+								+ x					
Urinary System Kidney Adenocarcinoma Urinary bladder	+ +	++	+ X +	+	++	++	+	+	+	+ +	+ +	+	+ +	++	A +	++	+	+ +	+	+	+	+ +	+	+	+	
Systemic Lesions Multiple organs Lymphoma malignant undifferentiated cell type	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	

# Table C2 Individual Ami

Individual Animal Tumor Pathology	oî F	Male	e	√lic	e	im	the	e 2	-¥(	ear	F	eed	I S	tuc	ly	oſ	HC	2 8	/ell	ØW	4:	1	10,0	MM	D p	pm	(continued	)
Number of Days on Study		7 3	730	7 3	730	730	730	7 3 1	7 3	7 3 1	731	7 3	7 3 1	7 3 1	7 3	7 3 1	7 3 1	731	7 3	7 3	7 3	7 3	7 3 1	7 3 1	7 3 1	7 3 1		
Carcass ID Number		3 3 2	3 3 4	3 4 1	3 4 2	3 5 1	3 5 2	3 2 1	333	3 5 4	3 6 1	3 6 3	3 6 4	3 7 2	3 7 3	3 8 2	3 9 2	4 0 1	4 0 2	4 0 3	4 1 1	4 1 2	4 1 3	4 2 1	4 2 3	4 2 4	Total Tissu Tumo	l les/ ors
Special Senses System Ear Eye Harderian gland Adenoma				+ x			+	+				_									+ + X						4 1 3 3	
Urinary System Kidney Adenocarcinoma Urinary bladder		+ +	+	++	+ +	+ +	· +	+	+	+	++	++	++	· +	++	+++++++++++++++++++++++++++++++++++++++	+ +	+	+	++	++	+	++++	+	+	· +	49 1 50	
Systemic Lesions Multiple organs Lymphoma malignant undifferentiated cell type		+	+	+	+	+ x	 - +	+	+	+	+	+	+	 - +	+	+	+	+	+	+	+	+	+	+	• +	 +	50	

# Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of HC Yellow 4

	0 ppm	5,000 ppm	10,000 ppm
Harderian Gland: Adenoma			<u> </u>
Overall rates <sup>a</sup>	1/50 (2%)	0/49 (0%)	3/50 (6%)
Adjusted rates <sup>b</sup>	3.6%	0.0%	86%
Ferminal rates <sup>C</sup>	1/28 (4%)	0/29 (0%)	3/35 (9%)
First incidence (dave)	730 (T)	_e	730 (T)
if table tests	· P-0.230	P-0.403N	P-0387
caristic regression tests	P-0.230	P-0 403N	P=0.387
Configure Armitage test	P-0177	1 -0.49514	1 -0.567
Fisher exact test	r=0.177	P=0.505N	P=0.309
Liver: Henatocellular Adenoma			
Overall rates	8/49 (16%)	7/22 (32%) <sup>f</sup>	4/48 (8%)
Adjusted rates	28.6%		11.4%
Terminal rates	8/28 (29%)		4/35 (11%)
First incidence (days)	730 (T)		730 (T)
ife table tests	,(1)		P = 0.083N
and more rearession tests			P = 0.083N
Tisher exact test			P=0.188N
Liver: Hepatocellular Carcinoma		f	
Overall rates	5/49 (10%)	7/22 (32%)*	9/48 (19%)
Adjusted rates	16.2%		24.7%
Terminal rates	3/28 (11%)		8/35 (23%)
First incidence (days)	694		617
Life table tests			P=0.326
Logistic regression tests			P=0.279
fisher exact test	· .		P=0.182
Liver: Hepatocellular Adenoma or Carcinoma		f	
Overall rates	13/49 (27%)	10/22 (45%)'	12/48 (25%)
Adjusted rates	43.0%		33.1%
Terminal rates	11/28 (39%)		11/35 (31%)
First incidence (days)	694		617
Life table tests			P = 0.262N
Logistic regression tests			P = 0.327N
Fisher exact test			P=0.524N
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	7/50 (14%)	8/29 (28%)	6/49 (12%)
Adjusted rates	23.0%	72.7%	17.1%
Terminal rates	5/28 (18%)	8/11 (73%)	6/35 (17%)
First incidence (days)	721	730 (T)	730 (T)
Life table tests	P = 0.259N	P=0.029	P=0.345N
Logistic regression tests	P=0.318N	P=0.005	P=0.395N
Cochran-Armitage test	P=0.464N	_	
Fisher exact test		P=0.119	P=0.516N

#### Lesions in Male Mice

### TABLE C3

Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of HC Yellow 4 (continued)

	0 ppm	5,000 ppm	10,000 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma	n		
Overall rates	8/50 (16%)	9/29 (31%)	7/49 (14%)
Adjusted rates	26.3%	73.6%	20.0%
Terminal rates	6/28 (21%)	8/11 (73%)	7/35 (20%)
First incidence (days)	721	687	730 (T)
Life table tests	P=0.251N	P=0.027	P=0.330N
Logistic regression tests	P=0.314N	P=0.003	P=0.385N
Cochran-Armitage test	P=0.468N		
Fisher exact test		P=0.101	P=0.517N
Skin (Subcutaneous Tissue): Fibrosarcoma			
Overall rates	6/50 (12%)	2/49 (4%)	3/50 (6%)
Adjusted rates	18.4%	4.8%	7.1%
Terminal rates	2/28 (7%)	0/29 (0%)	0/35 (0%)
First incidence (days)	508	291	484
Life table tests	P=0.129N	P=0.149N	P=0.179N
Logistic regression tests	P=0.182N	P=0.141N	P=0.217N
Cochran-Armitage test	P=0.170N		
Fisher exact test		P=0.141N	P=0.243N
Skin (Subcutaneous Tissue): Fibroma or Fibrosard	coma		
Overall rates	6/50 (12%)	3/49 (6%)	3/50 (6%)
Adjusted rates	18.4%	8.1%	7.1%
Terminal rates	2/28 (7%)	1/29 (3%)	0/35 (0%)
First incidence (days)	508	291	484
Life table tests	P=0.134N	P=0.256N	P=0.179N
Logistic regression tests	P=0.185N	P=0.252N	P=0.217N
Cochran-Armitage test	P=0.179N		
Fisher exact test		P=0.254N	P=0.243N
Stomach (Forestomach): Squamous Papilloma			
Overall rates	3/50 (6%)	2/49 (4%)	1/50 (2%)
Adjusted rates	10.7%	6.9%	2.9%
Terminal rates	3/28 (11%)	2/29 (7%)	1/35 (3%)
First incidence (days)	730 (T)	730 (T)	730 (T)
Life table tests	P=0.159N	P=0.484N	P=0.228N
Logistic regression tests	P=0.159N	P=0.484N	P=0.228N
Cochran-Armitage test	P=0.223N		
Fisher exact test		P = 0.510N	P=0.309N
All Organs: Hemangioma or Hemangiosarcoma			
Overall rates	3/50 (6%)	0/49 (0%)	0/50 (0%)
Adjusted rates	9.2%	0.0%	0.0%
Terminal rates	1/28 (4%)	0/29 (0%)	0/35 (0%)
First incidence (days)	519	-	-
Life table tests	P=0.031N	P = 0.128N	P=0.097N
Logistic regression tests	P=0.033N	P = 0.124N	P = 0.108N
Cochran-Armitage test	P=0.038N		
Fisher exact test		P=0.125N	P=0.121N

Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of HC Yellow 4 (continued)

	0 ррт	5,000 ppm	10,000 ppm
All Organs: Benign Tumors			
Overall rates	19/50 (38%)	17/49 (35%)	13/50 (26%)
Adjusted rates	60.9%	52.6%	37.1%
Terminal rates	16/28 (57%)	14/29 (48%)	13/35 (37%)
First incidence (days)	508	512	730 (T)
Life table tests	P=0.021N	P=0.374N	P=0.026N
Logistic regression tests	P=0.034N	P=0.465N	P=0.044N
Cochran-Armitage test	P=0.121N		
Fisher exact test		P=0.447N	P=0.142N
All Organs: Malignant Tumors			
Overall rates	16/50 (32%)	12/49 (24%)	16/50 (32%)
Adjusted rates	44.2%	30.9%	37.3%``
Terminal rates	8/28 (29%)	3/29 (10%)	9/35 (26%)
First incidence (days)	449	291	308
Life table tests	P=0.335N	P=0.288N	P=0.354N
Logistic regression tests	P=0.476N	P=0.270N	P=0.485N
Cochran-Armitage test	P=0.544		
Fisher exact test		P=0.272N	P=0.585N
All Organs: Benign or Malignant Tumors			
Overall rates	28/50 (56%)	23/49 (47%)	23/50 (46%)
Adjusted rates	77.7%	60.1%	54.1%
Terminal rates	20/28 (71%)	14/29 (48%)	16/35 (46%)
First incidence (days)	449	291	308
Life table tests	P=0.047N	P = 0.222N	P=0.050N
Logistic regression tests	P=0.061N	P=0.222N	P=0.066N
Cochran-Armitage test	P=0.184N		
Fisher exact test		P=0.242N	P=0.212N

(T)Terminal sacrifice

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.

<sup>b</sup> Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality

<sup>c</sup> Observed incidence at terminal kill

<sup>d</sup> 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 were found at the site in this group

<sup>f</sup> Tissue was examined microscopically only when it was observed to be abnormal at necropsy.

## Table C4

Historical Incidence of Thyroid Gland Follicular Cell Neoplasms in Untreated Male B6C3F, Mice<sup>a</sup>

.

Study		Incidence in Contr	rols
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G	Mason Research Institute		
4-Hydroxyacetanilide	2/49	1/49	3/49
HC Yellow 4	1/47	0/47	1/47
Pentaerythritol tetranitrate	1/46	1/46	2/46
Total	4/142 (2.8%)	2/142 (1.4%)	6/142 (4.2%)
Standard deviation	1.2%	1.2%	2.0%
Range	2%-4%	0%-2%	2%-6%
Overall Historical Incidence			
Total	14/856 (1.6%)	4/856 (0.5%)	18/856 (2.1%)
Standard deviation	1.7%	0.9%	1.8%
Range	0%-4%	0%-2%	0%-6%

<sup>a</sup> Data as of 3 April 1991

# Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of HC Yellow 4<sup>a</sup>

	0	ppm	5,00	0 ppm	10,00	0 ppm
Disposition Summary		. <u></u>				
Animals initially in study	70		70		70	
5-month interim evaluation	10		10		10	
5-month interim evaluation	10		10		10	
Early deaths						
Natural deaths	14		10		5	
Moribund kills	8		10		9	
Accidental death					1	
urvivors						
Terminal sacrifice	28		29		35	
Missing			1			
Animals examined microscopically	50		49		50	
Alimentary System						
Gallbladder	(39)		(9)		(46)	
Inflammation, chronic	3	(8%)			4	(9%)
ntestine small, ileum	(41)		(14)		(45)	. ,
Hyperplasia, lymphoid	1	(2%)	``'			
.iver	(49)		(22)		(48)	
Basophilic focus	()		()		1	(2%)
Clear cell focus	1	(2%)				
Eosinophilic focus					1	(2%)
Infarct			1	(5%)		. ,
Necrosis	9	(18%)	4	(18%)	2	(4%)
Thrombus		. ,	1	(5%)		
ancreas	(45)		(16)	. ,	(49)	
Inflammation, chronic	16	(36%)	ì	(6%)	<b>`</b> 11	(22%)
Vacuolization cytoplasmic	12	(27%)	2	(13%)	8	(16%)
Duct, dilatation		. /		. ,	1	(2%)
alivary glands	(50)		(17)		(49)	. ,
Inflammation, chronic active	33	(66%)	ìή	(41%)	<b>`2</b> ĺ	(43%)
stomach, forestomach	(46)	. /	(19)	. ,	(48)	. ,
Acanthosis	ì	(2%)			. ,	
Diverticulum	1	(2%)				
Hyperkeratosis	1	(2%)		•		
Stomach, glandular	(46)		(16)		(47)	
Hyperplasia			í í	(6%)		
Inflammation, chronic	9	(20%)	1	(6%)	8	(17%)
Mineralization	2	(4%)	1	(6%)	4	(9%)
Footh	(9)		(1)		(6)	
Dysplasia	`9́	(100%)	1	(100%)	5	(83%)
Cardiovascular System					<u> </u>	
Heart	(50)		(17)		(49)	
Absons	(30)	(2%)	(1)		()	
Inflammation, chronic	8	(16%)			7	(14%)
initiation, entoine	0	()				()

#### Lesions in Male Mice

### Table C5

Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of HC Yellow 4 (continued)

	٥	) isisuu	5,0	CO ppm	10,0	CO ppm
Endocrine System						
Adrenal gland, cortex	(50)	1	(17)		(48)	
Hyperplasia	ì	(14%)	1	(6%)	7	(15%)
Adrenal gland, medulla	(50)		(16)		(47)	(1070)
Hyperplasia	í	(2%)			2	(4%)
Islets, pancreatic	(45)		(15)		(49)	
Hyperplasia	8	(18%)				
Pituitary gland	(38)		(13)		(40)	
Pars distalis, cyst	1	(3%)	1	(8%)		
Pars distalis, hyperplasia	10	(26%)	1	(8%)	6	(15%)
Thyroid gland	(47)		(48)		(49)	
Inflammation, chronic			7	(15%)	29	(59%)
Folincie, cyst					2	(4%)
Follicle, inflammation, acute			1	(2%)		
Follicie, pigmentation			44	(92%)	48	(98%)
Follicular cell, hyperplasia			27	(56%)	41	(84%)
Interatitive pigmentation			44	(92%)	49	(100%)
merstitum, pigmentation			42	(88%)	49	(100%)
General Body System None						
Genital System						
Epididymis	(50)		(47)		(49)	
Granuloma sperm	ì	(2%)	~ /		1	(2%)
Inflammation, chronic active	16	(32%)	13	(28%)	13	(27%)
Penis	(5)	. ,	(8)		(4)	
Inflammation, chronic active	3	(60%)	4	(50%)	ź	(50%)
Preputial gland	(9)		(11)	. ,	(6)	
Abscess	3	(33%)	3	(27%)	ĺ	(17%)
Inflammation, chronic active	5	(56%)	8	(73%)	4	(67%)
Duct, dilatation	1	(11%)				
Prostate	(47)		(15)		(45)	
Inflammation, chronic active	34	(72%)	7	(47%)	20	(44%)
Information changes at	(49)		(21)		(49)	
Testes	11	(22%)	4	(19%)	14	(29%)
Succession and the second seco	(50)		(17)		(49)	
Germinal enithelium signt cell			1	(6%)	1	(2%)
Germinal epithenum, grant cen			. 1	(6%)	1	(2%)
Hematopoietic System	·····					<u> </u>
Spleen	(49)		(21)		(49)	
Depletion lymphoid	11	(22%)	(21)	(43%)	(40)	(10%)
Hematopoietic cell proliferation	6	(12%)	6	(29%)	5 K	(10%)
Hyperplasia, lymphoid	Ť	()	v	()	1	(2%)
Thymus	(28)		(9)		(29)	(270)
Cyst	8	(29%)	1	(11%)	4	(14%)
#### TABLE C5

Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of HC Yellow 4 (continued)

	0	ррт	5,00	Ю ррт	10,00	0 ppm
ntegumentary System				<u> </u>		
Skin	(49)		(32)		(48)	
Cyst epithelial inclusion Inflammation, chronic active	1 8	(2%) (16%)	4	(13%)	. 5	(10%)
Musculoskeletal System		<u></u>		<u>`</u> a		
Bone	(50)		(39)		(48)	
Joint, tarsal, hyperostosis	17	(34%)	24	(62%)	17	(35%)
Nervous System				······································		
Brain	(50)		(18)		(49)	
Thalamus, mineralization	29	(58%)	. 6	(33%)	25	(51%)
Respiratory System						
Lung	(50)		(29)	•	(49)	
Crystals			1	(3%)	-	
Alveolar epithelium, hyperplasia	1	(2%)			3	(6%)
Bronchiole, epithelium, hyperplasia	(40)		(14)		(47)	(2%)
NUSC Ovet	(47)	(2%)	(14)		(47)	
Inflammation, acute	6	(12%)			3	(6%)
Special Senses System None						
Urinary System				, , ,		
Kidney	(49)		(22)		(49)	
Abscess	2	(4%)			~	(())
Cyst Ukudana on banaia	1	(2%) (2%)			3	(0%) (2%)
Hydronephrosis Inflammation chronic active	1 22	(4%) (78%)	15	(68%)	1	(270) (90%)
Necrosis		(2%)	15	(0070)		(,,,,,)
Vacuolization cytoplasmic	1	(-//)	1	(5%)		
Papilla, mineralization			-		1	(2%)
Renal tubule, mineralization	7	(14%)	2	(9%)	4	(8%)
Urethra	(1)	-	(1)			
Inflammation, chronic active	1	(100%) ·	1	(100%)		
Urinary bladder	(44)		(17)		(50)	(00)
Calculus micro observation only			1	(0%) (12%)	1	(2%)
Inflammation obtains active	20	(64%)	2 5	(12%)	25	(50%)
initiammation, chronic active	28	(04%)	3	(2970)	20	(30%)

<sup>a</sup> Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.

# APPENDIX D SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR FEED STUDY OF HC YELLOW 4

Table D1	Summary of the Incidence of Neoplasms in Female Mice	
	in the 2-Year Feed Study of HC Yellow 4	149
Table D2	Individual Animal Tumor Pathology of Female Mice	
	in the 2-Year Feed Study of HC Yellow 4	152
Table D3	Statistical Analysis of Primary Neoplasms in Female Mice	
	in the 2-Year Feed Study of HC Yellow 4	168
TABLE D4	Summary of the Incidence of Nonneoplastic Lesions in Female Mice	
	in the 2-Year Feed Study of HC Yellow 4	171

### Lesions in Female Mice

# Table D1

Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of HC Yellow 4ª

	Φ	blow	_ <b>5,</b> 0%	naga CO	10,03	9 ppm
	-		· · ·	- <u> </u>		
Disposition Summary		• 1 ar	and the second		-	
Animals initially in study	70	1	70		70	
-month interim evaluation	10		10	•	10	
5-month interim evaluation	10	s. *	10		10	
Early deaths					_	
Natural deaths	4		2		2	
Moribund kills	3		10		5	
Survivors						
Terminal sacrifice	43		. 38		43	
Animals examined microscopically	50		50		50	
Alimentary System						
Gallbladder	(46)		(3)		(48)	
intestine large, cecum	(47)		(3)		(49)	
Intestine large, rectum	(49)		(3)		(47)	
Intestine small, duodenum	(46)		(0)		(50)	
Intestine small, ileum	(45)		(1)		(48)	
Intestine small jejunum	(47)		(41)		(49)	
iver	(50)		(19)		(50)	
Hemangiama	(50)	(2%)	(10)		(50)	
L'ensterellular corgineme	1	(270)				
Henatocellular adenoma	1	(270)	6	(22%)	1	(9%)
Hepatoceniular adenoma multiple	4 1	(070)	0	(33%)	4	(0%)
Hepatocenular agenoma, multiple	1	(2%)	2	(11%)		
riepatociolangiocarcinolia		(2%)	(1)			
Nesentery	(4)		(1)		(1)	
Pancreas	(48)		(3)		(49)	
Salivary glands	(50)		(2)		(50)	
Stomacn, lorestomacn	(49)		(/)	(000)	(50)	
Papilloma squamous	3	(0%)	2	(29%)	1	(2%)
Stomach, giandular	(49)		(6)		(50)	
footh	(2)				(1)	
Cardiovascular System			• i.			
Heart	(50)		(4)		(50)	
	N-7					
Endocrime System						
Adrenal gland, cortex	(50)		(3)		(50)	
Pituitary gland	(42)				(45)	
Pars distalis, adenoma	5	(12%)			1	(2%)
Thyroid gland	(48)		(49)		(50)	

General Body System None

-

Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of HC Yellow 4 (continued)

	0	ppm	5,00	00 ppm	10,00	00 ppm
Genital System						
Ovary	(50)		(47)		(50)	
Cystadenoma	ź	(4%)	• • •		3	(6%)
Granulosa cell tumor benign	1	(2%)			1	(2%)
Teratoma					1	(2%)
Uterus	(50)	• •	(24)		(50)	
Polyp stromal	2	(4%)	1	(4%)	,	·
Sarcoma stromal		· * · · · · · ·			1	(2%)
Hematopoietic System		- <del></del>	, ,		· · ·	
Bone marrow	(50)		·· (3)		(50)	
Osteosarcoma, metastatic, uncertain primary site	()				1	(2%)
Lymph node	(49)		(15)		(49)	
Lymph node, mandibular	(45)		··· (5)		(45)	
Adenocarcinoma, metastatic, harderian gland	ì	(2%)				-
Lymph node, mesenteric	(45)		(10)	·· 2 · · `	(44)	· ·
Spleen	(49)		(17)		(50)	
Hemangiosarcoma, metastatic, skeletal muscle			1	(6%)		
Thymus	(43)		(6)	. μ	(41)	
			······		• • • • • • • • • • • • • • • • • • •	<u>.</u>
Integumentary System	(24)	-	(			.) i
Mammary gland	(31)	( <b>AA</b> )	(2)	(consi	(37)	(0.01)
Adenocarcinoma	1	(3%)	1	(30%)	1	(3%)
SKIN	(30)	۰. ۰	(40)	i.	( <b>UC)</b> 	e e al.
Musculoskeletal System			L	х Ц. Эл		
Skeletal muscle	(2)		(1)		(2)	
Hemangiosarcoma	.,		ì	(100%)		
Osteosarcoma, metastatic, uncertain primary site					1	(50%)
Sarcoma	1	(50%)				
Nomenous Brundan				· · · ·		
Regin	<b>/50</b>		. (5)		(50)	
	(50)		(5)	· · ·	(50)	
Respiratory System						
Lung	(50)		(8)		(50)	
Adenocarcinoma, metastatic, harderian gland	1	(2%)				
Adenocarcinoma, metastatic, mammary gland		,			1	(2%)
Alveolar/bronchiolar adenoma	1	(2%)	2	(25%)	1	(2%)
Alveolar/bronchiolar adenoma, multiple	2	(4%)	•	•		
Alveolar/bronchiolar carcinoma	1	(2%)				
Alveolar/bronchiolar carcinoma, multiple					1	(2%)
Osteosarcoma, metastatic, uncertain primary site					1	(2%)
Mediastinum, alveolar/bronchiolar carcinoma,					-	( <b>AC</b> )
metastatic, lung					1	(2%)
l ma ab aa	740\		(2)		(50)	

122220

Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of HC Yellow 4 (continued)

	Ø	bibuu	5,00	0 ppm	10,00	to ppm
Special Senses System Harderian gland Adenocarcinoma Adenoma	(2) 1 1	(50%) (50%)	(1) 1	(100%)	(2) 1	(50%)
Urinary System Kidney Osteosarcoma, metastatic, uncertain primary site Urinary bladder	(50) (48)		(4) (4)		(50) 1 (49)	(2%)
Systemic Lesions Multiple organs <sup>b</sup> Lymphoma malignant histiocytic Lymphoma malignant hymphocytic Lymphoma malignant mixed Lymphoma malignant undifferentiated cell	(50) 1 1 6 2	(2%) (2%) (12%) (4%)	(50) 1 3 4 6	(2%) (6%) (8%) (12%)	(50) 1 5 2	(2%) (10%) (4%)
Tumor Summary Total animals with primary neoplasms <sup>c</sup> Total primary neoplasms Total animals with benign neoplasms Total benign neoplasms Total animals with malignant neoplasms Total animals with secondary neoplasms <sup>d</sup> Total secondary neoplasms Total animals with malignant neoplasms of uncertain primary site	30 39 21 23 14 16 1 2	 	24 30 13 14 15 16 1 1		20 24 11 13 11 11 3 6	,

<sup>a</sup> Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.

Number of animals with any tissue examined microscopically

<sup>c</sup> Primary tumors: all tumors except metastatic tumors

<sup>d</sup> Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

T	ABLE	<b>D2</b>
д.	ADLC	. Д.

Number of Days on Study Carcass ID Number Alimentary System Esophagus Gallbladder Intestine large Intestine large, cecum			2 6 3 4 5 4	4 6 3 5 2 4	4 6 5 4	5 3 2 5 1 2	5 3 3 4 9	6 2 5 4 4	6 3 4 5	7 3 1 4	7 3 1	7 3 1	7 3 1	7 3 - 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2								
Carcass ID Number Alimentary System Esophagus Gallbladder Intestine large Intestine large, cecum			4 5 4	5 2 4	5 4 4	5 1 2	4 9	4	5	4	4																		
Alimentary System Esophagus Gallbladder Intestine large Intestine large, cecum		<del></del>	5 4	2 4	4	1 2	9 4	4	~	-	-	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4		
<b>Limentary System</b> Esophagus Gallbladder Intestine large Intestine large, cecum							7	5	2	3 1	3 2	3 3	3 4	4 1	4 2	4 3	5 2	5 3	6 1	6 2	4 4	5 1	6 3	7 1	7 2	7 3	8 1	·	
Esophagus Gallbladder Intestine large Intestine large, cecum																													
Gallbladder Intestine large Intestine large, cecum			- +	+	+	+	М	+	+	+	+	+	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+		
Intestine large Intestine large, cecum			+	+	Å	À	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	М	+	+	+	+	+		
Intestine large, cecum			+	+	+	A	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
			. +	· +	Å	A	.+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, colon			+	+	Ā	A	+	+	+	÷	+	+	+	+	+	+	Ň	+	+	+	+	+	+	+	+	+	÷		
Intestine large, rectum			÷	+	- -	A	+	+	+	+	+	+	÷	÷	+	÷	+	+	÷	+	+	÷	+	÷	+	÷	÷		
Intestine small			Ā	1	Δ			Ļ	÷	÷	÷	÷	÷	+	÷	÷	÷	÷	÷	+	÷	+	÷	÷	÷.	÷	÷		
Intestine small duodenum			· 🚡			Δ.		- M	Ť	+	+	+	÷.	+	+	÷	- -	÷	+	÷	+	÷	+	÷	+	÷	+		
Intestine small, ducuenum			A					- T	+ +	т Т	- -	+	т +	1	÷	+	÷	พ่	÷	÷	÷	+	÷	÷	т Т	+	+		
Intestine small, ieiunum			Δ	÷	Δ	Δ.			÷	1	÷	÷	÷.	÷	÷	÷	<u>.</u>	+	÷.	÷	÷	÷	÷	+	÷		÷		
I iver				· •		. <u>А</u>	4	÷	4	1			÷	1	÷	÷.	÷	÷	÷	÷	÷	÷	÷	÷	÷	<u>+</u>			
Hemangioma			· <b>T</b>	т	т	т	Ŧ		x	т	Ŧ	Ŧ	т	<b>T</b>	т	.1	т	T	т	•	Ŧ	r	Ŧ	T.	т	т	T		
Henatocellular carcinoma									Λ												x								
Henatocellular adenoma												x									12		x		x				
Venatocellular adenoma multin	ما											Λ							x				Λ		Λ				
Hepatocenulai auchoma, multip	HC.																		Λ										
Mesenter			м		r						м																		
Bananaa			M	L IVI		а	-		+	т.	TAT I		1	Ŧ	Т	т	+	т	+	т	-	Т	-	Т	-	т	-		
Lancicas Solivoru alondo			, 191 	і т -		· T	т. 	·	т 		т 	т 	т ⊥	Ŧ	т т	т	т _	т 	Ť	т	т 	- T	т 	т 	т 	Ť	т 		
Salivary granus				ਾ	Ţ	· -	Ţ	Ţ		- T	Ŧ	T	T	т 	T	т 1	Ŧ	т т	Ŧ	Ŧ	Ŧ	· I	Ţ	Ť		Ť	Ţ		
Stomacn Stomach fannstannach			+	+	+	· +	Ť	+	+	+	Ť	*	+	+	+	Ŧ	+	Ť	+	Ţ	+	Ţ	+	Ţ	+	T	+		
Stomacn, Iorestomacn			. +	+	+	•	Ť	. <del>.</del>	+	+	M	+	Ŧ	Ŧ	+ v	Ŧ	Ŧ	Ŧ	+	Ŧ	Ŧ	Ŧ	Ŧ	+	Ŧ	Ŧ	Ŧ		
Papilloma squamous															<b>^</b>				•										
Stomach, glandular Tooth			А	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+		
Cardiovascular System								÷																				-	
Heart			+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Endocrine System											·									-									
Adrenal gland			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adrenal gland, cortex			+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adrenal gland, medulla			+	+	+	+	+	+	+	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Islets, pancreatic			M	[+]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Parathyroid gland			+	+	+	+	Μ	M	+	+	Μ	+.	+	М	+	+	М	+	+	+	I	+	М	М	+	Μ	+		
Pituitary gland			+	+		+	+	+	+	+	Μ	M	+	+	М	+	M	+	+	+	+	+	М	+	M	+	+		
Pars distalis, adenoma				x		•	•		•	•			-	-		•			,	•	-			•		•			
Thyroid gland			+	+	+	+	м	+	÷	+	+	+	+	+	+	+	М	+	+	+	+	+	+	·+	+	+	+		

None

+: Tissue examined microscopically A: Autolysis precludes examination

M: Missing tissue I: Insufficient tissue

X: Lesion present Blank: Not examined

### Lesions in Female Mice

Table D2

Individual Animal Tumor Pathology	of Fem	ala	8 ₪	/lico	e îi	n î	he	2-	Ye	81°	Fe	æd	St	tundi	y C	of 1	HC	¥	2110	<b>)</b> %%	4:	0	P	þш	<b>n</b> (	cont	inued)
Number of Days on Study	7 3 2	7 3 5	735	, , ,	7 3 5																						
Carcass ID Number	4 8 2	4 8 3	4 8 4	4 9 1	4 9 2	4 9 3	5 0 1	5 0 2	5 0 3	5 0 4	5 1 1	5 2 1	5 2 2	5 2 3	5 3 1	5 3 2	5 3 3	5 4 2	5 4 3	5 5 3	5 5 4	5 6 1	5 4 1	5 5 1	5	5 5 2	Total Tissues/ Tumors
Alimentary System																_											<u> </u>
Esophagus	+	+	+	+	+	+	+	+	+	+	+	М	: +	+	+	+	+	+	+	+	+	+	H	+ +	ł	+	47
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	Μ	[+]	+	+	+	+	+	+	+	+	-	⊦ -	ł	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4	+ +	F	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	Μ	[ +	+	+	+	+	+	+	+	+	H		ł	+	47
Intestine large, colon	+	+	+	М	+	+	+	+	+	Ŧ	+	М	+	+	+	+	+	+	+	+	+	+	4	+ +	۲	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4	+ -	ł	+	49
Intestine small	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	H	⊢ -	ł	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4	+ -	ŧ.	+	46
Intestine small, ileum	+	÷	+	+	+	+	+	+	+	+	+	+	М	[ + ]	+	+	+	+	+	+	+	+	H	+ -	ł	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	ंन		ł	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4		ł	+	50
Hemangioma																											1
Hepatocellular carcinoma																											1
Hepatocellular adenoma																			Х								4
Hepatocellular adenoma, multiple																											1
Hepatocholangiocarcinoma							Х																				1
Mesentery						+										+											2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	4	⊦ -	+	+	48
Salivary glands	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	⊦ -	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+ -	ŧ.	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	⊦ -	ŧ.	+	49
Papilloma squamous														Х	Х												3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	⊦ -	ł	+	49
Tooth																											2
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+ -	ł	+	50
Endocrime System																									•••••		
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		⊦ ۰	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	⊦ •	+	+	50
Adrenal gland, medulla	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	⊦ -	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+ •	ł	+	49
Parathyroid gland	+	+	Μ	M	+	+	+	М	Μ	( +	+	+	+	+	+	+	+	+	+	+	+	+	-	۰ ۱	ŧ	+	37
Pituitary gland	+	+	+	+	+	+	+	+	М	[ +	+	+	+	+	+	+	+	+	+	+	+	+	· -	+ •	+	+	42
Pars distalis, adenoma								Х		Х										Х	X						5
Thuroid aland	+	+	+	+	+	+	+	+	4	+	+	+	+	-	+	+	+	+	+	.+	+	+		+ •	÷	+	48

None

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TABLE D2

Individual Animal Tumor Pathology o	of Fen	181	e n	110	e n		ne	2-	Ye	ar	Fe	ea	St	uđ	y o		1Ç	Y	ello	)W	4:	U	P	pm	(00	ntinued)
· ·	2	4	4	5	5	6	6	7.	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	6	6	6	3	ž	2	ž	3	3	3	3	3	3	3	3	3	à	3	3	3	3	3	3	4	3	
amon of Days on Stady	3	3	6	2	3	5	4	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	
	<u> </u>						;				_							_	_		_					
	4	5	5	5	4	4	5	4	4	<b>4</b> .	4	4	4.	4	4	4	4	4	4	4	4	4	4	4	4	
Carcass ID Number	5	2	4	1	9	4	6	3	3	3	3	4	4	4	5	5	6	6	4	5	6	7	7	7	8	
	4	4	4.	2	4.	5	2	1.	2	3	4	1	2	3	2	3	1	2	4	1	3	1	2	3	1	
Conital System				_				•••						_		_					_					
	т	<u>т</u>	<b>т</b>	Ŧ	<b>–</b>	Ŧ	-	ъ	Ŧ	Ŧ	Т	ъ	ъ	+	Ŧ	1	ъ	Ŧ	ъ	Ŧ	+	-		. ــــــــــــــــــــــــــــــــــــ	т.	
Ovstadenoma	•	-	1	'	т		1	T	•	T	•	ľ	•	•	'		•	•	'		'	r	'	'	x	
Granulosa cell tumor benign																							x		~	
Oviduct	Δ																					. '	~			
Literus		<u> </u>	<u>ـ</u>	т	Т	Ŧ	т	т	Т	ъ	т		Т	Т	т	ж	т	+	Т	<u>т</u>	Т	<u>т</u>			+	
Polyp stromal	т	т	т	т	т	т	т	т	т	т	т	т	Ŧ	-1	т	T	т	т	x	т	т	Ŧ	т	т	т	
																									••	<u> </u>
Hematopoietic System																						-				
Bone marrow	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	1	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	Μ	+	+	+	+	+	+	+	+	_ <del>,+</del>	- +	+	I	
Adenocarcinoma, metastatic, harderian gland				x														• • *								
Lymph node, mesenteric	М	(+	+	+	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	Μ	( <del>+</del> 1	+	Μ	·
Spleen	Α	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	
Thymus	Μ	M	+	М	Μ	+	+	+	÷	+	+	+	Μ	+	+	+	+	+	+	+	+	+	+	+	+	
Internation: Curtom															,		• -							<del></del>		<del></del>
Mammun aland	·	т	Т	т	м	ш	м	м	т	м	м	м	ъ	<u>т</u>	Т	м	Т	т	<b>н</b>	Ŧ	<b>ж</b>		ند سر		Т	· . · ·
	.т	T	т.	т	141	v	TAT	141	т	141	141	141	т	т	т	141	т	т	т	т	т	т	т	т	т	
Adenocarcinoma						Â.									,											
Skin	+	+	+	Ŧ	+	+	Ŧ	ar.	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	Ţ	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	Ŧ	т	Ŧ	т	Ŧ	Ŧ	
										-,																
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Skeletal muscle			+		+																					
Sarcoma					x																					
Nervous System																	-			_						
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
													_							÷						`
kespiratory System																										÷
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma, metastatic, harderian																			15 V		-11			•		,
gland				х																						
Alveolar/bronchiolar adenoma																										
Alveolar/bronchiolar adenoma, multiple																										
A hard and man abiation annotation															_						÷	_	23			
Alveolar/oronchiolar carcinoma																		н.								
Aiveolar/oronchiolar carcinoma Nose	+	· +	+	+	+	+	+	+	+	+	+	+	+	+	м	+	+	т	+	-+-	M	1 +	+	• +	-	

### Lesions in Female Mice

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TABLE D2 \_

un ----

Individual Animal Tumor Pathology	of Fem	næl	<b>e</b> R	Лic	æ i	m (	he	2-	Ye	ar	Fe	æd	St	und	y o	of I	HC	Y	ella	<b>DW</b>	4:	0	PI	) Mile Mile Mile Mile Mile Mile Mile Mile	(00	ntinu	.ed)
Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7. 3 2	7 3 2	7 3 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		
Carcass ID Number	4 8 2	4 8 3	4 8 4	4 9 1	4 9 2	4 9. 3	5 0 1	5 0 2	5 0 3	5 0 4	5 1 1	5 2 1	5 2 2	5 2 3	5 3 1	5 3 2	5 3 3	5 4 2	5 4 3	5 5 3	5 5 4	5 6 1	5 4 1	5 5 1	5 5 2		Total Tissues/ Tumors
Genital System Ovary Cystadenoma Granulosa cell tumor benign Oviduct	· +	+	+	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50 2 1
Uterus Polyp stromal	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ ,		50 2
Hematopoietic System Bone marrow Lymph node Lymph node, mandibular	+ +	+ + +	+++++++	+++++++++++++++++++++++++++++++++++++++	+ + +	++++	+ + M	++++	+ + +	+ + M	+++++++++++++++++++++++++++++++++++++++	++++	+++++	+++++	+++++	++++	+ + M	+++++	++++	+++++	+++++	+++++	+++++++++++++++++++++++++++++++++++++++	+++++++++++++++++++++++++++++++++++++++	+++++		50 49 45
Adenocarcinoma, metastatic, harderian gland Lymph node, mesenteric Spleen Thymus	+ + +	· + · +	++++++	+++++++++++++++++++++++++++++++++++++++	+ + M	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	+ + +	M + +	+ ; + +	+ + +	+ + +	+ + M	+ +	+ + +	+ + +	+ + +	+ +	+++++	++++	+ + +		1 45 49 43
Integumentary System Mammary gland Adenocarcinoma Skin		1 + · +	₩ +	[ + · +	+	M +	+	+	M +	+ +	M +	: M	( M	ім +	( M +	+	+++	+	++	++	+	++	м +		I M +		31 1 50
Musculoskeletal System Bone Skeletal muscle Sarcoma	+	• +	+	· +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50 2 1
Nervous System Brain	+	· +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Respiratory System Lung Adenocarcinoma, metastatic, harderian gland Alveolar/bronchiolar adenoma Alveolar/bronchiolar adenoma, multiple Alveolar/bronchiolar carcinoma	+	. +		· +	+	+	+	+ x	+ x	+	+	+	+	+	+	+	+	+	+	+ x	+	+ x	+	+	, +		50 1 1 2 1
Nose Trachea	+ +	· + - +	+	• +	+	+ +	+ +	++	+ +	+ +	++	+ +	M +	[ + +	+ +	+ +	+ .+	+ +	+ +	+	+	+	• + • +	+	• + • +		47 49

TABLE	D2
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Individual Animal Tumor Pathology (	of Fen	nak	e N	lic	e iı	n th	1e	2-}	(ea	r Fe	ed	S	lud	y o	fł	ĮĊ	Y	ello	W	4:	Ģ	pp	m	(00)	ntinue	ed)
Number of Days on Study	2 6 3	4 6 3	4 6 6	5 3 2	5 3 3	6 2 5	6 3 4	7 3 : 1 :	7 7 3 3 1 1	7733	7 3 1	7 3 2														
Carcass ID Number	4 5 4	5 2 4	5 4 4	5 1 2	4 9 4	4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	5 6 2	4 4 3 : 1 :	4 4 3 3 3	4 3 3 3 4	4 4 1	4 4 2	4 4 3	4 5 2	4 5 3	4 6 1	4 6 2	4 4 4	4 5 1	4 6 3	4 7 1	4 7 2	4 7 3	4 8 1		
Special Senses System Eye Harderian gland Adenocarcinoma Adenoma	-		•	+ + X	•		•.					-							·· ,			•	•.			
Urinary System Kidney Urinary bladder	+ A	· +	+ A	+++	+ + +	+	++	+	+ ; + ;	+ + + +	+++	 + +	++	+++	;+ +	++++	+ +	+++	+++	+ +	+ +	++	++++	+++		
Systemic Lesions Multiple organs Lymphoma malignant histiocytic Lymphoma malignant lymphocytic Lymphoma malignant mixed Lymphoma malignant undifferentiated cell type		• +	+ x x	+ X	÷	+	+ X			+ +	+	·+	+	+	+ x	+	+ x	+	, +	+	+	+	+	ţ.		

Table D2 Individual Animal Tumor Pathole	ogy of	Fen	nalo	e R	Mic	œi	im (	the	2	-Ye	-81°	Fe	ed	St	nd	уo	K I	HC	: ¥	e]]	) W	4:	0	P	pm	(00	ontinu	ed)
Number of Days on Study		7 3 2	7 3 5	7 3 5	7 3 5																							
Carcass ID Number	·	4 8 2	4 8 3	4 8 4	4 9 1	4 9 2	4 9 3	5 0 1	5 0 2	5 0 3	5 0 4	5 1 1	5 2 1	5 2 2	5 2 3	5 3 1	5 3 2	5 3 3	5 4 2	5 4 3	5 5 3	5 5 4	5 6 1	5 4 1	5 5 1	5 5 2		Total Tissues/ Tumors
Special Senses System Eye Harderian gland Adenocarcinoma Adenoma																								+ ,x				1 2 1 1
Urinary System Kidney Urinary bladder	· ·	+	• +	+	· +	+ +	+++	+ +	++	· + · +	++++	+++	+ +	++	+ +	+ +	+ +	, + +	++	++	+ +	+ +	+	+	· + · +	• + • +		50 48
Systemic Lesions Multiple organs Lymphoma malignant histiocytic Lymphoma malignant hymphocytic Lymphoma malignant mixed Lymphoma malignant undifferentia cell type	ited	+ X	- + :	+	· +	+	+	+	+	• +	• +	+	+ x	+	+	+	+	+ x	+	+	+ x	+	• +	+	- +	· +		50 1 1 6 2

TABLE D2

																							_				 
Number of Days on Study	1 9 2	5 1 9	5 9 2	6 4 7	6 6 4	6 7 6	6 8 2	6 8 8	7 0 4	7 1 1	7 1 8	7 2 2	7 3 0														
Carcass ID Number	6 9 5	7 0 5	5 7 5	6 2 2	6 0 3	5 9 4	6 8 4	6 3 2	5 8 4	7 0 4	5 9 3	7 0 3	5 7 1	5 7 2	5 7 3	5 7 4	5 8 1	5 8 2	5 8 3	5 9 1	5 9 2	6 0 1	6 0 2	6 1 2	6 1 3		
Alimentary System		_			_			_			_						_									_	 
Esophagus	М	[+]	+																								
Galibladder	+	+	+																							;	
Intestine large	+	÷+	+																								
Intestine large, cecum	+	+	+			•																					
Intestine large, colon	+	+	+																								
Intestine large, rectum	+	+	+																								
Intestine small	+	+	+					+		+				+		+						+					
Intestine small, duodenum	+	+	+					+		+				+													
Intestine small, ileum	+	+	+					+		+				+		+						+					
Intestine small, jejunum	м	[+]	+					+		+				+													
Liver	+	+	+		+			+	+	+	+								+					+	• +		
Hepatocellular adenoma	-	•	-		·					-														X	ĊX		
Hepatocellular adenoma, multiple																			x							•	
Mesentery		+																		•							
Pancreas	+	+	+																								
Salivary glands	 M	, + 1	+																								
Stomach	+		+			+					+												+	-			
Stomach forestomach			_			+					÷.																
Papilloma squamous	1	1	'			1					×												'				
Stomach, glandular	+	+	+			+																	+	•			
Cardiovascular System Heart	+	+	+		+																				<u></u>		
Endocrine System								_									_			_							
Adrenal gland	+	+	·+																								
Adrenal gland, cortex	+	+	+																								•
Adrenal gland, medulla	+	+	+																								
Islets, pancreatic	+	+	+																								
Parathyroid gland	+	+	M	ſ																							
Pituitary gland	M	I M	I M	[																							
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	<b>í</b> +	• +	-	
General Body System None									_																		
Genital System										-																	
Ovary	+	+	+	• +	+	M	[ +	+	• +	+	+	+	+	+	+	+	+	+	+	+	- +	· +	- +	• +	- +	-	
Uterus	+	+	+	•	+	+	+		,	+			+	+	+			-	,		+		+		+	-	
Polyp stromal	·	•			•		•							•							x						
· · · · · · · · · · · · · · · · · · ·	·																						_				 

Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of HC Yellow 4: 5,000 ppm

Table D2

ol Fer	nale	<b>e</b> P	Mic	e i	n î	he	2-	Ye	ar i	Fe	ædi	St	ud	y C	of I	HC	Y	ello	<b>D</b> #V	4:	5	,M	20 j	ppm	(continued)
7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
6 2 1	6 3 1	6 3 3	6 1 1	6 4 1	6 4 2	6 5 1	6 5 2	6 5 3	6 5 4	6 6 1	6 6 2	6 6 3	6 6 4	6 7 1	6 7 3	6 7 4	6 8 1	6 8 2	6 8 3	6 9 1	6 9 2	6 9 3	7 0 1	7 0 2	Total Tissues Tumor
7	+ + { X	+++++	+			+ x							+				+ + + + + X	+ X + + X +			++++				2 3 3 3 3 11 9 11 8 18 6 2 1 3 2 7 7 7 2 6
																									4
	+ 4	<u> </u>		+	- +	+	+		+	+		· .	· -+	+	+	- +	+	· +		- +	4			+ +	3 3 3 2 49
]	M +		+ +	 <b>1</b>	+ +	• +	 + +	+	+	+	• +	· +	+	- +	- +	- +	+	- 4		+ +			- P	ví + + +	47 24
		7       7         3       3         0       0         6       6         2       3         1       1         +       +         +       +         +       +         +       +         +       +         +       +         +       +         +       +         +       +         +       +         +       +         +       +         -       -	7       7       7         3       3       3         0       0       0         6       6       6         2       3       3         1       1       3         +       +       +         +       +       +         +       +       +         +       +       +         +       +       +         M       +       -	$ \begin{array}{c}             7 & 7 & 7 & 7 \\            $	$\begin{array}{c} \text{Of } \mathbf{F} \text{ climate founde for a } \mathbf{f} \\ \hline 7 & 7 & 7 & 7 \\ 3 & 3 & 3 & 3 \\ 0 & 0 & 0 & 1 & 1 \\ \hline \\ 6 & 6 & 6 & 6 & 6 \\ 2 & 3 & 3 & 1 & 4 \\ 1 & 1 & 3 & 1 & 1 \\ \hline \\ \hline \\ & & + \\ $	7 $7$	7       7	7 $7$	$\begin{array}{c} \text{ for } \textbf{F} \text{ climate for a de } \textbf{for } f$	$\begin{array}{c} \text{ for } \mathbf{f}  fermine for new for the line 2 = 1 (can for the line for the line 2 = 1 (can for the line for the line 2 = 1 (can for the line for the li$	$\begin{array}{c}  the matrix for the formed for the limit the 2-1 team if the form of $	$\begin{array}{c}  the finite formed form the constraints of the form of th$	t       +         7	$\begin{array}{c} \text{OI}  \text{prelimine prince in the 2 = 1 can precess solution} \\ \hline 7 & 7 & 7 & 7 & 7 & 7 & 7 & 7 & 7 & 7$	$ \begin{array}{c}  & \text{ for $\mathbf{p}$ relimine poince $\mathbf{n}$ rest in $\mathbf{p}$ constraints $\mathbf{y}$ rest in $\mathbf{p}$ constraints $\mathbf{y}$ rest in $\mathbf{p}$ constraints $\mathbf{y}$ rest in $\mathbf{p}$ rest in $\mathbf{p}$ constraints $\mathbf{y}$ rest in $\mathbf{p}$ re$	To i premiane relation precision precision of the second status of the second statu	101       F CHILBRINE FUNCE INTERPOLATION FOR A Statuy of The         7	1       Feinesine Function for 2 = 1 cent precision Soundy of ArC       1         7       8       1<	101 Freemand Pointer in take 2 Freem Freed Standy of Interference         7       8       1	1       1	Image: control of the state of the stat	T       T	Y = Pellinalle value 2 = 1 cell       Peellinalle value 2 = 1 cell       Peellinalle value 2 = 1 cell       Y = 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1	T       T	10       Permane price in the 20 permin free constantly on the feature of the perminent of the permine

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TABLE D2

Individual Animal Tumor Pathology o	f Fen	nal	e N	/ic	e i	n t	the	2-	Ye	ar	Fe	ed	St	tud	уо	<u>f</u> ]	HC	Y	ello	)W	4:	5,	00	0 J	pm	l (con	tinue	(b:
Number of Days on Study	1 9 2	5 1 9	5 9 2	6 4 7	6 6 4	6 7 6	6 8 2	6 8 8	7 0 4	7 1 1	7 1 8	7 2 2	7 3 0															
Carcass ID Number	6 9 5	7 0 5	5 7 5	6 2 2	6 0 3	5 9 4	6 8 4	6 3 2	5 8 4	7 0 4	5 9 3	7 0 3	5 7 1	5 7 2	5 7 3	5 7 4	5 8 1	5 8 2	5 8 3	5 9 1	5 9 2	6 0 1	6 0 2	6 1 2	6 1 3			-
Hematopoietic System																_									,			
Bone marrow	+	+	+																									
Lymph node	+	+	+	.+	+			+	+	+	+		+		+		+	Μ			+	+						
Lymph node, mandibular	+	М	+	+	+					+											Μ							
Lymph node, mesenteric	M	[ +	М	+				+	+	+			+		+						+	+						
Spleen	M	[ +	+	+		+		+	+	+	+				+	+	+	+			+	+						
Hemangiosarcoma, metastatic, skeletal												•																
muscle			Х																									
Thymus	М	[ +	М	+					+					+		+												
Integumentary System																												
Mammary gland	м	M	+					+																				
Adenocarcinoma								х																				
Skin	Μ	[ +	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+		+	+	+			
Musculoskeletal System																									_			
Bone	+	+	+													+												
Skeletal muscle			+																									
Hemangiosarcoma			X																									
Nervous System													•															
Brain	+	+	+		÷						+																	
Respiratory System																												
Lung	+	+	+				+				+	+											+					
Alveolar/bronchiolar adenoma							х																Х					
Nose	+	+	+																									
Trachea	+	+	+																									•
Special Senses System			,																						_			
Harderian gland																·				+								
Adenoma																				х								
Urinary System																												
Kidney	+	+	+						+																			
Urinary bladder	+	+	+		+										•													
Systemic Lesions																						•						
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Lymphoma malignant histiocytic					Х																							
Lymphoma malignant lymphocytic				Х							X											<i></i>						
Lymphoma malignant mixed				,						X							х					X		,				
Lymphoma malignant undifferentiated		v						v	v												v			-				
cen type		Х						•	л												Λ							

#### Table D2

Individual Animal Tumor Pathology	ol F	em	ale	R	/lico	e in	n ·	the	2	-Y0	es l	F	BBC	1 S	tu	dy	Ø	B	IC	¥	ella	099	4:	5	<b>,</b> M	M	pp	🏛 (cont	inued)
Number of Days on Study		7 3 0	7 3 0	7 3 0	7 3 1	7 3 3 1	7 <sup>-</sup> 3 : 1 :	7 3 1																					
Carcass IID Number		6 2 1	6 3 1	6 3 3	6 1 1	6 4 1	6 4 2	6 5 1	6 5 2	6 5 3	6 5 4	6 6 1	6 6 2	6 6 3	6 6 4		5 ( 7 <sup>-</sup> 1 :	6 7 3	6 7 4	6 8 1	6 8 2	6 8 3	6 9 1	6 9 2	6 9 3	7 0 1	7 0 2	T T T	'otal 'issues/ 'umors
Hematopoietic System															-														
Bone marrow																													3
Lymph node				+																									15
Lymph node, mandibular				M																									5
Lympn node, mesenteric Spleen				+						ـ	L										ъ								10
Hemangiosarcoma, metastatic, skeletal				т						т											Ŧ								1
Thymus								+																	R	1			6
Integumentary System Mammary gland Adenocarcinoma Skin		.+	м		+	+	+	• +	+	+	-	+	 · 4	⊦ +		+			_	+	+	+	+	+	+		-		2 1 40
Musculoskeletal System Bone Skeletal muscle Hemangiosarcoma																													4 1 1
Nervous System Brain																													5
Respiratory System Lung Alveolar/bronchiolar adenoma Nose Trachea				<u> </u>																		-					+		8 2 3 3
Special Senses System Harderian gland Adenoma													_																1 1
Urinary System Kidney Urinary bladder																													4 4
Systemic Lesions Multiple organs Lymphoma malignant histiocytic Lymphoma malignant lymphocytic Lymphoma malignant mixed Lymphoma malignant undifferentiated cell type		+	+	+	+	+	+	- + X	-+	⊦ 4	⊦ +	- +	- 4	⊦ ⊣	<b>-</b> -	<b>+</b> - ·	Ŧ	+	+	+ x	+	+		• +	· -		+ +	F :	50 1 3 4
cen type				Λ	•																			~	•				v

TABLE D2

Individual Animal Tumor	Pathology	of Fer	nal	e I	Mic	e i	n t	he	2-	Ye	ar	Fe	ed	S	tud	y o	of I	HC	Y	ell	ow	4:	1	0,0	00	PI	om	
Number of Days on Study		5 5 4	5 6 1	5 7 8	6 1 0	6 1 3	6 4 7	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0		
Carcass ID Number		7 5 4	. 8 2 5	8 4 4	8 0 3	8 2 4	8 3 4	7 8 2	7 1 1	7 1 2	7 1 3	7 2 1	7 2 2	7 3 1	7 3 2	7 3 3	7 3 4	7 4 1	7 4 2	7 4 3	7 4 4	7 4 5	7 5 1	7 5 2	7 5 3	7 6 1	• • •	
Alimentary System																												
Esophagus		N	( +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Gallbladder		· -	- +	+	+	+	+	+	М	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large			• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, cecum		-	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, colon		-	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine large, rectum		4	- +	+	+	+	+	+	+	+	+	+	Μ	[+]	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small		-	• +	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	. +	+	+	+	+	+	· +	+		
Intestine small, duodenum		-	- +	+	+	÷	+	+	+	+	+	+	. +	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small, ileum		-	• +	+	Μ	+	+	+	Μ	: +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Intestine small, jejunum		. H	·A	+	+	+	+	+	+	+	+	+	+	+	+	. +	+	+	+	+	+	+	+	+	+	+		
Liver			• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Hepatocellular adenoma												Х								Х								
Mesentery			•																									
Pancreas		-	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +		
Salivary glands		-	• +	+	+	+	+	` <b>+</b>	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Stomach			• +	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	+	+		
Stomach, forestomach		-	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Papilloma squamous																												
Stomach, glandular		-	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Tooth		4	-																									
Cardiovascular System														•														 
Heart		4	+	.+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Endogrine System								•			•					~												
Adrenal gland		L	. بر	.ر		ъ	Ŧ	Ŧ	+	Ŧ	L.	-		<u>ـ</u> ـ			L	L.	L.			L	ىد.		L	. <b>.</b>		
Adrenal gland contex			۳ د .	т 	т 	т	т ⊥	т ⊥	т 	T _	T T	- -	- -	- -	т Т	т Т	T 1	т Т	т Ц	т –	т ц	т 	۳ بد	T L	۳ ــــ	т 		
Adrenal gland medulla		ר : لـ				- -	т —	т —	- -	- -	+ +	- <del>-</del>	- +	- +	- -	- -	+	- +	Ň	т Г –	т 	- + -	- <del>-</del>	, +	· +			
Islets nancreatic		ר لہ		- <del>-</del>	- <del>-</del>	+	+	- <del>-</del>	+	+	+	- -		- +	- <del>-</del>	- <del>-</del>	- <del>-</del> +	+	+		, 1	, _	- <del>-</del>	+				
Parathyroid gland		-	. M	r M	г <del>т</del> Г <del>т</del>	÷	+	м	+	+	M	· +	+	м	, ,	, +	Ń	, 1	Ņ	, 1 +		Ň	г. 4- Т	4				
Pitnitary gland	-	-		۱۹۱		+	+	+	+	+	+	+		M	 r .	+	14.	+	4							. Ń	ſ	
Pars distalis adenoma		· ·	r	T	Ŧ			•				•		141	• •	•	'		'		ľ	•		•	'	14	-	
Thyroid gland		• •	- +	+	+	+	+	<b>;</b> +	+.	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	+	• +	• +	•	
General Body System None						_													• •									

#### Lesions in Female Mice

Table D2

Individual Animal Tumor Pathology	of Fem	ala	• №	lic	e in	nî	he	2-`	Ye	r.	Fe	ed	St	nd	уc	of I	IC	Y	ella	<b>)</b> WV	4:	1	0,0	XX	P	m (continued)
	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
• •	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	7	7	7	7	7	7	7	7	7	8	8	8	8	8	8	8	8	.8	8	8	8	8	8	8	8	Total
Carcass IID Number	6	6	7	7	7	7	8	9	9	0	0	1	1	1	1	1	2	2	2	3	3	3	4	4	4	Tissue
	2	3	1	2	3	4	1	1	2	1	2	1	2	3	4	5	1	2	3	1	2	3	1	2	3	Tumor
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	М	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	· +	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	М	( +	+	+	+	+	49
Intestine large, rectum	M	(+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	М	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• +	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	• +	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• +	50
Hepatocellular adenoma																			Х				X	:		4
Mesenterv																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Μ	( +	+	+	• +	• +	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	• +	• +	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• +	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	• +	• +	50
Papilloma squamous		Х																								1
Stomach, glandular	+	+	+	+	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• +	50
Tooth																										1
Cardiovascular System													_													
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	+	• +	- +	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	- +	+	- +	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	+	+	- +	50
Adrenal gland, medulla	M	1+	М	[+]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	- +	+	• +	- +	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	+	M	1+	• +	+	+	- +	49
Parathyroid gland	+	+	+	+	I	+	Ι	+	Ι	+	М	M	: +	M	Ι	+	М	[ +	+	M	[ +	- R	1 +	- R	4 +	31
Pituitary gland	Ι	+	+	+	+	+	+	М	M	+	+	+	+	+	+	+	+	+	+	+	• •	- +	- +		- +	45
Pars distalis, adenoma																									Х	1
Thyroid gland	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- 4	- +	. 4		- +	50

None

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TABLE D2

Individual Animal Tumor Pathology	of Fer	nal	e I	Mic	e iı	n t	he	2-	Ye	ar	Fe	æd	St	ud	y o	<b>f</b> ]	HC	Y	elle	0W	4:	• 1	.0,0	000	ppn	1 (continue
Number of Days on Study	5 5 4	5 6 1	5 7 8	6 1 0	6 1 3	6 4 7	7 2 9	7 3 0	•																	
	7	. 8	8	8	8	8	7	7	7	7	7	7	7	7	7	7	7	7	7.	7	7	7	7	7	·7.	
Carcass ID Number	5	25	4 4	0 3	2 4	3 4	8 2	1 1	1 2	1 3	2 1	22	3 1	32	3 3	3 4	4 1	4 2	4 3	4 4	4 5	5 1	5 2	5 3	6 1	
Genital System	_																									
Ovary	+	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• +	+	
Cystadenoma		•	-		,	•		•	-	-			-				-	-	-			x	x x			
Granulosa cell tumor benign																										
Teratoma																										
Literus	-	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	+	+	
Sarcoma stromal				•	·		•	•					-	-	-				X							
Hematopoietic System																				,						
Bone marrow	+	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	• +	+	
Osteosarcoma, metastatic, uncertain																										
primary site		x																								
Lymph node	-	- +	+	+	+	+	+	М	(+	+	+	+	+	+	+	+	+	+	+	+	+	+	- +	• +	+.	
Lymph node, mandibular	4	- +	+	+	+	+	+	М	E +	+	м	( ÷	+	+	+	+	+	+	+	+	+	+	- +	• +	+	
Lymph node, mesenteric	-	- +	+	+	+	+	+	Μ	(+	+	+	+	+	+	+	+	+	+	+	+	+	+	- 4	- +	+	
Spleen	-	- +	+	. <u>+</u>	+	+	+	+	. +	+	+	÷	+	+	+	+	+	+	+	+	• +		- 4	• • +	+	
Thymus	4	- +	+	M	M	÷	÷	M	(+	+	+	÷	+	+	+	M	M	+	+	+	+	+	• +	• +	÷	
Integumentary System			,										÷	2			•									
Mammary gland	N	1 +	+	+	Μ	Μ	+	Μ	[ M	M	[ +	+	+	+	М	+	+	Μ	[+]	+	+	· +	- +	• +	+	
Adenocarcinoma		,									,															•
Skin	-	- +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	÷	+	+	+	+	+	- +	• +	+	
Musculoskeletal System							;	:					,													
Bone	-	+ +	+	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	· - +	- +	- +	+	
Skeletal muscle	-	+ +																								
Osteosarcoma, metastatic, uncertain																										
primary site		х																								
Nervous System															:		_								÷	
Brain	-	+ +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• +		- +	+	

Individual Animal Tumor Pathology	o (	Fem	ala	e R	Aic	e ii	n, i	the	2.	Ye	<b>8</b> ľ	Fe	æd	S	tud	У¢	dî 1	HC	: ¥	ell	0W	4:	1	0,0	MM		ppm	1 (continued)
Number of Days on Study		7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0		7 3 0	
Carcass ID Number		7 6 2	7 6 3	7 7 1	7 7 2	7 7 3	7 7 4	7 8 1	7 9 1	7 9 2	8 0 1	8 0 2	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 3 1	8 3 2	8 3 3	8 4 1	8 4 2	1	8 4 3	Total Tissues/ Tumors
Gemital System Ovary Cystadenoma Granulosa cell tumor benign Teratoma Uterus Sarcoma stromal		+	++	+	+	+	+	+ X +	++	+	+	+	+	+ x +	+ x +	+	+ +	+	+	+	+	+	+	+	• •		+	50 3 1 1 50 1
Hematopoletic System Bone marrow Osteosarcoma, metastatic, uncertain primary site Lymph node Lymph node, mandibular Lymph node, mesenteric Spleen Thymus		+ + M + +	+ +++++	+ + M + + + + + + + + + + + + + + + + +	+ + M + + +	+ ++++++	+ + + I + +	+ +++ + M	+ ++ + M + +	+ + + + + + + + + + + + + + + + + + + +	+ ++ M + +	+ + + + + + + + +	+ + + I M	+ + + + + + + + + + + + + + + + + + + +	+ +++++	+ +++++	+ +++++++++++++++++++++++++++++++++++++	+ ++ +++ M	+ + + + + + + + + + + + + + + + + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + M +	+ + + + +	+ + + + + + + + + + + + + + + + + + + +	+ + + + + +	· + · + · + · + [ +		+ + + + + + + + + + + + + + + + + + + +	50 1 49 45 44 50 41
Integumentary System Mammary gland Adenocarcinoma Skin		м +	+ X +	++	+ +	M +	M +	[+	+	+	+	+	M +	+ 1	+	+	+	++	+	+	M +	+ 1	+	+	• +		+	37 1 50
Musculoskeletal System Bone Skeletal muscle Osteosarcoma, metastatic, uncertain primary site		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +		+	50 2 1
Nervous System Brain		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	50

Individual Animal Tumor Pathology of	f Fen	nal	e N	Mic	e i	n t	he	2-	Ye	ar	Fe	ed	St	ud	уC	of I	HC	Y	elle	DW	4:	1	0,0	000	pp	<b>m</b> (e	conti	nued)
Number of Days on Study	5 5 4	5 6 1	5 7 8	6 1 0	6 1 3	6 4 7	7 2 9	7 3 0																				
Carcass ID Number	7 5 4	8 2 5	8 4 4	8 0 3	8 2 4	8 3 4	7 8 2	7 1 1	7 1 2	7 1 3	7 2 1	7 2 2	7 3 1	7 3 2	7 3 3	7 3 4	7 4 1	7 4 2	7 4 3	7 4 4	7 4 5	7 5 1	7 5 2	7 5 3	7 6 1			
Respiratory System Lung Adenocarcinoma, metastatic, mammary gland Alveolar/bronchiolar adenoma Alveolar/bronchiolar carcinoma, multiple	+	+	+	+ x	÷	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	⊦ 4	+			
Osteosarcoma, metastatic, uncertain primary site Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung Nose Trachea	+ +	x + +	++	X + +	+++	++	+++	+++	+ +	+ +	+ +	+ +	++	++	+ +	+++	+ +	++	+ +	++	+ +	+	N +	/ N ⊦ +	[+			
Special Senses System Ear Harderian gland Adenoma					_				+						+													
Urinary System Kidney Osteosarcoma, metastatic, uncertain primary site Urinary bladder	+	+ X +	+	+ +	+	+	+	+	++	+ +	+ +	++	++	+ +	+	+	+ +	+ +	++	+	+	+	+	+ + + +	+			
Systemic Lesions Multiple organs Lymphoma malignant histiocytic Lymphoma malignant mixed Lymphoma malignant undifferentiated cell type	+ x	+	+ x	+	+ x	+ X	+ x	+	+	+	+	+	+	+	+ x	+	+	÷	+	+	+	+	+	+ -∔	+			

# Lesions in Female Mice

TABLE D2 Individual Amimal Tumor Pathology of	Fer	nal	e I	Mio	ce i	im 1	the	2-	Ye	ær	Fe	æd	St	:wd	уa	of I	HIC	Y	elle	DW	4:	1	0,0	M	Dj	ppn	1 (continued)
Number of Days on Study	7 3 0	1	7 3 0																								
Carcass IID Number	7 6 2	7 6 3	7 7 1	7 7 2	7 7 3	7 7 4	7 8 1	7 9 1	7 9 2	8 0 1	8 0 2	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 3 1	8 3 2	8 3 3	8 4 1	8 4 2		8 4 3	Total Tissues/ Tumors
Respiratory System		- 4	. 4	- +			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			-	+	50
Adenocarcinoma, metastatic, mammary gland Alveolar/bronchiolar adenoma Alveolar/bronchiolar carcinoma,		Х		•	•	•		·	•	•	•		•	•	·			•	x	•		·					1 1
multiple Osteosarcoma, metastatic, uncertain primary site Mediastinum, alveolar/bronchiolar																											1
Nose Trachea	- -	- +	· -	- +	• +	· + · +	M +	( + +	+ +	M +	( + +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+	· -  · -	⊦ 4 ⊦ 4	F F	+ +	1 46 50
Special Senses System Ear Harderian gland Adenoma													+ X														1 2 1
Urinary System																											
Kidney Osteosarcoma, metastatic, uncertain primary site	-	1		⊦ +	- +	• +	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	• +	• •		⊦	+	50 1
Urinary bladder	4			+ +	- +	+	+	+	+	+	+	+	+	+	+	М	+	+	+	+	+	+	• -	+ -1	⊦	+	49
Systemic Lesions Multiple organs Lymphoma malignant histiocytic Lymphoma malignant mixed	-	⊦ ⊣ Հ		+ +	- +	• +	+	+	+	+	+	÷	+	+	+	+	+	+	+	+	• +	- +		┡╶┥	ł	+	50 1 5
cell type						х																					2

# Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of HC Yellow 4

	0 ppm	5,000 ppm	10,000 ppm
Liver: Hepatocellular Adenoma		<u> </u>	
Overall rates <sup>a</sup>	5/50 (10%)	8/18 (44%) <sup>e</sup>	4/50 (8%)
Adjusted rates <sup>b</sup>	11.6%		9.3%
Ferminal rates <sup>c</sup>	5/43 (12%)		4/43 (9%)
First incidence (days)	730 (T)		730 (T)
ife table tests <sup>d</sup>			P=0.500N
ogistic regression tests <sup>a</sup>			P=0.500N
ïsher exact test <sup>a</sup>			P=0.500N
iver: Hepatocellular Adenoma or Carcin	oma		
Dverall rates	6/50 (12%)	8/18 (44%) <sup>e</sup>	4/50 (8%)
Adjusted rates	14.0%		9.3%
Cerminal rates	6/43 (14%)		4/43 (9%)
irst incidence (days)	730 (T)		730 (T)
ife table tests		-	P=0.369N
ogistic regression tests			P=0.369N
ïsher exact test			P=0.370N
ung: Alveolar/bronchiolar Adenoma			
Dverall rates	3/50 (6%)	2/8 (25%) <sup>e</sup>	1/50 (2%)
Adjusted rates	7.0%		2.3%
erminal rates	3/43 (7%)		1/43 (2%)
ïrst incidence (days)	730 (T)		730 (Ť)
ife table tests			P=0.305N
ogistic regression tests			P=0.305N
isher exact test			P=0.309N
Lung: Alveolar/bronchiolar Adenoma or (	Carcinoma		
Dverall rates	4/50 (8%)	2/8 (25%) <sup>e</sup>	2/50 (4%)
Adjusted rates	9.3%		4.4%
Cerminal rates	4/43 (9%)		1/43 (2%)
irst incidence (days)	730 (T)		610
ife table tests			P=0.335N
ogistic regression tests			P=0.331N
isher exact test			P=0.339N
Dvary: Cystadenoma			
Overall rates	2/50 (4%)	0/47 (0%)	3/50 (6%)
Adjusted rates	4.7%	0.0%	7.0%
Ferminal rates	2/43 (5%)	0/36 (0%)	3/43 (7%)
First incidence (days)	730 (T) É	_f ` ´	730 (Ť)
life table tests	P=0.393	P=0.278N	P=0.500
ogistic regression tests	P=0.393	P=0.278N	P=0.500
Cochran-Armitage test <sup>d</sup>	P=0.391		
isher exact test	-	P=0.263N	P=0.500
Pituitary Gland (Pars Distalis): Adenoma	1		
Dverail rates	5/42 (12%)	0/0 <sup>e</sup>	1/45 (2%)
Adjusted rates	12.9%		2.6%
Cerminal rates	4/36 (11%)		1/38 (3%)
First incidence (days)	463		730 (T)
life table tests			P = 0.094N
ogistic regression tests			P=0.163N

Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of HC Yellow 4 (continued)

	0 ppm	5,010 ppm	10,000 ppm
Stomach (Forestomach): Squamous Papillor	ma		
Overall rates	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rates	7.0%	5.1%	2.3%
Terminal rates	3/43 (7%)	1/38 (3%)	1/43 (2%)
First incidence (days)	730 (T)	718	730 (T)
Life table tests	P=0.227N	P=0.551N	P=0.305N
Logistic regression tests	P=0.214N	P=0.505N	P=0.305N
Cochran-Armitage test	P=0.222N		
Fisher exact test		P=0.500N	P=0.309N
All Organs: Malignant Lymphoma (Histiccy	tic, Lymphocytic, Mixed, o	r Undifferentiated Cell	Type)
Overall rates	9/50 (18%)	14/50 (28%)	8/50 (16%)
Adjusted rates	19.4%	30.6%	16.6%
Terminal rates	6/43 (14%)	7/38 (18%)	3/43 (7%)
First incidence (days)	466	519	554
Life table tests	P=0.437N	P=0.151	P=0.481N
Logistic regression tests	P=0.527N	P=0.160	P=0.594
Cochran-Armitage test	P=0.451N		
Fisher exact test		P=0.171	P=0.500N
All Organs: Benign Tumors			
Overall rates	21/50 (42%)	13/50 (26%)	11/50 (22%)
Adjusted rates	46.6%	32.3%	25.6%
Terminal rates	19/43 (44%)	11/38 (29%)	11/43 (26%)
First incidence (days)	463	682	730 (T)
Life table tests	P=0.021N	P = 0.141N	P = 0.027N
Logistic regression tests	P = 0.014N	P = 0.060 N	P = 0.020N
Cochran-Armitage test	P=0.019N		
Fisher exact test		P=0.069N	P=0.026N
All Organs: Malignant Tumors			
Overall rates	14/50 (28%)	15/50 (30%)	12/50 (24%)
Adjusted rates	29.2%	32.0%	24.0%
Terminal rates	9/43 (21%)	7/38 (18%)	5/43 (12%)
First incidence (days)	466	519	554
Life table tests	P = 0.362N	P=0.435	D=0 395N
Logistic regression tests	P = 0.473N	P = 0.471	P=0.57514
Cochran-Armitage test	P = 0.368N	1 -0.4/1	10-14414
Fisher exact test	1 -0.0001	P=0.500	P=0.410N
All Opposes: Remion of Malianant Turner			
Weill mter Will Alguns: menism of Manufusur Inmors	20/50 //001	24/ED / 4001	01 100 1000
Adjusted meter	30/30 (60%)	24/30 (48%) 50 701	21/50 (42%)
nujusicu faits	01.2%	50.7%	42.0%
ICIMINAL FAICS	24/43 (36%)	15/38 (39%)	14/43 (33%)
rirst incluence (days)	403	519 D. 0.00131	554
Life table lesis	P=0.071N	P=0.321N	P=0.078N
Logistic regression tests	P=0.05/N	P=0.163N	P=0.072N
Eichen ann at tast	1 = 0.04514	B 017055	

Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of HC Yellow 4 (continued)

(T)Terminal sacrifice

<sup>c</sup> Observed incidence at terminal kill

<sup>d</sup> 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.

<sup>e</sup> Tissue was examined microscopically only when it was observed to be abnormal at necropsy.

f Not applicable; no tumors were found at the site in this group

<sup>&</sup>lt;sup>a</sup> 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.

<sup>&</sup>lt;sup>b</sup> Kaplan-Meier estimated tumor incidence at the end of the study after adjustment for intercurrent mortality

#### Table D4

Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of HC Yellow  $4^{\rm a}$ 

	Ø	ലാലാ	<b>5,</b> M	ю рры	10,00	Эррт
Disposition Summary						
Animals initially in study	70		70		70	
6-month interim evaluation	10		10		10	
15-month interim evaluation	10		10		10	
Early deaths						
Natural deaths	. 4		2		2	
Moribund kills	3		10		5	
Survivors						
Terminal sacrifice	43		38		43	
Animals examined microscopically	50		50		50	
Alimnemtary System						
Gallbladder	(46)		(3)		(48)	
Inflammation, chronic	10	(22%)	(9)		4	(8%)
Liver	(50)		(18)		(50)	
Basophilic focus	<b>(</b> )		. ,		ì	(2%)
Clear cell focus	2	(4%)				
Fatty change	2	(4%)				
Inflammation, chronic active	17	(34%)			23	(46%)
Necrosis	4	(8%)	1	(6%)	13	(26%)
Mesentery	(2)		(1)		(1)	
Fibrosis	1	(50%)				
Inflammation, chronic active	1	(50%)				
Necrosis	1	(50%)				
Pancreas	(48)		(3)		(49)	
Inflammation, chronic	25	(52%)			22	(45%)
Salivary glands	(50)	(0 <b>.01</b> )	(2)		(50)	
Inflammation, chronic	4	(8%)		(500)	22	11.00
Inflammation, chronic active	33	(00%)		(50%)	34	(04%)
Stomacn, Iorestomacn	(49)	(20%)	()		(50)	(60)
Acantinosis	1	(2%)			3	(0%)
Hyperiacial losis	1	(270)			2	(4%)
Hyperplasia, basal cell Hyperplasia, pseudoenitheliomatous					1	(7%)
Inflammation chronic active	3	(6%)	1	(14%)	1	(2%)
Ulcer	5	(070)	1	(1470)	1	(2%)
Cardiovascular System None						
Endocrine System						
Adrenal gland, cortex	(50)		(3)		(50)	
Hyperplasia	3	(6%)	.,			
Adrenal gland, medulla	(49)	· -	(3)		(47)	
Hyperplasia	1	(2%)			1	(2%)
Islets, pancreatic	(49)		(3)		(49)	
Hyperplasia	1	(2%)				
Pituitary gland	(42)				(45)	
Pars distalis, hyperplasia	9	(21%)			8	(18%)

Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of HC Yellow 4 (continued)

	0	ррт	5,00	Ю ррт	10,0	00 ррп
Endocrine System (continued)						
Thyroid gland	(48)		(49)		(50)	
Inflammation, acute					2	(4%)
Inflammation, chronic	1	(2%)	6	(12%)	6	(12%)
Inflammation, chronic active					2	(4%)
C-cell, hyperplasia					1	(2%)
Follicle, cyst	1	(2%)	1	(2%)	1	(2%)
Follicle, pigmentation			48	(98%)	50	(100%
Follicular cell, hyperplasia			3	(6%)	13	(26%)
Follicular cell, pigmentation			49	(100%)	50	(100%
Interstitium, pigmentation			46	(94%)	50	(100%)
General Body System						
lone			·			
Conidal Contorn		<u> </u>		•		
	(50)		(17)		(50)	
	(50)		(47)	(10)	(30)	(90%)
Angiectasis	14	(2007)	17	(4%)	4	(8%)
Cyst	14	(28%)	17	(30%)	43	(40%)
Cyst, multiple	4	(8%)	4	(9%)	11	(2%)
Hemorrhage	16	(2001)	9	(19%)	11	(22%)
Inflammation, chronic	10	(32%)	4	(9%)	2	(4%)
Mineralization			1	(2%)	2	(4%)
Ihrombus	(50)		(24)		1	(2%)
Jierus	(50)	(0.00)	(24)		(50)	
Endometriosis	1	(2%)				in and a
Endometrium, hydrometra	44	(000)	10	(500)	10	(20%)
Endometrium, hyperplasia	41	(82%)	12	(50%)	36	(12%)
Endometrium, metaplasia, squamous	_	-			1	(2%)
Endometrium, thrombus	1	(2%)				
Iematopoietic System						
Bone marrow	(50)		(3)		(50)	
Myelofibrosis	36	(72%)			42	(84%)
ymph node	(49)		(15)		. (49)	
Renal, hyperplasia, lymphoid	. ,		ì	(7%)	. ,	
ymph node, mesenteric	(45)		(10)		(44)	
Infiltration cellular, histiocyte	26	(58%)	Ì ź	(20%)	23	(52%)
spleen	(49)		(17)		(50)	. ,
Hematopoietic cell proliferation	6	(12%)	3	(18%)	` ź	(4%)
Hyperplasia, lymphoid	11	(22%)	4	(24%)	3	(6%)
Pigmentation				. ,	1	(2%)
Chymus	(43)		(6)		(41)	
		10 ml 1	• • •		· · · ·	1001

None

Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of HC Yellow 4 (continued)

	0 B	olow	5,03	M ppm	10,00	≫ ppm
Musculoskeletal System Bone Joint, tarsal, hyperostosis	(50)		(4) 1 (25%)		(50)	
Nervous System Brain Gliosis Thalamus, mineralization	(50) 34	(68%)	(5) 1 2	(20%) (40%)	(50) 19	(38%)
Respiratory System Lung Hemorrhage Alveolar epithelium, hyperplasia Nose Inflammation, acute	(50) 3 1 (47) 9	(6%) (2%) (19%)	(8) (3) 1	(33%)	(50) 5 1 (46) 2	(10%) (2%) (4%)
Special Senses System None						
Urimary System Kidney Inflammation, chronic Metaplasia, osseous Urinary bladder Inflammation, chronic	(50) 45 (48) 43	(99%) (99%)	(4) 3 (4) 2	(75%) (50%)	(50) 48 1 (49) 39	(96%) (2%) (80%)

<sup>a</sup> Incidences are expressed as the ratio of animals with lesions to the number of animals examined microscopically at the site.

# APPENDIX E GENETIC TOXICOLOGY

SALMONELLA	PROTOCOL	176
CHINESE HAN	ISTER OVARY CELL CYTOGENETICS ASSAYS	176
DROSOPHILA	PROTOCOL	177
RESULTS		178
Table E1	Mutagenicity of HC Yellow 4 in Salmonella typhimurium	179
Table E2	Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells	
	by HC Yellow 4	180
Table E3	Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells	
	by HC Yellow 4	181
Table EA	Induction of Sex-Linked Recessive Lethal Mutations in Drosophila melanogaster	
	by HC Yellow 4	182
Table ES	Induction of Reciprocal Translocations in Drosophila melanogaster	
	by HC Yellow 4	182

# **GENETIC TOXICOLOGY**

# SALMONELLA Protocol

Testing was performed as reported by Mortelmans *et al.* (1986). HC Yellow 4 was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at  $37^{\circ}$  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 HC Yellow 4. High dose was limited to 10,000  $\mu$ g per plate. All assays were repeated.

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

# **CHINESE HAMSTER OVARY CELL CYTOGENETICS ASSAYS**

Testing was performed as reported by Galloway *et al.* (1985, 1987) and as presented briefly below. HC Yellow 4 was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (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 trial consisted of concurrent solvent and positive controls and of at least three doses of HC Yellow 4; the high dose was limited by toxicity.

In the SCE test without S9, CHO cells were incubated for 26 hours with HC Yellow 4 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 HC Yellow 4 was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with HC Yellow 4, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no HC Yellow 4 and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 to 3 hours. Harvesting and staining procedures were the same as for cells treated without S9. For the SCE test, significant chemical-induced cell cycle delay was seen in the absence of S9; therefore, incubation time was lengthened in several of the cultures to ensure a sufficient number of scorable cells.

In the Abs test without S9, a delayed harvest protocol was used, based on the information obtained in the SCE tests. Cells were incubated in McCoy's 5A medium with HC Yellow 4 for 16.5 hours; Colcemid was added and incubation was continued for 2 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 HC Yellow 4 and S9 for 2 hours, after which the treatment medium was removed and the cells incubated for 10.5 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the the same manner as for the treatment without S9.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype  $(21 \pm 2 \text{ chromosomes})$ . All slides were scored blind and those from a single test were read by the same person. For the SCE test, 50 second-division metaphase cells were scored for frequency of SCE per cell from each dose level; 100 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 SCE data, both the dose-response curve and individual dose points were statistically analyzed. For a single trial, a statistically significant (P $\leq$ 0.05) difference for one dose point and a significant trend (P $\leq$ 0.015) was considered weak evidence for a positive response (+w); significant differences for two or more doses indicated the trial was positive (+) (Galloway *et al.*, 1987).

### DROSOPHILA Protocol

The assays for induction of mutations and chromosomal translocations were performed as described in Zimmering *et al.* (1985). HC Yellow 4 was supplied as a coded aliquot from Radian Corporation (Austin, TX). Initially, HC Yellow 4 was assayed in the sex-linked recessive lethal (SLRL) test by feeding for 3 days to adult Canton-S wild-type males no more than 24 hours old at the beginning of treatment. Because no response was obtained, the chemical was retested by injection into adult males. Because treatment by injection produced a positive result, the chemical was assayed for induction of reciprocal translocations (RT) using this same method of exposure.

To administer a chemical by injection, a glass Pasteur pipette was drawn out in a flame to a microfine filament and the tip was broken off to allow delivery of the test solution. Injection was performed either manually, by attaching a rubber bulb to the other end of the pipette and forcing through sufficient solution (0.2 to 0.3  $\mu$ L) to slightly distend the abdomen of the fly, or by attaching the pipette to a microinjector which automatically delivered a calibrated volume. Flies were anesthetized with ether and immobilized on a strip of double stick tape; the chemical was injected into the thorax under the wing with the aid of a dissecting microscope.

Toxicity tests were performed to set concentrations of HC Yellow 4 at a level which would induce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. For the SLRL test, oral exposure was achieved by allowing Canton-S males (10 to 20 flies per vial) to feed for 72 hours on a solution of HC Yellow 4 dissolved in 40% ethanol and diluted with 5% sucrose. In the injection experiments, 24- to 72-hour-old Canton-S males were treated with a solution of HC Yellow 4 dissolved in 40% ethanol diluted with 0.7% saline, and were allowed to recover for 24 hours. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days; sample sperm from successive matings were treated at successively earlier post-meiotic stages. F<sub>1</sub> heterozygous females were allowed to mate with their siblings and were then placed in individual vials.  $F_1$  daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event, and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. Presumptive lethal mutations were identified as occurring in vials containing no wild-type males after 17 days; these were retested. The feeding and injection experiments combined resulted in the testing of approximately 5,000 treated and 5,000 control chromosomes. The only exceptions occurred when the results of the first experiment were clearly positive (induced frequency of recessive lethal mutations equal to or greater than 1%); then the second trial was not run.

Recessive lethal data were analyzed by the normal approximation to the binomial test (Margolin *et al.*, 1983). A test result was considered to be positive if the P value was less than 0.01 and the mutation frequency in the tested group was greater than 0.10%, or if the P value was less than 0.05 and the frequency in the treatment group was greater than 0.15%. A test was considered to be inconclusive if (a) the P value was between 0.01 and 0.05 but the frequency in the treatment group was between 0.05 and 0.10 but the frequency in the treatment group was greater than 0.10%. A result was between 0.05 and 0.10 but the frequency in the treatment group was greater than 0.10 or if the P value was greater than 0.10%. A result was considered to be negative if the P value was greater than 0.10 or if the frequency in the treatment group was less than 0.10%.

For the RT test, the exposure regimen was the same as that for the SLRL test except that small mass matings were used (10 males and 20 females). Exposed males were mated to three X.Y,y; bw; st females for 3 days and discarded. The females were transferred to fresh medium every 3 to 4 days for a period of about 3 weeks to produce a total of six broods. The results of the SLRL test were used to narrow the germ cell stage most likely to be affected by the chemical; for example, if earlier germ cell stages seemed to exhibit increased sensitivity, mating of the males was continued and translocation tests carried out from the offspring derived from these earlier germ cell stages.  $F_1$  males were mated individually to X.Y,y; bw; st females and the progeny were examined for missing classes, which indicate the induction of a translocation in a germ cell of the parental male. The translocation data were analyzed according to the conditional binomial test (Kastenbaum and Bowman, 1970).

#### RESULTS

HC Yellow 4 (3 to 10,000  $\mu$ g/plate) was tested for induction of gene mutations in four strains of *Salmonella typhimurium* in a preincubation protocol with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9; results were positive for strains TA100, TA1537, and TA98 with and without S9. An equivocal response was noted in TA1535 in the absence of S9 activation; with S9 from either species, results were negative (Table E1; Mortelmans *et al.*, 1986).

HC Yellow 4 induced SCE in CHO cells in the absence, but not in the presence, of S9 activation (Table E2). In the two trials without S9, a significant increase in SCE was observed only at the highest dose tested (167 or 200  $\mu$ g/mL); these doses induced cell cycle delay and required an extended harvest to accumulate sufficient cells for analysis. With Aroclor 1254-induced male Sprague-Dawley rat liver S9, no significant increase in SCE was observed with concentrations of up to 1,700  $\mu$ g/mL HC Yellow 4; cell cycle delay was not noted with S9. When tested for induction of Abs in CHO cells, HC Yellow 4 was negative with and without S9 (Table E3). In the trial conducted without S9, a dose-related increase in aberrations was noted, but this increase was not significant either by trend analysis (P=0.027) or peak response (P>0.05); a delayed harvest protocol was necessary to offset chemical-induced cell cycle delay. With S9, no cell cycle delay was observed in either trial, and the response observed at the highest nonlethal dose tested in the first trial (3,000  $\mu$ g/mL) was not repeated in the second trial. A precipitate formed at the 2,500  $\mu$ g/mL concentration in trial 2 and no viable cells were present in the 3,000  $\mu$ g/mL cultures.

HC Yellow 4 induced SLRL mutations in germ cells of adult male *Drosophila melanogaster* when administered by injection at a dose of 10,000 ppm; results of the initial feeding test were negative (Table E4; Woodruff *et al.*, 1985). Following the positive result in the SLRL assay, HC Yellow 4 (10,000 ppm by injection) was tested for induction of RT in germ cells of male *D. melanogaster*; results of this assay were negative (Table E5; Woodruff *et al.*, 1985).

#### Genetic Toxicology

	Revertants/plate <sup>b</sup>											
Strain Dasz	-9	9	÷10% h	amster S9	+10% rat S9							
(µg/plate)	Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2						
TA100 0 3 10 22	166 ± 7.0	154 ± 12.6	138 ± 10.6	$ \begin{array}{r} 147 \pm 13.0 \\ 199 \pm 11.7 \\ 262 \pm 9.4^{c} \\ 723 \pm 10.7^{c} \end{array} $	156 ± 12.0	139 ± 4.8						
100 333 1,000 3,333 10,000	$133 \pm 2.8 \\ 181 \pm 7.8 \\ 307 \pm 8.7 \\ 617 \pm 38.5 \\ 283 \pm 21.7^{d}$	$157 \pm 7.0 \\ 186 \pm 33.8^{c} \\ 257 \pm 28.4^{c} \\ 528 \pm 37.9^{c} \\ 324 \pm 22.2^{c} \\ \end{cases}$	$\begin{array}{rrrr} 1,180 \ \pm \ \ 27.8 \\ 1,096 \ \pm \ 136.5 \\ 918 \ \pm \ \ 32.7 \\ 583 \ \pm \ \ 97.5 \\ 210 \ \pm \ \ 31.7 \end{array}$	$723 \pm 10.7$ 1,103 ± 7.6 <sup>c</sup> 1,121 ± 145.4 <sup>c</sup>	$153 \pm 14.7 \\ 169 \pm 2.3 \\ 175 \pm 6.1 \\ 313 \pm 20.6 \\ 369 \pm 25.4$	$143 \pm 9.0 \\ 152 \pm 3.3^{c} \\ 189 \pm 3.2^{c} \\ 302 \pm 4.2^{c} \\ 469 \pm 94.0^{c} \\ 1000$						
Trial summary Positive control <sup>e</sup>	Positive 482 ± 13.4	Positive $421 \pm 4.7$	Positive 1,978 ± 31.5	Positive 1,307 ± 20.1	Positive 1,703 ±202.1	Positive 764 ± 16.7						
TA1535 0 100 333 1,000 3,333 10,000	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	$\begin{array}{rrrrr} 11 \ \pm \ 2.1 \\ 15 \ \pm \ 2.8 \\ 20 \ \pm \ 3.2^{c} \\ 20 \ \pm \ 3.2^{c} \\ 22 \ \pm \ 5.0^{c} \\ 30 \ \pm \ 6.9^{c} \end{array}$	$16 \pm 0.9 \\ 10 \pm 3.2 \\ 13 \pm 2.1 \\ 14 \pm 3.2 \\ 14 \pm 4.1 \\ 41 \pm 9.7^{d}$	$13 \pm 2.6  12 \pm 1.7  4 \pm 1.3^{c}  4 \pm 1.7^{c}  9 \pm 1.5^{c}  23 \pm 2.4^{c} $						
Trial summary Positive control	Positive 452 ± 25.5	Equivocal 394 ± 2.3	Negative 606 ± 23.6	Equivocal 486 ± 14.9	<b>Equivocal 528 ± 24.8</b>	Negative 307 ± 5.5						
TA1537 0 10 33	$13 \pm 0.3$	$9 \pm 1.5$ 10 ± 2.0 13 ± 2.8 <sup>c</sup>	$16 \pm 2.1$	8 ± 0.6	$12 \pm 3.2$	9 ± 1.5						
100 333 1,000 3,333 10,000	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	$ \begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	$ \begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	$ \begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	$12 \pm 2.7 \\ 18 \pm 4.7 \\ 38 \pm 4.2 \\ 124 \pm 10.9 \\ 283 \pm 27.7$	$5 \pm 1.2 \\ 17 \pm 4.9^{c} \\ 27 \pm 1.5^{c} \\ 114 \pm 11.7^{c} \\ 239 \pm 11.8^{c} $						
Trial summary Positive control	Positive $382 \pm 35.8$	Positive 242 ± 23.5	Positive $367 \pm 4.4$	Positive 424 ± 22.5	Positive $308 \pm 36.0$	Positive $304 \pm 2.9$						
TA98 0 10 33	28 ± 2.2	$21 \pm 2.3$ $25 \pm 4.1$ $30 \pm 3.5^{\circ}$	$29 \pm 0.7$	$38 \pm 3.5$ $38 \pm 3.6$ $48 \pm 7.4^{c}$	$36 \pm 3.2$	$35 \pm 1.3$						
100 333 1,000 3,333 10,000	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	$40 \pm 10.9^{c} \\ 124 \pm 10.4^{c} \\ 252 \pm 6.9^{c}$	$96 \pm 9.5$ $111 \pm 9.7$ $138 \pm 12.9$ $310 \pm 49.1$ $323 \pm 38.5^{d}$	$75 \pm 6.4^{c}$ $105 \pm 7.1^{c}$ $154 \pm 8.5^{c}$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$						
Trial summary Positive control	Positive $767 \pm 21.9$	Positive 687 ± 40.0	Positive $1,503 \pm 69.9$	Positive $1,219 \pm 34.6$	Positive 1,080 ± 15.6	Positive $571 \pm 22.3$						

# TABLE E1 Mutagenicity of HC Yellow 4 in Salmonella typhimurium<sup>a</sup>

<sup>a</sup> Study performed at SRI, International. The detailed protocol and these data are presented in Mortelmans *et al.* (1986). Cells and HC Yellow 4 or solvent (dimethylsulfoxide) were incubated in the absence of exogenous metabolic activation (-S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague-Dawley rat liver. High dose was limited to 10,000 µg/plate; 0 µg/plate dose is the solvent control.

b Revertants are presented as mean  $\pm$  standard error from three plates.

<sup>c</sup> Precipitate on plate

<sup>d</sup> Slight toxicity

e 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.

Compound	Dose (µg/mL)	Total Cells	No. of Chromo- somes	No. of SCEs	SCEs/ Chromo- somes	SCEs/ Cell	Hrs in BrdU	Relative SCEs/Chromo- some (%) <sup>b</sup>
-S9								
Trial 1 Summary: Weak positive								
Dimethylsulfoxide		50	1,034	450	0.43	9.0	26.0	
Mitomycin-C	0.0010 0.0100	50 5	1,035 105	574 241	0.55 2.29	11.5 48.2	26.0 26.0	27.43 427.40
HC Yellow 4	16.7 50.0 167.0	50 50 50	1,032 1,028 1,030	427 463 575	0.41 0.45 0.55	8.5 9.3 11.5	26.0 33.0 33.0	-4.93 3.49 28.27*
								$P = 0.000^{d}$
Trial 2 Summary: Positive		·	1					
Dimethylsulfoxide		50	1,031	467	0.45	<b>9.3</b>	26.0	4.
Mitomycin-C	0.0010 0.0100	50 .5	1,034 105	631 226	0.61 2.15	12.6 45.2	26.0 26.0	34.73 375.19
HC Yellow 4	50.0 100.0 200.0	50 50 50	1,037 1,033 1,026	509 559 609	0.49 0.54 0.59	10.2 11.2 12.2	26.0 32.5 <sup>c</sup> 32.5 <sup>c</sup>	8.36 19.47 31.04*
								P=0.000
+ \$9								
<b>Trial 1</b> Summary: Negative				۰.			· · · · · · · · · · · · · · · · · · ·	
Dimethylsulfoxide		50	1,033	440	0.42	8.8	26.0	,
Cyclophosphamide	0.4 2.0	50 5	1,035 104	601 135	0.58 1.29	12.0 27.0	26.0 26.0	36.33 204.75
HC Yellow 4	167.0 500.0 1.700.0	50 50 50	1,037 1,029 1.033	395 401 421	0.38 0.38 0.40	7.9 8.0 8.4	26.0 26.0 26.0	-10.58 -8.51 -4.32
	_,,		-,					P=0.696

#### TABLE E2

Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by HC Yellow 4ª

\* Positive (≥20% increase over solvent control)

<sup>a</sup> Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed

description of the SCE protocol is presented by Galloway et al. (1985, 1987).

<sup>b</sup> Percent increase in SCEs/chromosome of culture exposed to HC Yellow 4 relative to those of culture exposed to solvent.

<sup>c</sup> Because HC Yellow 4 induced significant cell cylce delay, incubation time was lengthened to ensure a sufficient number of scorable (second-division metaphase) cells.

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

# TABLE E3

Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by HC Yellow 4ª

		-59					+ S9		
Duse (µg/mL	Total ) Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dase (49/mL)	Total Cells	No. of Abs	Albs/ Cell	Percent Cells with Abs
Trial 1 – Harv Summary: Neg	vest time: 18. ative	5 hours			Trial 1 – Harves Summary: Weak	t time: 12 positive	.5 hours		
Dimethylsulfor	ide				Dimethylsulforide	e			
20111011191201101	100	1	0.01	1.0	2	100	1	0.01	1.0
Mitomycin-C			·		Cyclophosphamid	ie			
0.0400	) 100	24	0.24	16.0	7.5	100	9	0.09	5.0
0.0625	5 25	15	0.60	36.0	37.5	25	20	0.80	32.0
HC Yellow 4					HC Yellow 4				
400	) 100	1	0.01	1.0	1,000	100	4	0.04	4.0
500	) 100	2	0.02	2.0	2,000	100	10	0.10	5.0
600	) 100	5	0.05	5.0	3,000	100	14	0.14	12.0°
				$P = 0.027^{c}$					P=0.001
					Trial 2 – Harves Summary: Negati	t time: 12 we	.5 hours		
					Dimethylsulfoxid	e			
					211101119120110110	100	3	0.03	3.0
					Cyclophosphamic	ie			
					7.5	100	17	0.17	14.0
					37.5	25	15	0.60	36.0
					HC Yellow 4				
•					1,500	100	5	0.05	5.0
					2,000	100	2	0.02	2.0
					2,500 <sup>d</sup>	100	3	0.03	3.0
, · · ·					3,000	0			
				·					
								-	P=0.660

Positive (P≤0.05) ۰ а

Study performed at Litton Bionetics, Incorporated. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985, 1987).

Ь Because HC Yellow 4 induced significant cell cycle delay, incubation time was lengthened to ensure a sufficient number of scorable (first-division metaphase) cells. c

Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose Precipitate formed at this concentration.

d

Route of		Incidence of	<b>Incidence</b> of	No. of Lethals/N	lo. of X Chro	mosomes Test	<u>ed</u>
Exposure	Dose (ppm)	Deaths (%)	Sterility (%)	Mating 1	Mating 2	Mating 3	Total <sup>b</sup>
Feeding	10,000 0	2	0	0/2,182 1/2,353	2/2,128 2/1,959	1/2,087 1/1,846	3/6,397 (0.05%) 4/6,158 (0.06%)
Injection	10,000 0	0	0	4/2,075 0/1,880	3/1,995 0/1,863	3/1,834 1/1,561	10/5,904 (0.17%)* 1/5,304 (0.02%)

Induction	of Sex	-Linked	Recessive	Lethal	Mutations	in	Drosonhila	melanog	aster by	HC	Yellow	4 <sup>a</sup>
**************************************			Treeson		YAT OF ORE OF CARD		2 COOPINI	TITUTE				-

\* Results were significant at the 5% level (Margolin et al., 1983).

<sup>a</sup> Study performed at Bowling Green State University. A detailed protocol of the sex-linked recessive lethal assay and these data are presented in Woodruff *et al.* (1985). Results of the feeding experiment were not significant at the 5% level (Margolin *et al.*, 1983).

<sup>b</sup> Combined total number of lethal mutations/number of X chromosomes tested for three mating trials.

### TABLE E5

Induction of Reciprocal Translocations in Drosophila melanogaster by HC Yellow 4ª

Route of Exposure	Dose (ppm)		Trans	<u>Trar</u> locations/	<u>isfers</u> Total F <sub>1</sub>	No. of	Total No. of	Total Translocations		
		1	2	3	4	5	6	Tests	Translocations	(%)
Injection	10,000	0/914	0/959	0/1,075	0/1,045	0/927	0/0	4,920	0	0.00
Concurrent	control							23,686	1	0.00
Historical co	ontrol							116,163	2	0.00

<sup>a</sup> Study performed at Bowling Green State University. A detailed protocol of the reciprocal translocation assay and these data are presented in Woodruff *et al.* (1985). Results were not significant at the 5% level (Kastenbaum and Bowman, 1970).

TABLE E4

# 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 14-Day Feed Studies of HC Yellow 4	184			
TABLE	F2	Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats				
		in the 13-Week Feed Studies of HC Yellow 4	185			
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 HC Yellow 4	186			
TABLE	FA	Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice				
		in the 14-Day Feed Studies of HC Yellow 4	187			
TABLE	F5	Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice				
		in the 13-Week Feed Studies of HC Yellow 4	188			
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 HC Yellow 4	189			
	0 ppm	5,000 ppm	10,000 ppm	20,000 ppm	40,000 ppm	80,000 ppm
------------------	-----------------	----------------------	-------------------------	-------------------------	-----------------------	----------------------------------
	<u> </u>					
n	5	5	5	5	5	5
Necropsy body wt	$183 \pm 8$	$175 \pm 6$	$170 \pm 5$	$150 \pm 6^{**}$	$107 \pm 3$	74 ± 3**
Brain						
Absolute	$1.69 \pm 0.04$	$1.72 \pm 0.02$	$1.74 \pm 0.03$	$1.63 \pm 0.01$	$1.62 \pm 0.02$	$1.54 \pm 0.04^{**}$
Relative	$9.27 \pm 0.20$	$9.83 \pm 0.30$	$10.25 \pm 0.17$	$10.95 \pm 0.41^{**}$	$15.15 \pm 0.32^{**}$	$20.85 \pm 0.58^{**}$
Heart						
Absolute	$0.66 \pm 0.04$	$0.62 \pm 0.02$	$0.61 \pm 0.03$	$0.55 \pm 0.04$	$0.38 \pm 0.02$	$0.59 \pm 0.33$
Relative	$3.61 \pm 0.08$	$3.55 \pm 0.08$	$3.58 \pm 0.12$	$3.63 \pm 0.11$	$3.61 \pm 0.23$	$8.08 \pm 4.50$
R. Kidney						
Absolute	$0.83 \pm 0.06$	$0.84 \pm 0.04$	$0.86 \pm 0.03$	$0.73 \pm 0.04$	$0.56 \pm 0.02^{**}$	$0.44 \pm 0.02^{**}$
Relative	$4.53 \pm 0.21$	$4.80 \pm 0.05$	$5.06 \pm 0.03^*$	$4.82 \pm 0.11^{\circ}$	$5.27 \pm 0.06^{**}$	$5.98 \pm 0.13^{**}$
Liver	•					
Absolute	$9.93 \pm 0.69$	$9.69 \pm 0.37$	$10.32 \pm 0.64$	$8.79 \pm 0.50$	$6.31 \pm 0.17^{**}$	$4.51 \pm 0.21^{**}$
Relative	$54.1 \pm 2.1$	$55.4 \pm 2.0$	$60.5 \pm 2.2$	$58.4 \pm 1.4$	$59.1 \pm 2.4$	$60.8 \pm 1.0^*$
Lungs						
Absolute	$0.94 \pm 0.07$	$1.17 \pm 0.13$	$1.25 \pm 0.11$	$1.22 \pm 0.11$	$0.97 \pm 0.12$	$0.89 \pm 0.17$
Relative	$5.13 \pm 0.31$	$6.69 \pm 0.68$	$7.37 \pm 0.59$	$8.06 \pm 0.46^*$	$9.01 \pm 1.07^{**}$	$11.78 \pm 1.70^{**}$
R. Testis		•				
Absolute	$1.08 \pm 0.04$	$1.10 \pm 0.04$	$1.05 \pm 0.04$	$1.05 \pm 0.03$	$0.77 \pm 0.06^{**}$	$0.34 \pm 0.03^{**}$
Relative	$5.91 \pm 0.12$	$6.27 \pm 0.21$	$6.17 \pm 0.25$	$7.02 \pm 0.26$	$7.20 \pm 0.51^*$	$4.65 \pm 0.39^*$
Thymus						
Absolute	$0.38 \pm 0.06$	$0.40 \pm 0.04$	$0.36 \pm 0.05$	$0.29 \pm 0.01$	$0.18 \pm 0.02^{-1}$	$0.02 \pm 0.00^{**}$
Relative	$2.12 \pm 0.35$	$2.29 \pm 0.19$	$2.07 \pm 0.27$	$1.91 \pm 0.06$	$1.71 \pm 0.15$	$0.31 \pm 0.03^{\bullet\bullet}$
Female						
n	5	5	5	5	5	4
Necropsy body wt	$148 \pm 2$	$140 \pm 5$	$132 \pm 2^{**}$	131 ± 3**	$101 \pm 3^{**}$	77 ± 5**
Brain						-
Absolute	$1.42 \pm 0.24$	$1.70 \pm 0.03$	$1.49 \pm 0.13$	$1.58 \pm 0.04$	$1.56 \pm 0.01$	$1.51 \pm 0.02$
Relative	9.59 ± 1.64	$12.13 \pm 0.31$	$11.26 \pm 0.93$	$12.07 \pm 0.26$	15.48 ± 0.39**	$20.02 \pm 1.40^{**}$
Heart						
Absolute	$0.59 \pm 0.01$	$0.52 \pm 0.03^{**}$	$0.50 \pm 0.02^{**}$	$0.49 \pm 0.01^{**}$	$0.38 \pm 0.01^{**}$	$0.29 \pm 0.02^{**}$
Relative	$4.01 \pm 0.13$	$3.68 \pm 0.11$	$3.75 \pm 0.09$	$3.71 \pm 0.07$	$3.78 \pm 0.11$	$3.73 \pm 0.13$
R. Kidney						
Absolute	$0.69 \pm 0.01$	$0.64 \pm 0.03$	$0.62 \pm 0.02^{\circ}$	$0.63 \pm 0.02^*$	$0.51 \pm 0.02^{**}$	$0.42 \pm 0.02^{**}$
Relative	$4.66 \pm 0.10$	$4.58 \pm 0.11$	$4.68 \pm 0.10$	$4.77 \pm 0.07$	$5.06 \pm 0.11^{**}$	5.47 ± 0.06**
Liver						
Absolute	$7.21 \pm 0.34$	7.27 ± 0.69	$6.23 \pm 0.26$	$6.70 \pm 0.26$	$5.47 \pm 0.19^*$	$4.30 \pm 0.83^{**}$
Relative	$48.6 \pm 2.3$	51.8 ± 4.5	47.1 ± 1.4	$50.9 \pm 1.1$	$54.2 \pm 1.8$	$54.6 \pm 8.4$
Lungs						
Absolute	$1.11 \pm 0.07$	$0.94 \pm 0.09$	$0.91 \pm 0.05$	$1.24 \pm 0.10$	$0.88 \pm 0.04$	$0.89 \pm 0.15$
Relative	$7.51 \pm 0.47$	$6.71 \pm 0.59$	$6.90 \pm 0.36$	$9.44 \pm 0.64$	$8.65 \pm 0.31$	$11.41 \pm 1.37^{**}$
Thymus						
Absolute	$0.38 \pm 0.04$	$0.39 \pm 0.15$	$0.34 \pm 0.04$	$0.29 \pm 0.05$	$0.27 \pm 0.06$	$0.08 \pm 0.02^*$
Relative	$2.56 \pm 0.27$	$2.70 \pm 0.93$	$2.60 \pm 0.29$	$2.21 \pm 0.39$	$2.70 \pm 0.64$	$1.09 \pm 0.27$

Organ	Weights and	Organ-Weight-to-Body-Weight	Ratios for R	lats in the	14-Day Feed	Studies
of HC	Yellow 4 <sup>a</sup>	·			1	

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

°° P≤0.01

Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

	mag 0	5,000 ppm	10,000 ppm	20 <b>,0</b> 39 ppm	40,020 ppm	80,000 ppm
Male				N		
n	10	10	10	9	10	10
Necropsy body wt	348 ± 7	$356 \pm 6$	$341 \pm 6$	$316 \pm 6^{\circ \circ}$	273 ± 9**	$244 \pm 5^{\circ \circ}$
Brain						
Absolute	$1.94 \pm 0.01$	$1.95 \pm 0.02$	$1.92 \pm 0.02$	$1.92 \pm 0.02$	$1.89 \pm 0.01^{\circ}$	$1.80 \pm 0.01^{\circ\circ}$
Relative	$5.61 \pm 0.13$	$5.48 \pm 0.08$	$5.65 \pm 0.08$	$6.10 \pm 0.08^{\circ}$	6.99 ± 0.27°°	$7.42 \pm 0.11^{\circ \circ}$
Heart						
Absolute	$0.93 \pm 0.02$	$0.97 \pm 0.03^{b}$	$0.94 \pm 0.02$	$0.95 \pm 0.03$	$0.91 \pm 0.03$	$0.78 \pm 0.02^{\circ\circ}$
Relative	$2.67 \pm 0.04$	$2.75 \pm 0.07^{b}$	$2.75 \pm 0.06$	2.99 ± 0.11°	$3.36 \pm 0.18^{\circ \circ}$	$3.20 \pm 0.07^{\circ \circ}$
R. Kidney						
Absolute	$1.14 \pm 0.03$	$1.28 \pm 0.02$	$1.23 \pm 0.04$	$1.14 \pm 0.03$	$1.10 \pm 0.02$	$1.09 \pm 0.03$
Relative	$3.28 \pm 0.12$	$3.61 \pm 0.07^{\circ}$	$3.59 \pm 0.08^{\circ}$	$3.61 \pm 0.07^{\circ}$	$4.05 \pm 0.12^{\circ \circ}$	$4.48 \pm 0.05^{\circ\circ}$
Liver						
Absolute	$13.83 \pm 0.25$	$15.35 \pm 0.58$	$14.91 \pm 0.52$	$13.78 \pm 0.36$	$12.93 \pm 0.40$	$13.82 \pm 0.36$
Relative	$39.8 \pm 0.9$	$43.1 \pm 1.3$	43.7 ± 1.3°	$43.9 \pm 0.7^{\circ}$	$47.6 \pm 2.0^{\circ\circ}$	56.6 ± 0.9°°
Lung						
Absolute	$1.45 \pm 0.06$	$1.67 \pm 0.07$	$1.51 \pm 0.04^{b}$	$1.62 \pm 0.12$	$1.54 \pm 0.07$	$1.52 \pm 0.08$
Relative	$4.21 \pm 0.23$	$4.70 \pm 0.19$	$4.47 \pm 0.16^{b}$	5.05 ± 0.38°	5.65 ± 0.21**	$6.20 \pm 0.27^{\circ\circ}$
R. Testis	_					
Absolute	$1.47 \pm 0.02^{b}$	$1.37 \pm 0.08$	$1.52 \pm 0.02$	$1.49 \pm 0.03$	$1.47 \pm 0.03^{b}$	$1.44 \pm 0.02$
Relative	$4.20 \pm 0.10^{b}$	$3.87 \pm 0.25$	$4.45 \pm 0.06$	$4.72 \pm 0.11^{\circ}$	$5.43 \pm 0.23^{\circ \circ b}$	5.93 ± 0.09**
Thymus						
Absolute	$0.26 \pm 0.02$	$0.24 \pm 0.01$	$0.24 \pm 0.01$	$0.25 \pm 0.01$	$0.30 \pm 0.02$	$0.23 \pm 0.01$
Relative	$0.74 \pm 0.04$	$0.69 \pm 0.02$	$0.70 \pm 0.03$	$0.79 \pm 0.04$	1.09 ± 0.05°°	$0.96 \pm 0.03^{\circ \circ}$
Female						
n	10	10	10	10	10	10
Necropsy body wt	$200 \pm 4$	$209 \pm 3$	$195 \pm 3$	$197 \pm 3$	188 ± 2°°	$177 \pm 2^{\circ \circ}$
Brain						
Absolute	$1.79 \pm 0.02^{b}$	$1.78 \pm 0.03$	$1.76 \pm 0.01$	$1.79 \pm 0.02^{b}$	$1.76 \pm 0.02$	$1.70 \pm 0.02^{\circ\circ}$
Relative	$8.86 \pm 0.12^{b}$	$8.54 \pm 0.15$	$9.02 \pm 0.10$	$9.00 \pm 0.09^{b}$	$9.37 \pm 0.14^{\circ \circ}$	9.61 + 0.14**
Heart						
Absolute	$0.62 \pm 0.01$	$0.63 \pm 0.02^{b}$	$0.63 \pm 0.01$	$0.65 + 0.01^{b}$	$0.57 + 0.01^{\circ b}$	$0.57 + 0.01^{\circ}$
Relative	$3.11 \pm 0.07$	$3.03 \pm 0.09^{b}$	$3.25 \pm 0.09$	$3.27 \pm 0.06^{b}$	$3.03 \pm 0.06^{b}$	$3.23 \pm 0.05$
R. Kidney						
Absolute	$0.70 \pm 0.03$	$0.75 \pm 0.01^{b}$	$0.73 \pm 0.01$	$0.73 \pm 0.01$	0.70 + 0.01	0.72 + 0.02
Relative	$3.50 \pm 0.13$	$360 \pm 0.05^{b}$	$373 \pm 0.05$	$3.71 \pm 0.06$	$3.72 \pm 0.05$	4.06 + 0.09**
Liver	0.00 - 0.10	5.00 2 0.05	5.75 2 0.05	5.71 ± 0.00	5.72 2 0.05	4.00 ± 0.07
Absolute	$7.84 \pm 0.28$	$7.93 \pm 0.36$	$677 + 011^{\circ\circ}$	$693 \pm 011^{\circ}$	696 + 0.09*	$799 \pm 0.22$
Relative	39.1 + 1.1	$379 \pm 15$	$348 \pm 08$	$352 \pm 0.01$	$371 \pm 0.6$	$450 \pm 10^{\circ\circ}$
Lungs		57.5 2 1.5	54.6 1 0.0	55.2 - 0.0	5/11 2 0.0	45.0 ± 1.0
Absolute	$1.10 \pm 0.05$	1.37 + 0.05**	$1.20 \pm 0.03$	$1.32 + 0.08^{\circ}$	1.24 + 0.06	1.32. + 0.04*
Relative	$5.48 \pm 0.22$	$6.57 \pm 0.21^{\circ}$	$6.17 \pm 0.16^{\circ}$	$6.67 + 0.34^{\circ\circ}$	$6.64 + 0.29^{\circ\circ}$	746 + 0.35 **
Thymus		V.U	0.1, ± 0.10	0.07 - 0.04	0.01 - 0.27	7.TV ± 0.55
Absolute	$0.18 \pm 0.01$	0.20 + 0.01	$0.23 \pm 0.01$ **	$0.22 \pm 0.01^{\circ}$	$0.21 \pm 0.01$	0.20 + 0.01
Relative	0.91 + 0.03	0.97 + 0.05	1.16 + 0.05**	1.11 + 0.05**	1 12 + 0.05**	1 14 + 0.0200
Relative	$0.91 \pm 0.03$	$0.97 \pm 0.03$	$1.10 \pm 0.05^{\circ\circ}$	$1.11 \pm 0.05$ **	$1.12 \pm 0.05^{\circ\circ}$	$1.14 \pm 0.03$

Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Studies of HC Yellow 4ª

° Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test  $^{\circ\circ}$  P≤0.01

Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean  $\pm$  standard error). a

	0 ppm	2,500 ppm	5,000 ppm
Male	*****		
n	9	10	10
Necropsy body wt	$463 \pm 8$	473 ± 7	$452 \pm 8$
Brain			
Absolute	$2.11 \pm 0.02$	$2.06 \pm 0.02$	$2.03 \pm 0.03$
Relative	$4.56 \pm 0.10$	$4.37 \pm 0.08$	$4.50 \pm 0.08$
R. Kidney			
Absolute	$1.52 \pm 0.02$	$1.43 \pm 0.03$	$1.42 \pm 0.04$
Relative	$3.30 \pm 0.08$	$3.04 \pm 0.08$	$3.15 \pm 0.07$
Liver			
Absolute	$15.81 \pm 0.34$	$15.61 \pm 0.33$	$15.13 \pm 0.42$
Relative	$34.2 \pm 0.8$	$33.0 \pm 0.6$	$33.5 \pm 0.6$
	0 ррт	5,000 ppm	10,000 ppm
Female			· ·
n	10	10	10
Necropsy body wt	$328 \pm 6$	$314 \pm 8$	$297 \pm 6^{**}$
Brain	,		
Absolute	$1.85 \pm 0.02$	$1.85 \pm 0.02$	$1.87 \pm 0.01$
Relative	$5.65 \pm 0.11$	$5.92 \pm 0.13$	$6.33 \pm 0.14^{**}$
R. Kidney			
Absolute	$0.888 \pm 0.024$	$0.812 \pm 0.016^{**}$	$0.805 \pm 0.015^{**}$
	$270 \pm 0.05$	$2.59 \pm 0.05$	$2.72 \pm 0.03$
Relative	2.70 ± 0.05		
Relative Liver	2.70 ± 0.05		
Relative Liver Absolute	$9.30 \pm 0.27$	$9.57 \pm 0.33$	$9.76 \pm 0.19$

Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluations in the 2-Year Feed Studies of HC Yellow 4<sup>a</sup>

\* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test

\*\* P≤0.01

<sup>a</sup> Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Day Feed Studies of HC Yellow 4ª

	0 ppm	1,250 ppm	2, <b>500</b> ppm	5,010 ppm	10,000 ppm	20,000 ppm
Male				<u>.</u>		
n	5	5	5	5	5	5
Necropsy body wt	$26.2 \pm 0.6$	$28.2 \pm 0.3$	$28.4 \pm 0.3$	$28.3 \pm 0.2$	$27.0 \pm 0.3$	$22.9 \pm 0.9^{\circ \circ}$
Brain						
Absolute	$0.460 \pm 0.004$	$0.451 \pm 0.009$	$0.475 \pm 0.007$	$0.475 \pm 0.008$	$0.471 \pm 0.010$	$0.462 \pm 0.005$
Relative	$17.6 \pm 0.3$	$16.0 \pm 0.4$	$16.7 \pm 0.3$	$16.8 \pm 0.4$	$17.4 \pm 0.3$	$20.3 \pm 0.7^{\circ \circ}$
Heart						
Absolute	$0.133 \pm 0.006$	$0.150 \pm 0.008$	$0.166 \pm 0.009^{\circ}$	$0.166 \pm 0.012^{\circ}$	$0.153 \pm 0.003$	$0.134 \pm 0.005$
Relative	$5.08 \pm 0.18$	$5.33 \pm 0.25$	$5.85 \pm 0.33$	$5.88 \pm 0.43$	$5.66 \pm 0.13$	$5.85 \pm 0.22$
R. Kidney						
Absolute	$0.278 \pm 0.010$	$0.300 \pm 0.013$	$0.327 \pm 0.006^{**}$	$0.323 \pm 0.008^{\circ}$	$0.292 \pm 0.009$	$0.243 \pm 0.009$
Relative	$10.6 \pm 0.2$	$10.6 \pm 0.4$	$11.5 \pm 0.2$	$11.4 \pm 0.3$	$10.8 \pm 0.3$	$10.6 \pm 0.3$
Liver						
Absolute	$1.34 \pm 0.02$	$1.57 \pm 0.04^{\circ\circ}$	$1.78 \pm 0.05^{\circ\circ}$	$1.83 \pm 0.04^{**}$	$1.66 \pm 0.07^{**}$	$1.34 \pm 0.04$
Relative	$51.3 \pm 0.2$	$55.6 \pm 1.5^{\circ}$	$62.5 \pm 1.2^{**}$	$64.8 \pm 0.9^{\circ \circ}$	$61.4 \pm 2.2^{**}$	$58.5 \pm 0.8^{\circ \circ}$
Lungs						
Absolute	$0.174 \pm 0.007$	$0.280 \pm 0.041^{\circ\circ}$	$0.228 \pm 0.007$	$0.231 \pm 0.005$	$0.208 \pm 0.009$	$0.223 \pm 0.029$
Relative	$6.64 \pm 0.19$	$9.93 \pm 1.48$	$8.02 \pm 0.20$	$8.17 \pm 0.23$	$7.70 \pm 0.33$	$9.95 \pm 1.72$
R. Testis						
Absolute	$0.108 \pm 0.006$	$0.108 \pm 0.003$	$0.119 \pm 0.002$	$0.115 \pm 0.004$	$0.115 \pm 0.004$	$0.112 \pm 0.002$
Relative	$4.12 \pm 0.23$	$3.83 \pm 0.07$	$4.18 \pm 0.05$	$4.08 \pm 0.18$	$4.26 \pm 0.13$	$4.92 \pm 0.18^{\circ \circ}$
Thymus						
Absolute	$0.039 \pm 0.006$	$0.050 \pm 0.002$	$0.056 \pm 0.003$	$0.046 \pm 0.005$	$0.049 \pm 0.006$	$0.035 \pm 0.004$
Relative	$1.5 \pm 0.2$	$1.8 \pm 0.1$	$2.0 \pm 0.1$	$1.6 \pm 0.2$	$1.8 \pm 0.2$	$1.6 \pm 0.2$
Female						
n	5	5	5	5	5	5
Necropsy body wt	$20.6 \pm 0.4$	$21.7 \pm 0.6$	$20.1 \pm 0.4$	$20.8 \pm 0.1$	$20.0 \pm 0.3$	$20.8 \pm 0.5$
Brain						
Absolute	$0.507 \pm 0.013$	$0.487 \pm 0.010$	$0.484 \pm 0.008$	$0.502 \pm 0.007$	$0.500 \pm 0.008$	$0.517 \pm 0.026$
Relative	$24.5 \pm 0.6$	$22.5 \pm 0.7$	$24.2 \pm 0.7$	$24.2 \pm 0.3$	$25.1 \pm 0.4$	$24.8 \pm 0.7$
Heart						
Absolute	$0.134 \pm 0.011$	$0.127 \pm 0.010$	$0.136 \pm 0.010$	$0.131 \pm 0.004$	$0.125 \pm 0.003$	$0.147 \pm 0.016$
Relative	$6.48 \pm 0.45$	$5.91 \pm 0.51$	$6.79 \pm 0.59$	$6.28 \pm 0.21$	$6.26 \pm 0.14$	$7.03 \pm 0.62$
R. Kidney						
Absolute	$0.196 \pm 0.009$	$0.199 \pm 0.005$	$0.200 \pm 0.011$	$0.209 \pm 0.006$	$0.187 \pm 0.005$	$0.202 \pm 0.015$
Relative	$9.51 \pm 0.47$	$9.19 \pm 0.34$	$9.96 \pm 0.60$	$10.05 \pm 0.25$	$9.35 \pm 0.13$	$9.72 \pm 0.61$
Liver			_			
Absolute	$1.17 \pm 0.05$	$1.32 \pm 0.04$	$1.30 \pm 0.01$	$1.35 \pm 0.05$	$1.25 \pm 0.05$	$1.44 \pm 0.08^{\circ \circ}$
Relative	$56.4 \pm 1.8$	$61.0 \pm 1.3$	$65.0 \pm 1.2^{\circ \circ}$	$64.8 \pm 2.1$ **	$62.8 \pm 2.0^{\circ \circ}$	69.4 ± 2.2**
Lungs						
Absolute	$0.231 \pm 0.018$	$0.221 \pm 0.011$	$0.249 \pm 0.016$	$0.221 \pm 0.010$	$0.219 \pm 0.010$	$0.231 \pm 0.022$
Relative	$11.2 \pm 0.9$	$10.3 \pm 0.8$	$12.4 \pm 0.9$	$10.6 \pm 0.4$	$11.0 \pm 0.6$	$11.1 \pm 0.8$
Thymus						
Absolute	$0.084 \pm 0.007$	$0.063 \pm 0.016$	$0.083 \pm 0.003$	$0.077 \pm 0.006$	$0.073 \pm 0.008$	$0.093 \pm 0.014$
Relative	$4.08 \pm 0.30$	$2.94 \pm 0.78$	$4.11 \pm 0.14$	$3.68 \pm 0.29$	$3.69 \pm 0.43$	$4.45 \pm 0.64$

<sup>o</sup> Significantly different (P≤0.05) from the control group by Wiliams' or Dunnett's test
 <sup>o</sup> P≤0.01
 <sup>a</sup> Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

Organ	Weights and	Organ-Weight-to-Body-Weight	<b>Ratios</b> for	r Mice in	n the	13-Week	Feed	Studies
of HC	Yellow 4 <sup>a</sup>							

	0 ррт	5,000 ppm	10,000 ppm	20,000 ррт	40,000 ppm	80,000 ppm
Male						
n	10	10	10	10	9	2
Necropsy body wt	$28.2 \pm 0.5$	$29.7 \pm 0.7$	$27.6 \pm 0.6$	$27.9 \pm 0.5$	$26.4 \pm 0.5$	$21.3 \pm 1.1$
Brain						
Absolute	$0.463 \pm 0.005$	$0.455 \pm 0.004$	$0.453 \pm 0.011$	$0.446 \pm 0.008^{6}$	$0.439 \pm 0.007$	$0.502 \pm 0.060$
Relative	$16.5 \pm 0.3$	$15.4 \pm 0.3$	$16.5 \pm 0.5$	$16.1 \pm 0.4^{\circ}$	$16.7 \pm 0.4$	$23.5 \pm 1.6^{\bullet \bullet}$
Heart						
Absolute	$0.144 \pm 0.005$	$0.155 \pm 0.007^{\circ}$	$0.149 \pm 0.007$	$0.133 \pm 0.006$	$0.121 \pm 0.004^*$	$0.124 \pm 0.026$
Relative	$5.10 \pm 0.14$	$5.23 \pm 0.19^{D}$	$5.40 \pm 0.24$	$4.75 \pm 0.21$	$4.61 \pm 0.19$	$5.76 \pm 0.92$
R. Kidney		. *				
Absolute	$0.251 \pm 0.011$	$0.283 \pm 0.005$	0.258 ± 0.006 <sup>D</sup>	$0.230 \pm 0.006$	$0.210 \pm 0.008^{**}$	$0.162 \pm 0.005^{**}$
Relative	$8.87 \pm 0.29$	$9.61 \pm 0.31$	$9.49 \pm 0.20^{\circ}$	$8.21 \pm 0.15$	$7.96 \pm 0.28^*$	$7.59 \pm 0.16^*$
Liver				۰.		
Absolute	$1.23 \pm 0.06$	$1.52 \pm 0.05^{**}$	$1.42 \pm 0.04^*$	$1.30 \pm 0.04^{\text{D}}$	$1.35 \pm 0.05$	$1.03 \pm 0.08$
Relative	$43.5 \pm 1.6$	$51.4 \pm 1.5^{**}$	$51.4 \pm 1.2^{\bullet\bullet}$	$46.6 \pm 0.7^{D}$	$51.1 \pm 1.5^{**}$	$48.5 \pm 1.1$
Lungs						
Absolute	$0.211 \pm 0.011$	$0.249 \pm 0.017$	$0.251 \pm 0.015$	$0.230 \pm 0.009$	$0.231 \pm 0.012$	$0.309 \pm 0.058^*$
Relative	$7.47 \pm 0.33$	$8.41 \pm 0.56$	$9.11 \pm 0.50$	$8.13 \pm 0.32$	$8.84 \pm 0.55$	$14.40 \pm 1.98^{**}$
R. Testis						
Absolute	$0.117 \pm 0.002$	$0.112 \pm 0.002$	$0.114 \pm 0.004$	$0.111 \pm 0.004$	$0.113 \pm 0.004^{\circ}$	$0.095 \pm 0.012^*$
Relative	$4.15 \pm 0.06$	$3.78 \pm 0.07^*$	$4.15 \pm 0.13$	$3.98 \pm 0.09$	$4.28 \pm 0.07^{\circ}$	$4.42 \pm 0.35$
Thymus						
Absolute	$0.033 \pm 0.002$	$0.041 \pm 0.002^*$	$0.041 \pm 0.003^{\circ}$	$0.043 \pm 0.002^{**}$	$0.042 \pm 0.003^{**}$	$0.043 \pm 0.010$
Relative	$1.16 \pm 0.07$	$1.38 \pm 0.07$	$1.48 \pm 0.10^*$	$1.56 \pm 0.08^{**}$	$1.61 \pm 0.10^{**}$	$2.02 \pm 0.37^{**}$
Female						*
n	10	10	10	9	. 9	3
Necropsy body wt	$24.8 \pm 0.6$	$23.8 \pm 0.3$	$22.6 \pm 0.2^{**}$	$21.0 \pm 0.3^{**}$	$18.7 \pm 0.2^{**}$	17.2 ± 0.8**
Brain						
Absolute	$0.479 \pm 0.004$	$0.471 \pm 0.006$	$0.443 \pm 0.008^{**}$	$0.470 \pm 0.006^{*}$	$0.433 \pm 0.006^{**}$	$0.431 \pm 0.011^{**}$
Relative	$19.4 \pm 0.5$	$19.8 \pm 0.2$	$19.6 \pm 0.4$	$22.3 \pm 0.4^{**}$	$23.2 \pm 0.3^{**}$	$25.1 \pm 0.6^{**}$
Heart						
Absolute	$0.114 \pm 0.002^{b}$	$0.121 \pm 0.005$	$0.115 \pm 0.003$	$0.116 \pm 0.006$	$0.096 \pm 0.003^{**}$	$0.092 \pm 0.009^*$
Relative	$4.63 \pm 0.10^{b}$	$5.06 \pm 0.16$	$5.08 \pm 0.15$	$5.51 \pm 0.27$ **	$5.16 \pm 0.15^{**}$	$5.34 \pm 0.28$
R. Kidney						
Absolute	$0.181 \pm 0.006$	$0.185 \pm 0.004$	$0.170 \pm 0.004^{b}$	$0.158 \pm 0.003^{\bullet\bullet}$	$0.136 \pm 0.003^{**}$	$0.136 \pm 0.010^{**}$
Relative	$7.31 \pm 0.22$	$7.78 \pm 0.13$	$7.50 \pm 0.17^{b}$	$7.46 \pm 0.11$	$7.25 \pm 0.18$	$7.87 \pm 0.25$
Liver						
Absolute	$1.245 \pm 0.043$	$1.205 \pm 0.049$	$1.136 \pm 0.027$	$1.115 \pm 0.089$	$0.810 \pm 0.021^{**}$	$0.883 \pm 0.080^{**}$
Relative	$50.2 \pm 1.0$	$50.5 \pm 1.7$	$50.2 \pm 0.9$	$52.7 \pm 4.1$	$43.3 \pm 1.0$	$51.3 \pm 3.7$
Lungs						
Absolute	$0.233 \pm 0.017$	$0.255 \pm 0.014$	$0.244 \pm 0.015$	$0.258 \pm 0.024$	$0.192 \pm 0.022$	$0.176 \pm 0.005$
Relative	9.43 ± 0.69	$10.66 \pm 0.51$	$10.79 \pm 0.64$	$12.14 \pm 1.05$	$10.23 \pm 1.16$	$10.30 \pm 0.64$
Thymus						
Absolute	$0.043 \pm 0.003$	$0.044 \pm 0.003$	$0.036 \pm 0.002$	$0.041 \pm 0.001$	$0.047 \pm 0.003$	$0.048 \pm 0.006$
Relative	$1.74 \pm 0.11$	$1.83 \pm 0.10$	$1.60 \pm 0.08$	$1.93 \pm 0.04$	$2.52 \pm 0.13^{**}$	$2.80 \pm 0.31^{**}$

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

°<sup>®</sup> P≤0.01 <sup>a</sup> Organ y

<sup>a</sup> Organ weights and body weights are given in grams; organ-weight-to-body weight ratios are given as mg organ weight/g body weight (mean ± standard error).

b n=9

 $c_{n=8}$ 

Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluations in the 2-Year Feed Studies of HC Yellow 4<sup>a</sup>

	ு நின்	5,000 ppm	10,009 ppm
Male			······································
n	10	10	10
Necropsy body wt	$37.4 \pm 1.7$	$33.7 \pm 1.6$	$30.8 \pm 0.8^{\circ \circ}$
Brain			
Absolute	$0.466 \pm 0.005$	$0.467 \pm 0.008$	$0.459 \pm 0.006$
Relative	$12.7 \pm 0.6$	$14.1 \pm 0.6$	$15.0 \pm 0.3^{\circ \circ}$
R. Kidney			
Absolute	$0.316 \pm 0.010$	$0.292 \pm 0.007$	$0.256 \pm 0.009^{\circ\circ}$
Relative	$8.52 \pm 0.29$	$8.77 \pm 0.32$	$8.30 \pm 0.17$
Liver			
Absolute	$1.51 \pm 0.07$	$1.42 \pm 0.07$	$1.28 \pm 0.04^{\circ}$
Relative	$40.3 \pm 1.0$	$42.2 \pm 1.2$	$41.7 \pm 0.8$
Female			
n	10	10	10
Necropsy body wt	$39.2 \pm 1.0$	$33.8 \pm 1.1^{\circ \circ}$	$27.7 \pm 1.0^{\circ\circ}$
Brain			
Absolute	$0.484 \pm 0.005$	$0.476 \pm 0.007$	0.464 ± 0.006°
Relative	$12.4 \pm 0.3$	$14.2 \pm 0.4^{\circ \circ}$	$16.9 \pm 0.5^{\circ \circ}$
R. Kidney			
Absolute	$0.206 \pm 0.005$	$0.198 \pm 0.004$	$0.176 \pm 0.008^{\circ\circ}$
Relative	$5.26 \pm 0.14$	5.90 ± 0.24°	$6.32 \pm 0.11^{\circ\circ}$
Liver			
Absolute	$1.39 \pm 0.03$	$1.32 \pm 0.03$	$1.17 \pm 0.03^{**}$
Relative	$35.7 \pm 0.9$	$39.4 \pm 1.1$ **	$42.3 \pm 0.7^{\circ \circ}$

° Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test

°° P≤0.01

<sup>a</sup> Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

## APPENDIX G HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

Table G1	Clinical Chemistry Data for Rats at the 6-Month Interim Evaluations	
	in the 2-Year Feed Studies of HC Yellow 4	192
Table G2	Hematology and Clinical Chemistry Data for Rats	
	at the 15-Month Interim Evaluations	
	in the 2-Year Feed Studies of HC Yellow 4	193
Table G3	Clinical Chemistry Data for Mice at the 6-Month Interim Evaluations	
	in the 2-Year Feed Studies of HC Yellow 4	195
Table G4	Hematology and Clinical Chemistry Data for Mice	
	at the 15-Month Interim Evaluations	
	in the 2-Year Feed Studies of HC Yellow 4	196

Analysis	0 ррт	5,000 ppm	10,000 ррт
Male			
n	10	9	
Thyroid-stimulating hormone (ng/mL)	395 ± 27	$452 \pm 46^{b}$	
Triiodothyronine (ng/dL)	$74 \pm 4$	69 ± 6	
Thyroxine $(\mu g/dL)$	$2 \pm 0$	$3 \pm 0$	
Female			
n	10	10	10
Thyroid-stimulating hormone (ng/mL)	<b>399 ±</b> 18	_c	355 ± 14*
Triiodothyronine (ng/dL)	$79 \pm 6$	· _ ·	$62 \pm 4$
Thyroxine (µg/dL)	$2 \pm 0$	<b>-</b> .	$2 \pm 0$

#### TABLE G1 Clinical Chemistry Data for Rats at the 6-Month Interim Evaluations in the 2-Year Feed Studies of HC Yellow 4<sup>a</sup>

\* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Mean  $\pm$  standard error. No male rats received doses of 10,000 ppm.

b n=10

c No measurements were taken for this dose group.

#### Hematology and Clinical Chemistry

#### Table G2

Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluations in the 2-Year Feed Studies of HC Yellow  $4^a$ 

Amalysis	0 ppm	2,500 ppm	5,010 ppm
Male			
n	10	10	10
Hematology			
Hematocrit (%)	$44.0 \pm 2.0$	$46.0 \pm 1.1$	$44.3 \pm 1.1$
Hemoglobin (g/dL)	$15.9 \pm 0.8$	$16.9 \pm 0.5$	$16.1 \pm 0.5$
Erythrocytes $(10^6/\mu L)$	$9.03 \pm 0.33$	$9.55 \pm 0.27$	$9.42 \pm 0.07$
Mean cell volume (fL)	$48.6 \pm 0.7$	$48.2 \pm 0.3$	$46.9 \pm 1.0^{\circ}$
Mean cell hemoglobin (pg)	$17.5 \pm 0.4$	$17.7 \pm 0.1$	$17.0 \pm 0.5$
Mean cell hemoglobin			
concentration (g/dL)	$36.1 \pm 0.4$	$36.8 \pm 0.3$	$36.2 \pm 0.3$
Leukocytes $(10^{3}/\mu L)$	$5.94 \pm 0.58^{b}$	$5.74 \pm 0.29$	$6.85 \pm 0.45$
Segmented neutrophils $(10^3/\mu L)$	$2.52 \pm 0.52^{b}$	$2.13 \pm 0.21$	$3.14 \pm 0.43$
Lymphocytes $(10^{3}/\mu L)$	$3.00 \pm 0.10^{b}$	$3.24 \pm 0.17$	$3.26 \pm 0.16$
Monocytes $(10^3/\mu L)$	$0.19 \pm 0.06^{b}$	$0.16 \pm 0.04$	$0.22 \pm 0.04$
Eosinophils $(10^3/\mu L)$	$0.07 \pm 0.02^{b}$	$0.08 \pm 0.02$	$0.06 \pm 0.02$
Nucleated erythrocytes $(10^3/\mu L)$	$0.07 \pm 0.04^{\mathrm{b}}$	$0.09 \pm 0.04$	$0.05 \pm 0.04$
n ·	9	9	10
Clinical chemistry			
Blood uses nitrogen (mg/dL)	154 + 13	154 + 1.7	$30.2 + 6.1^{\circ}$
Alkaline phosphatase (IU/L)	$146 \pm 5$	$144 \pm 9^{c}$	$155 \pm 7$
Alanine aminotransferase (IU/L)	$104 \pm 15$	$102 \pm 6$	$101 \pm 8$
Aspartate aminotransferase (IU/L)	$180 \pm 21$	$154 \pm 7$	$146 \pm 7$
Sorbitol dehydrogenase (SU/mL)	$948 \pm 103$	$625 \pm 26^{\circ}$	856 ± 86

Analysis	0 ppm	5,000 ppm	10,000 ppm
Female			
a	10	10	10
Hematology			
Hematocrit (%)	$44.4 \pm 0.2$	$44.3 \pm 0.3$	$43.9 \pm 0.3$
Hemoglobin (g/dL)	$16.1 \pm 0.1$	$16.1 \pm 0.1$	$15.8 \pm 0.1^*$
Erythrocytes $(10^6/\mu L)$	$8.28 \pm 0.05$	$8.32 \pm 0.08$	$8.24 \pm 0.08$
Mean cell volume (fL)	$53.7 \pm 0.2$	$53.2 \pm 0.3$	$53.3 \pm 0.2$
Mean cell hemoglobin (pg)	$19.5 \pm 0.1$	$19.3 \pm 0.1$	$19.1 \pm 0.1^{\circ}$
Mean cell hemoglobin			
concentration (g/dL)	$36.3 \pm 0.2$	$36.2 \pm 0.2$	$36.0 \pm 0.1$
Leukocytes $(10^{3}/\mu L)$	$3.41 \pm 0.19$	$3.58 \pm 0.11$	$4.08 \pm 0.26$
Segmented neutrophils $(10^3/\mu L)$	$1.13 \pm 0.08$	$1.23 \pm 0.09$	$1.59 \pm 0.22$
Lymphocytes $(10^3/\mu L)$	$2.07 \pm 0.15$	$2.11 \pm 0.09$	$2.25 \pm 0.10$
Monocytes $(10^3/\mu L)$	$0.11 \pm 0.02$	$0.16 \pm 0.01^{\circ}$	$0.18 \pm 0.02^*$
Eosinophils $(10^3/\mu L)$	$0.06 \pm 0.01$	$0.05 \pm 0.01$	$0.04 \pm 0.01$
Nucleated erythrocytes $(10^3/\mu L)$	$0.04 \pm 0.02$	$0.04 \pm 0.02$	$0.01 \pm 0.01$
Clinical chemistry	•		
Blood urea nitrogen (mg/dL)	$13.7 \pm 0.5$	$17.0 \pm 1.0^{*}$	$15.9 \pm 0.6^*$
Alkaline phosphatase (IU/L)	$145 \pm 6$	$148 \pm 7$	$148 \pm 6$
Alanine aminotransferase (IU/L)	$58 \pm 4$	57 ± 4	$75 \pm 13$
Aspartate aminotransferase (IU/L)	94 ± 6	96 ± 7	$115 \pm 17$
Sorbitol dehydrogenase (SU/mL)	$666 \pm 42$	$745 \pm 68$	872 ± 152

#### TABLE G2

Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Ev	valuations
in the 2-Year Feed Studies of HC Yellow 4 (continued)	

\* Significantly different (P $\le 0.05$ ) from the control group by Dunn's or Shirley's test \*\* P $\le 0.01$ a Mean  $\pm$  standard error. b n=8

b n=8c n=10

#### TABLE G3 Clinical Chemistry Data for Mice at the 6-Month Interim Evaluations

							• 1.1011000	 	
1m	the	2-Year	Feed	Studies	of HO	C Yellow	4 <sup>a</sup>		

Amalysis	0 ppm	5,000 ppm	10,000 ppm
Male			
n	10	10	10
Triiodothyronine (ng/dL) Thyroxine ( $\mu$ /dL)	$105 \pm 5$ $4.09 \pm 0.23$	99 ± 3 6.09 ± 0.25°°	$78 \pm 6^{\circ \circ}$ 6.32 ± 0.28 <sup>\circ</sup>
Female			
n	10	10	10
Triiodothyronine (ng/dL) Thyroxine (µ/dL)	$83 \pm 5^{b}$ 4.98 ± 0.18	$94 \pm 2$ 6.34 $\pm$ 0.30**	$70 \pm 4^{b}$ 6.51 ± 0.55**

<sup>oo</sup> Significantly different (P≤0.01) from the control group by Dunn's or Shirley's test <sup>a</sup> Mean  $\pm$  standard error. <sup>b</sup> n=9

Analysis	0 ррт	5,000 ppm	10,000 ppm
Male	м <u>и (* </u> ,		· <u> </u>
1	10	10	10
lematology			
Hematocrit (%)	$42.2 \pm 0.9$	$39.9 \pm 0.9$	$43.2 \pm 0.3$
Hemoglobin (g/dL)	$15.3 \pm 0.3$	$14.6 \pm 0.3$	$15.8 \pm 0.2$
Erythrocytes $(10^6/\mu L)$	$8.83 \pm 0.19$	8.27 ± 0.23	$9.02 \pm 0.11$
Mean cell volume (fL)	$47.8 \pm 0.2$	$48.2 \pm 0.7$	$47.9 \pm 0.5$
Mean cell hemoglobin (pg)	$17.3 \pm 0.2$	$17.7 \pm 0.2$	$17.5 \pm 0.2$
Mean cell hemoglobin concentration (g/dL)	$36.3 \pm 0.4$	$36.7 \pm 0.3$	$36.5 \pm 0.4$
Leukocytes $(10^{3}/\mu L)$	$5.23 \pm 0.56$	$5.33 \pm 0.70$	$4.46 \pm 0.58$
Segmented neutrophils $(10^3/\mu L)$	$2.81 \pm 0.50$	$1.55 \pm 0.18$	$1.05 \pm 0.22^{**}$
Lymphocytes $(10^3/\mu L)$	$1.98 \pm 0.17$	$3.41 \pm 0.59^*$	$3.05 \pm 0.44^*$
Monocytes $(10^3/\mu L)$	$0.07 \pm 0.02$	$0.09 \pm 0.03$	$0.06 \pm 0.02$
Eosinophils $(10^3/\mu L)$	$0.07 \pm 0.03$	$0.11 \pm 0.03$	$0.09 \pm 0.02$
Nucleated erythrocytes $(10^3/\mu L)$	$0.02 \pm 0.01$	$0.10 \pm 0.04^*$	$0.12 \pm 0.03^{**}$
1	10	9	10
Clinical chemistry			
Blood urea nitrogen (mg/dL)	$22.8 \pm 1.4$	$24.4 \pm 3.2$	$24.4 \pm 1.4$
Alkaline phosphatase (IU/L)	$48 \pm 5$	$46 \pm 2$	$52 \pm 2$
Alanine aminotransferase (IU/L)	$34 \pm 3^{b}$	$38 \pm 5$	$42 \pm 3^{b}$
Aspartate aminotransferase (IU/L)	$108 \pm 14^{b}$	$125 \pm 10$	$183 \pm 22^{**}$
Sorbitol dehydrogenase (SU/mL)	$1.858 \pm 73$	$1,845 \pm 143$	$1,651 \pm 103$

#### TABLE G4

Hematology and	<b>Clinical Chemistry</b>	Data for	Mice at	the 15-Month	Interim	Evaluations
in the 2-Year Fe	ed Studies of HC Y	ellow 4 <sup>a</sup>				

#### Hematology and Clinical Chemistry

#### Table G4

Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluations in the 2-Year Feed Studies of HC Yellow 4 (continued)

Analysis	0 ppm	5,010 ppm	10,000 ppm
Female		<u> </u>	
n	10	10	10
Hematology			
Hematocrit (%)	$43.4 \pm 0.6$	$43.8 \pm 0.4$	$43.6 \pm 0.7$
Hemoglobin (g/dL)	$15.3 \pm 0.2$	$15.1 \pm 0.1$	$15.4 \pm 0.2$
Erythrocytes $(10^6/\mu L)$	$9.29 \pm 0.12$	9.44 ± 0.10	9.57 ± 0.19
Mean cell volume (fL)	$46.5 \pm 0.2$	$46.4 \pm 0.2$	$45.6 \pm 0.3^{\circ}$
Mean cell hemoglobin (pg)	$16.5 \pm 0.1$	$15.9 \pm 0.1^{\circ \circ}$	$16.1 \pm 0.2^{\circ}$
Mean cell hemoglobin concentration (g/dL)	$35.3 \pm 0.3$	$34.4 \pm 0.2^{\circ}$	$35.2 \pm 0.2$
Leukocytes $(10^3/\mu L)$	$2.49 \pm 0.29$	$3.46 \pm 0.37$	$3.65 \pm 0.40^{\circ}$
Segmented neutrophils $(10^3/\mu L)$	$0.60 \pm 0.13$	$0.88 \pm 0.07^{\circ}$	$0.92 \pm 0.14^{\circ}$
Lymphocytes $(10^{3}/\mu L)$	$1.66 \pm 0.18$	$2.34 \pm 0.33$	$2.53 \pm 0.25^{\circ}$
Monocytes $(10^3/\mu L)$	$0.08 \pm 0.02$	$0.09 \pm 0.01$	$0.09 \pm 0.03$
Eosinophils $(10^3/\mu L)$	$0.07 \pm 0.02$	$0.04 \pm 0.01$	$0.04 \pm 0.01$
Nucleated erythrocytes $(10^3/\mu L)$	$0.04 \pm 0.01$	$0.05 \pm 0.02$	$0.02 \pm 0.01$
Clinical chemistry			
Blood urea nitrogen (mg/dL)	$13.8 \pm 1.0^{b}$	$18.0 \pm 2.3^{c}$	$20.2 \pm 1.9^{\circ b}$
Alkaline phosphatase (IU/L)	$81 \pm 6^{b}$	$83 \pm 3^{b}$	99 ± 7°
Alanine aminotransferase (IU/L)	$34 \pm 4$	$34 \pm 3^{b}$	45 ± 3°
Aspartate aminotransferase (IU/L)	$100 \pm 9$	$133 \pm 18$	$194 \pm 24^{\circ \circ b}$
Sorbitol dehydrogenase (SU/mL)	941 ± 74	947 ± 119	$1,004 \pm 57$

 $^\circ$  Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test  $^{\circ\circ}$  P≤0.01

<sup>a</sup> Mean  $\pm$  standard error. b

n=9 С

n=8

## APPENDIX HI CHIEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMEN	T AND CHARACTERIZATION	200
Preparation	and Analysis of Dose Formulations	201
Figure H1	Infrared Absorption Spectrum of HC Yellow 4	203
Figure H2	Nuclear Magnetic Resonance Spectrum of HC Yellow 4	204
Table H1	Preparation and Storage of Dose Formulations in the Feed Studies	
	of HC Yellow 4	205
Table H2	Results of Analysis of Dose Formulations Administered to Rats and Mice	
	in the 14-Day Feed Studies of HC Yellow 4	205
Table H3	Results of Analysis of Dose Formulations Administered to Rats and Mice	
	in the 13-Week Feed Studies of HC Yellow 4	207
Table H4	Results of Analysis of Dose Formulations Administered to Rats and Mice	
	in the 2-Year Feed Studies of HC Yellow 4	208
Table H5	Results of Referee Analysis of Dose Formulations	
	in the 13-Week and 2-Year Feed Studies of HC Yellow 4	210

199

### CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

#### **PROCUREMENT AND CHARACTERIZATION**

HC Yellow 4 was obtained from the Southland Corporation, Grant Meadow, New Jersey (lots 0-218 and 3-074), and from Prochemie International, Incorporated (lot 81031). Lot 0-218 was used in the 14-day, 13-week, and the first 11 months of the 2-year studies. Lot 3-074 was used in the next 7 months of the 2-year study, and lot 81031 was used the final 6 months of the 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). MRI reports on analyses performed in support of the HC Yellow 4 studies are on file at the National Institute of Environmental Health Sciences.

The three lots of dye, a fluffy, yellow powder, were identified as HC Yellow 4 by infrared, ultraviolet/visible, and nuclear magnetic resonance (NMR) spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra of HC Yellow 4, as shown in Figures H1 and H2 (Sadtler Standard Spectra).

The purity of the three lots was determined by elemental analysis, Karl Fischer water analysis, weight loss on drying, titration, ultraviolet/visible spectrophotometry (lot 0-218), thin-layer chromatography (TLC), and high-performance liquid chromatography (HPLC). Titration was performed by dissolving the sample in 50% aqueous ethanol containing 7.5% sodium citrate, followed by reduction of the nitro group with 0.5 N titanous chloride. TLC was performed on silica gel 60 F-254 plates with two solvent systems: A) methylene chloride:acetone:glacial acetic acid (70:26:4), and B) methanol:toluene (75:25). Visualization was accomplished with visible light, short (254 nm) and long (366 nm) wavelength ultraviolet light, a 2,6-dibromoquinonechloroimide spray (lot 0-218), and a spray of 0.4% methanolic solution of 2,6-dichloroquinonechloroimide followed by a spray of 10% aqueous sodium carbonate solution (lots 3-074 and 81031). HPLC was performed with a  $\mu$ Bondapak C<sub>18</sub> column in a mixture of two solvents: A) 0.005 M heptanesulfonic acid in water, with pH adjusted to approximately 2.00 with concentrated phosphoric acid and B) 0.005 M heptanesulfonic acid in methanol, with an equal volume of phosphoric acid added as solvent A, with a ratio of 80:20 A:B (lot 0-218), 67:33 A:B (lot 3-074), or 85:15 A:B (lot 81031), at a flow rate of 1 mL/minute. Visible detection was at 405 nm for all lots, and ultraviolet detection was at 254 nm for lots 3-074 and 81031.

For lot 0-218, elemental analyses for carbon, hydrogen, and nitrogen were in agreement with theoretical values. Karl Fischer water analysis indicated  $0.84 \pm 0.02\%$  water. Weight loss on drying indicated  $0.38 \pm 0.01\%$  water. Titration by reduction of the nitro group indicated a purity of  $105.6 \pm 1.2\%$ . TLC indicated one major spot, one trace impurity, and one slight impurity by solvent system A, and one homogeneous spot by solvent system B. HPLC indicated one major peak and three impurities; the area of the largest impurity was 6.5% relative to the major peak. The two remaining impurities had a combined area of 0.40% relative to the major peak. The identity of the major impurity was tentatively identified by mass spectroscopy and synthesis data as N-(2-hydroxyethyl)-2-hydroxy-4-nitroaniline, with a concentration of 7% to 8% of the total peak area estimated from HPLC data. A comparison of the chromatographic profiles of lot 0-218 and the manufacturer's pure standard of HC Yellow 4 indicated the relative purity of lot 0-218 was 93.4  $\pm$  0.7% and the concentration of the major impurity was 1/25th as large in the standard. Based upon the above data, the purity of Lot 0-218 was estimated at greater than 93%.

For lot 3-074, elemental analyses for carbon, hydrogen, and nitrogen were in agreement with theoretical values. Karl Fischer water analysis indicated  $0.33 \pm 0.06\%$  water. Weight loss on drying indicated  $0.15 \pm 0.02\%$  water. Titration by reduction of the nitro group indicated a purity of  $103.4 \pm 0.7\%$ .

#### **Chemical Characterization and Dose Formulation**

TLC indicated one major spot, one minor impurity, and one trace impurity by solvent system A, and one major spot and a slight trace impurity by solvent system B. HPLC indicated one major peak and four impurities with a combined area of 2.9% at 254 nm and 3.1% at 405 nm relative to the major peak. The largest of the impurities (approximately 2.5%) was tentatively identified as N-(2-hydroxyethyl)-2-hydroxy-4-nitroaniline. Major peak comparison of lots 0-218 and 3-074 indicated a purity of 105.1  $\pm$  0.4% for lot 3-074 relative to lot 0-218. Based upon the above data, the purity of lot 3-074 was estimated at greater than 97%.

For lot 81031, elemental analyses for carbon, hydrogen, and nitrogen were in agreement with theoretical values. Karl Fischer water analysis indicated less than 0.05% water. Weight loss on drying indicated 0.04  $\pm$  0.01% water. Titration by reduction of the nitro group, with concomitant analyses of lots 0-218 and 81031, indicated a purity of 101.1  $\pm$  0.3% for lot 0-218 and 100.6  $\pm$  0.8% for lot 81031. TLC indicated one major spot and three trace impurities by solvent system A, and one major spot and a minor impurity by solvent system B. HPLC indicated one major peak and six impurities with a combined area of 1.2% at 254 nm and one major peak was 0.3% of the major peak. Major peak comparison of lots 0-218 and 81031 indicated a purity of 105.1% for lot 81031 relative to lot 0-218. Based upon the above data, the purity of lot 81031 was estimated at greater than 98%.

All three lots were analyzed for the possible presence of nitrosamines by HPLC equipped with a thermal energy analyzer (Thermo Electron Corp., Waltham, MA). Two or three nonpolar nitrosamines with combined concentrations of less than 0.5 ppm were found in each lot. A polar nitrosamine present at approximately 1.1 ppm was found in lot 81031. Another peak present at approximately 100 ppm could not be confirmed as a polar nitrosamine.

Stability studies performed by HPLC with the system described for analysis of the purity of lot 0-218 but with a ratio of 10:90 A:B and a flow rate of 2.5 mL/minute, with acetophenone added as an internal standard, indicated that HC Yellow 4, when stored protected from light, was stable as a bulk chemical for 2 weeks at temperatures up to 60° C. During the 2-year studies, the stability of the bulk chemical was monitored by the study laboratory using HPLC, titration of the nitro group, and infrared spectroscopy; no degradation of HC Yellow 4 was seen throughout the studies.

#### Preparation and Analysis of Dose Formulations

The dose formulations were prepared by mixing HC Yellow 4 with feed in a Patterson-Kelly twin-shell blender (Table H1). Dose formulations were prepared weekly.

Homogeneity and stability analyses of the dosed feed preparations were conducted by the analytical chemistry laboratory. For the homogeneity analyses, the formulations were extracted with 100 mL acetonitrile and centrifuged, then further diluted with acetonitrile. The absorbance of the samples was measured versus acetonitrile by ultraviolet spectroscopy at 398 nm. For the stability studies, feed samples were extracted with 100 mL of methanol:hydrochloric acid (99:1 v/v) and centrifuged; the extracts were then diluted with water:methanol (80:20), and were injected into an HPLC system equipped with a  $\mu$ Bondapak C<sub>18</sub> column and a 365 nm detector. The mobile phase was a mixture of two solvents: A) 0.005 M heptanesulfonic acid, sodium salt, in water, with pH adjusted to 2.0 with phosphoric acid added as solvent A, with a ratio of 80:20 A:B. Homogeneity of these formulations was confirmed; stability of the formulation was established for at least 2 weeks when stored in the dark at temperatures up to 25° C.

Periodic analyses of the dose formulations of HC Yellow 4 were conducted at the study laboratory and at the analytical chemistry laboratory using spectroscopy at 398 nm. Dose formulations were analyzed once during the 14-day studies. For the 13-week studies, dose formulations were analyzed at the

beginning of the studies, after the third mix, midway through the studies, and at the end of the studies. During the 14-day and 13-week studies, all dose formulations for rats and mice were within 10% of target concentrations (Table H2, H3). During the 2-year studies, the first and one of every eight sets of the dose formulations were analyzed; all dose formulations for rats and mice were within 10% of the target concentrations. Results of the dose formulation analyses studies for the 2-year studies are presented in Table H4. Results of periodic referee analysis performed by the analytical chemistry laboratory indicated good agreement with the results obtained by the study laboratory (Table H5).

2.5 20 10 50 3 5 6 8 4 100 OCH\_CH\_OH NH-CH\_CH\_OH 80 PERCENT TRANSMISSION 60 40 20 0 4000 3500 3000 2500 2000 1500 1000 500 200 WAVENUMBER CM-1 200 cm<sup>-1</sup>/min (out) Instrument: Beckman SB. DB J. Davidson X Speed: Analyst: \_ SB/DB Energy Ratio: \_\_\_\_1:1 Resolution: \_\_2.5 x Standard Slit Cell: ~\_1% (w/w) in KBr pellet VSE: Gain: 2,42 x 10 -Spectrum No.: \_\_\_\_007N Period: 2 8/21/80 Date: Sample: HC Yellow No. 4 Lot No.: 0-218 Batch No.: 01 Ordinate Scale: \_\_0-100% T Trimmer comb used in reference beam

WAVELENGTH IN MICRONS



203

Chemical Characterization and Dose Formulation



FIGURE H2 Nuclear Magnetic Resonance Spectrum of HC Yellow 4

#### Chemical Characterization and Dose Formulation

#### Table H1

Preparation and Storage of Dose Formulations in the Feed Studies of HC Yellow 4

14-Day Studies	13-Week Studies	2-Year Studies
Preparation A premix with HC Yellow 4 and feed (wt:vol) was prepared using a mortar and pestle; premix and remainder of feed was layered into a blender with an intensifier bar and mixed for 15 min. Dose formulations were prepared weekly.	Same as 14-day studies.	Same as 14-day studies.
Chemical Lot Number 0-218	0-218	0-218 3-074 81031
Maximum Storage Time 14 days from date of preparation	14 days from date of preparation	14 days from date of preparation
Storage Conditions In double plastic bags, in the dark, at $0 \pm 5^{\circ}$ C	In double, clear plastic bags, at approximately 4° C	In double plastic bags (inner bag opaque) at $0 \pm 5^{\circ}$ C
Study Laboratory EG&G Mason Research Institute, Worcester, MA	Same as 14-day studies.	Same as 14-day studies.
Referee Laboratory Midwest Research Institute, Kansas City, MO	Same as 14-day studies.	Same as 14-day studies.

205

# TABLE H2 Results of Analysis of Dose Formulations Administered to Rats and Mice in the 14-Day Feed Studies of HC Yellow 4

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration <sup>a</sup> (ppm)	% Difference from Target
8 July 1981	9 July 1981	1.250	1.140	-9
		2,500	2,330	-7
		5,000	5,060	+1
	10 July 1981	10,000	9,800	-2
	. •	20,000	18,000	-10
		40,000	39,400	-2
		80.000	73.000	-9

<sup>a</sup> Results of duplicate analyses

#### Chemical Characterization and Dose Formulation

#### TABLE H3

Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Feed Studies of HC Yellow 4

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration <sup>a</sup> (ppm)	% Difference from Target
10 February 1982	11 February 1982	2,500	2,330	-7
	<b>,</b>	5,000	4,760	-5
		10,000	10,300	+3
	12 February 1982	20,000	19,200	-4
	•	40,000	39,200	-2
		80,000	76,500	-4
26 February 1982	3 March 1982	2,500	2.400	-4 <sup>b</sup>
		2,500	2,370	-5 <sup>c</sup>
		2.500	2,250	-10 <sup>d</sup>
		80,000	79,300	-1 <sup>b</sup>
		80,000	79,800	0 <sup>c</sup>
		80,000	79,500	-1 <sup>d</sup>
13 April 1982	15 April 1982	2,500	2,360	-6
•	•	5,000	5,320	+6
		10,000	10,400	+4
		20,000	21,000	+5
		40,000	39,200	-2
		80,000	76,900	-4
18 May 1982	19 May 1982	2,500	2,380	-5
•		5,000	4,690	-6
		10,000	9,540	-5
		20,000	19,600	-2
		40,000	38,600	-3
		80,000	78,000	-3

a Results of duplicate analyses
 b Sample selection from top left of twin-shell blender
 c Sample selection from top right of twin-shell blender
 d Sample selection from bottom of twin-shell blender

# TABLE H4Results of Analysis of Dose Formulations Administered to Rats and Micein the 2-Year Feed Studies of HC Yellow 4

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration <sup>a</sup> (ppm)	% Difference from Target
9 March 1983	14 March 1983	2.500	2.260	-10 <sup>b</sup>
		2.500	2.300	-8 <sup>c</sup>
		2.500	2,440	-3 <sup>d</sup>
		5.000	4,790	-4
		10.000	9.580	-4 <sup>b</sup>
		10.000	9.520	-5 <sup>c</sup>
		10,000	10,000	0 <sup>d</sup>
5 May 1983	6 May 1983	2.500	2,540	+2
5 may 1905	• may 1500	5.000	4,840	-3
		10,000	9,700	-3
7 July 1983	8 July 1983	2,500	2.380	-5 <sup>b</sup>
7 July 1905	0 <b>Suly</b> 1905	2,500	2,520	+1°
		2,500	2,340	-6 <sup>d</sup>
		5,000	4.870	-3
		10,000	10 100	+1 <sup>b</sup>
		10,000	10,000	0°
		10,000	9,580	-4 <sup>d</sup>
22 Sentember 1983	23 Sentember 1983	2.500	2.290	-8
		5,000	4 860	-3
		10,000	9,890	-1
15 December 1983	20 December 1983	2.500	2.540	+2
10 D 000 moor 1700		5.000	4.840	-3
	<i>,</i>	10,000	9,840	-2
9 February 1984	9 February 1984	2,500	2,370	-5
,	· · · · · · · · · · · · · · · · · · ·	5.000	4,710	-6
	·	10,000	9,980	0
5 April 1984	6 April 1984	2.500	2,290	-8
	<u>-</u>	5.000	4,730	-5
		10,000	9,800	-2
24 May 1984	25 May 1984	2.500	2,440	-3
<b>_</b> , <i>i</i>	<i></i> , <i>_</i>	5.000	5,470	+9 <sup>e</sup>
		10,000	10,040	0
	30 May 1984 <sup>f</sup>	5,000	4,790	-4
28 June 1984	29 June 1984	2,500	2,560	+3
		5.000	5,080	+2
		10,000	10,000	0
7 August 1984	9 August 1984	2,500	2,500	0
<b>U</b>	~	5,000	4,880	-2
		10,000	10.200	+7

#### Table H4

#### Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of HC Yellow 4 (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	% Difference from Target
16 October 1984	18 October 1984	2,500	2,440	-2
•		5,000	4,780	-4
		10,000	10,200	+2
18 December 1984	20 December 1984	2,500	2,300	-8
		5,000	4,780	-4
		10,000	9,700	-3
12 February 1985	13 February 1985	2,500	2,550	+2
•	•	5,000	5,020	+1
		10,000	10,000	• 0
26 March 1985	2 April 1985	2,500	2.440	-2
		5.000	5.020	0
		10,000	9,820	-2

8 Results of duplicate analyses

b Sample selection from top left of twin-shell blender Sample selection from top right of twin-shell blender

с

d Sample selection from bottom of twin-shell blender

е Variation between duplicate samples was >10%, and samples contained relatively large aggregates of HC Yellow 4. Samples remixed. f

Analysis results of remix

				· . ·		Determined (	Concentration (ppm)	
Date Prepared	,	Target	Concenti (ppm)	ation	Ŷ	Study Laboratory <sup>a</sup>	Referee Laboratory <sup>b</sup>	
13-Week Studies	· · · · · · · · · · · · · · · · · · ·						· · · · · · · · · · · · · · · · · · ·	· · ·
16 February 1982		: : : : : :	2,500	· · ·	• •	2,330	2,460 ± 60	•
2-Year Studies			•	. •.	×			· · · · · ·
9 March 1983 22 September 1983 9 February 1984 7 August 1984 12 February 1985		<i>1</i>	2,250 10,000 5,000 2,500 10,000		· ·	2,330 9,890 4,710 2,500 10,000	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	·

#### TABLE H5 Results of Referee Analysis of Dose Formulations in the 13-Week and 2-Year Feed Studies of HC Yellow 4

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Results of duplicate analysis Results of triplicate analysis. Mean  $\pm$  standard deviation

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

Table I1	Feed and Compound Consumption by Male Rats in the 2-Year Feed Study	
	of HC Yellow 4	212
Table 12	Feed and Compound Consumption by Female Rats in the 2-Year Feed Study	
	of HC Yellow 4	213
Table 13	Feed and Compound Consumption by Male Mice in the 2-Year Feed Study	
	of HC Yellow 4	214
Table I4	Feed and Compound Consumption by Female Mice in the 2-Year Feed Study	
	of HC Yellow 4	215

#### TABLE I1

#### Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of HC Yellow 4

	0 m	DIR		2.500 ppm			5.000 npm	
Week	Feed (g/day) <sup>a</sup>	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day) <sup>b</sup>	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
	17.1	107	16.5	103	400	16.7	104	808
2	16.8	159	16.0	153	262	16.0	152	527
4	19.2	222	17.7	216	205	18.0	211	427
5	20.2	246	19.6	242	202	18.9	239	395
8	20.4	291	20.2	286	177	19.2	283	338
9	21.0	308	19.5	305	160	20.3	301	337
13	20.5	343	19.7	342	144	18.9	338	279
17	24.8	367	21.8	367	149	20.3	. 363	280
21	22.8	388	21.2	384	138	20.4	380	268
25	24.2	406	21.8	410	133	21.0	405	259
29	26.6	420	22.3	426	131	21.5	421	256
33	22.1	433	20.2	434	116	20.2	431	235
37	23.4	439	19.8	439	113	19.4	431	225
41	23.7	449	19.8	449	110	20.3	446	227
45	22.4	461	19.2	458	105	20.5	454	226
49	24.4	465	20.4	467	109	21.1	463	228
53	19.2	465	16.1	465	87	16.1	465	173
57	16.5	472	15.8	473	84	16.3	473	. 172
61	15.8	478	. 15.9	482	82	15.9	478	166
65	15.8	473	16.2	481	84	16.5	479	172
69	14.8	472	14.6	480	76	15.2	488	156
73	14.9	473	15.5	487	80	15.5	489	159
77	15.1	466	15.4	479 <sup>.</sup>	80	15.3	481	159
81	14.7	464	15.4	477	81	15.6	481	162
85	14.9	456	15.4	472	81	16.2	483	167
89	15.4	445	14.9	454	82	16.1	473	170
93	13.9	435	13.1	441	74	14.6	463	158
97	15.0	434	14.7	439	84	13.6	445	153
101	15.0	416	14.5	430	84	13.5	439	153
1 <b>04</b>	15.4	413	15.0	417	90	15.5	440	176
*** • •						· ^.		
weeks 1.	13:	220	10.4	225	221	10.7	222	
Mean	19.3	239	18.4	235	221	· 18.3	433	444
SD <sup>2</sup>	1.7		1.7		87	1.5		1/9
CV-	8.9		9.3		39.3	8.0		40.2
Weeks 14	4-52:							
Mean	23.8	425	20.7	426	123	20.5	421	245
SD	1.4		1.1		15	0.6	*	21
CV	5.7		5.3		12.6	3.0	· . ·	8.6
Weeks 53	3-104:							•
Mean	15.5	454	15.2	463	82	15.4	470	164
SD	1.2		0.8		4	0.9		· 8
CV	80		5.4		4.8	6.1		4.8

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Grams of feed consumed per animal per day Milligrams of HC Yellow 4 consumed per day per kilogram body weight

с d

Standard deviation of weekly means Coefficient of variation = (standard deviation/mean) x 100

#### TABLE I2

Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of HC Yellow 4

			5,000 ppm		10,000 ppm			
	Feed	Body	Feed	Body	Dose/	Feed	Body	Dose/
Week	(g/acy)-	vergint (g)	( <b>g/di</b> ay)	vergint (g)	للعي (mg/lg/day) <sup>b</sup>	(ල/ගතy)	weight (g)	iday (mg/kg/day)
	•							
1	15.0	<del>9</del> 9	13.6	<del>9</del> 9	687	12.6	98	1,284
2	14.0	131	14.3	134	533	14.3	128	1,114
4	14.6	154	14.3	162	441	13.7	156	878
5	16.3	165	13.7	171	401	13.5	165	817
8	15.0	190	14.5	191	380	14.3	184	775
9	15.8	196	13.9	197	354	13.3	189	706
12	15.3	20-6	15.5	208	374	14.8	200	740
13	15.8	209	15.2	212	357	13.6	204	667
17	15.9	221	15.7	225	350	15.2	217	701
21	15.2	228	14.3	229	311	13.6	222	613
25	15.7	237	14.8	238	310	14.0	230	611
29	15.8	247	13.9	247	281	14.4	239	605
33	17.4	254	14.8	250	297	14.2	239	594
37	15.5	263	14.1	258	273	13.5	245	551
41	17.2	276	14.9	266	281	13.9	250	555
45	15.5	277	13.6	271	251	12.9	255	504
49	18.1	292	16.1	279	289	15.5	262	594
53	10.8	300	12.6	288	218	12.3	272	451
57	12.2	315	12.6	299	211	11.9	281	425
61	10.9	317	10.8	300	181	10.4	280	372
65	11.9	334	11.8	318	186	11.5	297	386
69	12.4	336	11.9	321	185	11.5	298	385
73	12.7	349	12.5	335	187	10.6	309	343
77	14.2	355	13.3	342	194	12.4	314	396
81	13.1	360	14.4	352	204	13.6	322	424
85	12.2	360	11.3	348	163	11.9	321	370
89	12.7	358	12.7	351	181	12.0	326	369
93	12.8	356	13.0	356	182	12.2	324	376
97	12.5	356	11.8	351	169	11.9	327	364
101	12.2	355	13.2	351	189	13.0	330	394
104	13.1	354	13.3	353	189	12.2	330	369
Veeks 1-	13:	. •						
<b>lean</b>	15.2	169	14.4	172	441	13.8	166	873
D <sup>c</sup>	0.7		0.7		116	0.7		217
V <sup>d</sup>	4.9		4.7		26.2	4.9		24.8
Veeks 14	-52:		•	_				
<b>Aean</b>	16.2	255	14.7	251	294	14.1	240	592
D	1.0		0.8	۰. ۲	28	0.8		54
X.	6.3		5.7 <sub>014</sub> >,		9.6	5.9	,	9.2
eeks 53	8-104:			e 1. e				
Aean	12.4	343	12.5	333	189	12.0	309	388
D	0.9		0.9		15	0.8		29
CV	6.9		7.3	· · ·	7.9	7.0		7.4

8

Grams of feed consumed per animal per day Milligrams of HC Yellow 4 consumed per day per kilogram body weight Standard deviation of weekly means Coefficient of variation = (standard deviation/mean) x 100 b

c d

TABLE I3

Feed	and	Compound	Consumption	ı by	' Male	Mice	in the	e 2-Year	Feed	Stud	y of ]	HC	Yellow -	4
------	-----	----------	-------------	------	--------	------	--------	----------	------	------	--------	----	----------	---

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0 ppm		om		5.000 ppm		10,000 ppm			
Week	Feed (g/day) <sup>2</sup>	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day) <sup>b</sup>	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	
2	4.9	23.9	5.1	23.9	1,075	6.0	23.7	2,527	
5	5.8	28.3	6.0	28.5	1,052	7.8	27.3	2,849	
9	5.7	31.7	6.2	31.4	980	7.1	30.4	2,337	
13	5.3	34.1	5.9	34.0	874	7.2	31.6	2,268	
17	5.9	36.5	6.0	35.7	834	6.9	32.7	2,102	
21	5.6	38.1	5.6	37.3	745	7.2	33.5	2,145	
25	5.7	38.4	5.9	38.0	771	7.9	33.8	2,343	
29	5.9	39.4	5.7	38.7	736	8.0	34.2	2,335	
33	6.4	39.3	7.4	39.1	947	8.0	32.0	2,498	
37	5.8	41.0	5.7	39.7	721	7.6	34.1	2,239	
41	5.8	41.3	6.1	39.4	769	8.1	33.5	2,422	
45	5.6	41.8	5.9	38.7	763	8.2	33.9	2,404	
49	4.9	42.5	5.4	38.6	706	7.1	34.6	2,059	
53	5.9	42.7	6.3	38.3	828	7.5	33.3	2,258	
57	5.3	42.0	5.7	37.3	763	7.7	33.3	2,304	
61	5.3	43.6	6.1	38.1	798	7.6	34.6	2,204	
65	5.8	43.7	5.8	38.0	760	8.0	34.3	2,318	
69	6.2	43.5	6.5	37.9	860	8.5	33.8	2,502	
77	11.2	42.2	14.1	37.3	1,889	17.5	33.2	5,276	
81	10.1	42.8	15.0	37.2	2,010	18.6	33.0	5,621	
85			5.5	35.2	774	6.0	31.0	1,923	
88	5.2	40.4	5.4	35.4	767	7.4	31.1	2,392	
93	4.8	37.6	4.1	34.7	586	5.1	31.1	1,654	
97	4.8	38.3	4.5	35.0	650	6.3	31.1	2,012	
101	5.2	38.2	5.0	35.0	713	6.8	30.2	2,246	
104	5.3	37.3	5.1	35.0	724	6.3	30.5	2,054	
Weeks 1-	13:		•						
Mean	5.4	29.5	5.8	29.5	995	7.0	28.3	2,495	
SD <sup>c</sup>	0.4		0.5		91	0.7		260	
CV <sup>d</sup>	7.9		7.8		9.1	10.6		10.4	
Weeks 14	4-52:						_	_	
vlean	5.7	39.8	6.0	38.4	777	7.7	33.6	2,283	
SD	0.4		0.6		74	0.5		154	
CV	6.7		9.7		9.5	6.3		6.8	
Weeks 53	3-104:								
Меап	6.3	41.0	6.8	36.5	932	8.7	32.3	2,674	
SD	2.1		3.5		458	4.2		1,253	
CV	33.8		50.8		49.1	48.8		46.9	

a b

Grams of feed consumed per animal per day Milligrams of HC Yellow 4 consumed per day per kilogram body weight Standard deviation of weekly means

c

d Coefficient of variation = (standard deviation/mean) x 100

#### Feed and Compound Consumption

TABLE I4

Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of HC Yellow 4

	er 0	mino		5,020 ppm			10,020 ppm		
Week	Feed (g/day) <sup>2</sup>	Body Weight (B)	Feed (g/day)	Body Weight (g)	Daze/ Day (mg/Lg/day) <sup>b</sup>	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	
2	5.2	18.3	5.5	18.0	1,528	6.2	17.8	3,498	
5	6.1	20.9	6.5	20.1	1,618	7.4	19.8	3,759	
9	5.9	23.2	6.1	22.6	1,344	6.6	21.7	3,028	
17	5.5	28.9	6.3	27.2	1,166	6.8	24.6	2,768	
21	5.7	31.5	6.0	29.3	1,021	6.8	26.5	2,553	
25	6.2	32.7	6.9	30.3	1,142	7.8	27.0	2,901	
29	7.6	34.4	7.8	32.4	1,207	8.1	27.9	2,907	
33	6.8	35.3	7.6	33.1	1,147	8.2	28.1	2,919	
37	6.8	35.9	7.1	33.1	1,069	7.2	28.5	2,529	
41	7.0	37.7	7.1	34.5	1,036	8.2	29.6	2,779	
45	5.1	38.4	6.3	35.4	895	6.0	29.6	2,011	
49	6.1	39.8	7.1	35.9	992	8.1	29.9	2,718	
53	5.4	40.2	6.6	36.0	914	6.3	29.9	2.108	
57	6.2	39.7	7.3	35.5	1.023	7.6	29.1	2.621	
61	64	41.1	6.6	37.1	889	6.9	29.8	2.307	
65	7.0	41.5	5.8	35.5	820	6.2	29.3	2.120	
69	82	42.2	73	36.1	1.010	7.7	30.4	2.542	
73	83	41.6	80	363	1,010	87	30.2	2,875	
77	79	42.0	82	37.7	1,095	87	31.4	2,784	
81	55	42.0	65	37.2	878	76	30.1	2,533	
85	88	A2 3	75	363	1 029	91	29.3	3,095	
80	70	AD 7	69	35.8	962	72	28.6	2,526	
02	7.5	42.7	6.9	35.0	955	7.2	28.5	2,594	
93	63	42.2	6.4	35.0	000 755	95	28.1	3 371	
101	74	41.7	6.6	25.0	936	84	27.8	3,009	
101	8.9	42.0	9.0	35.4	1,266	10.6	27.7	3,825	
Weeks 1	-13:								
Mean	5.7	20.8	6.0	20.2	1,497	6.7	19.8	3,428	
SD <sup>c</sup>	0.5		0.5		139	0.6		370	
CVd	8.9		8.3		9.3	9.3		10.8	
Weeks 1	4-52:								
Mean	6.3	35.0	6.9	32.4	1,075	7.5	28.0	2,676	
SD	0.8		. 0.6		99	0.8		288	
CV	13.0		8.7		9.8	11.0		10.8	
Weeks 5	3-104:								
Mean	7.2	41.7	7.1	36.1	984	8.0	29.3	2,736	
SD	1.1		0.8		114	1.2		475	

а b

Grams of feed consumed per animal per day Milligrams of HC Yellow 4 consumed per day per kilogram body weight Standard deviation of weekly means Coefficient of variation = (standard deviation/mean) x 100

c d

### 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	218
Table J2	Vitamins and Minerals in NIH-07 Rat and Mouse Ration	218
Table J3	Nutrient Composition of NIH-07 Rat and Mouse Ration	219
Table J4	Contaminant Levels in NIH-07 Rat and Mouse Ration	220

Ingredients <sup>b</sup>	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	

#### TABLE J1 Ingredients of NIH-07 Rat and Mouse Ration<sup>a</sup>

<sup>a</sup> NCI, 1976; NIH, 1978
 <sup>b</sup> 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<sup>a</sup>

	Amount	Source
Α	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D <sub>3</sub>	4,600,000 IU	D-activated animal sterol
K <sub>3</sub>	2.8 g	Menadione
d-a-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 <sub>12</sub>	4,000 μg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	<i>d</i> -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

	Mean 🛨 Standard					
Nutrients	Deviation	Range	Number of Samples			
Protein (% by weight)	$22.31 \pm 0.86$	21.00-24.30	23			
Crude fat (% by weight)	$5.30 \pm 0.66$	4.20-6.40	23			
Crude fiber (% by weight)	$3.59 \pm 0.33$	2.90-4.50	23			
Ash (% by weight)	$6.65 \pm 0.28$	5.96-7.27	23			
Annino Acids (% of total diet)						
Arginine	$1.308 \pm 0.606$	1.210-1.390	8			
Cystine	$0.306 \pm 0.084$	0.181-0.400	8			
Glycine	$1.150 \pm 0.047$	1.050-1.210	8			
Histidine	$0.576 \pm 0.024$	0.531-0.607	8			
Isoleucine	$0.917 \pm 0.029$	0.881-0.944	8			
Leucine	$1.946 \pm 0.055$	1.850-2.040	8			
Lysine	$1.270 \pm 0.058$	1.200-1.370	8			
Methionine	$0.448 \pm 0.128$	0.306-0.699	· 8			
Phenylalanine	$0.987 \pm 0.140$	0.665-1.110	8			
Threonine	$0.877 \pm 0.042$	0.824-0.940	8			
Tryptophan	$0.236 \pm 0.176$	0.107-0.671	8			
Tyrosine	$0.676 \pm 0.105$	0.564-0.794	8			
Valine	$1.103 \pm 0.040$	1.050-1.170	8			
Essential Fatty Acids (% of total diet)						
Linoleic	$2.393 \pm 0.258$	1.830-2.570	7			
Linolenic	$0.280 \pm 0.040$	0.210-0.320	7			
Vitamins						
Vitamin A (IU/kg)	$11,491 \pm 4,854$	4,200-22,000	23			
Vitamin D (IU/kg)	$4,450 \pm 1,382$	3,000-6,300	4			
a-Tocopherol (ppm)	37.95 ± 9.41	22.50-48.90	8			
Thiamine (ppm)	$20.00 \pm 5.29$	12.0-37.0	23			
Riboflavin (ppm)	$7.92 \pm 0.87$	6.10-9.00	8			
Niacin (ppm)	$103.38 \pm 26.59$	65.0-150.0	8			
Pantothenic acid (ppm)	$29.54 \pm 3.60$	23.0-34.0	8			
Pyridoxine (ppm)	$9.55 \pm 3.48$	5.60-14.0	8			
Folic acid (ppm)	$2.25 \pm 0.73$	1.80-3.70	8			
Biotin (ppm)	$0.254 \pm 0.042$	0.19-0.32	8			
Vitamin B <sub>12</sub> (ppb)	$38.45 \pm 22.01$	10.6-65.0	8			
Choline (ppm)	$3,089 \pm 329$	2,400-3,430	8			
Minerals						
Calcium (%)	$1.21 \pm 0.14$	0.91-1.43	23			
Phosphorus (%)	$0.95 \pm 0.06$	0.84-1.10	23			
Potassium (%)	$0.883 \pm 0.078$	0.772-0.971	6			
Chloride (%)	$0.526 \pm 0.092$	0.380-0.635	8			
Sodium (%)	$0.313 \pm 0.390$	0.258-0.371	8			
Magnesium (%)	$0.168 \pm 0.010$	0.151-0.181	8			
Sulfur (%)	$0.280 \pm 0.064$	0.208-0.420	8			
Iron (ppm)	$361 \pm 100$	255.0-523.0	8			
Manganese (ppm)	$91.97 \pm 6.01$	81.70-99.40	8			
Zinc (ppm)	54.72 ± 5.67	46.1064.50	8			
Copper (ppm)	$11.06 \pm 2.50$	8.090-15.39	8			
Iodine (ppm)	$3.37 \pm 0.92$	1.52-4.13	6			
Chromium (ppm)	$1.79 \pm 0.36$	1.04-2.09	8			
Cobalt (ppm)	$0.68 \pm 0.14$	0.490-0.780	4			

	Mean ± Standard				
Contaminants	Deviation <sup>a</sup>	Range	Number of Samples		
Arsenic (ppm)	0.56 ± 0.18	0.18-0.80	23		
Cadmium (pom) <sup>b</sup>	$0.11 \pm 0.03$	<0.10-0.20	23		
Lead (ppm)	$0.54 \pm 0.20$	0.24-1.00	23		
Mercury (ppm)	<0.05		23		
Selenium (ppm)	$0.33 \pm 0.05$	0.23-0.45	23		
Aflatoxins (ppb)	<5.0		23		
Nitrate nitrogen (ppm) <sup>c</sup>	$10.55 \pm 5.40$	2.50-22.0	23		
Nitrite nitrogen (ppm) <sup>c</sup>	$0.84 \pm 1.41$	<0.10-6.10	23		
HA (ppm)	<2.00	•	23		
BHT (ppm) <sup>d</sup>	$2.26 \pm 1.05$	<1.00-4.00	23		
Aerobic plate count (CFU/g) <sup>e</sup>	$140.291 \pm 151.986$	6,200-420,000	23		
Coliform (MPN/g) <sup>f</sup>	$313 \pm 555$	<3.00-2.400	23		
E. coli (MPN/g)	$9.39 \pm 30.64$	<3.00-150	23		
fotal nitrosoamines (ppb) <sup>g</sup>	$6.16 \pm 6.15$	0.80-30.30	23		
V-Nitrosodimethylamine (ppb) <sup>g</sup>	$5.46 \pm 6.19$	0.50-30.00	23		
V-Nitrosopyrrolidine (ppb) <sup>g</sup>	$0.70 \pm 0.73$	0.30-2.70	23		
esticides (ppm)	х.				
α-BHC <sup>h</sup>	<0.01		23		
8-BHC	<0.02		23		
7-BHC	<0.01		23		
s-BHC	< 0.01		23		
Heptachlor	< 0.01		23		
Aldrin	<0.01		23		
Heptachlor epoxide	<0.01		23		
DDE	<0.01		23		
DDD	<0.01		23		
DDT	<0.01		23		
HCB	<0.01		23		
Mirex	<0.01		23		
Methoxychlor	<0.05		23		
Dieldrin	<0.01		23		
Endrin	< 0.01		23		
Telodrin	<0.01		23		
Chlordane	<0.05		23		
Toxaphene	<0.1		23		
Estimated PCBs	<0.2		23		
Ronnel	<0.01		23		
Ethion	<0.02		23		
Trithion	< 0.05		23		
Diazinon	<0.1		23		
Methyl parathion	<0.02		23		
Ethyl parathion	<0.02		23		
Malathion <sup>i</sup>	$0.17 \pm 0.21$	0.05-0.81	23		
Endosulfan I	<0.01		23		
Endosulfan II	<0.01		23		
Endosulfan sulfate	< 0.03		23		

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

Feed Analyses

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

- <sup>a</sup> For values less than the limit of detection, the detection limit is given for the mean.
- <sup>b</sup> Three batches (milled on 22 February 1984, 14 March 1984, and 9 May 1984) contained 0.20 ppm; all others contained <0.10 ppm.
- <sup>c</sup> Sources of contamination: alfalfa, grains, and fish meal
- d Sources of contamination: analia, grans, and its Sources of contamination: soy oil and fish meal
- CFU = colony-forming unit
- f MPN = most probable number
- <sup>g</sup> All values were corrected for percent recovery.
- <sup>h</sup> BHC = hexachlorocyclohexane or benzene hexachloride
- i Twelve lots contained more than 0.05 ppm.

## APPENDIX K SENTINEL ANIMAL PROGRAM

Methods		224
Table K1	Murine Virus Antibody Determinations for Rats and Mice	
	im the 13-Week and 2-Year Feed Studies of HC Yellow 4	226

223
# 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, samples for viral screening were collected from five diet control animals of each sex. At the termination of the 13-week studies, the animals were bled. Blood collected from each animal was allowed to clot, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates, Inc. (Bethesda, MD) for determination of 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/N 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 serum was separated. The serum was 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

Hemagglutination Inhibition PVM Sendai KRV H-1

ELISA

RCV/SDA (sialodacryoadenitis virus) Mycoplasma pulmonis Mycoplasma arthritidis PVM Sendai

#### Time of Analysis

6 and 12 months 6 and 12 months 6, 12, 18, and 24 months 6, 12, 18, and 24 months

6, 12, 18, and 24 months 18 and 24 months

### Mice

During the 13-week studies, samples for viral screening were collected from five diet control animals of each sex. At the termination of the 13-week studies, the animals were bled. Blood collected from each animal was allowed to clot, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates, Inc. (Bethesda, MD) for determination of the antibody titers. The following tests were performed:

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

#### **ELISA**

MHV (mouse hepatitis virus)

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 serum was separated. The serum was 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

Hemagglutination Inhibition PVM Reovirus 3 GDVII Polyoma virus Sendai MVM Ectromelia virus K (papovavirus)

Complement Fixation Mouse adenoma virus LCM Time of Analysis

Study termination

6 and 12 months 6 and 12 months 6 and 12 months 6, 12, 18, and 24 months 6 and 12 months 6, 12, 18, and 24 months 6 and 12 months 24 months

6 and 12 months 6, 12, 18, and 24 months

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

# TABLE K1

Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Feed Studies of HC Yellow 4

	Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-Week	Studies		
Rats	13 weeks	4/10	PVM
Mice	13 weeks	0/10	None positive
2-Year St	udies		۲. ۲
Rats	6 months	0/10	None positive
	12 months	0/10	None positive
	18 months	0/9	None positive
	24 months	2/10	KRV
Mice	6 months	0/10	None positive
,	12 months	0/10	None positive
	18 months	0/9	None positive
	24 months	3/10	M. arthritidis <sup>a</sup>
		,	

<sup>a</sup> Possible Mycoplasma arthritidis

## NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS PRINTED AS OF MAY 1992

#### 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 Butyl Benzyl Phthalate 213 214 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 **Propyl Gallate** 240 Diallyl Phthalate (Mice) 242 Trichloroethylene (Rats and Mice) 243 244 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
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TR No.	CHEMICAL
274	Tris(2-ethylhexyl)phosphate
. 275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl) phosphonium Sulfate &
	Tetrakis(hydroxymethyl) phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	o-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C <sub>23</sub> , 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C <sub>12</sub> , 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	n-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene

- 317 Chlorpheniramine Maleate
- 318 Ampicillin Trihydrate
- 319 1,4-Dichlorobenzene
- 320 Rotenone
- 321 Bromodichloromethane
- 322 Phenylephrine Hydrochloride
- 323 Dimethyl Methylphosphonate
- 324 Boric Acid
- 325 Pentachloronitrobenzene
- 326 Ethylene Oxide
- 327 Xylenes (Mixed)
- 328 Methyl Carbamate
- 329 1,2-Epoxybutane
- 330 4-Hexylresorcinol
- 331 Malonaldehyde, Sodium Salt
- 332 2-Mercaptobenzothiazole
- 333 N-Phenyl-2-naphthylamine
- 334 2-Amino-5-nitrophenol
- 335 C.I. Acid Orange 3
- 336 Penicillin VK

312-103/60011

337 Nitrofurazone

# NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS PRINTED AS OF MAY 1992

TR No.	CIHIEMIICAI.	TR No.	CHIEMHICAL
338	Erythromycin Stearate	370	Benzofuran
339	2-Amino-4-nitrophenol	371	Toluene
340	Indianted Glycerol	372	3,3'-Dimethonybenzidine Dihydrochloride
341	Nitrofurantoin	373	Succinic Anhydride
342	Dichlorvos	374	Glycidol
343	Benzyl Alcohol	375	Vinyl Toluene
344	Tetracycline Hydrochloride	376	Allyl Glycidyl Ether
345	Razamone	377	o-Chlorobenzalmalononitrile
346	Chloroethane	378	Benzaldehyde
347	D-Limonene	379	2-Chloroacetophenone
348	e-Methyldopa Sezquihydrate	380	Epinephrine Hydrochloride
349	Pentechlorophenol	381	d-Carvone
350	Tribromomethane	362	Furtural
351	p-Chloroaniline Hydrochloride	385	Methyl Bromide
352	N-Methylolacrylamide	386	Tetranitromethane
353	2,4-Dichlorophenol	367	Amphetamine Sulfate
354	Dimethemane	386	Ethylene Thiourea
355	Diphenhydramine Hydrochloride	389	Sodium Azide
356	Furozemide	390	3,3'-Dimethylbenzidine Dihydrochloride
357	Hydrochlorothiazide	391	Tris(2-chloroethyl) Phosphate
358	Ochratovin A	392	Chlorinated Water and Chloraminated Water
359	8-Methosypzoralen	393	Sodium Fluoride
360	N,N-Dimethylaniline	395	Probenecid
361	Heyschloroethane	395	Monochloroacetic Acid
362	4-Vinyl-1-Cyclohesene Dieposide	399	Titanccene Dichloride
363	Bromoethane (Ethyl Bromide)	401	2,4-Diaminophenol Dihydrochloride
364	Rhodamine 6G (C.I. Basic Red 1)	405	C.I. Acid Red 114
365	Penteerythritol Tetranitrate	405	7-Butyrolactone
366	Hydroquinone	407	C.I. Pigment Red 3
367	Phenylbutazone	410	Naphthalene
368	Nalidinic Acid	415	Polysorbate 80
369	Alpha-Methylhenzyl Alcohol		•

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